NCC-WCH

Version 2.0

Preterm labour and birth

Appendix H: Evidence tables

NICE Guideline

Methods, evidence and recommendations

1st June 2015

Draft for Consultation

Commissioned by the National Institute for Health and Care Excellence

Disclaimer
Healthcare professionals are expected to take NICE clinical guidelines fully into account when exercising their clinical judgement. However, the guidance does not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of each patient, in consultation with the patient and/or their guardian or carer.

Funding
Registered charity no. 213280

Contents

0 Appendix H: Evidence tables

H.1 Information and support

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Young,E., Tsai,E., O'Riordan,A., A qualitative study of predelivery counselling for extreme prematurity, Paediatrics and Child Health, 17, 432-436, 2012 **Ref Id** 306684 **Country/ies where the study was carried out** Canada **Study type** Qualitative ethnographic study using semistructured, face-to-face interviews **Aim of the study** To determine how to improve predelivery counselling for delivery room resuscitation from parents of neonates born before 27 weeks'	**Sample size** Participants were recruited until saturation was achieved (ie, no new themes or ideas were generated by subsequent interviews). **Characteristics** N= 10 families N= 12 babies (2 sets of twins) **Gestational age at delivery:** 24 weeks n=4 (1 set of twins) 25 weeks n=2 26 weeks n=6 (1 set of twins) **Maternal age at delivery:** 22-37 years **High risk pregnancy:** 8/10 (80%) **Interviewees** Mother and father n=6 Mother only n=4 **Education level** College n=5 University n=4 Unknown n=1 **Emergent (<24 h) or**	**Interventions** Face-to-face, semi-structured interviews conducted at the hospital or the participants' homes. All but one of the interviews was conducted within four years of the child's birth (mean 3.2 years). Both parents were interviewed when possible. The majority of the interviews were jointly conducted by one of the two principal investigators and a research assistant. Interviews took 1 h to 2 h and were audiotaped and transcribed.	**Details** A constant comparative method was used (newly collected data were compared with previously collected data as interviews were completed). During the interview, the interviewers recorded their thoughts and interpretations and briefly discussed them afterwards. Each researcher independently hand-coded each transcript, noting words, phrases or sentences that represented phenomena giving similar phenomena the same label. After labelling, phenomena were grouped to create conceptual categories. The research team met	**Results** **Category 1: Content - Theme: Knowledge** None of the families had any previous knowledge regarding prematurity. (Family 1 did have two children who were EP births at 24 and 26 weeks' GA, but they responded in reference to their first child.) Before being counselled, most parents had assumed that with extreme preterm labour, there was no chance of survival. [He] told me all the issues…I didn't even think that… it was an option to even have a [baby at] 26 weeks…. We were, in all honesty and bluntness, prepared to have a burial for this child. We didn't know what to expect, or severe abnormalities, and we talked about it…through the night. (Family 3) All parents wanted information that was clearly stated regarding the likelihood of survival and what to expect at delivery. All parents desired to be fully informed of the immediate risks for their child. …what we needed would to be told that [they] would administer steroids, his best chances are that you last another 48 hours there could be complications if he doesn't, um, vis-à-vis, breathing… moment by moment until his birth happens and then [they'll] let you know what you have to face. (Family 4)	**Limitations** Theoretical approach 1.1 Is a qualitative approach appropriate? Appropriate 1.2 Is the study clear in what it seeks to do? Clear Study design 2.1 How defensible/rigorous is the research design/methodology? Defensible Data collection 3.1 How well was the data collection carried out? Appropriate Validity 4.1 Is the context clearly described? Clear 4.2 Were the methods reliable? Reliable Analysis 5.1 Are the data 'rich'? Yes 5.2 Is the analysis reliable? Reliable 5.3 Are the findings convincing? Convincing 5.4 Are the conclusions adequate? Adequate Ethics 6.1 Was the study approved by an ethics committee?

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
gestational age **Study dates** June 2005 and May 2007 **Source of funding** Clinical Teachers' Association at Queen's University Endowment Fund	**non-emergent (>24h) delivery** Emergent n=3 Non-emergent n=7 **Received predelivery counselling** Mother only n=3 Both parents n=7 **Recalled being offered choice regarding resuscitation** Yes n=4 No n=6 **Inital counsellor** Paediatric resident n=2 Neonatologist n=3 Neonatal team n=1 Neonatal nurse n=1 Obstetrician n=3 **Inclusion criteria** Parents with a child born between 23 to 26 weeks' GA admitted to the neonatal intensive care unit (NICU) at a tertiary care teaching hospital in Ontario from 1999 to 2006. Potential participants were identified by chart review and selected using purposive sampling. **Exclusion criteria** Families who had moved to, or lived		on several occasions to review the data analysis, noting an emergence of common themes.	One set of parents recounted the experience of having multiple members of the neonatal team counsel them about various aspects of the NICU including ongoing research projects. They believed that this manner of counselling lacked compassion and would have preferred fewer counsellors focusing on information of immediate relevance such as survival and prognosis. …it would almost be a bit more compassionate to tell people we'll deal with it once the baby comes then, you know, we'll see what problems arise, there could be some, but going into the great detail before added a lot of stress to the fact that we were early and all of those things just kept going through our head. (Family 4) **Category 1: Content - Theme: Resuscitation wishes** Most families did not recall explicitly being asked about their resuscitation wishes. We want to focus on just the baby and then if that happens, then we'll deal with it at that time. But we never had that opportunity, other than just between ourselves…they should bring it up and they should discuss it with the parents and then the parents have that opportunity to say, "no, we don't want to talk about it"… (Family 8) In retrospect, three couples (Families 3, 5 and 9) may not have chosen resuscitation, had they known all of the potential complications of prematurity. The parents who lost one twin (Family 9) believed the other twin suffered to such an extent while in the NICU that they would not have proceeded with resuscitation had they known "what was in store." One mother was counselled alone in the middle of the night and believed her	Yes 6.2 Is the role of the researcher clearly described? Yes

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	further than 2 h travelling time from Kingston General Hospital (Kingston, Ontario) Unable to converse in English			awareness was affected by medication. But, to be honest, if somebody would have told me that this is what my life would be like, I don't think that I would have chosen resuscitation. I might have chosen to hold (twin A) for the seven minutes that he cried and let him die. (Family 5) Even parents who had deferred the ultimate decision to the team indicated that parents should have clear opportunities to express their wishes. **Category 1: Content - Theme: Additional resources** All parents suggested that written information, in addition to verbal counselling, would have helped them feel informed and supported. The parents who were provided with pictures found that they enhanced their understanding (Family 1). One mother suggested having a video or a virtual tour of the NICU (Family 10) to help prepare for this experience. **Category 2: Process - Theme: Timing of counselling during pregnancy** Most of the families were seeing high-risk obstetricians during the pregnancy. They wished that they had received counselling about prematurity when the pregnancy was first deemed to be high risk. Three couples believed they were falsely reassured by their physician about the risks of preterm delivery (Families 3, 4 and 9). One mother, who finally conceived via in vitro fertilization after having multiple miscarriages due to an incompetent cervix, recalled: They were just saying don't worry about it though, so I said OK. But I knew when I got pregnant it was pretty iffy all the way. (Family 4)	

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				One couple (Family 1) did suggest that early information regarding prematurity would cause needless worry; this couple was one of two who did not need to see a high-risk specialist before delivery. Two couples (Families 3 and 6) commented that while the risks for conditions such as Down syndrome are discussed antenatally, there is no information routinely given about prematurity even though it is common. They suggested that written pamphlets be available at obstetricians' or family physicians' offices. **Category 2: Process - Theme: Timing of counselling during maternal hospitalization** Seven families waited in hospital more than 24 h, and even couples requiring emergent management waited a few hours before delivery occurred. One mother (Family 5) recalled being admitted twice with spotting at 24 and 25 weeks before going into labour at 26 weeks. She was not counselled until the third admission in the middle of the night. By then she was anemic and on medications that affected her awareness, and fell asleep during the conversation. **Category 2: Process - Theme: Ongoing counselling** After the initial emergency counselling, parents wanted the opportunity to hear the news again, together, if there was time (ie, if delivery was not imminent). The mother who was admitted for weeks after the initial counselling, due to an incompetent cervix, and her partner did not see the team until after the birth. …if they'd have come in even one or two at a time instead of six at a time, and spaced it out and then revisit a day later, just to even pop their head in to say hi, how are you	

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				doing. Oh, I'm OK….that would have made the just before the birth thing a whole lot easier… (Family 4) Although parents acknowledged that physicians are busy and cannot always cater to parents' schedules, they believed that a follow-up visit after parents have had a chance to digest information and formulate questions would improve the communication process. **Category 2: Process - Theme: Impact of counsellors' attitude** Parents indicated that counsellors' messages regarding the survival and prognosis of their EP neonate should be performed in a compassionate manner and that hope should be conveyed after the decision to resuscitate had been made. I don't know what the legalities are, but my feeling at the time was that oh, we needed a lot of positive reinforcement at that moment and what we got was the exact opposite. (Family 4) Parents believed that some counsellors were unnecessarily negative. One mother recalls a physician who simply stated that the team would not proceed with resuscitation. He said to me, OK, if the baby is born today, what we are going to do is just wrap it up, we won't do any heroics, we'll just wrap him up you can hold him for a little bit and then he'll probably just go. (Family 1) This mother recalled being devastated by this mental imagery and described how she subsequently avoided this particular physician throughout the child's course in the NICU.	
Full citation	**Sample size**	**Interventions**	**Details**	**Results**	**Limitations**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Gaucher,N., Payot,A., From powerlessness to empowerment: Mothers expect more than information from the prenatal consultation for preterm labour, Paediatrics and Child Health, 16, 638-642, 2011 **Ref Id** 307076 **Country/ies where the study was carried out** Canada **Study type** Qualitative study **Aim of the study** To explore mothers' concerns about preterm labour and their expectations regarding the prenatal consultation with a neonatologist. **Study dates** Jan - Jun 2007 **Source of funding** Clinical Teachers' Association at Queen's University Endowment Grant	N=5 of seven women who were approached. Information drawn from each interview was analyzed before the next participant was recruited, and women were enrolled until no additional themes were identified **Characteristics** Participants varied in age (ranging from 24 to 36 years) and gestational age (from 26 weeks to 30 2/7 weeks). They were from different social backgrounds and professions. The reasons for hospitalization and outcomes were also diverse: two women had their babies within days of the consultation, and the other three had full-term pregnancies after hospital discharge. **Inclusion criteria** Adult women, with a gestational age of between 26 and 32 weeks, who were admitted to the obstetrics department for preterm labour, had no contact with the neonatology team, were	In-depth interviews, using a semidirective format and lasting 30 min to 60 min, were audio recorded. Women were encouraged to speak freely about their situation and to elaborate on : - main current concerns and stressors - topics the neonatologist should discuss and explain - expectations from the consultation process - roles they believed the neonatologist should play for them	The study used a qualitative approach informed by grounded theory. Interviews were transcribed in their entirety and coded using the constant comparative method of content analysis. Transcriptions were coded, line by line, by the main researcher to construct themes. Each interview was reviewed independently by the second researcher. Codes and themes were systematically discussed between both researchers to confirm uniformity of analysis or until consensus was reached. Identified themes were used to construct a survey addressing women's expectations about the prenatal consultation for preterm labour. This tool was sent for correction to the initial participants six months after their interview. Women confirmed that the	***Main themes identified*** <u>1) Mothers' stressful experience</u> a) Mourning: Having faced bad news regarding several aspects of their health or pregnancy, women tried to adapt quickly from living a healthy pregnancy to preparing for the challenges of prematurity, and found this to be difficult; the roles they had been preparing to play as parents changed. Some women at risk of a hysterectomy faced the possibility of no longer being able to bear children. b) Perceptions of prematurity: All women had negative views about prematurity; several of them compared it with 'horror stories' or 'hell'.All women wished to avoid delivering prematurely. c) Isolation: Women felt isolated from their usual support systems: four had been transferred from another hospital and their families lived far from the institution used for the present study. They expected their hospitalization and bed rest to become prolonged, which was perceived as another difficult challenge to overcome. Furthermore, although isolated from their loved ones, participants believed that they had lost their intimacy or privacy during their hospitalization experience. d) Powerlessness: Women expressed a strong feeling of powerlessness and loss of control. They believed that they had to accept all treatments offered to them to obtain the best possible outcome for themselves and for their baby: "There is nothing we can do. We're a little powerless in all this. So we let ourselves go.	Theoretical approach 1.1 Is a qualitative approach appropriate? Appropriate 1.2 Is the study clear in what it seeks to do? Clear Study design 2.1 How defensible/rigorous is the research design/methodology? Defensible Data collection 3.1 How well was the data collection carried out? Appropriate Validity 4.1 Is the context clearly described? Clear 4.2 Were the methods reliable? Reliable Analysis 5.1 Are the data 'rich'? Yes 5.2 Is the analysis reliable? Reliable 5.3 Are the findings convincing? Convincing 5.4 Are the conclusions adequate? Adequate Ethics 6.1 Was the study approved by an ethics committee? Yes 6.2 Is the role of the researcher clearly described? Yes

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	able to read and write basic French or English, did not have an active psychiatric disorder and had no previously identified fetal malformations. **Exclusion criteria** Women with pregnancies of less than 26 weeks' gestation were excluded		main themes, their concerns and their expectations had been identified and represented in the survey.	We let go and we let them do anything to us." (Mother 5) They were overwhelmed by the number of events experienced in a short period of time; the uncertainty of these events added insecurity and stress: "Uncertainty, it's like vertigo or a precipice. And there is a lot of uncertainty. We don't know when I will deliver. We don't know how I will deliver. We don't know how it will go for the baby. We don't know what awaits the baby after. And we can get surprises, good or bad, for months after that. So it's a lot of uncertainty for a long time." (Mother 3) Main concerns: The baby's health and outcome were the main concerns for most women. One was most worried about her own medical condition. Another had been born prematurely herself, and focused on potential attachment difficulties as a parent and on a prolonged separation from her other children. All participants expressed some concerns about organizing their families' lives around a prolonged hospital stay: "Yesterday, I was preparing my children's things, but I didn't know what to prepare. I had to give them extra everything because I didn't know when I would be back. One of my children goes to school, one goes to daycare and the third one stays at home (…) and he's having his first birthday tomorrow. Now they are staying in two different households. One child is at my mother's house and two children are at my mother-in-law's." (Mother 2) Consultation as a stressor: Women were generally informed by the	

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				obstetrical team in charge of their medical care that they would meet with a neonatologist. However, one woman had not been told this and found out only when approached about participating in the present study; she asked to partake in the study and was, therefore, included after she met with the team responsible for her care. Similar to other participants, she perceived the consultation as an additional source of stress: "Simply knowing that we'll meet the neonatologist is a stressor in itself. It's something really big (…) The fact that I am being offered to meet the neonatologist before anything else makes me realize that, in my case, it is highly probable that I will deliver prematurely." (Mother 5) However, all of the participants looked forward to the consultation so that their questions would be answered; they also hoped that the neonatologist could somehow reassure them, although the information they sought was not perceived as reassuring in itself: "I think that the more the neonatologist will tell me, the more stressed I will be. But I don't like (…) not knowing the answers." (Mother 1) "I am looking forward to meeting them so that they can reassure us. Well, maybe not so that they can reassure us, but so that they can tell us the truth." (Mother 2) <u>2) Empowerment strategies – expectations from the consultation</u> a) Reassurance: Being reassured was the most important objective of the prenatal consultation.	

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				Women realized that they might receive worrisome information about possible complications related to prematurity. They hoped that the neonatologist would find ways to reassure them: "Being reassured and just knowing what to expect. Because right now, I don't really know what to expect. So it's those two aspects, I think. (…) And what I can do as a mother to make sure, really make sure, that my baby is healthy and happy. Because that's really what I want." (Mother 4) b) Information and content: All women expected to receive clear, precise details and statistics about short-term and long-term complications of prematurity specific to their medical condition and related to gestational age. Some anticipated themes were respiratory distress, neurological complications, sepsis, feeding difficulties and length of hospitalization. They hoped the neonatologist would describe some of the technology in the NICU. They reported having learned about prematurity and its complications from friends working in health care, from the media or from their own physicians. Only two of the participants underwent active follow-up for high-risk pregnancies before their enrollment in the present study. One woman suggested that parents visit the NICU before delivery, and believed that written documentation or pictures could be helpful. c) Parental roles and responsibilities: Women expected the neonatologist to explain what their responsibilities would be and what would be expected of them. They wanted help organizing their professional and family lives so they could be available for their baby. They wanted to know how	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				they would be allowed to touch or hold their babies, and wanted to discuss breastfeeding and feeding strategies. Some wanted to know how they might participate in decision-making processes regarding their baby's treatment plans. One woman expressed concern about excessive care and had prepared questions to ask the neonatologist about her legal rights: "I'm not sure the neonatologists would make the same decisions that I would and I am worried they might impose their decisions on us." (Mother 3) d) Consistency of information: Women expected all of the different medical teams involved in their care to communicate among one another to hold consistent discourses about their situation. They reported inconsistency between health care providers' messages as an added source of stress. 3) A trusting patient-doctor relationship: Expectations from the neonatologist a) Structure of the consultation: Women who were interviewed believed that the best time to meet the neonatology team was before labour and delivery. They hoped their spouse would be present. They believed that the neonatologists should explain their role first, and then volunteer information about prematurity and its possible complications. One woman suggested that they sit down during the consultation. They all expected the neonatologists to be open to listening to their concerns and to provide time to answer their questions: "Sometimes, I find it goes fast, that we don't have time to ask our questions. (…) It would only take the doctor an extra minute or two,	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				but it would save us from being anxious and having unanswered questions." (Mother 3) 2) Trust: It was very important that the neonatologist instill a feeling of trust. Women wanted to know that they were in the best place for their baby and themselves to receive optimal care: "We are handing over our lives and our baby's life into the hands of people we've never met before. So, if there's no trust, it's impossible." (Mother 3) 3) Support and strategies: Most women expected the neonatologist to offer support and help them develop strategies to cope with their situation: "It's very important to have a good doctor who can answer your questions and reassure you. (…) I mean, at least they're there to answer your questions and be supportive." (Mother 4) Some also thought that neonatologists should refer them to other members of the health care team to explore various aspects of the problem. One woman, who had undergone in vitro fertilization and fetal reduction, would have preferred to be referred to her own obstetrician for additional information and support	
Full citation Gupton,A., Heaman,M., Learning needs of hospitalized women at risk for preterm birth, Applied Nursing Research, 7, 118-124, 1994	**Sample size** A convenience sample of 34 womeen **Characteristics** The majority of women were white, married and	**Interventions** The Preterm Birth Learning Needs Questionnaire (PBLNQ) which included a rating scale and several open ended questions. The questionnaire was	**Details** The assistant head nurse explained the purpose of the study to each woman, invited them to participate and gave them a questionnaire.	**Results** **Rank ordering of means for importance teaching topics by women at risk of preterm birth (N=34)** Rank | Topic | Mean | SD	**Limitations** Theoretical approach 1.1 Is a qualitative approach appropriate? Appropriate Comments: Quantitative nethods also used 1.2 Is the study clear in

<table>
<tr><th>Study details</th><th>Participants</th><th>Interventions</th><th>Methods</th><th>Outcomes and Results</th><th>Comments</th></tr>
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<td>Ref Id

307215

Country/ies where the study was carried out

Canada

Study type
Descriptive study

Aim of the study
To identify the priority learning needs of hospitalised women at risk of preterm birth

Study dates
Not reported

Source of funding
Not reported</td>
<td>had completed high school education.
4/34 women had a previous preterm birth.
The mean gestational age was 31.3 weeks (range 26-36 weeks).
Reasons for hospitalisation included spontaneous premature rupture of membranes (35%), twin pregnancy with cervical dilation and/or contractions (18%), antepartum haemorrhage (12%), incomptent cervix, polyhydramnios, placenta previa and pre-eclampsia. Some subjects had more than one reason for hospitalisation.

Inclusion criteria
This was a convenience sample of women receiving care on a 12 bed antepartum unit in a tertiary care teaching hospital (over 4000 deliveries/year) in western Canada.

Exclusion criteria
Not stated, but given that this is a convenience sample, by implication, choosing not to complete the</td>
<td>pilot tested with 2 women and content validity of items was reviewed by 2 perinatal nurse experts.
The questionnare consisted of 18 topics commonly included in educational programs for women at risk of preterm birth.
Instructions for completion stated "The following list contains items which are often taught to those at risk for preterm birth. In your opinion which ones are important to be taught?". Each item was rated using a 20 point visual analogue scale ranging from 1 (not very important) to 20 (very important to know).
There were also 4 open ended questions:
1) What is the most important information for a mother who is at risk for pretem birth to know?
2) What concerns do you have about being considered at risk for preterm labour and birth?
3) Are there things that mothers at risk ofor preterm labour and</td>
<td>Completed and blank questionnaires were collected by the assistant head nurse. A completed questionnaire was considered to provide consent to participate.
Data analysis
Topics on the questionnaire were rank ordered from most important to least important. Responses to open-ended questions were examined using content analysis. Themes and recurring regularities were determined and data were categorised and coded. Quantitative and qualitative data were compared to identify convergence or divergence of conceptual themes.</td>
<td>
<table>
<tr><td>1</td><td>The consequences of prematurity for the baby</td><td>19.38</td><td>1.65</td></tr>
<tr><td>2</td><td>Problems of the newborn associated with preterm birth</td><td>19.29</td><td>1.66</td></tr>
<tr><td>3</td><td>How premature babies are cared for at home</td><td>19.21</td><td>1.82</td></tr>
<tr><td>4</td><td>How premature babies grow and develop</td><td>18.71</td><td>3.40</td></tr>
<tr><td>5</td><td>The signs and symptoms of preterm labour</td><td>18.53</td><td>2.60</td></tr>
<tr><td>6</td><td>How premature infants are care for in hospital</td><td>18.09</td><td>2.81</td></tr>
<tr><td>7</td><td>Treatments for preterm labour</td><td>17.91</td><td>3.13</td></tr>
<tr><td>8</td><td>Nutrition and prevention of preterm birth</td><td>17.35</td><td>3.83</td></tr>
<tr><td>9</td><td>How to get rest and relaxation to prevent preterm birth</td><td>16.74</td><td>4.47</td></tr>
<tr><td>10</td><td>What a neonatal intensive care unit looks like</td><td>16.29</td><td>5.22</td></tr>
<tr><td>11</td><td>How to change your lifestyle to reduce risk (eg quit smoking)</td><td>16.18</td><td>4.47</td></tr>
<tr><td>12</td><td>A description of those who are at risk for preterm birth</td><td>16.09</td><td>4.00</td></tr>
<tr><td>13</td><td>How to feel for contractions</td><td>15.97</td><td>5.86</td></tr>
</table>
</td>
<td>what it seeks to do? Clear

Study design
2.1 How defensible/rigorous is the research design/methodology? Defensible

Data collection
3.1 How well was the data collection carried out? Appropriate Comments: Detail is scant

Validity
4.1 Is the context clearly described? Clear Comments: Some definition of participants and setting provided, context bias not discussed
4.2 Were the methods reliable? Reliable/Unreliable/Not sure Comments:
Analysis
5.1 Are the data 'rich'? Poor
5.2 Is the analysis reliable? Reliable Comments : Detail regarding data handling is scant
5.3 Are the findings convincing? Convincing
5.4 Are the conclusions adequate? Adequate
Ethics
6.1 Was the study approved by an ethics committee? Not reported
6.2 Is the role of the</td>
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<tr><th>Study details</th><th>Participants</th><th>Interventions</th><th>Methods</th><th>Outcomes and Results</th><th>Comments</th></tr>
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<td></td>
<td>form would exclude a woman from the study</td>
<td>bither do not need to know or should be taught?
4) What would you tell someone (a friend or relative) to help them cope with being at risk for preterm birth?</td>
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<table>
<tr><td>14</td><td>How to tell when you are having contractions</td><td>15.94</td><td>6.14</td></tr>
<tr><td>15</td><td>How to reduce stress</td><td>15.91</td><td>4.87</td></tr>
<tr><td>16</td><td>The consequences of prematurity for the mother</td><td>15.88</td><td>4.88</td></tr>
<tr><td>17</td><td>Experiences and feelings of other women who have had a preterm labour/birth</td><td>14.68</td><td>5.78</td></tr>
<tr><td>18</td><td>A definition of preterm labour</td><td>14.5</td><td>5.13</td></tr>
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Responses to 4 open ended questions:

• Responses to the first two questions raised a theme of "concern for the baby's well being"

1) What is the most important information for a mother who is at risk for pretem birth to know?
22/34 (67%) indicated a need to know the possible risks or complications to the baby and the baby's chance of survival if premature birth should become a reality.
11/34 (32%) indicated a need for reassurance - to be told that "the baby will be OK" "for the staff to be supportive of the mother" - and assistance in coping - to know "how to prepare oneself psychologically and physically to face the stress, fear, etc"
9/34 (27%) indicated that it was most important for them to know ho a premature birth could be prevented
6/34 (18%) indicated that they wanted ongoing information on the condition of their
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<td>researcher clearly described? Not reported</td>
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Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				baby as their pregnancy progressed. 3/34 (9%) indicated that they wanted information on how to care for a premature baby *2) What concerns do you have about being considered at risk for preterm labour and birth?* 31/34 (91%) indicated concern regarding the baby's survival chances, possible complications or permanent disabilities associated with prematurity and fetall development, especially lung maturation Additional concerns: future care of the baby, how long the baby might be in hospital, whether it would be possible to breastfeed a premature baby, the uncertainty of the situation - "so many unknowns, so many 'ifs' cause fear" *3) Are there things that mothers at risk of preterm labour and either do not need to know or should be taught?* All those responding to this question expressed a desire to be told "everything" - "I like to know exactly what is going on and get all the facts straight, so I can prepare myself both physicallly and psychologically", "The more knowledge that I have the more positive I feel. Not knowing the possibilities is frightening", "...if you are prepared for the worst and it doesn't happen, it feels great. If it does, I think that being totally unprepared could cause serious problems - both personally and in your family" 3/34 (9%) indicated the need for honesty - "Up front honesty is the best way to go. This is enough of a surprise; you don't need any more surprises because you weren't told something", "I prefer to know as much as possible and appreciate honesty in my	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				doctros, coupled with human compassion" Several women included advice for those teaching women at risk: "Give information gradually so mother has time to absorb and accept at her own pace", "Don't tell them something they may have done or not done has increased the risk. It adds to the guilt", "The use of alarming-sounding medical terms that when defined aren't life-threatening [is frightening] - not taking down to a mother but make sure she's famiiliar with the phases and termninology you're using - don't assume someone else has already explained - don't get overly technical - quoting statistics doesn't reassure - you want to know how your baby is doing" *4) What would you tell someone (a friend or relative) to help them cope with being at risk for preterm birth?* 6/34 (18%) indicated to tell other women to rest and relax 6/34 (18%) indicated trusing in the health care system - "I would try to remind them how advanced medicine is and the chances for survival are high", "Reassure them that absolute care is taken when handling preterm labour - competent doctors and nurses, modern technology", "Make sure you know what is happening at all times. Listen closely to what you are told and obey the medical staff" 4/34 (12%) indicated the importance of keeping informed - "Informyourself - talk to others who have gone through it", "To seek professional help and infomration and not to listen to those who know little or nothing", "Ask as may questions as they can regarding effects of preterm labour on baby and mother and read articles/books on preterm	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				births" Advice to maintain a positive attitude was also given: "Don't go on a guilt trip", "Keep an optimistic and positive attitude no matter what", "Hope for the best, prepare for the worst", "Positive imagery and relaxation help"	
Full citation Griffin,T., Kavanaugh,K., Soto,C.F., White,M., Parental evaluation of a tour of the neonatal intensive care unit during a high-risk pregnancy, JOGNN - Journal of Obstetric, Gynecologic, and Neonatal Nursing, 26, 59-65, 1997 **Ref Id** 307382 **Country/ies where the study was carried out** USA **Study type** Qualitative study using naturalistic inquiry **Aim of the study** To describe parents' reaction to a prenatal	**Sample size** 13 expectant parents who had toured a NICU during a high-risk pregnancy **Characteristics** **Mothers' age** Mean 32.7 years (Range 20-42 years) **Mothers' mean educational level** 14.5 years (Range 11-18 years) **Fathers' age** Mean 34.3 years (Range 31-39 years) **Fathers' mean educational level** 13.3 years (Range 12-16 years) **Marital status** 10 parents were married	**Interventions** All parents described a similar format for the tour. Parents were taken directly into all patient care areas of the NICU and were in close proximity to the infants. The following types of intervention were given to parents: • health information, such as weight and gestational age for several infants who were not identified by name • description of equipment for the infant • roles of staff members • description of the parental role in the	**Details** Procedure Immediately after the tour, parents were informed about the study by the nurse who conducted the tour (typically the charge nurse). Parents who expressed and interest in participating were referred to a member of the research team who contacted the parent to schedule an interview. Immediate scheduling of the interview maximised the amount of information the parent recalled and decreased the possibility that the birth would take place before the first interview. Written consent was	**Results** 17 interviews were conducted. 6 parents completed only the first interview. 4 parents completed the first and second interviews. 3 parents completed only completed the second interview. 7/10 first interviews were conducted within 1 week of the tour 3/10 were conducted either 11 or 12 days after the tour The second interview was conducted 2-7 weeks after the baby's birth. 3 parents participated in a combined interview (within a week of birth) because their babies were born before the first interview could be performed 3 categories of information were described by the parents a) description of the tour, specifically how the tour was arranged and the type of information that was included in the tour b) benefits of the tour c) an evaluation of the way the tour was arranged and conducted, and advice from	**Limitations** Theoretical approach 1.1 Is a qualitative approach appropriate? Appropriate 1.2 Is the study clear in what it seeks to do? Clear Study design 2.1 How defensible/rigorous is the research design/methodology? Defensible Comment: a convenience sample was used Data collection 3.1 How well was the data collection carried out? Appropriate Validity 4.1 Is the context clearly described? Clear 4.2 Were the methods reliable? Reliable Analysis 5.1 Are the data 'rich'? Yes 5.2 Is the analysis reliable? Reliable 5.3 Are the findings convincing? Convincing 5.4 Are the conclusions adequate? Adequate

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
tour of the neonatal intensive care unit (NICU) during a high-risk pregnancy and identify advice they have for other parents and health care professionals who participate in such a tour **Study dates** Not stated **Source of funding** Association of Women's Health, Obstetric and Neonatal Nurses (AWHONN)	3 parents were single **Ethnicity** White n=7 Black n=6 Incomes varied from a range of $5,000-$9,999 to a range $75,000-$100,000 **Inclusion criteria** Participants were a convenience sample of 13 parents (10 mothers and 3 fathers) who had toured a mid-Western NICU during a high-risk pregnancy. Mothers were considered to have high risk pregnancies because of one of the following: preterm labour n=2 diabetes mellitus n=2 hypertensive disorders n=2 congenital malformation of the fetus n=2 pregnancy-induced thrombocytopenia n=1 preterm PROM n=1 **Exclusion criteria** Not stated	NICU, including the visitation policy Each participant was interviewed after the NICU tour and again after the birth of his or her baby if admitted to NICU. Separate interview guides, which consisted of open-ended questions and specific probes, were used for the first and second interviews. The first guide addressed: a) maternal obstetric history, including the reason for the the prenatal tour b) description of the tour c) reactions ot the tour d) advice for health care providers and other parents with a high-risk pregnancy The second guide addressed: a) a brief history of the neonate's condition b) the impact of the prenatal tour on the parent's experience in the NICU c) advice for health care	obtained before the first interview. A tape-recorded interview was conducted with each parent in the parent's home or in the hospital. A member of the research team reviewed the daily admission log for the NICU to determine if any of the mothers in the study had delivered a baby admitted to NICU. If so, a research contacted the parent to schedule the second interview once the baby was stable Data Audiotapes were transcribed and checked against the original tapes for accuracy. Major codes and subcodes were developed, based on a review of the typed transcripts. Each of the 17 transcripts was coded and 12/17 were double coded (independent coding	the parents **Benefits of the tour** Parents described benefits of the tour, including that it decreased their fears inspired hope for their baby's prognosis provided reassurance about care in te NICU prepared them for their baby's NICU hospitalisation All parents described at least one of these benefits, including 5 mothers who said the tour was overwhelming or difficult because of the appearance of newborns. 'Well, its just hard when you see something like that. They were so young and so precious and fighting for their lives…. But you are more put at ease by seeing the care that they do receive and the attention that you get. But it's still frightening to see babies that small' **Decreased their fears** Parents reported that because the tour was informative, it decreased their fears about the NICU and the type of care that their newborn might require. 'Because it's so difficult to handle when you don't know. I know it's scary at times and I think the more education that you can receive about it, the better prepared you are to handle it should it happen' Parents stated that just knowing that the NICU existed was helpful. 'Just to know that it was there. And I think it	Ethics 6.1 Was the study approved by an ethics committee? Yes 6.2 Is the role of the researcher clearly described? Yes

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
		providers and other parents with a high-risk pregnancy A special interview guide that included questions from the two guides was developed for parents whose babies were born shortly after the tour and before the first interview could be arranged. At the end of the first interview, each participant also completed a sociodemographic form.	by 2 researchers and comparison of transcripts) before entry into software for qualitative data. The research team analysed all coded data through construction of matrices, which were visual displays of the data that allowed for category identification and description. A summary of the results was sent to 3 parents for member check, a process whereby results are tested with participants	put my wife more relaxed and at ease the fact that they had a facility there that was nearby. We didn't have to worry about going to another hospital because they didn't have a special care nursery. Just the fact that it was there, we could see it, we know that it looked like and so if we were faced with that problem we were at least familiar with it.' The tour gave mothers information about the NICU they needed to share with other family members. One mother indicated that she had gained an understanding of the unit and was better prepared to talk to her child about the NICU. Three of four mothers who were not who were not accompanied on the tour by the fathers reported that they had shared information about the NICU with the fathers, which was comforting to them. One of these mothers described her husband's reaction to their infant's admission to the NICU 'My husband was calm because I had already told him what to expect' **Inspired hope for newborn's prognosis** For several mothers, the tour inspired hope for their newborn's prognosis, especially when the mothers saw very premature infants who were said to be progressing well. One mother said 'The tour gave me hope that he was going to be fine. Seeing babies younger than him thrive……and then seeing the babies approximately his age survive thriving and doing well' Another mother said	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				'It showed me that there is a lot more hope, and I thought about a few years ago or even 10 years ago, babies like this wouldn't have made it' One mother said that after the tour, she was determined to take better care of herself and adhere to her prescription for bed rest to decrease the chance that her infant would be born prematurely. **Provided reassurance about care in the NICU** Parents reported that the tour was comforting and reassuring becaue it gave them an opportunity to observe the type and quality of care that the infants received. One mother said 'I was a lost more comfortable now seeing how they are giving the care and just seeing the environment they are in' Parents felt encouraged when they observed the way that nurses cared for the infants. One mother said 'I saw the love, compassion and empathy that they showed for each of the babies there. So I knew he was going to be treated well' Another mother commented 'Knowing they do care about them and they do realise that they are human and not machines…. You could feel that they really cared and worried' It was especially helpful for the parents to	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				see so many nurses and physicians in the NICU, hearing specific information about primary nursing also helped some mothers to feel more comfortable. Those mothers explained that it was reassuring to know that their questions could be answered because the primary nurse would know their infant. **Prepared parents for their newborn's NICU hospitalisation** All parents whose infants subsequently were cared for in the NICU reported that the tour prepared them for the experience. These parents explained that it helped to acquaint them with the NICU before delivery. One father said '…..we didn't have to worry and wonder. It (the tour) made us understand how it all worked so that we were familiar with it when we did go there. And we didn't worry about what was going to be done because they explained everything beforehand. So, we pretty much knew exactly what their procedures were and how everything was dealt with instead of finding out as they did it…. The tour pretty much prepared us for what we were going to see when we went up there.' One mother speculated on how her reaction to her infant's hospitalisation in the NICU would have been had she not toured the NICU while she was pregnant. She said 'I think it would have been a much more negative experience had I not toured and when there and saw the tubes in my baby's throat and the tape and everything. I don't know if I would have been able to take	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				that….' For one mother, the tour's importance became evidence after her infant was born 'Well I didn't really think much of it until she was born. I thought, well this is an interesting place and all that, but after she was actually born and brought here I kept thinking to myself, I'm glad I came and saw the place before she was born. It kind of helped ease knowing where she was going to be. It made it a lot easier' Finally a mother who initially was overwhelmed after the tour expressed how it prepared her for her newborn's admission to the NICU. She said 'I knew what to expect once I was there. So, I relaxed, and it wasn't overwhelming after I had him and he went to the (NICU)' **Evaluation of arrangement and conducting of the tour** Parents evaluated and provided suggestions on the way the tour was arranged and conducted and offered advice to other parents. In general, all parents recommended that parents in similar circumstances should be offered a prenatal tour of the NICU. One father said, 'I think you should go to the hospital and should try to get a tour of it…. You shouldn't be intimidated by the hospital and all the goings on in a nursery…. you have to get over the fear and ask the right questions and be familiar with that'	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				Parents advised that more health care providers suggest tours to parents diagnosed with a high-risk pregnancy. Two mothers also recommended that other perinatal health care providers should tour the NICU so that they can be supportive to parents. One mother perceived that her need to tour the NICU was not supported by the staff on the antepartum unit. She said 'So, I think some of them should be a little bit more realistic and help the patient prepare for their early delivery much more, rather than saying"Oh, I don't think they should have taken her there" or "it's too much for her"…. If they can just empathise with the patient and be a little more positive, I think the whole stay there would be a lot better as a result' Parents also evaluated and gave specific advice in a number of areas, including tour arrangements type of information provided on the tour the behaviours and knowledge of the tour conductor **Arrangement of the tour** Parent's recommendations for timing of the tour varied. However, several recommended that parents tour the NICU soon after their pregnancies are identified as high-risk. One mother recommended that to minimise anxiety,, parents take the tour soon after deciding to do so. Parents who toured with their partners commented that having each other as a support person was helpful. They recommended that the tour be scheduled so	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				that the partner or other support person could accompany the parent. One mother said 'Now that's the part I wish I could have changed. I wished my husband or somebody had been with me. But nobody was with me ar the time.' One couple also recommended that the tour should be scheduled around other appointments to avoid an additional trip to the hospital' **Type of information given on the tour** Parents reported that it was important to receive detailed information on the following newborns who had a diagnosis or gestational age similar to what was anticipated for their newborn a description of equipment for their newborns roles of staff members a description of the parental role in the NICU, including the visitation policy A mother said ' Just by introducing me to people and explaining the various ages of and their survival and the babies that make it there. That was very comforting' A parent suggested that parents meet with the neonatologist before the tour. It was important for parents to hear about the parental role. One mother said, 'They said if your baby was there, you could come up at any time, if you were the	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				parent….. you could come in and they do encourage bonding with the baby, you can feed the baby, that type of thing. That did put me at ease.' However, all parents did not perceive that they received adequate information on the parental role. A mother said, 'The parental role during the tour could have been more explicit because I was sure of my role during the tour, what would be expected of me or what I could do as far as caring for my baby.' The need for more specific information became apparent to parents after their infants were cared for in the NICU. These parents indicted that they waned more information on expectations for their role in the NICU, breastfeeding, sibling visitation, and the potential for the newborn to be transferred from the NICU to another unit before discharge. Two parents suggested that handouts would supplement or reinforce information that was given during the tour and assis parents to inform family and friends about the NICU. Parents reported that the tour should be individualised to meet the specific needs of parents. Parents perceived the tour as individualised when they went as a couple or an individual rather than in a group, had an opportunity to ask questions, and saw newborns who had a diagnosis or gestational age similar to that expected for their newborn. Therefore it was critical for the nurse conducting the tour to know the parents' maternal-fetal diagnosis. Several	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				parents made additional suggestions, such as having an opportunity to go on a second tour or changing the order in which the NICU patient care areas are shown; these demonstrate the parents' individual needs **Behaviour/knowledge of the tour conductor** Most parents reported that the nurses who conducted the tours were knowledgeable and comforting. These nurses were describe as compassionate, concerned, helpful, and considerate of the time parents needed to understand the information and ask questions. One mother said 'She was a warm lady… putting her hand on my arm, and just somebody touching me made me feel like (I was) relaxed…' One father stated that the nurse who conducted the tour 'knew what was going on and knew the staff, and the staff apparently thought a lot of her…'	
Full citation Sawyer,A., Rabe,H., Abbott,J., Gyte,G., Duley,L., Ayers,S., Parents' experiences and satisfaction with care during the birth of their very preterm baby: A qualitative study, BJOG: An International Journal of Obstetrics and Gynaecology, 120, 637-643, 2013	**Sample size** n=39 (25 mothers and 7 couples). Subjects were recruited from two of three participating hospitals (n = 24 and 15) **Characteristics** Ethnicity: n = 39 White European 29 (74(%), Indian 3 (8(%), Pakistani 2 (5(%),	**Interventions** The interview schedule consisted of 10 open-ended questions used as a guide to explore parents' experiences and satisfaction with care during the birth The interviewer could ask the interviewee to elaborate on the original response or to follow a line of inquiry introduced by the interviewee. Cues and	**Details** A letter of invitation was posted or given to parents if they had been on the neonatal unit for longer than 2 weeks. The study researcher contacted responders to discuss the study and arrange the interview. All interviews were carried out by a psychologist with	**Results** **Overall satisfaction with care** Question: 'Overall, how satisfied would you say you were with the care that you received during the birth?' Extremely satisfied with care and nothing could be improved = 31/39 (80%) parents Generally satisfied with care but certain things could have been improved (eg provision of information) = 7/39 (18%) Dissatisfied with her care = 1/39 (2%) **Factors associated with parents' experiences of care** Four main themes emerged as important determinants of positive or negative	**Limitations** Theoretical approach 1.1 Is a qualitative approach appropriate? Appropriate 1.2 Is the study clear in what it seeks to do? Clear Study design 2.1 How defensible/rigorous is the research design/methodology? Defensible Data collection 3.1 How well was the data collection carried out?

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Ref Id 307400 **Country/ies where the study was carried out** England **Study type** Qualitative study using semi-structured interviews **Aim of the study** To assess the experiences and satisfaction with care of parents during very preterm birth and to identify domains associated with their positive and negative experiences of care. **Study dates** June 2011 and November 2011 **Source of funding** National Institute of Health Research Programme Grants for Applied Research funding scheme	Filipino 2 (5%), Other 3 (8%) Marital status: n = 39 Married/living with partner 37 (94(%), Partner 1 (3(%), Separated 1 (3(%) Education: n = 39 None 2 (5%) GCSEs/O levels 9 (23%), A levels/Diploma/City & Guilds 12 (31%), Undergraduate 6 (15%) Postgraduate 2 (5%) Professional 8 (21%) Employed: n = 33 Income: n = 37 <£10 000 3 (8%), £10 000–19 999 7 (19%), £20 000–29 999 15 (41%), £30 000–39 999 6 (16%), >£40 000 6 (16) Gestation at birth (weeks): n = 32 31–32 11 (35%), 30–31 3 (9%), 29–30 3 (9%), 28–29 3 (9%), 27–28 4 (13%), 26–27 4 (13%), 25–26 1 (3%) 24–25 3 (9%) Type of birth: n = 32 Vaginal 13 (40%), Caesarean 19 (60%), Multiple Birth 11 (34%) Parity: n = 32 1 = 24 (75%), 2 = 6 (19%), 3 = 2 (6%)	prompts were also used to discuss the topic further. Sociodemographic information was collected using a questionnaire and medical records were checked for obstetric and neonatal information	experience of interviewing women in the perinatal period. Parents were informed that the interviewer was not associated with the hospital so as to encourage open and honest responses. Parents were interviewed in a quiet room in the hospital (n=5) or at their home (n=34). Couples were interviewed separately, with the exception of two couples that asked to be interviewed together. Recorded interviews lasted approximately 45 minutes and were anonlymised and transcribed. Data collection ended when no new information emerged from the interviews and data saturation had been achieved. Qualitative analysis of the transcripts used inductive thematic analysis to identify, describe, and analyse themes and patterns within	experiences of care during preterm birth. 1) Staff professionalism 2) Staff empathy 3) Involvement of fathers 4) Birth environment 1) **Staff professionalism** Positive experiences of care were associated with information and explanation, staff being calm in a crisis, and staff appearing confident and in control. Negative experiences of care were associated with staff being perceived as not listening to the woman. <u>Information and explanation</u> 33/39 parents (39 mothers, 4 fathers and 6 mothers in a couple) mentioned this theme. Provision of information was really important and was mentioned by 33 participants (85%). They wanted to be told what would happen during the birth (particularly if they were having a caesarean section), what type of anaesthetic would be administered, and what was going to happen to their baby when he or she was born.The anaesthetist was someone who stood out in participants' minds in terms of providing detailed information and explanations. *"so we actually go down into the operating theatre and again the anaesthesiologist was there and talking to [us] as she said 'I will stay with you the whole time'....and she talked us through everything that was happening and for both of us that was just outstanding, absolutely"* (1 Mother, C/S). It was perceived that someone taking the time to explain what was happening helped them cope with the situation and made the experience less 'traumatic' *"it was a traumatic experience. I think, if it hadn't been explained to us exactly step by*	Appropriate Validity 4.1 Is the context clearly described? Clear 4.2 Were the methods reliable? Reliable Analysis 5.1 Are the data 'rich'? Yes 5.2 Is the analysis reliable? Reliable 5.3 Are the findings convincing? Convincing 5.4 Are the conclusions adequate? Adequate Ethics 6.1 Was the study approved by an ethics committee? Yes 6.2 Is the role of the researcher clearly described? Yes

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	Inclusion criteria - Baby born before 32 weeks of gestation in the previous 6 months - spoke English well. Single parents and individuals within a couple were eligible to partitipcate Parents of babies who died were included. **Exclusion criteria** Women were not approached if attending clinicians considered that they were too unwell to participate. No further details were provided		the data.Transcripts were read to gain familiarity with the data and identify initial codes of interest. Codes were sorted into potential themes, and collated. Themes were reviewed in relation to the generated codes and the entire data set and were were named and defined.	*step it would have been more traumatic...It was just so much easier, because they did go out of their way and they explained absolutely everything to you"* (2 Father, C/S). Participants also wanted information to be explained in a way they could easily understand. *"They told you everything that was going on, what was happening. They make sure you understood, make sure he [father] understood what was going on"* (7 Mother, C/S). One mother wanted more information than she was given during the birth. She had some medical knowledge, and would have liked to know about what was happening throughout her operation in more detail. *"So you feel prodding, and I wasn't told much. I felt I wasn't told much when I was actually in there and hadn't, I didn't know when they'd started to open me up, cut me open...So I didn't know what they were doing, water's, broken my waters....None of that was ever communicated to me."* (8 Mother, C/S). Six participants (15%) commented that the different members of staff introduced themselves and told them what they would be doing. This helped them feel less like they were in a room with people they did not know. *"I mean they were all very, I remember there being 16 people in the room and they were all introducing themselves and what they did"* (6 Mother, C/S). <u>Staff calm in a crisis</u> 11/39 parents (7 mothers, 1 fathers and 3 mothers in a couple) mentioned this theme. Nineteen participants (49%) described	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				feeling frightened of what was going to happen during the birth and for the outcome of their baby. However, the calm attitude of the staff helped them feel more comfortable and at ease. *"you're not as frightened. It's daunting going in a room when you've never been in. All your bits are going to be on show. And you're worried about your children. Are they gonna survive? Are they gonna be born stillborn? You know....they were so relaxed, they made me feel so comfortable"* (4 Mother, C/S). *"I think it was them staying relaxed. Even though it was a rush, it was a stressful time, you could see that, but they were very good at staying calm. But I suppose that's their job in a way, but they were actually very good at it"* (19 Mother, C/S). <u>Confident and in control</u> 8/39 parents (8 mothers, no couples) mentioned this theme. The confidence displayed by staff was important to participants as it demonstrated capability and control. One woman described that the surgeon in charge of her operation portrayed total confidence. *"And the way he mastered the team, I got the absolute… he had an air of confidence and er control of the entire team. He knew what every person was doing. And he was very commanding as well"* (5 Mother, V). Having confidence in the staff seemed to make it easier to hand over control to them. One woman described that she did not feel that she needed to be in control. She trusted the staff and was happy for them to take control of the situation. *"Absolute confidence in the staff. I didn't feel like I needed to know every step of the*	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				way. I was able to just step back, realise that control was not mine. The control was where it should be, with professionals, and they would take good care of them [the babies]" (5 Mother, V). Four mothers (10%) described the doctors as being firm with them, but said this was exactly what they needed. They wanted the staff to take control of the situation and tell them what to do. *"it was very very quick, very shouty: 'you have to do this, you have to do this now'. It was made very clear to me if I didn't push he wouldn't survive. Erm, which was absolutely fantastic, which was what needed to be done"* (3 Mother, V). <u>Staff not listening to the woman</u> 8/39 parents (6 mothers, 1 father and 1 mother in a couple) mentioned this theme. This area contributed to a negative experience of care for participants. Seven mothers (18%) expressed disappointment that the staff did not always listen to what they had to say. These women described telling staff that they felt they were in labour and close to giving birth, and often the staff did not believe or trust what they were saying, which left women feeling ignored and frustrated. *"And then when I started to get pains, I started to tell the midwives, or the nurses that were there. And felt that they didn't actually believe me, because they put me on monitors. And where my waters had gone, the monitors don't pick up the contractions as well. So they were just saying 'no, no, no, the contractions are not real.....basically [you] can't be feeling this amount of pain"* (19 Mother, C/S). One woman described how she tried to tell	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				the midwife that she was about to have her baby, but was not listened to, and as a result no staff were present at the birth. *"The only kind of downside to it, was I kept saying to her, all my family have very quick labours..... I kept saying to her I need to push I need to push and she said I've only checked you half an hour ago, you're only 3cm ..... and she went I'm just popping out the room.....and at that point I just pushed and her head popped out, and no one was in the room apart from me and my partner"*(23 Mother, V). **2) Staff empathy** 21/39 parents (15 mothers, 1 fathers and 5 mothers in a couple) mentioned this theme. Participants' experiences of their care during the birth were also influenced by the interpersonal interactions with care providers, in particular by caring and emotional support, and encouragement and reassurance. <u>Caring and emotional support</u> Twenty-one participants (54%) spoke about the 'warm and friendly' attitude of the staff. In terms of satisfaction with their experience it was important that they were treated in a pleasant manner. Two very different quotes illustrate the importance of the staff treating them as an individual and receiving personalised care. *"I just found our experience very good, it was very I suppose personal in a sense. I wasn't, I didn't feel like a piece of meat. I felt like a human.....and people were caring"* (3 Mother, V). *"But the midwives that should have shown me compassion in the beginning didn't. They were just not bothered"* (30 Mother, V).	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				Mothers spoke about the importance of a member of staff always being with them, and this generally referred to the presence of a midwife. *"one of the nurses just steps out the way, holds your hand, and talks to you.....So it's just nice to have someone there, talking to you and holding your hand and sort of walking you through everything instead of everyone buzzing around"* (2 Mother, C/S). One mother whose baby was born with many complications and died less than 24 hours after the birth described how the caring and supportive attitude of one midwife made her experience of the birth less traumatic than it could have been. *"the midwives were incredible, so during the birth,...we had this amazingly lovely kind of West African um midwife who was, oh just love, like lovely, so nice so, supportive and caring and empathetic and everything that you could possibly want and just really supportive and, so the birth process itself actually, in the scheme of things was relatively easy thing then to go to because I felt very supportive... and she was so lovely"* (32 Mother, V). <u>Encouragement and reassurance</u> 23/39 parents (16 mothers, 3 fathers and 4 mothers in a couple) mentioned this theme. Twenty-three participants (59%) mentioned wanting encouragement and reassurance from the staff. They understood that staff have to be realistic about the situation and the prognosis for their baby, but found it really helpful and encouraging if the staff were able to reassure them in some way. *"Obviously so they can't lie... but just kind of being positive I think really really helps um 'cause you know, it's it's quite terrifying not*	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				having had an operation before and um you know you don't quite know what to expect and things so just people you know just reassuring you, saying nice things" (14, C/S Mother). *"And that's what you want is reassurance, that time, and so yeah, it was very good"* (1 Father, C/S)". Encouragement from the staff also influenced their experience with care at birth. One woman who was feeling scared and tired described how a midwife encouraged her to continue. *"Yeah we were whisked upstairs and at that point I couldn't feel the hand moving so I really freaked out. One of the midwives was there and she could feel a pulse, calm down, gave me cuddles, really calmed me down and said 'you're ok, you've got to do this, you'll get through it.' Really sort of geed me up and gave me that extra bit of strength really*" (3 Mother, V). Another mother described how praise from a midwife contributed positively to her experience. *"you know she was constantly praising "you, you're doing really well, just breathe through it", you know and things like that whereas you get some midwives who just aren't the nicest, so um, the fact that she was as nice as she was"* (23 Mother, V). **3) Involvement of the father** 16/39 parents (7 mothers, 5 fathers and 4 mothers in a couple) mentioned this theme. It was important to the mothers that the baby's father was involved in the birth, and the extent to which staff involved them contributed to a positive or negative experience with care. For example, two women (5%) described how the staff tried to	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				delay the caesarean section so the father could get there for the birth. Three women (8%) also discussed that they had planned their partner's involvement in the birth, and therefore appreciated any effort the staff made to make them feel more involved. *"He got there really quick. But they involved him, once they brought him [to the operating theatre], they told him everything while he was getting changed, what to expect."* (2 Mother, C/S). *"I found it reassuring that they were very happy with [husband] to be sort of looking over their shoulders and sticking his nose in and whatever, so there was no "stand over there dad"* (12 Mother, C/S). Four women (10%) talked of regret that the baby's father was not able to participate more and was not encouraged to feel more involved in the birth by the staff. *"Erm he found it very awkward...When they were being born he just sat out there, wasn't really able to participate...So he felt like a spare part.....when we were rushed to the surgical unit… there were so many people in the room, he felt he didn't know where to stand. He didn't want to get in the way. He knew he needed to get there..let everyone get on with their job. But he felt in the way"* (5 Mother, V). *"I don't think anyone even really spoke to [the father], I mean I I'm reflecting on it now, I don't think anyone did, how was he involved, he wasn't involved at all, so yeah how are you feeling, is there anything I can do, yeah"* (31 Mother, V). It was also important to fathers that they were encouraged to feel involved in the birth. One of the fathers interviewed described how fathers are not normally made to feel	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				involved in the birth, but that this time he was involved from the start. *"Because normally they don't talk to you. To a woman, they say 'right we've got to do this, got to do that' so the lady knows exactly what's happening to her and why. For the bloke.....'Stay down the pub and we'll give you a ring when it's all done and you can come up when it's all nice and clean, in a blanket.' But with [name of hospital], it was completely different"* (2 Father, C/S). **4) Birth environment** 17/39 parents (11 mothers, 3 fathers and 3 mothers in a couple) mentioned this theme. Participants discussed features of the delivery suite and operating theatre that contributed to their positive experience at the birth. Five participants (13%) described that the radio was playing during the birth, which made the environment seem less frightening. *"you know they didn't make it scary in any way at all, they were all quite happy, I think the radio was playing, which was good, you know things like that. The environment didn't seem scary"* (1 Mother, C/S). Three women (8%) also commented on the views from the windows of the operating theatre. It helped them feel 'connected' with the outside world and help take their mind off things. *"it can take your mind off it a bit rather than just sort of grey walls um so yea so I mean that's very much what we remember actually and often sort of comment on it you know to people"* (14 Mother, C/S).	
Full citation Hodnett,Ellen D., Fredericks,Suzanne,	**Sample size** 17 RCTs were included in the systematice	**Interventions** Oakley 1990 Intervention group:	**Details** The Cochrane Pregnancy and	**Results** Postnatal depression Intervention Group : 92/230	**Limitations** NICE Methodology Checklist for systematic

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Weston,Julie, Support during pregnancy for women at increased risk of low birthweight babies, Cochrane Database of Systematic Reviews, -, 2010 **Ref Id** 60207 **Country/ies where the study was carried out** Canada **Study type** Cochrane systematic seview **Aim of the study** To assess the effects of programs that offer additional social support compared with routine care, for pregnant women believed at high risk for giving birth to babies that are either preterm or weigh less than 2500 gm, or both, at birth. To determine whether effectiveness of support was mediated by timing of onset (early versus later in pregnancy) or type of provider (healthcare professional or lay	review. 2 trials reported outcomes relevant to this review **Characteristics** <u>Oakley 1990</u> Country: UK Participants : 509 women (Intervention group n=255, Control group n=254) Inclusion criteria: 1) History of a low birthweight (< 2500 gm) baby 2) < 24 gestational weeks 3) singleton pregnancy 4) fluent in English 5) attending antenatal booking clinics at 4 UK hospitals. The sample was socially disadvantaged: 77% were working class, 18% had unemployed partners, and 41% were smoking on entry <u>Villar 1992</u> Country : 4 centres in Argentina, Brazil, Cuba and Mexico Participants: 2235 pregnant women (Intervention Group = 1115 Control Group = 1120) at risk for giving birth to a low birthweight baby, between 15-22 gestational weeks in	usual antenatal care plus social support by the research midwife at her hospital. The social support intervention consisted of, at a minimum, 3 home visits - at 14, 20, and 28 weeks' gestation - plus 2 telephone contacts or brief home visits between these times. The midwife was also on-call to the mothers 24 hours/day. Semi-structured interview guides provided the basis for flexible and open-ended communication between midwives and mothers.98% of those in the intervention group had at least one home visit Control group: usual antenatal care. <u>Villar 1992</u> Intervention group: aimed at increasing social support and reducing stress and anxiety in pregnancy. A minimum of 4 home visits by specially trained female social workers or obstetrical nurses. The aims of the visits were to strengthen the woman's social	Childbirth Group's Trials Register was searched in January 2010. This register contains trials identified from: 1. quarterly searches of the Cochrane Central Register of Controlled Trials (CENTRAL); 2. weekly searches of MEDLINE; 3. handsearches of 30 journals and the proceedings of major conferences; 4. weekly current awareness alerts for a further 44 journals plus monthly BioMed Central email alerts. No language restrictions were applied. Data collection and analysis Trials were evaluated for methodological quality and appropriateness for inclusion, without consideration of their results. Selection of studies Two review authors independently assessed for inclusion all the potential studies we	Control Group : 10/228 RR = 0.85 (0.69 to 1.05) <u>Less than very satisfied with antenatal care</u> Intervention Group: 51/945 Control Group 45/942 RR = 1.13 (0.76 to 1.67)	<u>reviews</u> The review addresses an appropriate and clearly focused question that is relevant to the guideline review question : Yes The review collects the type of studies you consider relevant to the guideline review question : Yes The literature search is sufficiently rigorous to identify all the relevant studies: Yes Study quality is assessed and reported: Yes An adequate description of the methodology used is included, and the methods used are appropriate to the question : Yes <u>Individual studies</u> <u>Oakley 1990</u> Adequate sequence generation Low risk of bias: Randomization organized in balanced blocks, stratified by centre. The allocations were based on a table of random numbers Allocation concealment Low risk of bias: Enrolling midwife telephoned the coordinating centre to get group assignment Blinding Unclear risk of bias: There

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
woman). **Study dates** Content reviewed as up to date at 3 May 2010 **Source of funding** None	centres in: Rosario,Argentina; Pelotas, Brazil; Havana, Cuba; and Mexico City. Inclusion criteria: Risk was defined as one or more of the following: 1) previous LBW or preterm infant 2) previous fetal or infant death 3) age < 18 4) body weight < = 50 kg, height < = 1.5 m, 5) low family income according to locally adapted cutoff points 6) < 3 years of school 7) smoking or heavy alcohol consumption 8) residence apart from the child's father **Inclusion criteria** Randomized controlled trials (RCTs) comparing a program of additional support during at-risk pregnancy by either a professional (social worker, midwife or nurse) or a specially trained lay person, or both, in an effort to reduce the likelihood of preterm birth or low birthweight; random allocation to treatment and control	network, and to provide direct emotional support and health education. In addition, a special support office - for women to visit without prior appointments or to telephone - was available at each study hospital for all women in the intervention group.90% of women in the intervention group received at least one home visit. Control group: standard antenatal care (not described).	identified as a result of the search strategy. Any disagreement was resolved through discussion or, if required, a third person was consulted. Data extraction and management Two review authors extracted the data using an agreed data extraction form. Discrepancies were resolved through discussion or, if required, a third person was consulted. Data was entered into RevMan and checked for accuracy. Where trial information was unclear, attempts were made to contact the authors of the original reports for clarification Assessment of risk of bias Two review authors independently assessed risk of bias. Any disagreement was resolved through consultation with a third assessor.		was no mention of blinding. Incomplete outcome data addressed Low risk of bias: Medical record data were collected on all but 2 cases. The 6-week questionnaire was completed by 94% of the sample.One-year follow up was obtained on 71% of the sample and 7-year follow up on 47% and no data from them were used in this review. The 1-year and 7-year questionnaires were only mailed to those completing the 6-week questionnaire Selective reporting Low risk of bias: Satisfaction with care was only reported for the intervention group and thus not used in this review. All other outcomes were reported for both groups Other bias Low risk of bias: No other sources of bias noted. Villar 1992 Sequence generation Low risk of bias: The Data Coordinating Centre produced computer generated numbers in balanced blocks of 20 and stratified by centre Allocation concealment Low risk of bias: A sequence of sealed opaque envelopes

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	groups.'Additional support' was defined as some form of emotional support (e.g. counseling, reassurance, sympathetic listening) with or without additional information or advice, or both, occurring during home visits, clinic appointments, and/or by telephone.The additional support could also include tangible assistance (e.g. transportation to clinic appointments, assistance with the care of other children at home). We included studies if the additional support was provided during pregnancy and continued until the birth of the baby, or into the postnatal period. **Exclusion criteria** Trials were excluded if the intervention was solely an educational intervention or if the intervention was of brief duration (e.g. two to three weeks) and not intended to continue until the birth of the baby. We also excluded				was used by a single investigator in each hospital to assign women to groups Blinding Low risk of bias: for all outcomes, data collection at 36 weeks' gestation, postpartum in hospital and at 40 days was blinded Incomplete outcome data addressed Low risk of bias: for all outcomes, in-hospital data collection was done for 93% of the sample and follow up at 40 days postpartum was done for 85%. Data from the follow up at 36 weeks' gestation was not usable as some of the sample had delivered by that gestation Selective reporting Low risk of bias: All outcomes were reported. Other bias Low risk of bias: No other sources of bias noted.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	trials of smoking cessation programs or mind-body interventions for pregnant women.				

H.2 Prophylactic vaginal progesterone and prophylactic cervical cerclage

H.2.1 Prophylactic progesterone

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Dodd,Jodie M., Jones,Leanne, Flenady,Vicki, Cincotta,Robert, Crowther,Caroline A., Prenatal administration of progesterone for preventing preterm birth in women considered to be at risk of preterm birth, Cochrane Database of Systematic Reviews, -, 2013 **Ref Id** 287641 **Country/ies where the study was carried out** Australia	**Sample size** N=9 trials **Characteristics** **Akbari 2009** **Country**: Iran **Participants**: 150 women randomised: 75 to each group. **Inclusion criteria:** 1. Single child pregnancy with the exact age of conception based on LMP was determined and was verified by sonogram before reaching 20 weeks. If the LMP was not available the exact age of pregnancy was based on 2 sonograms that were verified on at least 2 separate weeks 2. Women with a history of 1 or 2 previous early childbirths before reaching 37 weeks of pregnancy or women with a history of prophylactic cervical cerclage or uterine anomalies (unicornuate uterus, bicornuate uterus,	**Interventions** Vaginal or oral progesterone compared to no treatment or placebo	**Details** The Cochrane Pregnancy and Childbirth Group's Trials Register was searched in January 2013. This trial register contains trials identified from: - monthly searches of the Cochrane Central Register of Controlled Trials (CENTRAL) - weekly searches of MEDLINE - weekly searches of EMBASE - handsearches of 30 journals and the proceedings of major conferences - weekly current awareness alerts for a further 44 journals plus	**Results** **Women with a history of spontaneous preterm birth** **Vaginal progesterone versus no treatment** Perinatal mortality Progesterone group = 3/69 No treatment group = 10/72 RR 0.31 (95% CI 0.09 to 1.09) [Fixed effect; 1 trial Akbari 2009] Neonatal death Progesterone group = 3/69 No treatment group = 10/72 RR 0.31 (95% CI 0.09	**Limitations** **Akbari 2009** **Random sequence generation (selection bias)** Unclear risk: Not clear "150 women that had passed the entrance criterion to the study were divided randomly into two groups of 75." **Allocation concealment (selection bias)** Unclear risk: Not reported. **Incomplete outcome data (attrition bias)** Unclear risk: 3 individuals from the control group and 4 from the group receiving progesterone were excluded from the study – reasons for exclusion not clear – but in table of results, 6 people appear to be missing from denominator for the progesterone group (report 69) and not 4 as

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Study type Cochrane systematic review **Aim of the study** To assess the benefits and harms of progesterone administration for the prevention of preterm birth in women and their infants. **Study dates** The inital search was performed in 2008 and rerun in January 2013; review content was assessed as up-to-date by the authors in January 2013 **Source of funding** **Funding for the reviewers** • Mater Research Sport Centre, Mater Health Services Brisbane, South Brisbane, Queensland, Australia. • Department of Maternal Fetal Medicine, Mater Mothers' Hospital, South Brisbane, Queensland, Australia. • The University of Adelaide, Discipline of Obstetrics and Gynaecology, Australia.	septate uterus, arcuate uterus, uterus didelphys) 3. Older than 18 years, younger than 35 years. **Exclusion criteria:** 1. Rupture of membranes PROM 2. Large known fetal anomalies 3 Cervix dilatation larger than 4 cm 4. Contraindications for tocolysis including fetal distress, chorioamnionitis, pre-eclampsia, and haemodynamic instability 5. Allergies to progesterone (dizziness, mygan, visual disturbances, depression, and increased blood sugar during previous consumption of this drug were considered allergic reactions to the hormone.) 6. Not following up with patients 7. Multiple pregnancies 8.The existence of an illness in the mother that necessitated medication, such as high blood pressure, cancer, tension, thromboembolic disease, Kennedy's disease, illnesses that are treated for asthma with oral beta-adrenergic 9. Age younger than 18 or older than 35 10. Existence of IUGR fetuses 11. Unwarranted vaginal bleeding **Intervention Group**: 100 mg of prophylactic vaginal progesterone (Cyclogest) daily between 24th and 34th week of gestation. **Control Group**: Monitoring but no treatment. **Cetingoz 2011** **Country:** Turkey		monthly BioMed Central email alerts No language restrictions were applied. **Data collection and analysis** Two review authors independently assessed all potentially eligible studies for inclusion to this update. Disagreements were resolved through discussion or if necessary a third author was consulted. Two review authors independently extracted data from included studies using a predesigned data extraction form which was then entered into RevMan and checked for accuracy. Further details were requested from authors of the original reports where details were unclear. Risk of bias was assessed by two review authors according to the following criteria, which were judged to be at high, low or unclear risk of bias: - random sequence generation (selection	to 1.09) [Fixed effect; 1 trial Akbari 2009] Preterm birth less than 34 weeks Progesterone group = 4/119 (3.4%) No treatment group = 19/122 (15.6%) RR 0.27 (95% CI 0.05 to 1.38) [Random effects: 2 trials Akbari 2009 and Majhi 2009] Preterm birth less than 37 weeks Progesterone group = 14/119 (11.8%) No treatment group = 42/122 (34.4%) RR 0.34 (95% CI 0.2 to 0.59) [Fixed effect; 2 trials Akbari 2009 and Majhi 2009] Neonatal sepsis Progesterone group = 0/119 (0%) No treatment group = 7/122 (5.7%) RR 0.13 (95% CI 0.02 to 1.01) [Fixed effect; 2 trials Akbari 2009 and Majhi 2009] **Vaginal progesterone versus placebo** Perinatal mortality	described? Results presented for 69 women in progesterone group and 72 in control. **Selective reporting (reporting bias)** Low risk: All expected outcomes appear to have been reported. **Other bias** Unclear risk:Unclear. **Blinding of participants and personnel (performance bias)** Unclear risk: Not reported. **Blinding of outcome assessment (detection bias)** Unclear risk: Not reported. **Cetingoz 2011** **Random sequence generation (selection bias)** Low risk: Computer-generated random-number list - "Patients were allocated according to randomised number table". **Allocation concealment (selection bias)** Low risk:Random-number list generated centrally by research hospital pharmacy. **Incomplete outcome data (attrition bias)** Low risk: 170 high-risk women were eligible – 10 women were excluded before randomisation due to abortion (n = 2), delivery between 20 and 24 weeks (n = 7) and application of cervical cerclage (n = 1). 160 women were randomised – 10 lost during follow-up, 6 from the placebo group and 4 from

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Funding for the Cochrane Editorial Group • National Institute for Health Research, UK. NIHR Programme of centrally-managed pregnancy and childbirth systematic reviews of priority to the NHS and users of the NHS:10/4001/02	**Participants**: 160 women randomised: 84 allocated to intervention and 76 allocated to placebo. **Inclusion criteria:** High-risk pregnant women: twin pregnancies, pregnancies with at least 1 spontaneous preterm birth, uterine malformation. **Exclusion criteria:** Not stated. **Intervention Group:** micronized progesterone (100 mg) administered daily by vaginal suppository between 24 and 34 weeks of gestation. **Control Group:** placebo (100 mg) administered daily by vaginal suppository between 24 and 34 weeks of gestation. **da Fonseca 2003** **Country**: Brazil **Participants**: 157 women considered to be at 'high risk' for preterm birth due to history of previous preterm birth, cervical suture, uterine malformation. **Intervention Group**: Nightly intravaginal pessary of either 100 mg progesterone or placebo from 24 weeks until 28 weeks' gestation, or birth if earlier. **Fonseca 2007** **Country**: Centres in UK, Chile, Brazil and Greece **Participants**: 250 women undergoing transvaginal ultrasound assessment of cervical length, where the cervical length was measured to be 15 mm or less. Women with both singleton and multiple pregnancies were eligible to participate (226 singleton and 24 with twin pregnancies). **Intervention Group**: Nightly		bias) - allocation concealment (selection bias) - incomplete outcome data (attrition bias) - selective reporting (reporting bias) - other bias (not covered by above criteria) - blinding of participants and personnel (performance bias) - blinding of outcome assessment (detection bias) Dichotomous data results were presented as summary risk ratio with 95% confidence intervals. Mean differences were used for continuous data if outcomes were measured in the same way between trials. Standardised mean differences to combine trials that measured the same outcome, but used different methods, if required. Due to insufficient information in the included trials, analyses were not adjusted to account for clustering (to take into account the non-independence of babies from in multiple pregnancy).	Progesterone group = 11/309 (3.6%) Placebo group = 11/302 (3.6%) RR 0.98 (95% CI 0.43 to 2.22) [Fixed effect; 1 trial O'Brien 2007] Intrauterine fetal death Progesterone group = 5/309 (1.6%) Placebo group = 4/302 (1.3%) RR 1.22 (95% CI 0.33 to 4.51) [Fixed effect; 1 trial O'Brien 2007] Neonatal death Progesterone group = 6/309 (1.9%) Placebo group = 7/302 (2.3%) RR 0.84 (95% CI 0.28 to 2.46) [Fixed effect; 1 trial O'Brien 2007] Preterm birth less than 34 weeks Progesterone group = 4/109 (3.7%) Placebo group = 22/104 (21.2%) RR 0.17 (95% CI 0.06 to 0.48) [Fixed effects; 2 trials Cetingoz 2011 and da Fonseca 2003] Preterm birth less	intervention group. 150 women analysed (intervention group - n = 80 - prior preterm birth = 37; uterine malformation = 4; twin gestation = 39) and (placebo group - n = 70 - prior preterm birth = 34; uterine malformation = 8; twin gestation = 28). Analysis was performed according to ITT principle. **Selective reporting (reporting bias)** Unclear risk: Yes – all expected outcomes reported. **Other bias** Unclear risk: Groups were similar in regard to age, pregravid BMI, parity, abortion, and ratio of high-risk groups according to baseline characteristics table. There were no statistically significant differences in demographics. This study included singleton and twin pregnancies - Odd ratio presented, but does not state whether any adjustments made in the analysis. **Blinding of participants and personnel (performance bias)** Low risk: “The participating women, their care-givers, and the research personnel were unaware of the woman’s study-group assignments.” **Blinding of outcome assessment (detection bias)** Unclear risk: Not reported. **da Fonseca 2003**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	intravaginal pessary of either 200 mg micronised progesterone or placebo from 24 weeks until 33 + 6 weeks' gestation, or birth if earlier. **Glover 2011** **Country**: USA. **Participants**: 36 women randomised, 20 allocated to progesterone group and 16 allocated to placebo group. **Inclusion criteria:** Women < 20 weeks' gestation and had at least 1 prior spontaneous preterm birth of a live-born singleton infant between 200/7 weeks and 366/7 weeks' gestation. **Exclusion criteria:** Multiple gestations, the presence of major fetal anomalies, progesterone use in current pregnancy, the presence of a cervical cerclage and the presence of a placenta previa. **Intervention group**: 400 mg (2 200-mg capsules) of oral micronized progesterone MP. Administration of the tables was initiated between 16+0 and 19+6 weeks and was continued until the completion of the 33rd week of gestation. **Control group**: control group took 2 identical placebo capsules for the same time period. **Hassan 2011** **Country**: Multicentre – 44 centres in 10 countries, USA. **Participants**: 465 women randomised, 236 allocated to progesterone and 229 to placebo. **Inclusion criteria**: singleton gestation, gestational age between 19 + 0 and 23		Heterogeneity was assessed using T^2, I^2, and Chi^2 statistics. Heterogeneity was regarded as substantial if an I^2 was greater than 30% and either the T^2 was greater than zero, or there was a low P value (less than 0.10) in the Chi^2 test for heterogeneity. **Subgroup analysis** The following subgroup analyses were done: - time of treatment commencing (before 20 weeks' gestation versus after 20 weeks' gestation) - route of administration (intramuscular, intravaginal, oral, intravenous) - different dosage regimens (divided arbitrarily into a cumulative dose of less than 500 mg per week and a dose of greater than or equal to 500 mg per week) All outcomes were considered in subgroup analyses.	than 37 weeks Progesterone group = 148/418 (35.4%) Placebo group = 160/406 (39.4%) RR 0.67 (95% CI 0.37 to 1.21) [Random effects; 3 trials Cetingoz 2011, da Fonseca 2003 and O'Brien 2007] Preterm birth less than 37 weeks - Therapy started before 20 weeks Progesterone group = 129/309 (41.7%) Placebo group = 123/302 (40.7%) RR 1.03 (95% CI 0.85 to 1.24) [Fixed effect; 1 trial O'Brien 2007] Preterm birth less than 37 weeks - Therapy started after 20 weeks Progesterone group = 19/109 (17.4%) Placebo group = 37/104 (35.6%) RR 0.49 (95% CI 0.3 to 0.78) [Fixed effect; 2 trials Cetingoz 2011 and da Fonseca 2003] **Oral progesterone versus placebo** Adverse drug reaction	**Random sequence generation (selection bias)** Low risk: Random number table. **Allocation concealment (selection bias)** Low risk: Adequate, sequential sealed opaque envelopes. **Incomplete outcome data (attrition bias)** Low risk: 15 women (less than 1%) post-randomisation exclusions. **Selective reporting (reporting bias)** Low risk: The published report includes all expected outcomes (incidence of preterm delivery; frequency of uterine contractions). **Other bias** Low risk: "The two groups were found similar in regard to age, risk factors for preterm delivery, and obstetric history." **Blinding of participants and personnel (performance bias)** Low risk: Caregivers and participants blinded. **Fonseca 2007** **Random sequence generation (selection bias)** Unclear risk: Method of randomisation generation not stated. **Allocation concealment (selection bias)** Low risk: Adequate, central randomisation and identical appearing treatment packs. **Incomplete outcome data**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	+ 6 weeks, transvaginal sonographic cervical length between 10 and 20 mm, without signs and symptoms of preterm labour. **Exclusion criteria**: planned cerclage, acute cervical dilation, allergic reaction to progesterone, current or recent progestogen treatment within 4 weeks, chronic medical conditions that would interfere with study participation or evaluation of the treatment, major fetal anomaly or known chromosomal abnormality, uterine anatomic malformation, vaginal bleeding, known or suspected clinical chorioamnionitis. **Intervention Group**: daily micronised vaginal progesterone gel – women self-administered the study drug once daily in the morning. Each applicator delivered 1.125 g gel containing 90 mg progesterone. **Control Group**: an identical appearing placebo - each applicator delivered 1.125 g gel containing 90 mg placebo. **Majhi 2009** **Country**: India. **Participants**: 50 women randomised: 50 allocated to progesterone and 50 allocate to no treatment. **Inclusion criteria**: women at high risk for preterm birth, having a singleton pregnancy and current gestation 16-24 weeks. High risk was defined by history of at least once prior spontaneous preterm birth of a singleton infant > 20 and < 37 weeks due to spontaneous labour or preterm rupture of fetal membranes. **Exclusion criteria**: women with			Progesterone group = 5/74 (6.8%) Placebo group = 7/74 (9.5%) RR 0.71 (95% CI 0.24 to 2.15) [Fixed effect; 1 trial Rai 2009] Perinatal mortality Progesterone group = 3/74 (4.1%) Placebo group = 7/74 (9.5%) RR 0.43 (95% CI 0.12 to 1.59) [Fixed effect; 1 trial Rai 2009] Neonatal death Progesterone group = 4/119 (3.4%) Placebo group = 19/122 (15.6%) RR 0.27 (95% CI 0.05 to 1.38) [Fixed effect; 1 trial Rai 2009] Preterm birth less than 34 weeks Progesterone group = 22/74 (29.7%) Placebo group = 37/74 (50%) RR 0.59 (95% CI 0.39 to 0.9) [Fixed effect; 1 trial Rai 2009] Preterm birth less than 37 weeks - therapy started after	**(attrition bias)** Low risk: Complete follow-up. **Selective reporting (reporting bias)** Low risk: All expected outcomes are reported. **Other bias** Low risk: "There were no significant differences in baseline characteristics between the placebo and progesterone groups". Singleton and twin pregnancies - adjustment made for infant outcomes, " the analyses of infant outcomes used robust standard errors and were clustered on a maternal identifier to account for the non-independence of twin pairs." **Blinding of participants and personnel (performance bias)** Low risk: Blinding of participants, caregivers, outcome assessors. **Blinding of outcome assessment (detection bias)** Low risk: Blinding of participants, caregivers, outcome assessors. **Glover 2011** **Random sequence generation (selection bias)** Low risk: "Randomization was done by the hospital's research pharmacy using a standard randomization table methodology for two groups." **Allocation concealment (selection bias)** Low risk: Central allocation –

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	multifetal gestation, congenital malformation in the fetus, current or planned cervical cerclage or with any associated medical disorder were excluded. **Intervention Group**: 100 mg natural micronised progesterone capsule intravaginally once daily at bedtime from 20-24 weeks' gestation until 36 weeks. **Control Group**: no placebo – just managed according to the institute protocol. **O'Brien 2007** **Country**: 53 centres worldwide **Participants**: 659 women with a history of prior spontaneous preterm birth. **Exclusions**: adverse reaction to progesterone, progesterone treatment within 4 weeks of randomisation, medical conditions, suspected genital tract malignancy, thromboembolic disease, fetal anomaly, multiple pregnancy, planned cervical cerclage. **Intervention Group:** Nightly vaginal progesterone gel (90 mg) **Control Group**: placebo. **Rai 2009** **Country**: Delhi. **Participants**: 150 women randomised: 75 allocated to progesterone and 75 allocated to placebo. **Inclusion criteria**: asymptomatic women aged between 18 and 35 years who were between 18 and 24 weeks of pregnancy, with a history of at least 1 spontaneous preterm delivery			20 weeks Progesterone group = 5/19 (26.3%) Placebo group = 8/14 (57.1%) RR 0.46 (95% CI 0.19 to 1.11) [Fixed effect; 1 trial Glover 2011] Pregnancy prolongation (weeks) Progesterone group = Mean 15.57 SD 7.38 n=74 Placebo group = Mean 11.1 SD 7.01 n=74 MD 4.47 higher (95% CI 2.15 to 6.79) [Fixed effect; 1 trial Rai 2009] **Women with ultrasound identified short cervix** **Vaginal progesterone versus placebo** Perinatal mortality Progesterone group = 11/371 (3%) Placebo group = 19/361 (5.3%) RR 0.56 (95% CI 0.27 to 1.17) [Fixed effect; 2 trials Fonseca 2007 and Hassan 2011] Intrauterine fetal	pharmacy controlled: "After subjects were randomized to their respective group, the research pharmacy dispensed a 1-month supply of either progesterone or placebo tablets in identical prescription bottles, which were labelled identically as "progesterone study medication." **Incomplete outcome data (attrition bias)** Low risk: 45 patients were eligible for randomisation – 9 women didn't complete the initial evaluation or failed to present to the pharmacy for randomisation and were excluded. 36 were randomised, but it appears that 3 were excluded as only 33 analysed. 3 more participants were excluded – 1 from the MP group as became apparent that she had not had previous spontaneous preterm birth as she had been induced for severe eclampsia; 1 from the placebo group had a spontaneous abortion at 14 weeks; and another from placebo group did not complete her prenatal care at this centre and delivered elsewhere. Analysis appears to be ITT: 2 women ended their participation in the study – but both delivered at this institution and were included in their respective group for all analyses. **Selective reporting (reporting bias)**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	(between 20 weeks and 36 weeks plus 6 days) and with a singleton live pregnancy. **Exclusion criteria**: women with first trimester bleeding, PROM, multiple pregnancy, fetal anomalies or active liver disease were excluded. **Intervention Group**: 100 mg oral micronised progesterone – twice a day from recruitment (18-24 weeks) until 36 weeks or delivery. **Control Group**: placebo - twice a day from recruitment (18-24 weeks) until 36 weeks or delivery. **Inclusion criteria** All published and unpublished randomised controlled trials, in which progesterone was administered for the prevention of preterm birth, subdivided by the reason women were considered to be at risk for preterm birth. **Exclusion criteria** • RCTs that utilised quasi-randomised methodology or cross-over design • RCTs progesterone was administered for the acute treatment of actual or threatened preterm labour (that is, where progesterone was administered as an acute tocolytic medication) • progesterone was administered in the first trimester only for preventing miscarriage.			<u>death</u> Progesterone group = 6/371 (1.6%) Placebo group = 7/361 (1.9%) RR 0.82 (95% CI 0.28 to 2.42) [Fixed effect; 2 trials Fonseca 2007 and Hassan 2011] <u>Neonatal death</u> Progesterone group = 5/371 (1.3%) Placebo group = 12/361 (3.3%) RR 0.41 (95% CI 0.15 to 1.15) [Fixed effect; 2 trials Fonseca 2007 and Hassan 2011] <u>Preterm birth less than 28 weeks</u> Progesterone group = 12/235 (5.1%) Placebo group = 23/223 (10.3%) RR 0.5 (95% CI 0.25 to 0.97) [Fixed effect; 1 trial Hassan 2011] <u>Preterm birth less than 34 weeks</u> Progesterone group = 26/125 (20.8%) Placebo group = 45/125 (36%) RR 0.58 (95% CI 0.38 to 0.87) [Fixed effect; 1 trial	Unclear risk: In methods reports that neonatal mortality will be reported – but was not reported. **Other bias** Low risk: Similar baseline characteristics – no statistically significant differences between groups. **Blinding of participants and personnel (performance bias)** Low risk: "The study subjects' physicians were aware of the study participation but were blinded to the group assignment." **Blinding of outcome assessment (detection bias)** Unclear risk: Not reported. **<u>Hassan 2011</u>** **Random sequence generation (selection bias)** Low risk: Randomisation allocation was 1:1 and was accomplished using a centralised interactive voice response system. Randomisation was stratified according to centre and risk strata (previous preterm birth between 20 and 35 weeks or no previous preterm birth) using a permuted blocks strategy with a block size of 4. **Allocation concealment (selection bias)** Low risk: Reported that allocation concealment accomplished in 3 ways: 1. participant study kits at each site were numbered independently from the treatment

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				Fonseca 2007] Preterm birth less than 37 weeks Progesterone group = 71/235 (30.2%) Placebo group = 76/223 (34.1%) RR 0.89 (95% CI 0.68 to 1.16) [Fixed effect; 1 trial Hassan 2011] Neonatal sepsis Progesterone group = 10/371 (2.7%) Placebo group = 17/361 (4.7%) RR 0.58 (95% CI 0.15 to 2.25) [Random effects; 2 trials Fonseca 2007 and Hassan 2011]	assignments in the randomisation blocks 2. IVR system specified which kit number was to be dispensed to the subject 3. the study drug packaging, applicators and contents were identical in appearance. **Incomplete outcome data (attrition bias)** Low risk: 733 women eligible, 268 declined, 465 randomised. 1 lost to follow-up from progesterone group and 6 from placebo group. ITT analysis performed. **Selective reporting (reporting bias)** Low risk: All expected outcomes reported upon. **Other bias** Low risk: Baseline characteristics were similar between groups. **Blinding of participants and personnel (performance bias)** Low risk: Described as double blind. **Blinding of outcome assessment (detection bias)** Unclear risk: Not reported. **Majhi 2009** **Random sequence generation (selection bias)** Low risk: Computer-generated random-number tables. **Allocation concealment (selection bias)** Low risk: Sequentially numbered opaque sealed envelopes –

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
					provided centrally by Dept Biostatistics and investigators were not involved in the randomisation procedure. **Incomplete outcome data (attrition bias)** Low risk: 118 women met the inclusion criteria; 100 women consented and were included – 50 assigned to each group. There was no attrition during follow-up. **Selective reporting (reporting bias)** Low risk: All expected outcomes reported upon. **Other bias** Unclear risk: Both groups were similar in all characteristics except bacterial vaginosis, which was commoner in the study group. It was treated in both groups. **Blinding of participants and personnel (performance bias)** Unclear risk: Not reported – no placebo used though – so participants would have been aware of assignment. **Blinding of outcome assessment (detection bias)** Unclear risk: Not reported. **O'Brien 2007** **Random sequence generation (selection bias)** Low risk: Random number table. **Allocation concealment (selection bias)** Low risk: Adequate, identical appearing treatment packs.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
					Incomplete outcome data (attrition bias) Low risk: Outcome data available for 611 of 659 women randomised (7.3% women lost to follow-up). **Selective reporting (reporting bias)** Low risk: All expected outcomes reported (preterm birth; maternal, fetal and neonatal outcomes). **Other bias** Low risk: Baseline characteristics similar between groups **Blinding of participants and personnel (performance bias)** Low risk: Women, caregivers and outcome assessors blinded. **Blinding of outcome assessment (detection bias)** Low risk: Women, caregivers and outcome assessors blinded. **Rai 2009** **Random sequence generation (selection bias)** Low risk: "computer-generated numbers table." **Allocation concealment (selection bias)** Low risk: Central allocation suggested - random number table provided by the Department of Biostatistics. **Incomplete outcome data (attrition bias)** Low risk: 150 assessed for eligibility, all enrolled and randomised. 75 randomised to each group –

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
					and 1 lost to follow-up from each group – 74 analysed in each group. ITT not mentioned – but 74 from each group analysed. **Selective reporting (reporting bias)** Low risk: All expected outcomes appear to have been reported . Other bias Low risk: Baseline characteristics similar. **Blinding of participants and personnel (performance bias)** Low risk: "The patients and the medical staff were blinded to the study medication allocation until after the last patient had delivered and the study was complete." **Blinding of outcome assessment (detection bias)** Unclear risk: Not reported.
Full citation Romero,R., Nicolaides,K., Conde-Agudelo,A., Tabor,A., O'Brien,J.M., Cetingoz,E., Da,Fonseca E., Creasy,G.W., Klein,K., Rode,L., Soma-Pillay,P., Fusey,S., Cam,C., Alfirevic,Z., Hassan,S.S., Vaginal progesterone in women with an asymptomatic sonographic short cervix in the midtrimester decreases preterm delivery and	**Sample size** n=5 RCTS n=775 women n=827 babies **Characteristics** **<u>Cetingoz 2011</u>** **Country:** Turkey **Participants:** 160 women randomised: 84 allocated to intervention and 76 allocated to placebo. **Inclusion criteria:** High-risk pregnant women: twin pregnancies, pregnancies with at least 1 spontaneous preterm birth, uterine malformation. **Exclusion criteria:** Not stated.	**Interventions** Intervention: vaginal progesterone Control: placebo.	**Details** The study used Preferred Reporting Items for Systematic reviews and Meta-analyses (PRISMA) guideline for IPD meta-analysis. Literature search performed via MEDLINE, EMBASE, CINAHL, LILACS, Cochrane Central Register of Controlled Trials (CENTRAL), Web of Science, Google Scholar and six research	**Results** **Vaginal progesterone or placebo** Total participants in 5 trials: n=775 women, 827 infants. <u>Preterm birth 33 weeks or fewer (singleton pregnancy)</u> Progesterone group = 41/365 (11%) Placebo group = 72/358 (20%)	**Limitations** No serious limitations

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
neonatal morbidity: a systematic review and metaanalysis of individual patient data, American Journal of Obstetrics and Gynecology, 206, 124-19, 2012 **Ref Id** 223143 **Country/ies where the study was carried out** Various **Study type** Systematic review of individual patients data (IPD) **Aim of the study** To evaluate the efficacy of vaginal progesterone in asymptomatic women with a sonographic short cervix (25mm or less) in the mid-trimester for reduction of preterm birth and improvement of neonatal morbidity and mortality. **Study dates** Search was performed up to 31st December 2011 **Source of funding** Supported in part by Intramural Research	**Intervention Group:** micronized progesterone (100 mg) administered daily by vaginal suppository between 24 and 34 weeks of gestation. **Control Group:** placebo (100 mg) administered daily by vaginal suppository between 24 and 34 weeks of gestation. **Co-intervention:** None **Fonseca 2007** **Country:** Centres in UK, Chile, Brazil and Greece **Participants:** 250 women undergoing transvaginal ultrasound assessment of cervical length, where the cervical length was measured to be 15 mm or less. Women with both singleton and multiple pregnancies were eligible to participate (226 singleton and 24 with twin pregnancies). **Intervention Group:** Nightly intravaginal pessary of either 200 mg micronised progesterone or placebo from 24 weeks until 33 + 6 weeks' gestation, or birth if earlier. **Co-intervention**: cervical cerclage (1 in interventional group and 0 in control group) **Hassan 2011** **Country:** Multicentre – 44 centres in 10 countries, USA. Participants: 465 women randomised, 236 allocated to progesterone and 229 to placebo. **Inclusion criteria:** singleton gestation, gestational age between 19 + 0 and 23 + 6 weeks, transvaginal sonographic cervical length between 10 and 20 mm, without signs and symptoms of preterm labour.		registers of ongoing trials. No language restriction applied and specified search terms were used. Society for Maternal-Fetal Medicine and international meetings on preterm birth, reference lists of identified studies, textbooks, previously published systematic reviews and review articles were also searched. Outcomes were available for patients with a pre-randomisation cervical length of 25mm or smaller. The pre-specified primary outcome measure was preterm birth ≤33 weeks. Intervention Two studies used vaginal progesterone capsules or pessaries 200mg/d, two used vaginal progesterone gel 90mg/d, and the other used vaginal progesterone suppositories 100mg/d. The treatment was started at 24 weeks of gestation in two trials, between 20 and 23 weeks of gestation in two trials, and between 18 and 22 weeks of	RR 0.56 (95% CI, 0.40 to 0.80) Preterm birth 35 weeks or fewer (singleton pregnancy) Progesterone group = 67/365 (18.3%) Placebo group = 100/358 (28%) RR 0.67 (95% CI, 0.51 to 0.87) Preterm birth 28 weeks or fewer (singleton pregnancy) Progesterone group = 20/365 (5.5%) Placebo group = 39/358 (10.9%) RR 0.51 (95% CI, 0.31 to 0.85) Perinatal mortality (singleton pregnancy) Progesterone group = 12/365 (3.3%) Placebo group = 18/358 (5.0%) RR 0.64 (95% CI 0.31 to 1.31) Intrauterine fetal death (singleton pregnancy) Progesterone group = 6/365 (1.6%) Placebo group = 7/358 (1.9%) RR 0.82 (95% CI 0.28 to 2.42)	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Programme, National Institute of Health, department of Health and Human Services	**Exclusion criteria:** planned cerclage, acute cervical dilation, allergic reaction to progesterone, current or recent progestogen treatment within 4 weeks, chronic medical conditions that would interfere with study participation or evaluation of the treatment, major fetal anomaly or known chromosomal abnormality, uterine anatomic malformation, vaginal bleeding, known or suspected clinical chorioamnionitis. **Intervention Group:** daily micronised vaginal progesterone gel – women self-administered the study drug once daily in the morning. Each applicator delivered 1.125 g gel containing 90 mg progesterone. **Control Group:** an identical appearing placebo - each applicator delivered 1.125 g gel containing 90 mg placebo. **Co-intervention:** emergency cerclage (10 in interventional group and 6 in control group) **O'Brien 2007** **Country:** 53 centres worldwide **Participants:** 659 women with a history of prior spontaneous preterm birth. **Exclusions:** adverse reaction to progesterone, progesterone treatment within 4 weeks of randomisation, medical conditions, suspected genital tract malignancy, thromboembolic disease, fetal anomaly, multiple pregnancy, planned cervical cerclage. **Intervention Group:** vaginal progesterone gel (90		gestation in one trial. **Data collection and analysis** Two review authors independently assessed all potentially eligible studies for inclusion to this update. Disagreements were resolved through discussion. Risk of bias was assessed by two review authors according to the Cochrane risk of bias criteria, which were judged to be at high, low or unclear risk of bias: - random sequence generation (selection bias) - allocation concealment (selection bias) - incomplete outcome data (attrition bias) - selective reporting (reporting bias) - other bias (not covered by above criteria) - blinding of participants and personnel (performance bias) - blinding of outcome assessment (detection bias) Additionally the quality of the randomisation	Neonatal death (singleton pregnancy) Progesterone group = 6/365 (1.6%) Placebo group = 11/358 (3.0%) RR 0.53 (95% CI 0.20 to 1.39) Neonatal sepsis (singleton pregnancy) Progesterone group = 11/365 (3.0%) Placebo group = 14/358 (3.9%) RR 0.80 (95% CI 0.37 to 1.74) Bronchopulmonary dysplasia Progesterone group = 4/249 (1.6%) Placebo group = 5/231 (2.1%) RR 0.76 (95% CI 0.21 to 2.79) I^2 was 50% or less in all analyses.The results were robust to sensitivity analyses, the Egger test of funnel plot asymmetry was not significant.	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	mg) administered daily between 18-22 to 37 weeks of gestation. **Control Group:** placebo (100 mg) administered daily by vaginal suppository between 24 and 34 weeks of gestation. **Co-intervention:** None **Rode 2011** **Country:** Denmark, Austria **Participants:** n = 42 **Inclusion criteria: w**omen with diamniotic twin pregnancy **Exclusion criteria:** adverse reaction to progesterone or peanut as active treatment contained peanut oil, progesterone treated for twin to twin transfusion, intentional fetal reduction, medical conditions, rupture of membranes, thromboembolic disease, fetal anomaly, known liver disease, known or suspected malignancy in genital or breasts. **Intervention:** Vaginal progesterone pessary **Co-intervention:** emergency cerclage (2 in interventional group and 2 in control group) **Inclusion criteria** All published and unpublished randomised controlled trials in which asymptomatic women with a sonographic short cervix in the midtrimester were randomly allocated to receive vaginal progesterone or placebo/no treatment for the prevention of preterm birth were considered for inclusion.		processes were assessed using Individual Patient Data (IPD) to review the chronological randomisation sequence and pattern of assignment and the balance of baseline characteristics. Inconsistencies or missing data were discussed with the trial investigators and corrections were made if necessary. Data extraction IPD was obtained from all eligible trial authors. Authors were asked to provide anonymised patient level data about baseline characteristics, experimental intervention, control intervention, co-interventions and pre-specified outcome measures for every randomised patient. A two stage method was used to synthesis IPD data. Trial level summary data was generated from IPD and combined using both fixed and random effects models. Heterogeneity was assessed using I^2 and		

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	Exclusion criteria • RCTs that utilised quasi-randomised • Progesterone was administered for women with threatened preterm labour, second trimester bleedings, or premature rupture of membranes. • Did not report clinical outcomes • progesterone was administered in the first trimester only for preventing miscarriage.		one-stage models were used to assess any differences in effectiveness subgroups. Stratified analysis performed according to pregnancy type (singleton versus multiple). Funnel plots and Egger tests were used to test for funnel plot asymmetry which may indicate publication or other biases. **Subgroup analysis** The following subgroup analyses were done: - Cervical length (<10mm, 10-20mm, 21-25mm) - Obstetric history - Maternal age - Race - Body mass index - Trial characteristics (daily dose)		

H.2.2 Prophylactic cervical cerclage

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Alfirevic,Z., Stampalija,T., Roberts,D., Jorgensen,A.L., Cervical stitch (cerclage) for preventing preterm birth in singleton pregnancy, Cochrane Database of Systematic Reviews, 4, CD008991-, 2012 **Ref Id** 220799 **Country/ies where the study was carried out** Various **Study type** Systematic review of randomised controlled trials **Aim of the study** To assess whether the use of a cervical stitch in singleton pregnancies considered to be at high risk of pregnancy loss based on woman's history and/or ultrasound finding of short cervix and/or physical exam improves subsequent obstetric care and fetal outcome	**Sample size** N = 12 trials N = 3328 women **Characteristics** * additional information which had to be accessed from the full text of the trials because it was not reported in the systematic review **Althuisius, 2001** **Inclusion criteria:** High risk of preterm labour as diganosed by serial transvaginal ultrasonography cervical length < 25mm before gestational age 27 weeks **Exclusion criteria:** Women with pregnancies complicated by fetal congenital /chromosomal anomalies, premature rupture of membranes (PROM), membranes bulging into the vagina or intrauterine infection in the current pregnancy **Sample size:** N = 67 **Intervention:** Therapeutic cerclage with bed rest *suture similar to McDonald **Comparator:** Bed rest only **Other details of care provided:** None given. *All women received amoxicillin/clavulanic acid 1g intravenously every 6 h and metronidazole 500mg intravenously every 8 h for 24 h followed by amoxicillin/clavulanic acid 500mg orally every 8 h and metronidzaole 500mg orally every 8 h for 6 days.	**Interventions** Cervical stitch (cerclage) compared with no cervical stitch or any alternative preventative treatment (e.g. progesterone), plus any comparison of different cerclage protocols (history-versus ultrasound-versus physical exam-indicated cerclage)	**Details** The Cochrane Pregnancy and Childbirth Group's Trials Register was searched in October 2011. This trial register contains trials identified from: - quarterly searches of the Cochrane Central Register of Controlled Trials (CENTRAL) - weekly searches of MEDLINE - weekly searches of EMBASE - handsearches of over 30 journals and the proceedings of major conferences - weekly current awareness alerts for a further 44 journals plus monthly BioMed Central email alerts No language restrictions were applied. **Data collection and analysis** Three review authors independently assessed all potentially eligible studies for inclusion. Disagreements were resolved through discussion. Two review authors independently extracted data from included studies using a predesigned data extraction form. Where authors provided individual	**Results** **1. All perinatal losses (including miscarriage, stillbirth and neonatal deaths)** **a. Cerclage vs. no cerclage** Cerclage: 100/1196 Control: 128/1195 RR 0.78 (95% CI 0.61 to 1.00) I^2 = 0% [Fixed effect; 8 trials: Ezechi, 2004; Rush, 1984; MRC/RCOG, 1993; To, 2004; Althuisius, 2001; Berghella, 2004; Rust, 2000; Owen, 2009] - *History-indicated cerclage vs. no cerclage* Cerclage: 62/770 Control: 77/769 RR 0.80 (95% CI 0.58 to 1.10) I^2 = 0% [Fixed effect; 3 trials: Ezechi, 2004; Rush, 1984; MRC/RCOG, 1993] - *One-off ultrasound-indicated cerclage vs. no cerclage*	**Limitations** **Risk of bias of included studies, as assessed by the review authors and indirectness assessed by NCC-WCH techincal team** Additional notes from NCC-WCH technical team are marked with * None of the participants or clinical staff were blinded to the intervention and it was unclear in all studies whether outcome assessors were blinded. Use of terms 'recue cerclage' or 'emergency cerclage' are those used in the original papers. **Althuisius, 2001** - 3 women lost to follow up and 1 woman excluded due to bulging membranes - Intention-to-treat analysis - Adequate allocation concealment, unclear method of random sequence generation - 2/6 (12.5%) women in the comparator group received "rescue" cerclage - Indirectness: none **Beigi, 2005** - Unclear allocation concealment and method of random sequence generation

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Study dates The search was performed in October 2011; review content was assessed as up-to-date by the authors in February 2012 **Source of funding** University of Liverpool, UK	Women allocated to the intervention group also received indomethacin suppository (100mg 2 h before and 6 h after the operation). Women in both groups were restricted to 48 h bed rest following randomisation. Management after discharge home in both groups did not include prophylactic tocolysis, steroids or home uterine monitoring. ***Country:** The Netherlands **<u>Beigi, 2005</u>** **Inclusion criteria:** singleton pregnancies with an obstetric history of spontaneous midtrimester loss or early preterm delivery (between 15 and 32 weeks) accompanied by painless and progressive dilatation of cervix and/or PROM without preceding contractions, in the absence of other possible causes of midtrimester loss or early preterm delivery (PTD) were included **Exclusion criteria:** multiple pregnancies, major fetal defect, intrauterine fetal death **Sample size:** N = 97 **Intervention:** elective cerclage - cerclage placement between 12 and 15 weeks gestation *McDonald suture **Comparator:** serial transvaginal sonography (biweekly, beginning at 14 weeks gestation) of the cervix. Emergency cerclage performed if endocervical canal length shortened to 20mm or less. *Cerclage performed between 14 and 24 weeks **Other details of care provided:**		patient data this was transferred to agreed forms by two review authors. In studies that included both singleton and twin pregnancies the review authors included only data on singletons. Data were analysed using Review Manager. Risk of bias was assessed by the review authors according to the following criteria, which were judged to be at high, low or unclear risk of bias: - random sequence generation (selection bias) - allocation concealment (selection bias) - blinding of participants and personnel (performance bias) - blinding of outcome assessment (detection bias) - incomplete outcome data (attrition bias) - selective reporting (reporting bias) - other bias (not covered by above criteria) As far as possible, analyses were done on an intention-to-treat basis, where women were analysed in the group to which they were allocated regardless of whether they	Cerclage: 2/26 Control: 3/30 RR 0.77 (95% CI 0.14 to 4.25) I^2 = not applicable [Fixed effect; 1 trial: To, 2004] - *Serial ultrasound-indicated cerclage in high risk for preterm labour vs. no cerclage* Cerclage: 24/253 Control: 37/256 RR 0.66 (95% CI 0.41 to 1.06) I^2 = 28% [Fixed effect; 4 trials: Althuisius, 2001; Berghella, 2004; Rust, 2000; Owen, 2009] - *One-off ultrasound-indicated cerclage in low/unspecified risk for preterm labour vs. no cerclage* Cerclage: 12/147 Control: 11/140 RR 1.01 (95% CI 0.46 to 2.22) I^2 = 23% [Fixed effect; 3 trials: Berghella, 2004; Rust, 2000; To, 2004]	- Unclear whether intention-to-treat analysis - *28/52 (54%) women in the comparator group underwent received cerclage. - Indirectness: none **Berghella, 2004** - Adequate allocation concealment and method of random sequence generation - Review authors believe intention-to-treat analysis although not clearly stated by study authors - *4/31 (13%) women in the intervention arm did not receive cerclage following randomisation - 3 declined and 1 was 4cm dilated and the cerclage could not be placed - *2/30 (7%) women in the comparator arm underwent rescue cerclage. - *Unclear how many women in each group received betamethosone, tocolytics and antibiotics. - Indirectness: 7% of the study population had a twin pregnancy (although review authors used individual patient data for singletons only). Women with advanced cervical dilatation or membrane bulging in to the vagina were not excluded from the study.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	*Women in the intervention group received prophylactic antibiotics but not tocolytics, home uterine monitoring or prophylactic inpatient bed rest. Women in the comparator group did not receive prophylactic tocolytics, routine antibiotics, hospitalisation or home uterine monitoring. 28/52 (54%) women in the comparator group underwent emergency cerclage. ***Country:** Iran **Berghella, 2004** **Inclusion criteria:** Singleton and twin pregnancies, high risk of preterm delivery, *short cervix < 25mm or significant funnelling (> 25%) between 14+0 weeks and 23+6 weeks gestation (serial ultrasound; low risk women identified incidentally were also included) **Exclusion criteria:** Prophylactic cerclage placed on the basis of historic high-risk criteria, last pregnancy delivered at term, major fetal anomaly, triplets or higher multiple gestations, previous inclusion in another trial, current drug abuse, regular contractions that led to preterm labour after identification of abnormal cervix by ultrasonography **Sample size:** N = 61 **Intervention:** Cerclage with bed rest *cerclage placement within 3 days of hospital admission. McDonald suture at 14 to 24 weeks **Comparator:** *Preterm labour education, advise to begin bed rest,		received the allocated intervention. Heterogeneity was assessed using T^2, I^2, and Chi^2 statistics. Heterogeneity was regarded as substantial if T^2 was greater than zero and either I^2 was greater than 30% or there was a low P value (less than 0.10) in the Chi^2 test for heterogeneity. A random-effects model was used if there was clinical or statitistical heterogeneity. **Subgroup analysis** The following subgroup analyses were done: - cervical stitch based on previous obstetric history versus no cerclage - cervical stitch based on one-off ultrasound scan versus no cerclage - cervical stitch based serial ultrasound scanning of the cervix in high risk for preterm birth versus no cerclage - cervical stitch based on one-off ultrasound scanning of the cervix in low risk for preterm birth versus no cerclage - cervical stitch based on physical exam in high risk for preterm birth versus no cerclage	**b. Cerclage versus progesterone** Cerclage: 14/42 Control: 11/37 RR 1.12 (0.58 to 2.16) I^2 = not applicable [Fixed effect; 1 trial: Keeler, 2009] **c. History-indicated cerclage versus ultrasound-indicated cerclage** History-indicated cerclage: 14/125 Ultrasound-indicated cerclage: 10/122 RR 1.37 (95% CI 0.63 to 2.96) I^2 = not applicable [Fixed effect; 1 trial: Simcox, 2009] **2. Serious neonatal morbidity*** **a. Cerclage vs. no cerclage** Cerclage: 39/407 Control: 42/411 RR 0.95 (95% CI 0.63 to 1.43) I^2 = 0% [Fixed effect; 4 trials: To, 2004; Berghella, 2004; Rust, 2000; Owen, 2009] - *One-off ultrasound-	**Ezechi, 2004** - Unclear whether women with multiple pregnancy were included but review authors obtained individual patient date for singletons only for analysis - Method of randomisation and allocation concealment not reported - Unclear whether intention-to-treat analysis - Indirectness: none detected **Keeler, 2009** - Adqeuate allocation concealment and method of random sequence generation - Intention-to-treat analysis - The study authors planned to recruit 160 women but stopped the trial after 3 years of recruitment (n = 79) as interim analysis showed no difference in outcome between treatment groups - Indirectness: 4/42 (9.5%) women in the intervention group and 5/37 (13.5%) in the comparator arm underwent rescue cerclage. **Lazar, 1984** - Unclear allocation concealment and method of random sequence generation - Unclear whether intention-to-treat analysis - Results are a first analysis

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	with bathroom privileges, at home **Other details of care provided:** *Rescue cerclage was allowed if cervical dilatation of ≥ 1 cm was detected on digital examination. Betamethasone was offered at 24 weeks for overt preterm labour or PROM. Antibiotics and tocolytics were left to the discretion of the obstetrician (no further details reported) ***Country:** USA **<u>Ezechi 2004</u>** **Inclusion criteria:** Women with previous preterm delivery **Exclusion criteria:** Not stated **Sample size:** N = 81 **Intervention:** Cerclage at 14 weeks gestation *McDonald suture **Comparator:** No cerclage **Other details of care provided:** None reported **Country:** Nigeria **<u>Keeler, 2009</u>** **Inclusion criteria:** Women with risk factors (previous preterm birth, second trimester loss, cervical surgery, uterine anomaly) for spontaneous PTB were screened with serial transvaginal ultrasound beginning at 16 weeks. Women at "low risk" also screened as part of routine anatomical survey. Women found to have a cervical length ≤ 25 mm offered enrolment *between 16 and 24 weeks gestation **Exclusion criteria:** Known fetal			*indicated cerclage vs. no cerclage* Cerclage: 2/26 Control: 3/30 RR 0.77 (95% CI 0.14 to 4.25) I^2 = not applicable [Fixed effect; 1 trial: To, 2004] *-Serial ultrasound-indicated cerclage in high risk for preterm labour vs. no cerclage* Cerclage: 25/234 Control: 30/241 RR 0.84 (95% CI 0.51 to 1.37) I^2 = 0% [Fixed effect; 3 trials: Berghella, 2004; Rust, 2000; Owen, 2009] *- One-off ultrasound-indicated cerclage in low/unspecified risk for preterm labour vs. no cerclage* Cerclage: 12/147 Control: 9/140 RR 1.40 (95% CI 0.61 to 3.23) I^2 = 03% [Fixed effect; 3 trials: Berghella, 2004; Rust, 2000; To, 2004]	following recruitment of first 500 women to decide whether to continue the trial - Women in cerclage group were more likely to have had previous abortions. Bias largely from one of the centres of the multicentre trial, analyses excluding data from this centre showed no difference to analyses including that centre's data. - *26/238 (11%) women in the comparator group underwent cerclage (unclear whether this was "rescue" cerclage) - *Variation in the number of women receiving tocolytics between the treatment groups - Indirectness: none **MRC/RCOG, 1993** - Adequate allocation concealment and unclear method of random sequence generation - Intention-to-treat analysis - 2% of women were lost to follow up - 586/647 (90.6%) women in the intervention group received cerclage. 49/645 (7.6%) in the comparator group underwent cerclage. - *Likely to be variation in the care protocol between groups and centres - Indirectness: 2% of the study population had a twin

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	chromosomal or structural anomaly, multiple gestation, known allergy to progesterone, ruptured membranes, vaginal bleeding, evidence of an active intra-amniotic infection (diagnosed clinically or by amniocentesis), prolapse of endocervical membranes beyond the external cervical os, persistent uterine activity accompanied by cervical change or an obstetrically indicated delivery **Sample size:** N = 79 **Intervention:** McDonald cerclage at 16 to 24 weeks **Comparator:** Weekly intramuscular injections of 17OHP-C *until 36 weeks gestation **Other details of care provided:** *At gestational ages < 24 weeks rescue cerclages were allowed if membranes prolapsed beyond the level of cerclage in the intervention group or if membranes prolapsed beoynd the level of the external cervical os in the comparator group ***Country:** USA **<u>Lazar, 1984</u>** **Inclusion criteria:** Women's eligibility for inclusion was assessed using a scoring system (*at each visit between 10 and 28 weeks gestation); points were given to two kinds of risk factors "permanent" (factors present before the index pregnancy) and "evolving" (factors that appeared or changed during the pregnancy). Women with a score ≥ 20 points at			**b. Cerclage vs. progesterone** Cerclage: 9/42 Control: 7/37 RR 1.13 (0.47 to 2.74) I^2 = not applicable [Fixed effect; 1 trial: Keeler, 2009] **c. History-indicated cerclage vs. ultrasound-indicated cerclage** History-indicated cerclage: 7/125 Ultrasound-indicated cerclage: 4/122 RR 1.71 (95% CI 0.51 to 5.69) I^2 = not applicable [Fixed effect; 1 trial: Simcox, 2009] *as defined by the trialists. It was not clear from Cochrane review how serious neonatal morbidity is defined. See Other information for individual trial definitions of morbidity **<u>3. Stillbirth</u>** **a. Cerclage vs. no cerclage**	pregnancy (although review authors use individual patient data for singletons only). **Owen, 2009** - Adequate allocation concealment and method of random sequence generation - Intention-to-treat analysis - 138/149 (92.6%) women in the intervention group received cerclage. 14/153 (9.2%) women in the comparator group underwent cerclage - 10 received emergency cerclage and 4 received off-protocol cerclage. - Indirectness: none **Rush, 1984** - Unclear allocation concealment and method of random sequence generation - Intention-to-treat analysis - 1/98 (1%) woman found to have a dilated cervix at 18 weeks gestation in the comparator group received cerclage. 1/96 (1%) woman in the intervention group refused cerclage. - *Variation in the number of women receiving tocolytics between the two groups - Indirectness: none **Rust, 2000** - Unclear allocation concealment and method of

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	the first visit were deemed to be ineligible for the trial, as were women with a score < 9 points at the first or subsequent visits. Women were eligible as soon as a score ≥ 9 had been reached and they remained in the trial whether or not the score subsequently rose to ≥ 20 **Exclusion criteria:** Previous late spontaneous abortion of living fetus at 14–28 weeks, cervix torn up to the lateral cul de sac, cervix opening including inner os (1 finger width), enlargement of uterine isthmus ≥ 1 cm width demonstrated at hysterogram, twin pregnancies **Sample size:** N = 506 **Intervention:** Cerclage *McDonald suture **Comparator:** No cerclage **Other details of care provided:** *154/268 (57.5%) women in the intervention group and 96/238 (40.3%) in the comparator group received tocolytics (no details about antibiotic or steroid treatment) ***Country:** France **MRC/RCOG, 1993** **Inclusion criteria:** Women whose obstetricians were uncertain whether to recommend cervical cerclage, most of whom had a history of early delivery or cervical surgery *latest gestation at trial entry 29 weeks **Exclusion criteria:** not reported **Sample size:** N = 1292 **Intervention:** Cerclage as soon as possible *74% of obstetricians			Cerclage: 15/905 Control: 17/898 RR 0.89 (95% CI 0.45 to 1.75) I² = 0% [Fixed effect; 5 trials: Rush, 1984; MRC/RCOG, 1993; To, 2004; Althuisius, 2001; Berghella, 2004] *- History-indicated cerclage vs no cerclage* Cerclage: 12/731 Control: 12/727 RR 1.00 (95% CI 0.45 to 2.20) I² = 0% [Fixed effect; 2 trials: Rush, 1984; MRC/RCOG, 1993] *- One-off ultrasound-indicated cerclage vs. no cerclage* Cerclage: 0/26 Control: 2/30 RR 0.23 (95% CI 0.01 to 4.58) I² = not applicable [Fixed effect; 1 trial: To, 2004] *- Serial ultrasound-indicated cerclage in high risk for preterm labour vs. no*	random sequence generation - Intention-to-treat analysis - *3/31 (9.7%) women in the intervention group and 1/30 (3.3%) women in the comparator group received rescue cerclage. - Indirectness: 11% of the study population had a multiple pregnancy (although the review authors use individual patient data for singletons only). **Simcox, 2009** - Adequate allocation concealment and method of random sequence generation - Intention-to-treat analysis - 5/248 (2%) women were excluded following randomisation - 3 were subsequently identified as not fitting eligibility criteria and 2 elected to terminate the pregnancy after detection of fetal anomaly - 9 women did not received the randomisation intervention - Significantly more women in the scanning group received progesterone - 39% vs 25% - Indirectness: *decision to give a cerclage in history-indicated arm was made before randomisation. Review authors state that 20% of women in comparator arm received cerclage

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	inserted the suture in bites with no dissection, 14% used a sub-epithelial suture with no dissection and 18% used dissection **Comparator:** No cerclage **Other details of care provided:** *a request was made to keep ancillary treatment with betamimetics and bedrest to a minimum for all women, otherwise subsequent care was left to the clinician responsible (no further details provided) ***Country:** UK, France, Hungary, Norway, Italy, Belgium, Zimbabwe, South Africa, Iceland, Ireland, the Netherlands, Canada **Owen, 2009** **Inclusion criteria:** Multiparous, single gestation women with at least 1 prior spontaneous preterm birth between 10+0 and 33+6 weeks gestation with a cervical length < 25 mm found on serial transvaginal ultrasonography **Exclusion criteria:** Fetal anomaly, planned history-indicated cerclage for a clinical diagnosis of cervical insufficiency, clinically significant maternal-fetal complications that would increase the risk of preterm birth, uterine anomalies **Sample size:** N = 302 **Intervention:** Cerclage *performed after 16 weeks and within 96 hours of qualifying scan, McDonald suture **Comparator:** No cerclage **Other details of care provided:** Women in the comparator group			*cerclage* Cerclage: 0/44 Control: 0/38 RR 0.00 (95% CI 0.00 to 0.00) I^2 = 0% [Fixed effect; 2 trials: Althuisius, 2001; Berghella, 2004] - *One-off ultrasound-indicated cerclage in low/unspecified risk for preterm labour vs. no cerclage* Cerclage: 3/104 Control: 3/103 RR 0.95 (95% CI 0.20 to 4.59) I^2 = 0% [Fixed effect; 2 trials: Berghella, 2004; To, 2004] **b. History-indicated cerclage versus ultrasound-indicated cerclage** History-indicated cerclage: 1/125 Ultrasound-indicated cerclage: 2/122 RR 0.49 (95% CI 0.04 to 5.31) I^2 = not applicable [Fixed effect; 1 trial: Simcox, 2009] **4. Neonatal deaths**	**To, 2004** - Adequate allocation concealment and method of random sequence generation - Intention-to-treat analysis - 122/127 (96.1%) women in the intervention group received cerclage. 2/126 (1.6%) women in the comparator group underwent cerclage - Indirectness: none **Other information** **Individual trial defintions of serious morbidity** The GDG had pre-specified sepsis and bronchopulmonary dysplasia as outcomes of interest. Only one trial (To, 2004) reported the number of events for each outcome making up their chosen composite outcome of serious morbidity. All other trials defined serious morbidity as the following: **Althuisius 2001** Admission to neonatal intensive care unit and/or neonatal death **Berghella, 2004** Composite morbidity: any of respiratory distress syndrome, intraventricular haemorrhage, necrotising enterocolitis or sepsis

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	could receive a physical examination indicated cerclage for acute cervical insufficiency diagnosed on clinical examination. *Early in the trial, in response to a published trial of 17-OHP-C, progesterone for preterm birth prevention became an option for study participants and an additional randomisation stratum was added, reflecting the woman's intention to use progesterone. 117 women were randomised within the progesterone stratum - the effect of the woman's plan to use progesterone on preterm birth < 35 weeks was null. No details provided about steroid or antibiotic use. **Country:** USA **<u>Rush, 1984</u>** **Inclusion criteria:** 2, 3, or 4 previous pregnancies ended spontaneously before 37 completed weeks or at least 1 previous pregnancy ended spontaneously between 14 and 36 completed weeks **Exclusion criteria:** > 35 years of age, smoking > 5 cig/day, cardiac disease, hypertension, diabetes, thyroid disease, recurring first trimester abortions, multiple gestation in present pregnancy, congenital uterine abnormality, uterine fibromyomata, previous cervical surgery - cone biopsy, trachelorrhaphy, cervical cerclage, cervix < 2.0cm long or dilated at entry **Sample size:** N = 194 **Intervention:** Cervical suture - *entry			**<u>before discharge</u>** **a. Cerclage vs. no cerclage** Cerclage: 20/1173 Control: 27/1136 RR 0.73 (95% CI 0.42 to 1.28) I^2 = 0% [Fixed effect; 6 trials: Lazar, 1984; MRC/RCOG, 1993; Rush, 1984; To, 2004; Althuisius, 2001; Berghella, 2004] *- History-indicated cerclage vs. no cerclage* Cerclage: 13/999 Control: 19/965 RR 0.67 (95% CI 0.33 to 1.36) I^2 = 0% [Fixed effect; 3 trials: Lazar, 1984; Rush, 1984; MRC/RCOG, 1993] *- One-off ultrasound-indicated cerclage vs. no cerclage* Cerclage: 2/26 Control: 1/30 RR 2.31 (95% CI 0.22 to 24.01) I^2 = not applicable [Fixed effect; 1 trial: To, 2004]	**Keeler, 2009** Severe morbidity: respiratory distress syndrome requiring mechanical ventilation > 24 hours, intraventriuclar haemorrhage, neonatal sepsis or necrotising enterocolitis **Owen, 2009** Definition of serious morbidity not clearly reported **Rust, 2000** Serious morbidity: mechanical ventilation, respiratory distress, necrotising enterocolitis, intraventricular haemorrhage, sepsis, other life-threatening morbidity **Simcox, 2009** Definition of serious morbidity not clearly reported **To, 2004** Major adverse outcome before hospital discharge: bronchopulmonary dysplasia, intraventricular haemorrhage, retinopathy of prematurity, positive fetal blood culture **<u>Bronchopulmonary dysplasia</u>** **To, 2004** Cerclage: 4/123 (3%) Control: 4/121 (3%) The review authors used as

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	to the trial between 15 and 21 weeks gestation, McDonald cerclage commonly performed day after entry to the trial **Comparator:** No suture **Other details of care provided:** *12/96 (12.5%) women in the intervention group and 8/98 (8.2%) in the comparator group received tocolytics**.** No details provided about steroid or antibiotic use. ***Country:** South Africa **Rust, 2000** **Inclusion criteria:** High or low risk women with demonstrable dilatation of the internal os and either prolapse of membranes at least 25% of the total cervical length or a distal cervical length < 2.5cm, getstational age between 16 and 24 weeks **Exclusion criteria:** Membrane prolapse beyond the external os, any fetal lethal congenital or chromosomal anomaly, clinical evidence of abruption placenta, unexplained vaginal bleeding, chorioamnionitis, persistent uterine activity accompanied by cervical change or any other contraindication for cerclage procedure **Sample size:** N = 61 **Intervention:** McDonald cerclage at 16 to 24 weeks **Comparator:** No cerclage **Other details of care provided:** *All women were treated as inpatients with bed rest, received 48–72 hours of enpiric therapy with clindamycin			*- Serial ultrasound-indicated cerclage in high risk for preterm labour vs. no cerclage* Cerclage: 1/44 Control: 1/38 RR 0.87 (95% CI 0.13 to 5.89) I^2 = 0% [Fixed effect; 2 trials: Althuisius, 2001; Berghella, 2004] *- One-off ultrasound-indicated cerclage in low/unspecified risk for preterm labour vs. no cerclage* Cerclage: 4/104 Control: 6/103 RR 0.63 (95% CI 0.18 to 2.18) I^2 = 0% [Fixed effect; 2 trials: Berghella, 2004; To, 2004] **b. History-indicated cerclage vs. ultrasound-indicated cerclage** History-indicated cerclage: 1/125 Ultrasound-indicated cerclage: 4/122 RR 0.24 (95% CI 0.03 to 2.15)	the denominator the number of women who were randomised even though some babies could not have attained the outcome, e.g. if there was a stillbirth then a baby could not achieve the outcome of 'admission to special care baby unit'. **Definitions of maternal pyrexia** **To 2004** Fever of 38°C or more on two occasions during antenatal hospital stay **MRC/RCOG 1993** Puerperal fever of 38°C or more **Rush 1984** Fever 38°C or more on at least one occasion during the puerperium The review authors used individual patient data for the following studies: Althuisius, 2001; Berghella, 2004; MRC/RCOG, 1993; Rush, 1984; Rust, 2000; To, 2004 In studies that included both singleton and multiple pregnancies, the review authors used only data on singletons

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	(900mg every 9 h) and indomethacin (100mg by rectum as a loading dose followed by 50mg orally every 6 h) and underwent amniocentesis before randomisation. Women assigned to the intervention group continued clindamycin and indomethacin for 24 h after the procedure. Women in the comparator group had withdrawal of clindamycin and indomethacin 24 h after randomisation. ***Country:** USA **<u>Simcox, 2009</u>** **Inclusion criteria:** Singleton pregnancy with at least 1 previous spontaneous delivery between 16+0 and 34+0 weeks, *gestational age < 24+0 weeks **Exclusion criteria:** Woman unable to give informed consent **Sample size:** N = 248 **Intervention:** History-indicated cerclage was offered if the treating clinicians considered that the obstetric history justified a cerclage. There were no proscribed minimum criteria for a history-indicated suture. The decision to insert a cerclage or not, based on history, was made in every case before randomisation by the attending clinician and then carried out if the woman was randomised to the history arm **Comparator:** Cervical length assessment by transvaginal ultrasonography every 2 weeks from entry into the trial until 24+0 weeks gestation. If the cervix shortened to ≤			I^2 = not applicable [Fixed effect; 1 trial: Simcox, 2009] **<u>5. Miscarriage</u>** **a. Cerclage vs. no cerclage** Cerclage: 47/1048 Control: 55/1043 RR 0.84 (95% CI 0.58 to 1.22) I^2 = 0% [Fixed effect; 7 trials: Ezechi, 2004; Rush, 1984; MRC/RCOG, 1993; To, 2004; Althuisius, 2001; Berghella, 2004; Rust, 2000] *- History-indicated cerclage vs. no cerclage* Cerclage: 39/770 Control: 45/769 RR 0.86 (95% CI 0.57 to 1.30) I^2 = 0% [Fixed effect; 3 trials: Ezechi, 2004; Rush, 1984; MRC/RCOG, 1993] *- One-off ultrasound-indicated cerclage vs. no cerclage* Cerclage: 0/26 Control: 0/30 RR 0.00 (95% CI	Single centre trials (all others were multicentre): Beigi, 2005; Ezechi, 2004; Keeler, 2009; Rush, 1984; Rust, 2000 NB: outcome data for all perinatal losses and serious neonatal morbidity in the study To, 2004 are the same. Individual patient data for Rust 2000 are double the study population reported in the published paper (127 and 61, respectively)

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	20 mm a cervical cerclage was inserted **Other details of care provided:** *25/126 (19.8%) women in the history-indicated group received a cerclage stitch and 39/119 (32.8%) women in the ultrasound scanning group received a cerclage stitch (data reported in abstract, JOG 2007 suppl 1, not in main report of study) **Country:** UK **<u>To, 2004</u>** **Inclusion criteria:** Singleton pregnancy, cervical length ≤ 15 mm in single ultrasound scan, gestational age 22–24 weeks **Exclusion criteria:** Major fetal abnormalities, painful regular uterine contractions, history of ruptured membranes, cervical cerclage in situ, dilated cervix found during transvaginal ultrasonography **Sample size:** N = 253 **Intervention:** Shirodkar cerclage **Comparator:** No cerclage **Other details of care provided:** *All women were given prophylactic corticosteroids (two doses of dexmethasone, 12 mg intramuscularly, 12 h apart) at 26–28 weeks gestation. No other interventions were routinely recommended (tocolytics, antibiotics or bed rest). Women assigned to intervention group received a single dose of intravenous erythromycin (500mg) intraoperatively. **Country:** UK, Brazil, South Africa,			0.00 to 0.00) I^2 = not applicable [Fixed effect; 1 trial: To 2004] *- Serial ultrasound-indicated cerclage in high risk for preterm labour vs. no cerclage* Cerclage: 6/105 Control: 9/104 RR 0.65 (95% CI 0.25 to 1.66) I^2 = 0% [Fixed effect; 3 trials: Althuisius, 2001; Berghella, 2004; Rust, 2000] *- One-off ultrasound-indicated cerclage in low/unspecified risk for preterm labour vs. no cerclage* Cerclage: 2/147 Control: 1/140 RR 1.72 (95% CI 0.16 to 18.22) I^2 = 0% [Fixed effect; 3 trials: Berghella, 2004; Rust, 2000; To, 2004] **b. Cerclage versus progesterone** Cerclage: 5/42 Control: 3/37	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	Slovenia, Greece, Chile **Inclusion criteria** Randomised trials comparing cervical stitch in singleton pregnancies considered to be at high risk of pregnancy loss **Exclusion criteria** Cross-over trials and quasi-randomised studies Multiple pregnancy			RR 1.47 (0.38 to 5.73) I^2 = not applicable [Fixed effect; 1 trial: Keeler, 2009] **c. History-indicated cerclage versus ultrasound-indicated cerclage** History-indicated cerclage: 16/170 Ultrasound-indicated cerclage: 9/174 RR 1.71 (95% CI 0.55 to 5.30) I^2 = 46% [Random effect; 2 trials: Beigi, 2005; Simcox, 2009] **6. Preterm birth before 37 completed weeks** **a. Cerclage vs. no cerclage** Cerclage: 389/1464 Control: 480/1434 RR 0.80 (95% CI 0.69 to 0.95) I^2 = 39% [Random effects; 9 trials: Ezechi, 2004; Lazar, 1984; Rush, 1984; MRC/RCOG, 1993; To, 2004; Althuisius, 2001; Berghella, 2004; Rust, 2000; Owen,	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				2009] *- History-indicated cerclage vs. no cerclage* Cerclage: 215/1038 Control: 249/1007 RR 0.86 (95% CI 0.59 to 1.27) I^2 = 62% [Random effects; 3 trials: Ezechi, 2004; Lazar, 1984; Rush, 1984; MRC/RCOG, 1993] *- One-off ultrasound-indicated cerclage vs. no cerclage* Cerclage: 9/26 Control: 19/30 RR 0.55 (95% CI 0.30 to 0.99) I^2 = not applicable [Random effects; 1 trial: To, 2004] *- Serial ultrasound-indicated cerclage in high risk for preterm labour vs. no cerclage* Cerclage: 110/253 Control: 144/257 RR 0.78 (95% CI 0.60 to 1.02) I^2 = 38% [Random effects; 4 trials: Althuisius,	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				2001; Berghella, 2004; Rust, 2000; Owen, 2009] *- One-off ultrasound-indicated cerclage in low/unspecified risk for preterm labour vs. no cerclage* Cerclage: 55/147 Control: 68/140 RR 0.80 (95% CI 0.55 to 1.16) I^2 = 31% [Random effects; 3 trials: Berghella, 2004; Rust, 2000; To, 2004] **b. Cerclage versus progesterone** Cerclage: 22/42 Control: 22/37 RR 0.88 (0.60 to 1.30) I^2 = not applicable [Fixed effects; 1 trial: Keeler, 2009] **c. History-indicated cerclage versus ultrasound-indicated cerclage** History-indicated cerclage: 5/45 Ultrasound-indicated cerclage: 8/52 RR 0.72 (95% CI 0.25 to 2.05)	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				I^2 = not applicable [Fixed effect; 1 trial: Beigi, 2005] **<u>7. Preterm delivery before 34 completed weeks</u>** **a. Cerclage versus no cerclage** Cerclage: 210/1196 Control: 277/1196 RR 0.79 (95% CI 0.68 to 0.93) I^2 = 0% [Random effects; 8 trials: Ezechi, 2004; Rush, 1984; MRC/RCOG, 1993; To, 2004; Althuisius, 2001; Berghella, 2004; Rust, 2000; Owen, 2009] *- History-indicated cerclage vs. no cerclage* Cerclage: 106/770 Control: 138/769 RR 0.76 (95% CI 0.40 to 1.46) I^2 = 57% [Random effects; 3 trials: Ezechi, 2004; Rush, 1984; MRC/RCOG, 1993] *- One-off ultrasound-indicated cerclage vs. no cerclage*	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				Cerclage: 6/26 Control: 11/30 RR 0.63 (95% CI 0.27 to 1.46) I^2 = not applicable [Random effects; 1 trial: To, 2004] *- Serial ultrasound-indicated cerclage in high risk for preterm labour vs. no cerclage* Cerclage: 65/253 Control: 90/257 RR 0.77 (95% CI 0.55 to 1.10) I^2 = 23% [Random effects; 4 trials: Althuisius, 2001; Berghella, 2004; Rust, 2000; Owen, 2009] *- One-off ultrasound-indicated cerclage in low/unspecified risk for preterm labour vs. no cerclage* Cerclage: 33/147 Control: 38/140 RR 0.82 (95% CI 0.55 to 1.22) I^2 = 0% [Random effectst; 3 trials: Berghella, 2004; Rust, 2000; To, 2004]	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				b. History-indicated cerclage versus ultrasound-indicated cerclage History-indicated cerclage: 19/125 Ultrasound-indicated cerclage: 18/122 RR 1.03 (95% CI 0.57 to 1.87) I^2 = not applicable [Fixed effect; 1 trial: Simcox, 2009] **<u>8. Preterm birth before 28 completed weeks</u>** **a. Cerclage vs. no cerclage** Cerclage: 118/1196 Control: 148/1196 RR 0.80 (95% CI 0.64 to 1.00) I^2 = 0% [Fixed effect; 8 trials: Ezechi, 2004; Rush, 1984; MRC/RCOG, 1993; To, 2004; Althuisius, 2001; Berghella, 2004; Rust, 2000; Owen, 2009] *- History-indicated cerclage vs no cerclage* Cerclage: 60/770 Control: 73/769 RR 0.82 (95% CI	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				0.59 to 1.13) I² = 0% [Fixed effect; 3 trials: Ezechi, 2004; Rush, 1984; MRC/RCOG, 1993] *- One-off ultrasound-indicated cerclage vs. no cerclage* Cerclage: 3/26 Control: 5/30 RR 0.69 (95% CI 0.18 to 2.62) I² = not applicable [Fixed effect; 1 trial: To, 2004] *- Serial ultrasound-indicated cerclage in high risk for preterm labour vs. no cerclage* Cerclage: 36/253 Control: 52/257 RR 0.71 (95% CI 0.48 to 1.04) I² = 0% [Fixed effect; 4 trials: Althuisius, 2001; Berghella, 2004; Rust, 2000; Owen, 2009] *- One-off ultrasound-indicated cerclage in low/unspecified risk for preterm labour vs. no cerclage*	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				Cerclage: 19/147 Control: 18/140 RR 1.01 (95% CI 0.55 to 1.83) I^2 = 0% [Fixed effect; 3 trials: Berghella, 2004; Rust, 2000; To, 2004] **b. Cerclage versus progesterone** Cerclage: 10/42 Control: 7/37 RR 1.26 (0.53 to 2.97) I^2 = not applicable [Fixed effect; 1 trial: Keeler, 2009] **c. History-indicated cerclage versus ultrasound-indicated cerclage** History-indicated cerclage: 14/125 Ultrasound-indicated cerclage: 10/122 RR 1.37 (95% CI 0.63 to 2.96) I^2 = not applicable [Fixed effect; 1 trial: Simcox, 2009] **9. Baby discharged home healthy** **a. History-indicated cerclage vs. no cerclage**	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				Cerclage: 85/96 Control: 88/98 RR 0.99 (95% CI 0.89 to 1.09) I² = not applicable [Fixed effect; 1 trial: Rush, 1984] **b. Cerclage versus progesterone** Cerclage: 28/42 Control: 21/37 RR 1.17 (0.82 to 1.67) I² = not applicable [Fixed effect; 1 trial: Keeler, 2009] **10. Serious respiratory morbidity (respiratory distress syndrome [RDS] or oxygen dependency)** **a. Cerclage vs. no cerclage** Cerclage: 26/418 Control: 24/421 RR 1.11 (95% CI 0.66 to 1.88) I² = 0% [Fixed effect; 5 trials: Rush, 1984; To, 2004; Althuisius, 2001; Berghella, 2004; Owen, 2009] - *History-indicated*	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				cerclage vs. no cerclage Cerclage: 3/96 Control: 1/98 RR 3.06 (95% CI 0.32 to 28.93) I^2 = not applicable [Fixed effect; 1 trial: Rush, 1984] *- Serial ultrasound-indicated cerclage in high risk for preterm labour vs. no cerclage* Cerclage: 18/192 Control: 18/190 RR 0.98(95% CI 0.53 to 1.81) I^2 = 0% [Fixed effect; 3 trials: Althuisius, 2001; Berghella, 2004; Owen, 2009] *- One-off ultrasound-indicated cerclage in low/unspecified risk for preterm labour vs. no cerclage* Cerclage: 4/104 Control: 3/103 RR 1.63 (95% CI 0.39 to 6.86) I^2 = 0% [Fixed effect; 2 trials: Berghella, 2004; To, 2004]	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				b. History-indicated cerclage versus ultrasound-indicated cerclage History-indicated cerclage: 3/125 Ultrasound-indicated cerclage: 2/122 RR 1.46 (95% CI 0.25 to 8.61) I^2 = not applicable [Fixed effect; 1 trial: Simcox, 2009] **<u>11. Necrotising entercolitis</u>** **a. Cerclage vs. no cerclage** Cerclage: 3/195 Control: 2/177 RR 0.81 (95% CI 0.16 to 4.12) I^2 = 0% [Fixed effect; 3 trials: Althuisius, 2001; Berghella, 2004; Owen, 2009] *- Serial ultrasound-indicated cerclage in high risk for preterm labour vs. no cerclage* Cerclage: 3/192 Control: 2/170 RR 0.81 (95% CI 0.16 to 4.12) I^2 = 0% [Fixed effect; 3 trials:	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				Althuisius, 2001; Berghella, 2004; Owen, 2009] *- One-off ultrasound-indicated cerclage in low/unspecified risk for preterm labour vs. no cerclage* Cerclage: 0/3 Control: 0/7 RR 0.00 (95% CI 0.00 to 0.00) I^2 = 0% [Fixed effect; 1 trial: Berghella, 2004] **12. Apgar < 7 at 5 minutes** **a. Serial ultrasound-indicated cerclage in high risk for preterm labour vs. no cerclage** Cerclage: 19/148 Control: 29/153 RR 0.68 (95% CI 0.40 to 1.15) I^2 = not applicable [Fixed effect; 1 trial: Owen, 2009] **13. Caesarean section** **a. Cerclage vs. no cerclage** Cerclage: 257/1425 Control: 212/1392	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				RR 1.19 (95% CI 1.01 to 1.40) I² = 0% [Fixed effect; 8 trials: Lazar, 1984; Rush, 1984; MRC/RCOG, 1993; To, 2004; Althuisius, 2001; Berghella, 2004; Rust, 2000; Owen, 2009] *- History-indicated cerclage vs. no cerclage* Cerclage: 143/999 Control: 115/965 RR 1.21 (95% CI 0.96 to 1.52) I² = 0% [Fixed effect; 3 trials: Lazar, 1984; Rush, 1984; MRC/RCOG, 1993] *- One-off ultrasound-indicated cerclage vs. no cerclage* Cerclage: 7/26 Control: 6/30 RR 1.35 (95% CI 0.52 to 3.50) I² = not applicable [Fixed effect; 1 trial: To, 2004] *- Serial ultrasound-indicated cerclage in high risk for preterm*	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				labour vs. no cerclage Cerclage: 70/253 Control: 65/257 RR 1.10 (95% CI 0.82 to 1.46) I^2 = 0% [Fixed effect; 4 trials: Althuisius, 2001; Berghella, 2004; Rust, 2000; Owen, 2009] *- One-off ultrasound-indicated cerclage in low/unspecified risk for preterm labour vs. no cerclage* Cerclage: 37/147 Control: 26/140 RR 1.31 (95% CI 0.84 to 2.04) I^2 = 0% [Fixed effect; 3 trials: Berghella, 2004; Rust, 2000; To, 2004] **14. Maternal side effects (vaginal discharge, bleeding, pyrexia not requiring antibiotics)** **a. Cerclage vs. no cerclage** Cerclage: 83/491 Control: 49/462 RR 2.25 (95% CI	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				0.89 to 5.69) I² = 66% [Random effects; 3 trials: Lazar, 1984; Rush, 1984; To, 2004] *- History-indicated cerclage vs. no cerclage* Cerclage: 71/364 Control: 47/336 RR 1.57 (95% CI 0.76 to 3.24) I² = 48% [Random effects; 2 trials: Lazar, 1984; Rush, 1984] *- One-off ultrasound-indicated cerclage in low/unspecified risk for preterm labour vs. no cerclage* Cerclage: 12/127 Control: 2/126 RR 5.95 (95% CI 1.36 to 26.06) I² = not applicable [Random effects; 1 trial: To, 2004] **b. History-indicated cerclage versus ultrasound-indicated cerclage** History-indicated cerclage: 6/122 Ultrasound-indicated	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				cerclage: 11/121 RR 0.54 (95% CI 0.21 to 1.42) I² = not applicable [Fixed effect; 1 trial: Simcox, 2009] **15. Maternal infection requiring intervention** **a. History-indicated cerclage versus ultrasound-indicated cerclage** History-indicated cerclage: 0/125 Ultrasound-indicated cerclage: 1/122 RR 0.33 (95% CI 0.01 to 7.91) I² = not applicable [Fixed effect; 1 trial: Simcox, 2009] **16. Composite outcome of perinatal deaths plus serious neonatal morbidity** **a. Cerclage vs no cerclage** Cerclage: 67/407 Control: 83/410 RR 0.82 (95% CI 0.61 to 1.09) I² = 0% [Fixed effect; 4 trials: To, 2004; Berghella, 2004; Rust, 2000;	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				Owen, 2009] *- One-off ultrasound-indicated cerclage vs. no cerclage* Cerclage: 3/26 Control: 6/30 RR 0.58 (95% CI 0.16 to 2.08) I^2 = not applicable [Fixed effect; 1 trial: To, 2004] *- Serial ultrasound-indicated cerclage in high risk for preterm labour vs. no cerclage* Cerclage: 42/234 Control: 57/240 RR 0.75 (95% CI 0.53 to 1.07) I^2 = 0% [Fixed effect; 3 trials: Berghella, 2004; Rust, 2000; Owen, 2009] *- One-off ultrasound-indicated cerclage in low/unspecified risk for preterm labour vs. no cerclage* Cerclage: 22/147 Control: 20/140 RR 1.08 (95% CI 0.61 to 1.89) I^2 = 0% [Fixed effect; 3 trials:	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				Berghella, 2004; Rust, 2000; To, 2004]	
Full citation Berghella,V., Rafael,T.J., Szychowski,J.M., Rust,O.A., Owen,J., Cerclage for short cervix on ultrasonography in women with singleton gestations and previous preterm birth: a meta-analysis, Obstetrics and Gynecology, 117, 663-671, 2011 **Ref Id** 222462 **Country/ies where the study was carried out** Various **Study type** Systematic review of randomised controlled trials **Aim of the study** To review randomised trials on cerclage for prevention of preterm birth in asymptomatic singleton gestations with both previous preterm	**Sample size** N = 5 trials N = 504 women **Characteristics** Details of included studies not reported in the review. All studies included in this review were also included in Alfirevic, Z., et al. Cervical stitch (cerclage) for preventing preterm birth in singleton pregnancy. Cochrane Database of Systematic Reviews, 4, CD008991-, 2012, which is reported above in this evidence table. Information is repeated here for ease of reference. [*information taken from full text of trial because it was not reported in systematic review] **Althuisius, 2001** **Inclusion criteria:** High risk of preterm labour as diganosed by serial transvaginal ultrasonography cervical length < 25mm before gestational age 27 weeks **Exclusion criteria:** Women with pregnancies complicated by fetal congenital /chromosomal anomalies, premature rupture of membranes (PROM), membranes bulging into the vagina or intrauterine infection in the current pregnancy **Sample size:** N = 67 **Intervention:** Therapeutic cerclage with bed rest	**Interventions** Cervical cerclage compared with no cerclage	**Details** MEDLINE, PUBMED, EMBASE and the Cochrane Library were searched from 1966 to March 2010. No language restrictions were applied. Data extraction was performed by two independent investigators. Differences were resolved by common review of the data. Primary authors of each included trial provided raw data, including all women randomised, so that patient-level meta-analysis could be performed. Two independent anaylses of the primary data files were performed using Review Manager. The two analyses were compared and any difference resolved by review of individual patient data. All anaylses maintained intention-to-treat group assignment of the original trials. In tests of heterogeneity, P<0.10 was considered significant. Where there was no significant heterogeneity, a fixed-effect model was used, otherwise a random-effects model was used.	**Results** **Preterm birth <37 weeks** Cerclage: 105/250 No cerclage: 154/254 RR 0.70 (95% CI 0.58 to 0.83) I^2 = not reported [Fixed effect: 5 trials; Althuisius 2001; Berghella 2004; Owen 2009; Rust 2001; To 2004] **Preterm birth <35 weeks** Cerclage: 105/254 No cerclage: 71/250 RR 0.70 (95%CI 0.55 to 0.89) I^2 = 0% [Fixed effect: 5 trials; Althuisius 2001; Berghella 2004; Owen 2009; Rust 2001; To 2004] **Preterm birth <32 weeks** Cerclage: 48/250 No cerclage: 75/254 RR 0.66 (95% CI 0.48 to 0.91) I^2 = not reported [Fixed effect: 5 trials;	**Limitations** All included studies were judged to have an adequate method of randomisation and allocation concealment and no serious risk of bias. NCC-WCH technical team did not identify indirectness in any of the included studies. **Other information** 404/908 women (44.5%) were excluded from this review: no previous preterm birth = 342, multiple pregnancy = 55, cervical length >25mm = 5, cervical length <25 mm between 24 and 27 weeks gestation = 2 Individual patient data from each of the included studies was used. One study provided data for more women randomised than were included in the original publication. The definition of composite neonatal morbidity is unclear. Where the original trialists have defined their measure of neonatal morbidity it is reported below, however it is unclear whether the review authors used the same definitions in their analysis.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
birth and short cervical length on second-trimester transvaginal ultrasonography **Study dates** The search was performed in March 2010 **Source of funding** Not reported	**Comparator:** Bed rest only **Other details of care provided:** None given. *All women received amoxicillin/clavulanic acid 1g intravenously every 6 h and metronidazole 500mg intravenously every 8 h for 24 h followed by amoxicillin/clavulanic acid 500mg orally every 8 h and metronidzaole 500mg orally every 8 h for 6 days. Women allocated to the intervention group also received indomethacin suppository (100mg 2 h before and 6 h after the operation). Women in both groups were restricted to 48 h bed rest following randomisation. Management after discharge home in both groups did not include prophylactic tocolysis, steroids or home uterine monitoring. ***Country:** The Netherlands **Berghella, 2004** **Inclusion criteria:** Singleton and twin pregnancies, high risk of preterm delivery, *short cervix < 25mm or significant funnelling (> 25%) between 14+0 weeks and 23+6 weeks gestation (serial ultrasound; low risk women identified incidentally were also included) **Exclusion criteria:** Prophylactic cerclage placed on the basis of historic high-risk criteria, last pregnancy delivered at term, major fetal anomaly, triplets or higher multiple gestations, previous inclusion in another trial, current drug abuse, regular contractions that led to preterm labour after identification of		**Subgroup analyses** The following subgroup analyses were planned: - cervical length <25mm - cervical length 16 - 24.9mm - cervical length ≤15.9mm - cervical length <25mm at <20 weeks gestation - previous preterm birth at <24 weeks gestation	Althuisius 2001; Berghella 2004; Owen 2009; Rust 2001; To 2004] **Preterm birth <28 weeks** Cerclage: 32/250 No cerclage: 51/254 RR 0.64 (95% CI 0.43 to 0.96) I^2 = not reported [Fixed effect: 5 trials; Althuisius 2001; Berghella 2004; Owen 2009; Rust 2001; To 2004] **Preterm birth <24 weeks** Cerclage: 13/250 No cerclage: 28/254 RR 0.48 (95% CI 0.26 to 0.90) I^2 = not reported [Fixed effect: 5 trials; Althuisius 2001; Berghella 2004; Owen 2009; Rust 2001; To 2004] **Perinatal mortality** Cerclage: 22/250 No cerclage: 35/254 RR 0.65 (95% CI 0.40 to 1.07) I^2 = not reported [Fixed effect: 5 trials; Althuisius 2001; Berghella 2004;	**Althuisius 2001** Neontatal morbidity: admission to neonatal intensive care unit and/or neonatal death **Berghella, 2004** Composite morbidity: any of respiratory distress syndrome, intraventricular haemorrhage, necrotising enterocolitis or sepsis **Owen, 2009** Definition of serious morbidity not clearly reported **Rust, 2000** Serious morbidity: mechanical ventilation, respiratory distress, necrotising enterocolitis, intraventricular haemorrhage, sepsis, other life-threatening morbidity

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	abnormal cervix by ultrasonography **Sample size:** N = 61 **Intervention:** Cerclage with bed rest *cerclage placement within 3 days of hospital admission **Comparator:** *Preterm labour education, advise to begin bed rest, with bathroom privileges, at home **Other details of care provided:** *Rescue cerclage was allowed if cervical dilatation of ≥ 1 cm was detected on digital examination. Betamethasone was offered at 24 weeks for overt preterm labour or PROM. Antibiotics and tocolytics were left to the discretion of the obstetrician (no further details reported) ***Country:** USA **Owen, 2009** **Inclusion criteria:** Multiparous, single gestation women with at least 1 prior spontaneous preterm birth between 10+0 and 33+6 weeks gestation with a cervical length < 25 mm found on serial transvaginal ultrasonography **Exclusion criteria:** Fetal anomaly, planned history-indicated cerclage for a clinical diagnosis of cervical insufficiency, clinically significant maternal-fetal complications that would increase the risk of preterm birth, uterine anomalies **Sample size:** N = 302 **Intervention:** Cerclage *performed within 96 hours of qualifying scan **Comparator:** No cerclage **Other details of care provided:**			Owen 2009; Rust 2001; To 2004] **Composite perinatal mortality and morbidity** Cerclage: 39/250 No cerclage: 63/254 RR 0.64 (95% CI 0.45 to 0.91) I^2 = 0% [Fixed effect: 5 trials; Althuisius 2001; Berghella 2004; Owen 2009; Rust 2001; To 2004]	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	Women in the comparator group could receive a physical examination indicated cerclage for acute cervical insufficiency diagnosed on clinical examination. *Early in the trial, in response to a published trial of 17-OHP-C, progesterone for preterm birth prevention became an option for study participants and an additional randomisation stratum was added, reflecting the woman's intention to use progesterone. 117 women were randomised within the progesterone stratum - the effect of the woman's plan to use progesterone on preterm birth < 35 weeks was null. No details provided about steroid or antibiotic use. **Country:** USA **Rust, 2000** **Inclusion criteria:** High or low risk women with demonstrable dilatation of the internal os and either prolapse of membranes at least 25% of the total cervical length or a distal cervical length < 2.5cm, getstational age between 16 and 24 weeks **Exclusion criteria:** Membrane prolapse beyond the external os, any fetal lethal congenital or chromosomal anomaly, clinical evidence of abruption placenta, unexplained vaginal bleeding, chorioamnionitis, persistent uterine activity accompanied by cervical change or any other contraindication for cerclage procedure **Sample size:** N = 61 **Intervention:** McDonald cerclage				

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	Comparator: No cerclage **Other details of care provided:** *All women were treated as inpatients with bed rest, received 48–72 hours of enpiric therapy with clindamycin (900mg every 9 h) and indomethacin (100mg by rectum as a loading dose followed by 50mg orally every 6 h) and underwent amniocentesis before randomisation. Women assigned to the intervention group continued clindamycin and indomethacin for 24 h after the procedure. Women in the comparator group had withdrawal of clindamycin and indomethacin 24 h after randomisation. ***Country:** USA **To, 2004** **Inclusion criteria:** Singleton pregnancy, cervical length ≤ 15 mm in single ultrasound scan, gestational age 22–24 weeks **Exclusion criteria:** Major fetal abnormalities, painful regular uterine contractions, history of ruptured membranes, cervical cerclage in situ, dilated cervix found during transvaginal ultrasonography **Sample size:** N = 253 **Intervention:** Shirodkar cerclage **Comparator:** No cerclage **Other details of care provided:** *All women were given prophylactic corticosteroids (two doses of dexmethasone, 12 mg intramuscularly, 12 h apart) at 26–28 weeks gestation. No other interventions were routinely recommended (tocolytics, antibiotics				

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	or bed rest). Women assigned to intervention group received a single dose of intravenous erythromycin (500mg) intraoperatively. **Country:** UK, Brazil, South Africa, Slovenia, Greece, Chile **Inclusion criteria** Randomised trials of women with singleton gestations, previous spontaneous preterm birth, and a short cervical length in the second trimester randomised to cerclage or no cerclage **Exclusion criteria** Cerclage trials evaluating history-indicated cerclage (placed for the sole indication of poor obstetrical history) or cerclage indicated on physical examination (placed for second trimester cervical dilatation detected on physical examination).				

H.2.231 **Health economics**

Bibliographic details	Interventions and comparisons	Data Sources	Time horizon & Method	Results	Reviewer comment
Full citation Pizzi,L.T., Seligman,N.S., Baxter,J.K., Jutkowitz,E., Berghella,V., Cost and cost effectiveness of vaginal progesterone gel in reducing preterm	**Study dates** Not stated **Intervention** Vaginal Progesterone (VP) **Comparison(s)**	**Source of effectiveness data** Randomised multicenter controlled trial (RCT): PREGNANT. The trial was based in 44 sites in ten countries. **Source of cost data**	**Time horizon and discount rate** Time Horizon: NA Discount Rate: NA **Method of eliciting health valuations (if applicable)**	**Cost per patient per alternative** Per mother VP USD 23,079 Placebo USD 36,436 **Effectiveness per patient per alternative** Incremental benefit for	**Limitations** RCTs are are based on multiple countries so applying US costs models difficult. Costs include the cost of testing for a short cervix and cervical cerclage in

Bibliographic details	Interventions and comparisons	Data Sources	Time horizon & Method	Results	Reviewer comment
birth: an economic analysis of the PREGNANT trial, Pharmacoeconomics, 32, 467-478, 2014 **Ref Id** 323625 **Economic study type** Cost effectiveness analysis **Country(ies) where the study was done** USA **Perspective & Cost Year** Perspective: US healthcare payer Cost Year: 2011 **Source of funding** Watson Pharmaceuticals (now Actavis)	Placebo	Services costed include cervical length screening, VP gel, antenatal hospitalization, cerclage, maternal and neonatal costs. Assessment of costs based on published reimbursement sources and scientific literature. Published sources include Current Procedural Terminology, wholesale prices for progesterone, Medicare reimbursement rates, published literature Luke 1996, St John 2000, Institute of Medicine 2007. **Other data sources e.g. transition probabilities**	NA **Modelling approach** A Decision Tree model was used to simulate the outcomes associated with each of the different treatments to predict costs and age of gestation.	VP as 0.0426 preterm births averted **Incremental cost-effectiveness** VP dominates **Other reporting of results** **Uncertainty** Probabilistic sensitivity analysis	some instances. Some of the cost data was based published evidence that studied twins. **Other information**
Full citation Cahill,A.G., Odibo,A.O., Caughey,A.B., Stamilio,D.M.,	**Study dates** Published in June 2010. Study dates not stated.	**Source of effectiveness data** Published evidence	**Time horizon and discount rate** Time Horizon: NA	**Cost per patient per alternative** Based on a population of 4 million deliveries:	**Limitations** Absence of detail regarding cost build up, specific sources of data,

Bibliographic details	Interventions and comparisons	Data Sources	Time horizon & Method	Results	Reviewer comment
Hassan,S.S., Macones,G.A., Romero,R., Universal cervical length screening and treatment with vaginal progesterone to prevent preterm birth: a decision and economic analysis, American Journal of Obstetrics and Gynecology, 202, 548-548, 2010 **Ref Id** 281888 **Economic study type** Cost effectiveness analysis **Country(ies) where the study was done** USA **Perspective & Cost Year** Perspective: Not Stated Cost Year: Not Stated **Source of funding** The Perinatology	**Intervention** Vaginal progesterone **Comparison(s)** No treatment	**Source of cost data** Published evidence. Underlying assumptions and scope was not stated. **Other data sources e.g. transition probabilities**	Discount Rate: NA **Method of eliciting health valuations (if applicable)** NA **Modelling approach** Decision Analytic Cost-Utility analysis	Vaginal progesterone: USD 333.0 mln No treatment: USD 462.4 mln **Effectiveness per patient per alternative** Preterm births prevented Vaginal progesterone: 95,920 No treatment: 0 **Incremental cost-effectiveness** Vaginal progesterone dominates **Other reporting of results** **Uncertainty** Probabilistic sensitivity analysis. A single value was reported. Limited applicability to outcome of interest.	perspective and study dates. There was also no list of references. As such claims in this study cannot be verified. Data in the report is based on single values. There are no confidence intervals. Other information

Bibliographic details	Interventions and comparisons	Data Sources	Time horizon & Method	Results	Reviewer comment
Research Branch, Division of Intramural Research, Eunice Kennedy Shriver National Institute of Child Health and Human Development, NIH/DHHS					

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H.3 Diagnosing preterm prelabour rupture of membranes (P-PROM)

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
Full citation Jain,K., Morris,P.G., A clinical study to evaluate the usefulness of the MAST test in diagnosing pre-labour rupture of membranes, Journal of Obstetrics and Gynaecology, 18, 33-36, 1998 **Ref Id** 257993 **Country/ies where the study was carried out** UK **Study type** Nested case-control study	**Sample size** n = 100 **Characteristics** Not specified **Inclusion Criteria** - Between 24 and 42 weeks' gestation - With a history suggestive of P-PROM **Exclusion Criteria**	**Tests** <u>Test</u> MAST test: detects Insulin-like growth factor binding protein-1 in amniotic fluid <u>Reference test/Gold standard</u> Not clearly specified. Might have used following observation: - Pooling of the liquor in the posterior fornix in speculum examination - Intact amniotic sac at birth	Methods Women with admission history of pre- labour rupture of membrane and suspected diagnosis of PROM were included in the study. From n = 100 women recruited with gestational age 24 to 42 weeks, n = 34 women had gestational age 24 to 36 weeks and n = 66 women were between 37 to 42 weeks gestation. . A routine admission history was taken, queries made on duration of membrane rupture, associated vaginal bleeding and timing of recent sexual intercourse. Routine examination performed and observation recorded. A sterile speculum was then performed and the following observation and recording were then made: pooling of the liquor in the posterior fornix, the amine test to detect the presence of the bacterial vaginosis, a high vaginal swab (HVS) for culture and sensitivity, the MAST test to	**Results** <u>MAST test 24 to 36 weeks n = 34</u> True positive n = 4 False positive n = 0 True negative n = 30 False negative n = 0 Sensitivity: 100% Specificity: 100% PPV(Positive predictive value): 75% NPV(negative predictive value):100% <u>MAST test 24 to 42 weeks n = 100</u> True positive n = 25 - n = 20/25 liquor	**Limitations** - Unclear who performed the test and whether he was blinded to the previous test result - Unclear reference test/gold standard <u>Study quality - QUADAS 2 checklist</u> Was a consecutive or random sample of patients enrolled? No Did the study avoid inappropriate exclusions? Unclear Were the index test results interpreted

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
Aim of the study To evaluate the efficiency of insulin-like growth factor binding protein-1 as a marker for the detection of pre-labour rupture of membranes **Study dates** Not specified **Source of funding** Not specified	- Women with clinically obvious flooding of liquor		detect the presence of IGFBP-1 to confirm or rolling out the history of rupture of membranes. To conduct the MAST test sample were taken from vaginal fluid by a sterile dacron swab when performing the speculum examination. In order to saturate the swab with vaginal fluid or discharge the swap was holding it in situ for 10- 15 seconds. The dipstick is then removed, place on a level surface and the result interpreted after 5 minutes. Women with a negative result were discharged home and those with positive result were managed according to the routine practice with regard to diagnosis of PROM.	was seen on speculum all had intact - n = 13/25 liquor were not seen on speculum (n = 8/13 had intact amniotic sac) - Spontaneous onset of labour n = 16/25 - Induction of labour n = 8/25 - Elective caesarean n = 1/25 False positive n = 8 - Spontaneous onset of labour n = 5/8 - Induction of labour n = 2/8, - Elective caesarean n = 1 True negative n = 67 - n = 67/67 did not have liquor seen on speculum and all had intact amniotic sac. - Spontaneous onset of labour n = 58/67 - Induction of labour n = 5/67 - Elective caesarean n = 4/67 False negative n = 0 Sensitivity: 100% Specificity: 89% PPV: 75% NPV: 100%	without knowledge of the results of the reference standard? Unclear If a threshold was used, was it pre-specified? Unclear Is the reference standard likely to correctly classify the target condition? Unclear Were the reference standard results interpreted without knowledge of the results of the index test? Unclear Was there an appropriate interval between index test(s) and reference standard? Unclear Did all patients receive a reference standard? Yes Did patients receive the same reference standard? Unclear Were all patients included in the analysis? No

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
Full citation Tagore,S., Kwek,K., Comparative analysis of insulin-like growth factor binding protein-1 (IGFBP-1), placental alpha-microglobulin-1 (PAMG-1) and nitrazine test to diagnose premature rupture of membranes in pregnancy, Journal of Perinatal Medicine, 38, 609-612, 2010 **Ref Id** 258127 **Country/ies where the study was carried out** Singapore **Study type** Prospective cohort study **Aim of the study** To compare insulin-like growth factor binding protein-1 (IGFBP-1) (non-phosphorylated), placental alpha-microglobulin-1 (PAMG-1) and nitrazine test to diagnose premature rupture of membrane to allow gestation-specific management. **Study dates** May 2008 to April 2009 **Source of funding**	**Sample size** n = 100 **Characteristics** - Gestation 17 to 37 weeks - 6/100 women had twin pregnancy - 6/100 women were at < 24 weeks - 41/100 women diagnosed as having PROM on the final review of medical records - 59/100 women did not have PROM on the final review of medical records - Mean age: 28.1 (range 14 - 41 SD 6.1) - 82/100 women were hospitalised ranging from 1 to 30 days for further assessment - 69/100 women were received steroids with tocolysis - out of n = 31 women who did not receive steroids and tocolysis, n = 3 women were diagnosed with PROM **Inclusion Criteria** - Women with signs or symptoms of premature rupture of	**Tests** <u>Tests</u> - Actim PROM: Insulin-like growth factor binding protein-1 (IGFBP-1) (non-phosphorylated) - AminSure: placental alpha-microglobulin-1 (PAMG-1) - Nitrazine test <u>Reference test/Gold standard</u> Based on the presence of three or more of the following conditions: - Pooling of the clear fluid during speculum examination - Oligohydraminous on ultrasound - Sign and symptoms of chorioamnionitis - Preterm birth within a week of presentation along with convincing history of leaking liquor Women's medical record was reviewed after birth	**Methods** Study performed in a tertiary referral centre, n = 100 consecutive women between 17 and 37 weeks who presented to labour ward with sign and symptoms of PROM were recruited. A confirmed diagnosis (gold standard) was based on the presence of three or more of the following conditions: pooling of the clear fluid during speculum examination, oligohydraminous on ultrasound, sign and symptoms of chorioamnionitis and preterm birth within a week of presentation along with convincing history of leaking liquor. Amniotic fluid index (AFI) < 6 was considered as an oligohydramnios. Chorioamnionitis was diagnosed based on the clinical and biochemical factors (maternal temperature > 38 ^{0} C, uterine tenderness, maternal tachycardia, fetal tachycardia, maternal leucocytosis, CRP). Speculum examination was performed to assess pooling of the liquor. Rapid test strips performed by placing a swab in the cervical-vaginal secretions for detection of PAMG-1 and IGFBP-1. Nitrozine test was performed using Amnicato, a sterile swab impregnated with nitrozine and a pH indicator. Residents or on-call consultants performed the tests. <u>Analysis</u> Performed using McNemar χ^2 test.	**Results** n = 82 women were hospitalised from 1 - 30 days for further assessment. n = 69 women received steroids with tocolysis. <u>Live birth</u> n = 105/106. n = 1 intrauterine death due to placental abruption and P-PROM at 32 weeks <u>NICU admission</u> n = 27/106 <u>Mean latency from diagnosis of PROM to birth</u> 10.7 days <u>PAMG-1</u> n = 100 False positive (FP): n = 0 False negative (FN): n = 3 Sensitivity: 92.7% Specificity: 100% Positive predictive value (PPV): 100% Negative predictive value (NPV): 95.2%	**Limitations** Unclear if the clinicians that performed the test were blinded to the results of the other previous tests Unclear if the same clinician performed all tests Indirectness: n =6 women had twin pregnancies <u>Study quality - QUADAS 2 checklist</u> Was a consecutive or random sample of patients enrolled? Yes Did the study avoid inappropriate exclusions? No Were the index test results interpreted without knowledge of the results of the reference standard? Unclear If a threshold was used, was it pre-specified? Unclear Is the reference standard likely to correctly classify the target condition? Unclear Were the reference

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
Funded by KK Hospital, Singapore Research Grant and the AmniSure Kits by Niche Medical Pte Limited	membranes (PROM) - Between 17 and 37 week of gestation **Exclusion Criteria** Not specified			IGFBP-1 n = 94 women FP: n = 3 FN: n = 5 Sensitivity: 87.5% Specificity: 94.4% PPV: 92.1% NPV: 91.1%. Nitrazine test n = 98 was FP: n = 35 FN: n = 6 Sensitivity: 85% Specificity: 39.7% PPV: 49.3% NPV: 79.3%	standard results interpreted without knowledge of the results of the index test? Unclear Was there an appropriate interval between index test(s) and reference standard? Unclear Did all patients receive a reference standard? Yes Did patients receive the same reference standard? Yes Were all patients included in the analysis? Yes

H.14 Antenatal prophylactic antibiotics for women with P-PROM

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Mercer,B., Antibiotics in the management of PROM and preterm labor, Obstetrics and Gynecology Clinics of North America, 39, 65-76, 2012 **Ref Id**	**Sample size** n = 7 studies (n = 1173 women) **Characteristics** n = 7 studies met the inclusion criteria: Data extracted from Kenyon 2010 **Amon 1988a** Participants: n = 82 women Treatment: n = 43	**Interventions** Prophylactic antibiotic	**Details** Statistical analysis were performed using Review Manger (RevMan) version 5.0. Mantel-Heanszel chi square, using a fixed model were performed. No more details provided	**Results** **Any antibiotic versus placebo/no treatment** Intraventricular haemorrhage Number of studies: n = 7 Any antibiotic: n = 74/572 (12.9%)	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
222976 **Country/ies where the study was carried out** Various **Study type** Systematic review **Aim of the study** Further analysis of the studies included in Kenyon 2010 (restricted to the studies that compared antibiotic treatment with placebo or no treatment)	Control: n = 39 Inclusions: 20-34 weeks pregnant. Singleton pregnancy only, preterm prelabour rupture of membranes (PPROM) confirmed by sterile speculum. Interventions: Treatment group: ampicillin 1g intravenously (IV) every 6 hours for 24 hours. Maintained on oral 500mg ampicillin 6 hourly until delivery. In labour they were recommenced on 1g intravenous ampicillin. **Christmas 1992** Participants: n = 94 women Treatment: n = 48 Control: n = 46 Inclusions: singleton pregnancies 20 - 34 weeks with PPROM confirmed by sterile speculum. Exclusions: - penicillin allergy - prior antibiotic therapy - clinical evidence of intra-amniotic infection - evidence of labour or fetal distress. Interventions: - Treatment: 24 hours IV ampicillin 2g every 6 hours for 4 doses; gentamycin 90mg loading dose 60mg every 8 hours for 3 doses. Then oral amoxicillin + clavulanic acid 500mg 3 x day for 7 days. - Control: IV fluids without antibiotics for 24 hours. **Fuhr 2006** Participants: n = 105 pregnant treatment n = 47			Placebo: n = 105/590 (17.8%) RR 0.73 (0.56 to 0.95) Sepsis Number of studies: n = 5 Any antibiotic: n = 53/485 (10.9%) Placebo: n = 82/489 (16.8%) RR 0.67 (0.49 to 0.91) Delivery delayed ≥ 7 days Number of studies: n = 6 Any antibiotic: n = 237/515 (46%) Placebo: n = 139/537 (25.9%) RR 1.8 (1.52 to 2.13) Stillbirth Number of studies: n = not reported Any antibiotic: n = 2/228 (0.8%) Placebo: n = 6/225 (2.6%) RR 0.42 (0.11 to 1.58) Clinical amnionitis Number of studies: n = 6	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	Control n = 58 Inclusion: women with PROM between 24+0 and 32+6 weeks. Exclusion: criteria not clearly stated nor whether multiple pregnancies included. Interventions: Metzlocillin 2g given 3 x day for 7 days or placebo. All women given corticosteroids and tocolytics IV. Conducted in 5 centres in Germany - dates not given. **Johnston 1990** Participants n = 85 women. Inclusions: mothers with singleton gestations between 20-34 weeks with PPROM confirmed by sterile speculum for pooling, ferning and nitrazine paper testing. Exclusions: - penicillin allergy - taking antibiotics at the time of PPROM - fever > 100.4 degrees Fahrenheit - signs of chorioamnionitis - in active labour (defined by 3 or more contractions per 10 minute period for 1 hour or presented with cervical dilatation > 3 cm confirmed at the time of sterile speculum). Fetal indications for exclusion were the presence of fetal distress, defined as repetitive late deceleration or sustained bradycardia, or congenital abnormality on ultrasound. Interventions: IV mezlocillin for 48 hours followed by oral ampicillin until delivery or matched (IV + oral) placebo.			Any antibiotic: n = 55/527 (9.6%) Placebo: n = 70/537 (1.30%) RR 0.81 (0.58 to 1.13)	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	No doses noted. After randomisation no tocolytic steroids given. Study drugs discontinued if infection diagnosed. Study carried out in a single centre - University Medical Centre - Jacksonville Florida. All women had infection screen on admission. No digital examination allowed. No comment as to losses to follow up or recruitment period. **Lockwood 1993** Participants: n = 75 women Treatment: n = 38 placebo n = 37 Inclusion: women with a single fetus at 24-34 completed weeks (accurate gestational age), admitted with PROM. No digital examination unless active labour. Women had infection screening. Exclusions: - abruption - lethal fetal abnormalities - clinical chorioamnionitis - maternal illness - diabetes; pregnancy induced hypertension (PIH) - lupus - severe maternal disease - fetal growth retardation - fetal distress - cervical cerclage - active herpes. Women having received antibiotics for existing infection were also excluded. Interventions: Piperacillin 3g IV 6				

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	hourly 72 hours or placebo. Recruitment in 3 centres (USA) from January 1987 to January 1992. 3 babies (1 in the experimental group and 2 in controls) were lost to follow up. Free of other bias?: Unclear - no information given. **Mercer 1997** Participants: 1867 women screened. n = 804 eligible. n = 614 agreed to participate. n = 29 twin gestations. Group B Strep positive: n = 118/614. Inclusion criteria: membrane rupture within 36 hours of randomisation; cervical dilatation 3cm or less on usual examination; < 5 contractions in 6 minutes, at 24-32 weeks gestation Exclusion criteria: - non-reassuring fetal testing; - vaginal bleeding - maternal or fetal indication for delivery - cervical cerclage in place - antibiotics within the last 5 days - corticosteroids within last 7 days - allergy to penicillin or erythromycin - maternal infection or medical disease - ultrasound evidence of placenta praevia - fetal weight < 10th centile for gestational age - malformation. Previous successful tocolysis was not an exclusion criterion. Tocolysis and corticosteroids were prohibited after randomisation.				

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	Interventions: Ampicillin 2g 6 hourly and erythromycin 250mg 6 hourly IV for 48 hours, then oral amoxacillin 250mg every 8 hours and erythromycin 333mg 8 hourly for 5 days and a matching placebo regimen. For twin pregnancies adverse outcomes considered present if 1 twin affected. Study carried out in 11 centres - USA. From February 1992 to January 1995. 3 women lost to follow up. **Owen 1993** Participants n = 118 randomised 1 lost to follow up. Treatment: n = 59 Controls: n = 58 Inclusions: 24 to 34 weeks gestation. PPROM confirmed by speculum. Exclusions in labour: - clinical evidence of infection suspected fetal compromise - membrane rupture over 2 days - fetal abnormality - antibiotics in last 7 days - multiple pregnancy - cervical cerclage - prompt delivery required. Interventions: IV 1g ampicillin 6 hourly for 24 hours then 500mg ampicillin orally every 6 hours. If allergic to penicillin 500mg erythromycin used 6 hourly. Treatment continued with delivery or diagnosis of chorioamnionitis. **Inclusion criteria** The analysis was restricted to:				

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	- the studies that compared antibiotic treatment with placebo or no treatment - women requited at 34 week gestation or less - initiated therapy with intravenous treatment **Exclusion criteria** Not specified				
Full citation Kenyon,S., Pike,K., Jones,D.R., Brocklehurst,P., Marlow,N., Salt,A., Taylor,D.J., Childhood outcomes after prescription of antibiotics to pregnant women with preterm rupture of the membranes: 7-year follow-up of the ORACLE I trial, Lancet, 372, 1310-1318, 2008 **Ref Id** 254356 **Country/ies where the study was carried out** Uk **Study type** Long term follow up of a multicentre trial (161 centres, 135 in the UK)	**Sample size** Participants: n = 4826 women At entry to ORACLE study: Erythromycin and co-amoxiclav n = 737 Erythromycin n = 754 Co-amoxiclav n = 808 Placebo n = 775 **Characteristics** <u>Maternal age (years)</u> Erythromycin and co-amoxiclav: 28.8 (24.2 - 32.8) Erythromycin: 28.4 (23.7 - 23.6) Co-amoxiclav: 28.8 (24.4 - 32.6) Placebo: 28.7 (24.2 - 32.7) <u>Gestational age (days)</u> Erythromycin and co-amoxiclav: 226 (209 - 238) Erythromycin: 225 (205 - 234) Co-amoxiclav: 225 (208 - 238.5) Placebo: 226 (205 - 238) <u>Multiple birth</u> Erythromycin and co-amoxiclav: 57 (24.4%) Erythromycin: 191 (25.3%) Co-amoxiclav: 46 (5.7%) Placebo: 49 (6.3%)	**Interventions** Co-amoxiclav 375mg QDS, erythromycin 250mg QDS orally for 10 days or until delivery matched placebo (2 x 2 factorial design).	**Details** UK follow up at 7 years of age of the 4378 children of the 4148 eligible women who joined the ORACLE trial (The ORACLE trial looked at the antibiotics erythromycin and co-amoxiclav used in PPROM and spontaneous premature labour in the hope of delaying or preventing premature labour) using a parental questionnaire. Women and children were traced with the help of UK Office of National Statistics (ONS) and by contact with their family doctor. An information leaflet was sent to the parents and two weeks later the study questionnaire was sent. Those involved in tracing data entry were reminded blind to the allocated treatment. Data to assess health and educational outcomes were double entered and their validity were checked. Data was collected via a patent-completion postal questionnaire. Functional impairment was assessed	**Results** **Any erythromycin versus no erythromycin** <u>Stillbirths</u> Any erythromycin: n = 42/2323 (1.8%) No erythromycin: n = 44/2389 (1.8%) RR 0.98 (0.64 to 1.50) <u>Deaths in first year</u> Any erythromycin: n = 107/2323 (4.6%) No erythromycin: n = 124/2389 (5.2%) RR 0.88 (0.68 to 1.15) <u>Deaths after first year</u> Any erythromycin: n = 7/2323 (0.3%) No erythromycin: n = 4/2389 (0.2%) RR 1.79 (0.52 to 6.12) <u>Total deaths</u> Any erythromycin: n = 156/2323 (6.7%)	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Aim of the study To determine the long-term effects on children of these interventions **Study dates** 2008 **Source of funding** Sponsored by University Hospitals of Leicester	**Inclusion criteria** Under 37 weeks pregnant with PROM. Multiple pregnancies included. **Exclusion criteria** n = 661 women (246 due to perinatal death, 376 randomised outside UK and 39 women withdrew).		using the Mark III Multi-Attribute Health Status classification system. Educational attainment was evaluated for children in England using data from National Curriculum Tests at 7 years of age (Key Stage 1). n = 2 women lost to follow up and 15 women were excluded due to protocol violations. 4809 women analysed. For twin pregnancies adverse outcomes were considered present if one twin affected.	No erythromycin: n = 172/2389 (7.2%) RR 0.93 (0.74 to 1.16) Cerebral palsy Any erythromycin: n = 46/1590 (2.9%) no erythromycin: n = 41/1671 (2.5%) RR 1.18 (0.77 to 1.81) Developmental problems - ADHD from SDQ or parental report Any erythromycin: n = 109/1590 (6.9%) No erythromycin: n = 135/1671 (8.1%) RR 0.84 (0.64 to 1.09) Educational attainment - reading Any erythromycin: n = 360/1596 (22.6%) No erythromycin: n = 363/1671 (22.1%) RR 1.03 (0.99 to 1.81) Educational attainment - writing Any erythromycin: n = 418/1596 (26.2%) No erythromycin: n = 426/1671 (25.9%) RR 1.01 (0.97 to 1.05)	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				Educational attainment - maths Any erythromycin: n = 257/1596 (16.1%) No erythromycin: n = 257/1671 (15.7%) RR 1.01 (0.97 to 1.06) **Any co-amoxiclav versus no co-amoxiclav** Stillbirths Any co-amoxiclav: n = 45/2336 (1.9%) No co-amoxiclav: n = 41/2376 (1.7%) RR 0.97 (0.73 to 1.71) Deaths in first year Any co-amoxiclav: n = 113/2336 (4.8%) No co-amoxiclav: n = 118/2376 (5.0%) RR 0.97 (0.75 to 1.27) Deaths after first year Any co-amoxiclav: n = 5/2336 (0.2%) No co-amoxiclav: n = 6/2376 (0.3%) RR 0.85 (0.26 to 2.78) Total deaths Any co-amoxiclav: n = 163/2336 (7.0%) No co-amoxiclav: n = 165/2376 (6.9%) RR 1.01 (0.80 to	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				1.26) Cerebral palsy Any co-amoxiclav: n = 39/1632 (2.4%) No co-amoxiclav: n = 48/1629 (2.9%) RR 0.81 (0.53 to 1.24) Developmental problems - ADHD from SDQ or parental report Any co-amoxiclav: n = 124/1632 (7.6%) No co-amoxiclav: n = 120/1629 (7.4%) RR 1.03 (0.80 to 1.34) Educational attainment - reading Any co-amoxiclav: n = 354/1623 (21.8%) No co-amoxiclav: n = 369/1615 (22.8%) RR 0.98 (0.94 to 1.02) Educational attainment - writing Any co-amoxiclav: n = 405/1623 (25.0%) No co-amoxiclav: n = 439/1615 (27.2%) RR 0.98 (0.94 to 1.01) Educational attainment - maths Any co-amoxiclav: n	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				= 250/1623 (15.4%) No co-amoxiclav: n = 439/1615 (16.3%) RR 0.99 (0.95 to 1.03)	
Full citation Kenyon,Sara, Boulvain,Michel, Neilson,James P., Antibiotics for preterm rupture of membranes, Cochrane Database of Systematic Reviews, -, 2013 **Ref Id** 299864 **Country/ies where the study was carried out** Various **Study type** Systematic review **Aim of the study** To assess the effect of administering antibiotics to women with preterm rupture of membranes (PROM) on maternal and neonatal outcomes. **Study dates**	**Sample size** Trials: 22 Women: n = 6872 **Characteristics** Randomised and quasi-randomised trials: **Amon 1988a** Participants: n = 82 women Treatment: n = 43 Control: n = 39 Inclusion: 20-34 weeks pregnant. Singleton pregnancy only, preterm pre-labour rupture of membranes (PPROM) confirmed by sterile speculum. Intervention: Treatment group: ampicillin 1g intravenously (IV) every 6 hours for 24 hours. Maintained on oral 500mg ampicillin 6 hourly until delivery. In labour they were recommenced on 1g intravenous ampicillin. **Camli 1997** Participants: n = 31 Inclusion: women with premature rupture of the membranes between 28-34 weeks gestation. PPROM confirmed by speculum. Exclusions:	**Interventions** Antibiotic versus placebo	**Details** Searching for studies The Trials Search Co-coordinator was contacted on 30 September 2013, and asked to search the Cochrane Pregnancy and Childbirth Group's Trials Register. In addition, CENTRAL, MEDLINE, CINAHL and Dissertation Abstracts were searched. The reference list of identified studies was also searched, and any studies assessed for eligibility. No language restrictions were applied. Data collection and analysis Two review authors independently assessed studies for inclusion. They then extracted data into a pre-designed form and resolved discrepancies through discussion or if required the third review authors was consulted. Data were entered into RevMan and checked for accuracy. If there was any unclear information, the authors were contacted to provide details. Quality assessment Risk of bias was assessed independently by two authors using the The Cochrane Collaboration's	**Results** **Any antibiotic versus placebo** Maternal death Number of studies: n = 3 Any antibiotic: n = 0/369 (0%) Placebo: n = 0/394 (0%) RR NC Perinatal death/ death before discharge Number of studies: n = 12 Any antibiotic: n = 276/4315 (6.4%) Placebo: n = 138/1986 (6.9%) RR 0.93 (0.76 to 1.14) Neonatal necrotising enterocolitis Number of studies: n = 11 Any antibiotic: n = 100/4273 (2.3%) Placebo: n =	**Limitations** - Trials in which post-randomisation exclusions occurred are included provided there was no evidence that these occurred preferentially in one or other arm of the trials.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Content was assessed as up to date: 26 November 2013 **Source of funding** University of Liverpool, UK University of Geneva, Switzerland Leicester Royal Infirmary, UK University of Birmingham, UK	- Women going into active labour within 24 hours who needed induction of labour. - Multiple pregnancy and fetal malformations. - Women with serious medical conditions or who needed antibiotic treatment for a known infection. - Women who had received antibiotics in the last 10 days or who were allergic to penicillin. **Christmas 1992** Participants n = 94 women Treatment: n = 48 Control: n = 46 Inclusions: singleton pregnancies 20 - 34 weeks with PPROM confirmed by sterile speculum. Exclusions: - Penicillin allergy - Prior antibiotic therapy. - Clinical evidence of intra-amniotic infection - Evidence of labour or fetal distress. Intervention: 24 hours IV ampicillin 2g every 6 hours for 4 doses; gentamycin 90mg loading dose 60 mg every 8 hours for 3 doses. Then oral amoxicillin + clavulanic acid 500mg 3 x day for 7 days. Control IV fluids without antibiotics for 24 hours. **Cox 1995** Participants: n = 62 Inclusion: women PPROM between 24 and 29 weeks pregnant. Not stated whether multiple pregnancy included. Interventions: Co-amoxiclav 3g 6		tool for assessing risk of bias. The following criteria were considered: - Sequence generation - Allocation concealment - Blinding: due to the intervention, it would not be possible to blind participants or those providing care; however, the authors report that they did consider whether outcome assessors were blinded - Incomplete outcome data: low risk was defined 20% or less missing data, and high risk as more than 20% missing data - Selective reporting bias: established by cross checking the outcomes reported in the methods and results sections of the publication - Other sources of bias Missing data Levels of attrition were noted for the studies. Sensitivity analysis was done to explore the effect of including studies with high attrition. All analyses were carried out on an intention-to-treat basis. Denominators were the number randomised, minus any women whose outcomes were known to be missing. Analysis Statistical analysis was done in RevMan. A random effects model was used. This was because the authors felt that there was sufficient clinical heterogeneity to expect that	58/1958 (3%) RR 1.09 (0.65 to 1.83) **All penicillin (excluding co-amoxiclav)** Maternal death Number of studies: n = 1 All penicillin: n = 0/40 (0%) Placebo: n = 0/45 (0%) RR NC Perinatal death/ death before discharge Number of studies: n = 4 All penicillin: n = 71/165 (4.2%) Placebo: n = 10/167 (6%) RR 0.78 (0.31 to 1.97) Neonatal necrotising enterocolitis Number of studies: n = 3 All penicillin: n = 5/124 (4%) Placebo: n = 6/138 (4.3%) RR 0.85 (0.25 to 2.97)	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	hourly for 4 doses then co-amoxiclav 500mg 6 hourly for 5 days or matching placebo. Data extracted from abstract only. Further data requested from the author but not made available. Study took place between May 1991 and April 1994 in Dallas, Texas. **Ernest 1994** Drugs and placebo were prepared by research nurses. Participants: n = 148 Treatment: n = 77 Placebo: n = 71 Inclusion: women at 21-37 weeks with premature rupture of the membranes preterm confirmed with positive nitrazine test and 'fern' of amniotic fluid or by seeing vaginal pool of amniotic fluid from os. No tocolytics or steroids given. Multiple pregnancies included. Exclusions: not clearly stated. Interventions: 4 hourly IV 1 million units benzylpenicillin for 12-24 hours - oral 250mg penicillin twice daily before delivery or a matched placebo. Study conducted from March 2 1989 to May 29 1991, in a single site (North Carolina, USA). 4 women were excluded because of protocol violation in placebo arm (antibiotics given) **Fuhr 2006** Participants: n = 105 pregnant Treatment: n = 47 Control: n = 58		the underlying treatment effect would differ.	Neonatal infection including pneumonia Number of studies n = 5 Other antibiotic: n = 6/258 (2.3%) Placebo: n = 25/263 (9.5%) RR 0.3 (0.13 to 0.68) **Beta lactum (including co-amoxiclav)** Perinatal death/ death before discharge Number of studies: n = 2 All penicillin: n = 80/1236 (6.5%) Placebo: n = 46/644 (7.1%) RR 0.62 (0.15 to 2.55) Neonatal necrotising enterocolitis Number of studies: n = 2 All penicillin: n = 29/1236 (2.3%) Placebo: n = 3/644 (0.47%) RR 4.72 (1.57 to	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	Inclusion: women with PROM between 24+0 and 32+6 weeks. Exclusion: criteria not clearly stated nor whether multiple pregnancies included. Interventions: Metzlocillin 2g given 3 x day for 7 days or placebo. All women given corticosteroids and tocolytics IV. Conducted in 5 centres in Germany - dates not given. **Garcia 1995** Participants: n = 60 pregnant women. Inclusion: PPROM under 36 weeks singleton pregnancy. Ruptured membranes confirmed by sterile speculum examination, ferning test and nitrazine test. No steroids or tocolytics given after randomisation. Exclusions: - > 37/40 - Discrepancy of over 2 standard deviations between scan and estimated due dates - Bleeding - Contractions - Fetal distress - Fetal malformation - Fetal death - Chorioamnionitis on admission - Antibiotics given during previous 10 days Interventions: Erythromycin 500mg 6 hourly orally until delivery. Matched placebo given until delivery. Women recruited during 1992 from single centre in Madrid, Spain. No losses to follow up.			14.23) Neonatal infection including pneumonia Number of studies: n = 1 Beta lactum: n = 0/31 (0%) Placebo: n = 1/31 (3.2%) RR 0.33 (0.01 to 7.88) **Macrolide (including erythromycin)** Perinatal death/ death before discharge Number of studies: n = 4 Macrolide: n = 84/1354 (6.2%) Placebo: n = 56/784 (7.1%) RR 0.83 (0.43 to 1.6) Neonatal infection including pneumonia Number of studies: n = 3 Macrolide: n = 19/163 (11.7%) Placebo: n = 25/171 (14.6%)	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	Paper in Spanish. **Grable 1996** Participants: n = 60 women Inclusions: ≤ 35 weeks with documented PPROM. Exclusions: - Non-reassuring stress test - Presence of chorioamnionitis - Abruptio placenta - Pre-eclampsia - Multiple pregnancy - penicillin allergy Intervention: IV ampicillin 2g every 6 hours for 24 hours followed by 500mg oral ampicillin until delivery or discharge. Matched placebos. Study divided into Group B strep (GBS) positive and negative patients. Unclear whether clinician knew of positive culture. **Johnston 1990** Participants n = 85 women. Inclusions: women with singleton gestations between 20-34 weeks with PPROM confirmed by sterile speculum for pooling, ferning and nitrazine paper testing. Exclusions: - Penicillin allergy - Taking antibiotics at the time of PPROM - Had fever > 100.4 degrees Fahrenheit - Had signs of chorioamnionitis - Were in active labour (defined by 3 or more contractions per 10 minute period for 1 hour or presented with cervical			RR 0.79 (0.45 to 1.37) Neonatal necrotising enterocolitis Number of studies: n = 3 Macrolide: n = 21/1322 (1.6%) Placebo: n = 19/754 (2.5%) RR 0.88 (0.45 to 1.69) **Other antibiotic versus placebo** Maternal death Number of studies: n = 2 Antibiotic: n = 0/329 (0%) Placebo: n = 0/349 (0%) RR NC Perinatal death/ death before discharge Number of studies: n = 3 Antibiotic: n = 84/1354 (6.2%) Placebo: n = 26/391 (6.6%) RR 1.13 (0.68 to 1.88)	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	dilatation > 3 cm confirmed at the time of sterile speculum). Fetal indications for exclusion: - Presence of fetal distress, defined as repetitive late deceleration or sustained bradycardia - Congenital abnormality on ultrasound. Interventions: IV mezlocillin for 48 hours followed by oral ampicillin until delivery or matched (IV + oral) placebo. No doses noted. After randomisation no tocolytic steroids given. Study drugs discontinued if infection diagnosed. Study carried out in a single centre - University Medical Centre - Jacksonville Florida. All women had infection screen on admission. No digital examination allowed. No comment as to losses to follow up or recruitment period. **Kenyon 2001** Participants: n = 4826 women Inclusion: under 37 weeks pregnant with PROM. Multiple pregnancies included. Exclusions: n = 661 women (246 due to perinatal death, 376 randomised outside UK and 39 women withdrew). Interventions: Co-amoxiclav 375mg QDS, erythromycin 250mg QDS orally for 10 days or until delivery matched placebo (2 x 2 factorial design). Multicentre trial (161 centres, 135 in the UK). n = 2 women lost to follow up			Neonatal infection including pneumonia Number of studies: n = 12 Any antibiotic: n = 85/823 (10.3%) Placebo: n = 141/857 (16.4%) RR 0.67 (0.52 to 0.85) Neonatal infection including pneumonia Number of studies: n = 3 Other antibiotic: n = 60/371 (16.2%) Placebo: n = 90/392 (23%) RR 0.71 (0.53 to 0.95) Neonatal necrotising enterocolitis Number of studies: n = 4 Other antibiotic: n = 25/402 (6.2%) Placebo: n = 30/421 (7.1%) RR 0.89 (0.54 to 1.47) Birth before 37 weeks gestation Number of studies:	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	and 15 women were excluded due to protocol violations. 4809 women analysed. For twin pregnancies adverse outcomes were considered present if one twin affected. Consumers involved in drawing up of protocol and information for women. **Kurki 1992** Participants: n = 101 women Inclusion: Women between 23-36 weeks pregnant with visible leakage of amniotic fluid who did not go into labour within 12 hours of admission. Sterile speculum, digital examination and infection screening was performed on admission. Multiple pregnancies included. Interventions: 2 doses of IV penicillin (5mu) or matched placebo. Department of Obstetrics and Gynaecology, Helsinki, Finland. No mention of where the study was conducted Results in 76 women not randomised but admitted during the same period are also reported. **Lockwood 1993a** Participants: n = 75 women Treatment n = 38 Placebo n = 37 Inclusion: women with a single fetus at 24-34 completed weeks (accurate gestational age), admitted with PROM. No digital examination unless active labour. Women had infection screening. Exclusions:			n = 3 Antibiotic: n = 3104/3642 (85.2%) Placebo: n = 1102/1289 (85.5%) RR 1 (0.98 to 1.03) Major adverse drug reaction Number of studies: n = 3 Antibiotic: n = 0/3913 (0%) Placebo: n = 0/1547 (0%) RR NC Maternal infection after delivery prior to birth Number of studies: n = 4 Antibiotic: n = 729/3942 (16.4%) Placebo: n = 306/1604 (19.1%) RR 0.91 (0.8 to 1.02) Chorioamnionitis Number of studies: n = 11 Antibiotic: n = 126/767 (18.5%) Placebo: n = 196/792 (24.7%) RR 0.66 (0.46 to 0.96)	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	- Abruption - Lethal fetal abnormalities - Clinical chorioamnionitis - Maternal illness (diabetes, pregnancy induced hypertension [PIH], lupus) - Other severe maternal disease - Fetal growth retardation - Fetal distress - Cervical cerclage - Active herpes - Women having received antibiotics for existing infection were also excluded. Interventions: Piperacillin 3g IV 6 hourly 72 hours or placebo. Recruitment in 3 centres (USA) from January 1987 to January 1992. 3 babies (1 in the experimental group and 2 in controls) were lost to follow up. Free of other bias?: Unclear. No information given. **Magwali 1999** Participants: n = 171 women Treatment: n = 84 Control: n = 87 in no treatment group. Inclusion: PROM 26-36 weeks gestation drainage of liquor confirmed by sterile speculum. Exclusions: - Clinical signs of chorioamnionitis - Multiple pregnancy - Those with any contraindication to continuing the pregnancy and those who had just completed a course of antibiotics for another reason. Interventions: Co-amoxiclav for 5 days. No mention of daily frequency or mg of			Birth 7 days of randomisation Number of studies: n = 7 Antibiotic: n = 2388/4145 (57.6%) Placebo: n = 1221/1820 (67.1%) RR 0.79 (0.71 to 0.89) Positive blood culture Number of studies: n = 3 Antibiotic: n = 234/3654 (6.4%) Placebo: n = 104/1307 (8%) RR 0.79 (0.63 to 0.99) Neonatal encephalopathy Number of studies: n = 1 Antibiotic: n = 0/30 (0%) Placebo: n = 0/30 (0%) RR NC Serious childhood disability at approximately 7 years Number of studies: n = 1 Antibiotic: n =	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	drugs. **McGregor 1991** Participants: n = 65 women Treatment: n = 28 Control: n = 27 Excluded: n = 10 (15%) Inclusion: Women between 23-34 completed weeks gestation with PROM. Sterile speculum. No corticosteroids administered. Singleton pregnancies. Exclusions: - Active labour - Presence of maternal or fetal complication to necessitate delivery (fetal distress, prolapsed cord, pregnancy-induced hypertension, abruptio placentae) - Placenta praevia - Cervical cerclage - Known infection requiring antibiotic treatment - Use of vaginal or oral antibiotics in last 2 weeks - Presence of known uterine or fetal abnormality - History of vaginal bleeding in last month - Serious existing maternal disease - History of allergy or intolerance to erythromycin. Interventions: Erythromycin 333mg 3 x daily or placebo 7 days or until active labour started. Study period: July 1986-June 1988 University Hospital Denver. No breakdown between stillbirths and neonatal deaths.			938/2375 (39.5%) Placebo: n = 311/796 (39.1%) RR 1.01 (0.91 to 1.12) **Antibiotics versus no antibiotic and/or placebo** Perinatal death/death before discharge Number of studies: n = 18 Antibiotic: n = 299/4604 (6.5%) Placebo: n = 172/2268 (7.6%) RR 0.89 (0.74 to 1.08) **Antibiotics versus no antibiotic (no placebo)** Perinatal death/death before discharge Number of studies: n = 6 Antibiotic: n = 23/289 (8%) no antibiotics: n = 34/282 (12.1%) RR 0.69 (0.41 to 1.14)	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	Mercer 1992 Participants: n = 220 Treatment: n = 106 Control: n = 114 Inclusions: women 20-34/6 weeks pregnant with PPROM - sterile speculum and evaluation of cervix. Amniocentesis done for infection screen. Multiple pregnancies included. Exclusions: - PPROM > 72 hours duration - Cervical dilatation > 4 cm - Progressive labour - Vaginal bleeding - Temperature 99 degrees Fahrenheit or greater - Active infection requiring antibiotic therapy - Antibiotic therapy within 1 week prior to admission - Active hepatic disease - Erythromycin allergy - Cervical cerclage or medical condition requiring delivery - Intrauterine growth restriction (IUGR) (< 10 centile) - Congenital abnormalities - Evidence of fetal distress - Unsuccessful tocolysis on admission for preterm labour. Interventions: Oral 333mg erythromycin. 8 hourly from randomisation to delivery with matched placebo. Study carried out in a single centre (Memphis, Tennessee, USA). March 1989-August 1990. Women had infection screen before				

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	randomisation. 3 lost to follow up. **Mercer 1997** Participants: 1867 women screened. n = 804 eligible. n = 614 agreed to participate. n = 29 twin gestations. Group B Strep positive: n = 118/614. Inclusion criteria: membrane rupture within 36 hours of randomisation; cervical dilatation 3cm or less on usual examination; < 5 contractions in 6 minutes, at 24-32 weeks gestation Exclusion criteria: - Non-reassuring - Vaginal bleeding - Maternal or fetal indication for delivery - Cervical cerclage in place - Antibiotics within the last 5 days - Corticosteroids within last 7 days - Allergy to penicillin or erythromycin - Maternal infection or medical disease - Ultrasound evidence of placenta praevia - Fetal weight < 10th centile for gestational age - Malformation Previous successful tocolysis was not an exclusion criterion. Tocolysis and corticosteroids were prohibited after randomisation. Interventions: Ampicillin 2g 6 hourly and erythromycin 250mg 6 hourly IV for 48 hours, then oral amoxacillin 250mg every 8 hours and erythromycin 333mg 8 hourly for 5 days and a matching placebo regimen.				

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	For twin pregnancies adverse outcomes considered present if 1 twin affected. Study carried out in 11 centres - USA. From February 1992 to January 1995. 3 women lost to follow up. **Morales 1989** Participants Randomised: 41 = GP1, 43 = GP2, 37 = GP3, 44 = GP4. Intervention: antenatal steroids + ampicillin. 4-p groups - GP1 - neither, GP2 steroids only, GP3 antibiotic only, GP4 both. Inclusion: 26-34 weeks pregnant singleton gestation. PROM confirmed by sterile speculum L/S ratio (amniotic fluid Lecithin Sphingomyelin) less than 2.0. Exclusions: - In labour within 12 hours of randomisation women with uterine tenderness - Foul smelling lochia or fetal tachycardia on admission - Women allergic to penicillin - Congenital abnormality with L/S ratio greater than 2.0 or not obtained. Interventions: 2g IV ampicillin every 6 hours until results of cervical cultures negative. **Ovalle Salas 1997** Participants: n = 88 women. Treatment: n = 42 Control: n = 46 Inclusions: women with PPROM 24-34 weeks, PPROM diagnosed with sterile speculum-pooling, ferning and				

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	nitrazine tests. No digital examination performed. Exclusions: - Significant haemorrhage - Placental abruption - Use of antibiotics within 30 days before screening for study - Fetal anomaly or death - Multiple gestation - Documented allergy to clindamycin or gentamicin - Uterine abnormality - Presence of intrauterine contraceptive device (IUCD) - Fetal distress - Clinical chorioamnionitis - Maternal medical complications necessitating delivery or any condition precluding expectant management and intrauterine growth retardation (< 10th centile for gestational age). Interventions: Clindamycin 600mg IV every 6 hours for 48 hours + 4 mg/kg/day gentamycin IV for 48 hours followed by Clindamycin 300mg orally every 6 hours for 5 days + gentamycin 2 mg/kg/day intramuscularly (IM) every 12 hours for 5 days. Matching placebo. Conducted in November 1990-September 1994. 3 sites: 2 Chile, 1 USA. Women had infection screen. 1 lost to follow up in placebo arm. Trial stopped after intermediate evaluation showed treatment group had better outcome. **Owen 1993a** Participants: n = 118 randomised 1 lost				

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	to follow up. Treatment: n = 59 Controls: n = 58 Inclusions: 24 to 34 weeks gestation. PPROM confirmed by speculum. Exclusions: - Clinical evidence of infection suspected fetal compromise - Membrane rupture over 2 days - Fetal abnormality - Antibiotics in last 7 days - Multiple pregnancy - Cervical cerclage - Prompt delivery required Interventions: IV 1g ampicillin 6 hourly for 24 hours then 500mg ampicillin orally every 6 hours. If allergic to penicillin 500mg erythromycin used 6 hourly. Treatment continued with delivery or diagnosis of chorioamnionitis. **Svare 1997** Participants: n = 67 Treatment: n = 30 Control: n = 37 Inclusion: women randomised. 26+0 - 33+6 rupture of membranes, leakage of amniotic fluid at vaginal speculum examination. Preceding onset of uterine contractions. Singleton pregnancies. Interventions: Ampicillin 2g IV 6 hourly. 24 hours - pivampicillin 500g orally 8 hourly for 7 days plus IV metronidazole 500mg every 8 hours for 24 hours, followed by metronidazole 400mg orally every 8 hours for 7 days or identical placebo. Conducted in				

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	October 1991-April 1994. 6 centres around Copenhagen. Data sent from the author and extracted from PhD thesis. **Inclusion criteria** - Randomised and quasi-randomised trials comparing antibiotics versus placebo, given to women with preterm rupture of membranes. - Trials in which post-randomisation occurred were included provided there was no evidence that it occurred in favour of one or other arm of the trial. **Exclusion criteria** - Trials where non randomised cohorts were amalgamated with randomised participants if the result of the randomised participants were not reported separately. - Trials where outcomes for over 20% of the participants were not reported				

H.4.1.31 **Health economics**

Bibliographic details	Interventions and comparisons	Data Sources	Time horizon & Method	Results	Reviewer comment
Full citation Colbourn,T., Asseburg,C., Bojke,L., Philips,Z., Claxton,K., Ades,A.E., Gilbert,R.E., Prenatal screening and treatment strategies to prevent group B streptococcal and other	**Study dates** June 2005 to June 2006 **Intervention** Vaccination + intravenous penicillin, vaccination + oral erythromycin, intravenous penicillin, and	**Source of effectiveness data** Vaccination effectiveness based on expert opinion. Effectiveness of antibiotics based on published literature.	**Time horizon and discount rate** Time Horizon: Llifetime Discount Rate (costs): Not stated Discount Rate (QALYs): 3%	**Cost per patient per alternative** Gains over no treatment Prelabour ROM > 2 hours Vaccination + intravenous penicillin GBP –2.28	**Limitations** Other information

Bibliographic details	Interventions and comparisons	Data Sources	Time horizon & Method	Results	Reviewer comment
bacterial infections in early infancy: Cost-effectiveness and expected value of information analyses, Health Technology Assessment, 11, 21-108, 2007 **Ref Id** 59896 **Economic study type** Cost-utility analysis **Country(ies) where the study was done** UK **Perspective & Cost Year** Perspective: NHS Cost Year: 2005 **Source of funding** HTA programme	oral erythromycin. **Comparison(s)** No treatment	**Source of cost data** Long-term healthcare costs of disability were taken from published literature Trotter 2002 Costs of delivery was taken from Petrou (129 lookup date). Duration of hospital stay was taken from the BPSU database. The costs per night of stay in each type of hospital ward were derived from the PSSRU. The costs of testing were based on the cost of staff , materials and laboratory costs. The costing of this was found in the PSSRU ,BNF, published literature, market value of materials. Drug costs were taken from the BNF. The cost of vaccine was based on the mean of four expert opinions.	Method of eliciting health valuations (if applicable) EQ-5D was used to estimate utilities for health children. For children with disabilities, published literature, Oostenbrinka 2002, was used where utilities based on EQ-5D was used. Life expectancy was estimated using ONS data and published literature Katz 2003 **Modelling approach** A Decision Tree model was used to simulate the various complications of group B streptococcal and other bacterial infections in early infancy.	Vaccination + oral erythromycin GBP –2.73 Intravenous penicillin GBP –2.17 Oral erythromycin GBP –2.52 **Effectiveness per patient per alternative** Gains over no treatment Prelabour ROM > 2 hours Vaccination + intravenous penicillin 0.000844 Vaccination + oral erythromycin 0.000843 Intravenous penicillin 0.000621 Oral erythromycin 0.000583 **Incremental cost-effectiveness** Reports ICER for intravenous compared to oral. With vaccination: ICER intravenous penicillin to oral erythromycin GBP	

Bibliographic details	Interventions and comparisons	Data Sources	Time horizon & Method	Results	Reviewer comment
		Other data sources e.g. transition probabilities		471,000 Without vaccination: ICER intravenous penicillin to oral erythromycin GBP 9,470 **Other reporting of results** **Uncertainty** Probabilistic sensitivity analysis	

H.5 Identifying infection in women with P-PROM

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
Full citation Carroll,S.G., Papaioannou,S., Nicolaides,K.H., Assessment of fetal activity and amniotic fluid volume in the prediction of intrauterine infection in preterm prelabor amniorrhexis, American Journal of Obstetrics and Gynecology, 172, 1427-1435, 1995	**Sample size** N = 89 **Characteristics** <u>Gestational age at assessment</u> Range 20 to 36 weeks **Inclusion Criteria**	**Tests** - Nonstress test - Fetal heart rate (tachycardia and FHR variation) - Biophysical profile score - Amniotic fluid index	**Methods** Amniocentesis and cordocentesis were performed for diagnosis of intrauterine infection in women with preterm prelabour amniorrhexis who were referred for further assessment. Diagnosis of preterm prelabour amniorrhexis was confirmed by ultrasonographic demonstration of decreased or absent amniotic fluid and	**Results** **<u>Nonreactive nonstress test as predictor of intrauterine infection</u>** Prevalence of intrauterine infection - defined as positive fetal blood culture: 14/89 (15.7%) All values calculated by NCC from data in Table IV Sensitivity: 50 % (23.81 to 76.19) Specificity: 41.33% (30.19 to 52.48) PPV: 13.73% (4.28 to 23.17) NPV: 81.58% (69.25 to 93.9) LR+: 0.85 (0.48 to 1.49) LR-: 1.21 (0.67 to 2.18)	**Limitations** Unclear whether consecutive women were included; exclusion criteria not reported Unclear whether results of reference standard were interpreted without knowledge of index test Amniotic fluid culture results not available for 15/89 women; reasons not reported

<table>
<tr><th>Bibliographic details</th><th>Participants</th><th>Tests</th><th>Methods</th><th>Outcomes and results</th><th>Comments</th></tr>
<tr>
<td>Ref Id

258724

Country/ies where the study was carried out

UK

Study type

Case-series

Aim of the study
To evaluate fetal biophysical profile score, amniotic fluid index and fetal heart rate pattern in predicting positive fetal blood and amniotic fluid cultures in samples obtained antenatally from pregnancies that were complicated by preterm prelabour amniorrhexis

Study dates
June 1992 to February 1994

Source of funding
Not reported</td>
<td>Preterm prelabour amniorrhexis confirmed by ultrasonographic demonstration of decreased or absent amniotic fluid and visualisation of Nitrazine-positive fluid in the vagina

Exclusion Criteria
Not reported</td>
<td></td>
<td>visualisation of Nitrazine-positive fluid in the vagina.

Amniocentesis and cordocentesis were performed with a single uterine transabdominal entry of a 20-gauge needle under ultrasonographic guidance. Umbilical venous blood was obtained and tests confirmed all samples contained only fetal blood. Amniotic fluid was cultured by standard microbiologic techniques and was also inoculated into Mycofast liquid cultures for Ureaplasma urealyticum and Mycoplasma hominis (International Mycoplasma, Toulon, France). The first 1ml of fetal blood and amniotic fluid were not used for microbiologic investigations.

Computerised fetal heart rate (FHR) analysis was performed after monitoring for 60 min with the Sonicaid system 8000 (Sonicaid, Chichester, UK) and a Hewlett-Packard 8040A FHR monitor (Hewlett-Packard, Boeblingen, Germany). Baseline FHR was measured in beats per min and FHR variation measured as the mean minute range of pulse intervals around the baseline. FHR baseline and variation</td>
<td>Nonstress test
<table>
<tr><th></th><th>Reference Test +ve</th><th>Reference Test -ve</th></tr>
<tr><td>Predictive Test +ve</td><td>7</td><td>44</td></tr>
<tr><td>Predictive Test -ve</td><td>7</td><td>31</td></tr>
</table>
</td>
<td>Timing of nonstress test not reported

Applicability of nonstress test before 28 weeks? (gestational age range of included women 20 to 36 weeks, mean gestational age not reported)

Other information
Study evaluated biophysical profile and amniotic fluid index as predictors of infection - data for nonstress test only were extracted as this was the test of interest in review protocol

Data not extracted for fetal tachycardia and reduced fetal heart rate variation as cut-offs for a positive predictive test were not adequately defined

Nonstress test not described

Data not extracted for amniotic fluid culture results as there were missing data; reasons for missing data not reported

Prevalence of intrauterine infection - defined by positive amniotic fluid culture: 28/74 (37.8%)</td>
</tr>
</table>

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
			were corrected for gestational age.		Use of antibiotics not reported
Full citation Del Valle,G.O., Joffe,G.M., Izquierdo,L.A., Smith,J.F., Gilson,G.J., Curet,L.B., The biophysical profile and the nonstress test: poor predictors of chorioamnionitis and fetal infection in prolonged preterm premature rupture of membranes, Obstetrics and Gynecology, 80, 106-110, 1992 **Ref Id** 259048 **Country/ies where the study was carried out** USA **Study type** Case-series **Aim of the study** To evaluate the role of fetal biophysical profile and the nonstress test in the management of prolonged preterm premature rupture of membranes (PROM)	**Sample size** N = 68 **Characteristics** **Maternal age (mean ± SD)** 26.2 ± 5.6 years **Gestational age at PROM (mean ± SD)** 31.3 ± 3.2 weeks **Gestational age at PROM (mean ± SD)** 32.8 ± 2.9 weeks **Latency (mean ± SD)** 10.9 ± 11.1 days **Inclusion Criteria** - Proved premature rupture of membranes - absence of labour - absence of chorioamnionitis or fetal distress on admission - time between rupture of membranes and	**Tests** - Biophysical profile - Nonstress test	**Methods** On admission women were examined with a sterile speculum to confirm ruptured membranes. If initial evaluations demonstrated fetal and neonatal wellbeing and there was no evidence of labour or infection expectant management was instituted. Women were hospitalised and placed on bed rest. Prophylactic antibiotics were not used. Fetal surveillance consisted of daily kick counts, daily nonstress test (NST) and biophysical profile every 48 to 72 hours after 26 weeks gestation. NST was performed for a 20-min period, extended to 40 min if nonreactive. Reactivity was defined as two or more accelerations of the fetal heart rate of at least 15 beats per minute (bpm) over baseline for at least 15 seconds. Nonreactive tests were evaluated with a biophysical profile to assess fetal well-being. An abnormal NST was defined as a nonreactive one with late or	**Results** **Abnormal nonstress test as predictor of neonatal infection (neonatal sepsis and neonatal pneumonia)** Prevalence of neonatal infection: 5/68 (7%) All values calculated by NCC-WCH using data reported in Table 2 Sensitivity: 33.33% (2.53 to 64.13) Specificity: 96.61% (91.99 to 100) PPV: 60.00% (17.06 to 100) NPV: 90.48% (83.23 to 97.72) LR+: 9/83 (1.89 to 50.99) LR-: 0.69 (0.43 to 1.09) **Abnormal nonstress test as predictor of clinical chorioamnionitis** Prevalence of clinical chorioamnionitis: 10/68 (15%) All values calculated by NCC-WCH using data reported in Table 2 Sensitivity: 30.00% (1.60 to 58.40) Specificity: 89.66% (81.82 to 97.49) PPV: 33.33% (2.53 to 64.13) NPV: 88.14% (79.88 to 96.39) LR+: 2.9 (0.86 to 9.75) LR-: 0.78 (0.52 to 1.18) **Nonstress test**	**Limitations** Retrospective case series Unclear whether consecutive women were included Unclear whether results of reference standard were interpreted without knowledge of index test Gestational age range for inclusion not reported (mean and standard deviation suggest a small percentage may have had a gestational age > 37 weeks) **Other information** Only data for nonstress test have been extracted (biophysical profile not a test of interest specified in review protocol) Authors also report data for reactive/nonreactive nonstress test Authors report in results text that for predicting neonatal infections the sensitivity and specificity for NST are 60%

<table>
<tr><th>Bibliographic details</th><th>Participants</th><th>Tests</th><th>Methods</th><th>Outcomes and results</th><th>Comments</th></tr>
<tr>
<td>Study dates
September 1988 - December 1990

Source of funding
Not reported</td>
<td>onset of labour of at least 48 hours

Exclusion Criteria
- Transported to the study institution more than 48 hours after PROM
- Last biophysical profile more than 72 hours before delivery
- Signs of intra-amniotic infection, labour, or fetal compromise on admission
- Births before 26 weeks</td>
<td></td>
<td>repetitive, severe variable decelerations.

Clinical chorioamnionitis was based on maternal temperature ≥ 38°C and one or more of the following: maternal tachycardia, fetal tachycardia, purulent cervical discharge, labour, uterine irritability, and absence of other sources of infection. Women were treated with antibiotics and delivered as soon as chorioamnionitis was diagnosed.

Neonatal sepsis was diagnosed in infants with suggestive clinical findings and positive blood cultures within the first 24 hours of life. Neonatal pneumonia was based on clinical and radiological findings within the first 24 hours of life. Neonates with "suspected" or "rule out" sepsis were excluded from the analysis.

Data were analysed retrospectively</td>
<td>
<table>
<tr><th></th><th>Reference Test +ve</th><th>Reference Test -ve</th></tr>
<tr><td>Predictive Test +ve</td><td>3</td><td>2</td></tr>
<tr><td>Predictive Test -ve</td><td>6</td><td>57</td></tr>
</table>
Nonstress test
<table>
<tr><th></th><th>Reference Test +ve</th><th>Reference Test -ve</th></tr>
<tr><td>Predictive Test +ve</td><td>3</td><td>6</td></tr>
<tr><td>Predictive Test -ve</td><td>7</td><td>52</td></tr>
</table>
</td>
<td>and 90%, respectively. When NCC calculated predictive values using data in Table 2, the positive and negative predictive values were 60% and 90%, respectively

Results of last NST before delivery were evaluated</td>
</tr>
<tr>
<td>Full citation

Farb,H.F., Arnesen,M., Geistler,P., Knox,G.E., C-reactive protein with</td>
<td>Sample size
N = 31</td>
<td>Tests
Serum C-reactive protein</td>
<td>Methods
Women admitted to the Abbott-North-western Minneapolis Children's Perinatal Center from June to</td>
<td>Results
<u>CRP >2 mg/dl as a predictor of clinical chorioamnionitis</u>
Prevalence of clinical chorioamnionitis: 9/31 (29.0%)</td>
<td>Limitations
Unclear whether consecutive women were included

Only 24/31 placentas were</td>
</tr>
</table>

<table>
<tr><th>Bibliographic details</th><th>Participants</th><th>Tests</th><th>Methods</th><th>Outcomes and results</th><th>Comments</th></tr>
<tr>
<td>premature rupture of membranes and premature labor, Obstetrics and Gynecology, 62, 49-51, 1983

Ref Id

258087

Country/ies where the study was carried out

USA

Study type

Case-series

Aim of the study
To test the diagnostic validity of C-reactive protein (CRP) in identifying or predicting the development of chorioamnionitis

Study dates
June to November 1981

Source of funding
Not reported</td>
<td>Characteristics
None reported

Inclusion Criteria
Confirmed diagnosis of PROM (free flow of amniotic fluid observed from the cervix, or nitrazine-positive and ferning present on examination of vaginal fluid) between 20 and 36 weeks' gestation

Exclusion Criteria
Intercurrent illnesses such as systemic lupus erythematosus or rheumatoid arthritis in which serum levels of (CRP) may be elevated</td>
<td></td>
<td>November 1981 with a confirmed diagnosis of PROM. Amniotic fluid was cultured for bacteria following successful amniocentesis. Women were given betamethasone, with prompt delivery occurring 1) 48 hours after first dose of betamethasone, 2) in the event tocolytic drugs were unable to prevent labour and 3) when a clinical diagnosis of chorioamnionitis or fetal distress was made.

Clinical chorioamnionitis was defined as temperature ≥ 37.5°C or white blood cell count rise of at least 50% above the admission white blood cell count with either uterine tenderness or fetal tachycardia. Histologic chorioamnionitis was defined as histopathologic findings of chorioamnionitis (amnion and chorion), funisitis (wall of the umbilical cord vessels) and intervillisitis.

Serial blood samples of serum CRP determinations were obtained on admission and every 12 hours until delivery. CRP levels were not determined until after delivery and therefore had no role in the care of the women. CRP levels were measured using a</td>
<td>All values calculated by NCC from data in Figure 1
Sensitivity: 55.56% (23.09 to 88.02)
Specificity: 72.73% (54.12 to 91.34)
PPV: 45.45% (16.03 to 74.88)
NPV: 80.00% (62.47 to 97.53)
LR+: 2.04 (0.83 to 5.00)
LR-: 0.61 (0.28 to 1.33)

<u>CRP >2 mg/dl as a predictor of histologic choroamnionitis</u>
Prevalence of histologic chorioamnionitis: 5/24 (21%)

All values calculated by NCC from data in Figure 2. Histologic data for 24/31 women
Sensitivity: 80% (44.94 to 100)
Specificity: 68.42% (47.52 to 89.32)
PPV: 40% (9.64 to 70.36)
NPV: 92.86% (79.37 to 100)
LR+: 2.53 (1.15 to 5.60)
LR-: 0.29 (0.05 to 1.73)

C-reactive protein - clinical reference test
<table>
<tr><th></th><th>Reference Test +ve</th><th>Reference Test -ve</th></tr>
<tr><td>Predictive Test +ve</td><td>5</td><td>6</td></tr>
<tr><td>Predictive Test -ve</td><td>4</td><td>16</td></tr>
</table>
</td>
<td>available for histologic examination

Time that samples used in analysis were taken is unclear

Antibiotic use not reported

Other information
41 women in preterm labour and 18 women with "a variety of high-risk conditions" were also included in the study. The study reports outcomes separately for the pPROM and preterm labour groups, and so data for pPROM only have been extracted</td>
</tr>
</table>

<table>
<tr><th>Bibliographic details</th><th>Participants</th><th>Tests</th><th>Methods</th><th>Outcomes and results</th><th>Comments</th></tr>
<tr><td></td><td></td><td></td><td>nephelometric immunochemisttry system (Beckman Instruments Incorporated, Fullerton, CA, USA). Serum samples were pretreated by a 1:6 dilution and a polymeric buffer reaction media and centrifuged to remove interfering turbidity after a 5-min incubation. Sensitivity of the system is 1.8 mg/dl and the procedure is linear to 20 mg/dl. A CRP of 2 mg/dl or more was considered elevated.</td><td>C-reactive protein - histological reference test<table><tr><th></th><th>Reference Test +ve</th><th>Reference Test -ve</th></tr><tr><td>Predictive Test +ve</td><td>4</td><td>6</td></tr><tr><td>Predictive Test -ve</td><td>1</td><td>13</td></tr></table></td><td></td></tr>
<tr><td>Full citation

Fisk,N.M., Fysh,J., Child,A.G., Gatenby,P.A., Jeffery,H., Bradfield,A.H., Is C-reactive protein really useful in preterm premature rupture of the membranes?, British Journal of Obstetrics and Gynaecology, 94, 1159-1164, 1987

Ref Id

258332

Country/ies where the study was carried out

Australia

Study type</td><td>Sample size
N = 55

(n = 51 singleton pregnancies)

Characteristics
Not reported

Inclusion Criteria
- 26 to 36 weeks gestation
- Ruptured membranes confirmed by demonstration of pooling of amniotic fluid in the posterior</td><td>Tests
Serum C-reactive protein</td><td>Methods
Women admitted to King George V Hospital between March 1985 and June 1986 with ruptured membranes at 26 to 36 weeks gestation were enrolled.

Venepuncture for CRP, white blood cell count, differential and film was performed daily throughout latency. CRP was measured by rate nephelometry (Beckman Instruments Inc, Fullerton, CA, USA), using a single point calibration based on purified CRP and monospecific antisera (Quantimetric 2, Kallestad, Austin, TX, USA). A value</td><td>Results
<u>CRP as a predictor of histological acute diffuse chorioamnionitis</u>
Prevalence: 30/51 (58.8%)

Predictive values as reported by study authors in Table 1 *95% confidence intervals, LR+ and LR- and data presented in 2x2 tables below calculated by NCC technical team

CRP cut-off >20 mg/l
Sensitivity: 50% (32.11 to 67.89)
Specificity: 81% (64.16 to 97.25)
PPV: 79% (60.62 to 97.28)
NPV: 53% (35.83 to 70.42)
LR+: 2.63 (1.01 to 6.80)
LR-: 0.62 (0.41 to 0.93)

CRP cut-off 30 mg/l
Sensitivity: 47% (28.81 to 64.52)</td><td>Limitations
Unclear whether consecutive women were included

Other information
5/60 women were excluded from the analysis: two women received antibiotics, one woman declined further venepuncture, one woman was discharged after amniotic fluid drainage ceased for 7 days and one woman developed a respiratory tract infection

Of the 55 women analysed, 51 women had a singleton pregnancy and 4 women had</td></tr>
</table>

<table>
<tr><th>Bibliographic details</th><th>Participants</th><th>Tests</th><th>Methods</th><th>Outcomes and results</th><th>Comments</th></tr>
<tr>
<td>Case-series

Aim of the study
To ascertain the C-reactive protein (CRP) level above which the test becomes highly predictive of infection

Study dates
March 1985 to June 1986

Source of funding
Not reported</td>
<td>fornix
- Indications for conservative expectant management

Exclusion Criteria
- Clinical signs of infection
- History of chronic inflammatory conditions</td>
<td></td>
<td>was not assigned to measurements below 6mg/l. CRP results were not available to the investigators or clinicians involved until after the woman was discharged.

Management was at the discretion of the attending physician and usually included betamethasone administration at gestations < 34 weeks and tocolysis with oral and parenteral salbutamol, if required, a at gestations < 32 weeks.

Clinical chorioamnionitis was defined as uterine tenderness, purulent amniotic fluid and maximum temperature ≥ 37.5°C (maternal temperature recorded every 4 hours). Histological acute diffuse chorioamnionitis was assessed by one of two perinatal pathologists, using a membrane roll technique to examine a thin strip of membranes from the placental edge of the site of rupture. Focal inflammation confined to the site of membrane rupture was not considered an infective phenomenon</td>
<td>Specificity: 90% (77.92 to 100)
PPV: 88% (71.29 to 100)
NPV: 54% (37.78 to 70.79)
LR+: 4.9 (1.24 to 19.33)
LR-: 0.59 (0.41 to 0.85)

CRP cut-off 35 mg/l
Sensitivity: 40% (22.47 to 57.53)
Specificity: 95% (86.13 to 100)
PPV: 92% (77.82 to 100)
NPV: 53% (36.76 to 68.51)
LR+: 8.4 (1.18 to 59.77)
LR-: 0.63 (0.46 to 0.86)

CRP cut-off 40 mg/l
Sensitivity: 37% (19.42 to 53.91)
Specificity: 100% (100 to 100)
PPV: 100% (100 to 100)
NPV: 52.5% (37.02 to 67.98)
LR+: NC
LR-: 0.63 (0.48 to 0.83)

C-reactive protein
<table>
<tr><th></th><th>Reference Test +ve</th><th>Reference Test -ve</th></tr>
<tr><td>Predictive Test +ve</td><td>15</td><td>4</td></tr>
<tr><td>Predictive Test -ve</td><td>15</td><td>17</td></tr>
</table>
C-reactive protein</td>
<td>a multiple pregnancy (8%). Predictive values were calculated for singleton pregnancies only.

11 women had a CRP level >40mg/l and all had histological chorioamnionitis. None of the women had all three clinical signs of chorioamnionitis at the time of blood collection, although five women had one of the three signs.

Last taken CRP values were analysed; in 44 women the last CRP was taken within 24h of delivery, and 7 women had their last CRP value taken 24-48h before delivery

CRP elevation often preceded delivery or clinical infection by several days

White blood cell count, neutrophil count and blood film did not correlate with chorioamnionitis (data not reported)</td>
</tr>
</table>

<table>
<tr><th>Bibliographic details</th><th>Participants</th><th>Tests</th><th>Methods</th><th>Outcomes and results</th><th>Comments</th></tr>
<tr><td></td><td></td><td></td><td></td><td>
<table>
<tr><th></th><th>Reference Test +ve</th><th>Reference Test -ve</th></tr>
<tr><td>Predictive Test +ve</td><td>14</td><td>2</td></tr>
<tr><td>Predictive Test -ve</td><td>16</td><td>19</td></tr>
</table>
C-reactive protein
<table>
<tr><th></th><th>Reference Test +ve</th><th>Reference Test -ve</th></tr>
<tr><td>Predictive Test +ve</td><td>12</td><td>1</td></tr>
<tr><td>Predictive Test -ve</td><td>18</td><td>20</td></tr>
</table>
C-reactive protein
<table>
<tr><th></th><th>Reference Test +ve</th><th>Reference Test -ve</th></tr>
<tr><td>Predictive Test +ve</td><td>11</td><td>0</td></tr>
<tr><td>Predictive Test -ve</td><td>19</td><td>21</td></tr>
</table>
</td><td></td></tr>
<tr><td>Full citation</td><td>Sample size
N = 251</td><td>Tests
- Fetal heart</td><td>Methods
As part of a prospective</td><td>Results
<u>Fetal heart rate > 170 bpm at admission</u></td><td>Limitations
Unclear whether consecutive</td></tr>
</table>

<table>
<tr><th>Bibliographic details</th><th>Participants</th><th>Tests</th><th>Methods</th><th>Outcomes and results</th><th>Comments</th></tr>
<tr>
<td>Garite,T.J., Freeman,R.K., Chorioamnionitis in the preterm gestation, Obstetrics and Gynecology, 59, 539-545, 1982

Ref Id

258765

Country/ies where the study was carried out

USA

Study type

Case-series

Aim of the study
To identify the maternal and fetal/neonatal complications of chorioamnionitis in preterm gestation and to look at ways of distinguishing women who have infection or are destined to develop infection

Study dates
May 1997 - July 1980

Source of funding
Not reported</td>
<td>(n = 237 analysed by NCC-WCH)

Characteristics
Not reported

Inclusion Criteria
Women with premature rupture of membranes between 28+0 and 34+6 weeks

Exclusion Criteria
Not reported</td>
<td>rate
- White blood cell count</td>
<td>randomised study to evaluate the use of corticosteroids in in women with premature rupture of membranes (PROM), all women with PROM between 28+0 and 34+6 weeks were coded prospectively (women selected from patients at University of California Irvine Medical Center and private maternal transports at Women's Hospital, Memorial Medical Center of Long Beach). Rupture of membranes was documented by sterile speculum examination confirming pooling of fluid, alkaline pH by Nitrazine paper and ferning. Women were then evaluated for clinical signs of chorioamnionitis, including maternal and fetal tachycardia, leukocytosis, uterine tenderness and purulent foul-smelling vaginal discharge. Diagnosis of chorioamnionitis was restricted to women with temperatures ≥ 38°C for whom other causes of fever (such as urinary tract infection [UTI]) were absent. No histological confirmation of chorioamnionitis was performed.

Antibiotics were not given prior to delivery unless</td>
<td>Prevalence of clinical chorioamnionitis: 36/237 (15%)
All values and confidence intervals calculated by NCC-WCH using data presented in Table 1, for women who developed chorioamnionitis and women who did not (women with chorioamnionitis on admission excluded from analysis)

Sensitivity: 5.56% (0 to 13.04)
Specificity: 100% (100 to 100)
PPV: 100% (100 to 100)
NPV: 85.53% (81.03 to 90.03)
LR+: 0.94 (0.87 to 1.02)
LR-: 0 (0 to 0)

<u>Maternal white blood cell count > 20,000 at admission</u>
Prevalence of clinical chorioamnionitis: 36/237 (15%)
All values and confidence intervals calculated by NCC-WCH using data presented in Table 1, for women who developed chorioamnionitis and women who did not (women with chorioamnionitis on admission excluded from analysis)

Sensitivity: 5.56% (0 to 13.04)
Specificity: 95.02% (92.02 to 98.03)
PPV: 16.67% (0 to 37.75)
NPV: 84.89% (88.21 to 89.57)
LR+: 1.12 (0.26 to 4.89)
LR-: 0.99 (0.91 to 1.08)

White blood cell count
<table>
<tr><th></th><th>Reference Test +ve</th><th>Reference Test -ve</th></tr>
</table>
</td>
<td>women were included

Other information
Method of fetal heart rate (FHR) monitoring not reported

11 women had chorioamnionitis at admission - data not extracted. Data reported separately for women who developed chorioamnionitis (n = 36) and women who did not develop chorioamnionitis (201) - these data have been extracted into the evidence table</td>
</tr>
</table>

<table>
<tr><th>Bibliographic details</th><th>Participants</th><th>Tests</th><th>Methods</th><th>Outcomes and results</th><th>Comments</th></tr>
<tr><td></td><td></td><td></td><td>chorioamnionitis was diagnosed.

All maternal data were coded prospectively. Neonatal data were coded after discharge.</td><td>
<table>
<tr><td>Predictive Test +ve</td><td>2</td><td>10</td></tr>
<tr><td>Predictive Test -ve</td><td>34</td><td>191</td></tr>
</table>

Fetal heart rate - clinical reference test
<table>
<tr><th></th><th>Reference Test +ve</th><th>Reference Test -ve</th></tr>
<tr><td>Predictive Test +ve</td><td>2</td><td>0</td></tr>
<tr><td>Predictive Test -ve</td><td>34</td><td>201</td></tr>
</table>
</td><td></td></tr>
<tr><td>Full citation

Hawrylyshyn,P., Bernstein,P., Milligan,J.E., Soldin,S., Pollard,A., Papsin,F.R., Premature rupture of membranes: the role of C-reactive protein in the prediction of chorioamnionitis, American Journal of Obstetrics and Gynecology, 147, 240-246, 1983

Ref Id

258979

Country/ies where the study was carried out</td><td>Sample size
N = 54

Characteristics
Not reported

Inclusion Criteria
- Confirmed PROM by alkaline pH on nitrazine paper
- Between 20 and 34 weeks gestation

Exclusion Criteria</td><td>Tests
- C-reactive protein (CRP)
- White blood cell (WBC) count
- Erythrocyte sedimentation rate (ESR)
- Band count</td><td>Methods
All women presenting to the Perinatal Unit at Mount Sinai Hospital in Toronto from 1 July 1981 to 31 March 1982 with confirmed PROM before 34 weeks' gestation were eligible for study entry.

PROM was confirmed by alkaline pH on nitrazine paper after a history suggestive of PROM was taken. In uncertain cases PROM was confirmed by speculum examination to assess pooling of fluid in the posterior vaginal fornix.</td><td>Results
Prevalence of histological amnionitis: 26/52 (50%)
<u>CRP > 1.25 mg/dl as predictor of histological amnionitis</u>
Values presented in Table II *95% confidence intervals, LR+, LR- and 2x2 data calculated by NCC technical team

Sensitivity: 88% (76.18 to 100)
Specificity: 96% (88.76 to 100)
PPV: 96% (87.84 to 100)
NPV: 89% (77.83 to 100)
LR+: 23.00 (3.35 to 157.97)
LR-: 0.12 (0.04 to 0.35)

<u>WBC count >12,500/mm³ as predictor of histological amnionitis</u>
Values presented in Table II *95%</td><td>Limitations
Unclear if consecutive women were included

Time that samples used in analysis were taken is unclear

Other information
2/54 women were excluded from the study because they had positive introital swabs and received antibiotics for several days before delivery - therefore 52 women analysed. A further nine women were discharged</td></tr>
</table>

<table>
<tr><th>Bibliographic details</th><th>Participants</th><th>Tests</th><th>Methods</th><th>Outcomes and results</th><th>Comments</th></tr>
<tr>
<td>Canada

Study type

Case-series

Aim of the study
To delineate better the accuracy and clinical usefulness of ancillary aids aimed at diagnosing chorioamnionitis in PROM

Study dates
1 July 1981 to 31 March 1982

Source of funding
Not reported</td>
<td>Not reported</td>
<td></td>
<td>Management was left to the discretion of attending physicians. Most women were managed expectantly. Corticosteroids were routinely administered (12mg Celestone, two doses, 12h apart). During the first 48h, whenever regular uterine activity developed, tocolytic therapy was instituted. Routine prophylactic antiobiotics were not used.

All women were monitored for chorioamnionitis on a daily basis according to a standardised protocol, including WBC count, differential or band count, ESR, CRP determination and clinical assessment. Amniocentesis was not routinely performed. At delivery, anaerobic and aerobic cultures of endometrial cavity and amniotic membranes were routinely obtained. Placentas were examined histologically and classified as having mild or severe inflammation on basis of leukocytes per microscopic high power field.

WBC counts were performed on automated Coulter-S counter. CRP samples were collected and stored independently and results</td>
<td>confidence intervals, LR+, LR- and 2x2 data calculated by NCC technical team

Sensitivity: 80% (65.62 to 95.92)
Specificity: 62% (42.84 to 80.24)
PPV: 67% (51.29 to 84.20)
NPV: 76% (57.97 to 94.41)
LR+: 2.10 (1.25 to 3.54)
LR-: 0.31 (0.13 to 0.73)

C-reactive protein
<table>
<tr><th></th><th>Reference Test +ve</th><th>Reference Test -ve</th></tr>
<tr><td>Predictive Test +ve</td><td>23</td><td>1</td></tr>
<tr><td>Predictive Test -ve</td><td>3</td><td>25</td></tr>
</table>
White blood cell count
<table>
<tr><th></th><th>Reference Test +ve</th><th>Reference Test -ve</th></tr>
<tr><td>Predictive Test +ve</td><td>21</td><td>10</td></tr>
<tr><td>Predictive Test -ve</td><td>5</td><td>16</td></tr>
</table>
</td>
<td>undelivered after up to 6 weeks' hospitalisation as leakage of amniotic fluid had ceased. All nine women were subsequently delivered with no evidence of chorioamnionitis.

Clinical chorioamnionitis, defined by febrile morbidity (38°C at or within 12 hours of delivery) occurred in only seven women. There were nine perinatal deaths directly related to prematurity or its sequelae.

A control group of 74 women selected at random was used to define the normal range of laboratory parameters being studied (upper limit of normal defined as two standard deviations above the mean for normally distributed data and the 95th percentile for other distributions). Upper limit of normal for CRP defined as 1.25mg/dl and WBC as 12.5 x 10^3

Data for ESR and band count not extracted as these were not tests specified in the review protocol</td>
</tr>
</table>

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
			were unavailable to attending physicians, therefore results did not influence care management decisions. A rate nephelometric assay was performed suing a Beckman Immunochemistry Analyser with CRP reagent kit (Beckman Instruments Inc., Fullterton, CA, USA)		
Full citation Ismail,M.A., Zinaman,M.J., Lowensohn,R.I., Moawad,A.H., The significance of C-reactive protein levels in women with premature rupture of membranes, American Journal of Obstetrics and Gynecology, 151, 541-544, 1985 **Ref Id** 259068 **Country/ies where the study was carried out** USA **Study type** Case-series **Aim of the study** To evaluate the sensitivity	**Sample size** N = 100 **Characteristics** <u>Maternal age (mean ± standard error of the mean [SEM])</u> 24.5 ± 5.2 years <u>Gestational age (mean ± SEM)</u> 31 (SEM not reported) <u>Duration of PROM (mean ± SEM)</u> 150 ± 21.7 hours <u>Mode of delivery</u> Sponatenous vaginal delivery: 47% Outlet forceps delivery: 40% Caesarean section: 13%	**Tests** - Serum C-reactive protein - Fetal heart rate (FHR) - Maternal temperature - White blood cell (WBC) count	**Methods** All women admitted to Chicago Lying-in Hospital between 1 August 1980 and 30 July 1982 with premature rupture of membranes (presence of gross pooling of amniotic fluid or Nitrazine-positive fluid in the vaginal vault). Women were managed conservatively and evaluated with the following tests: uterine cervical culture tested for group B streptococci, Neisseria gonorrhoeae and Chlamydia trachomatis; real-time sonogram to rule out congenital malformation and to identify pockets of amniotic fluid; amniocentesis (with consent) to evaluate fetal lung maturity and tested for infection (Gram stain and aerobic and anaerobic bacterial cultures); blood drawn for daily complete	**Results** **<u>CRP > 2 mg/dl as predictor of clinical chorioamnionitis</u>** Prevalence of clinical chorioamnionitis: 18/100 (18%) Predictive values as reported by study authors in Table III *95% CI, LR+, LR- and 2x2 table calculated by NCC techincal team using reported sensitivity and specificity, and reported prevalence of clinical chorioamnionitis. Calculated PPV and NPV differ from those reported in the original study Sensitivity: 82% (66.12 to 100) Specificity: 55% (44.11 to 65.65) PPV: 28.85 % (NCC calculated) (16.53 to 41.16); 36% (reported) NPV: 93.75% (NCC calculated) (86.90 to 100); 91% (reported) LR+: 1.85 (1.35 to 2.53) LR-: 0.30 (0.11 to 0.87) **<u>CRP >2 mg/dl as predictor of histologic chorioamnionitis</u>** Prevalence of histologic chorioamnionitis:	**Limitations** Report suggests consecutive women were included; exclusion criteria not reported Time that samples used in analysis were taken is unclear **Other information** 18 women developed clinical chorioamnionitis; histologic chorioamnionitis was diagnosed in the placentas of 63 women (16 women had both clinical and histologic chorioamnionitis) Note there are differences in the PPV and NPV reported by authors and the PPV and NPV calculated by NCC technical team for both clinical and histological chorioamnionitis

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
and specificity of C-reactive protein (CRP) in the management of women with premature rupture of membranes **Study dates** 1 August 1980 to 30 July 1982 **Source of funding** Mother's Aid Research Fund, The Chicago Lying-In Hospital	**Inclusion Criteria** - Between 26 and 35 weeks gestation - Premature rupture of membranes (presence of gross pooling of amniotic fluid or of nitrazine-positive fluid in the vaginal vault) - No signs or symptoms of chorioamnionitis - No labour contractions **Exclusion Criteria** Not reported		blood cell count with differential WBC count and CRP determination. Fetal heart rate, maternal temperature, uterine tenderness or contractions were evaluated every 8 hours. Conservative management was interrupted if clinical evidence of chorioamnionitis developed. Labour was induced if maternal temperature was ≥ 38°C, if the uterus became tender and irritable, or if foul-smelling amniotic fluid was noted and if fetal tachycardia developed (> 180 bpm) Rate nephelometric assay to determine CRP was performed using Beckman immunochemistry analyser (automated model) with C-reactive protein reagent kit (Beckman Instruments Inc., Fullerton, CA, USA). CRP results were not available for clinical management. All placentas and amniotic membranes were histologically evaluated for evidence of inflammation and/or infection. Criteria to define histologic chorioamnionitis: 1. polymorphonuclear leukocyte infiltration of extraplacental membranes; 2. accumulation	63/100 (63%) Predictive values as reported by study authors in Table IV *95% CI, LR+, LR- and 2x2 table calculated by NCC techincal team using reported sensitivity and specificity, and reported prevalence of histologic chorioamnionitis. Calculated PPV and NPV differ from those reported in the original study Sensitivity: 67% (55.03 to 78.31) Specificity: 81% (68.46 to 93.70) PPV: 85.71% (NCC calculated) (75.92 to 95.51); 90% (reported) NPV: 58.82% (NCC caclulated) (45.32 to 72.33); 50% (reported) LR+: 3.52 (1.77 to 7.02) LR-: 0.41 (0.28 to 0.60) **FHR >160/min as predictor of clinical chorioamnionitis** Prevalence of clinical chorioamnionitis: 18/100 (18%) Predictive values as reported by study authors in Table III *95% CI, LR+, LR- and 2x2 table calculated by NCC techincal team using reported sensitivity and specificity, and reported prevalence of clinical chorioamnionitis. Sensitivity: 22% (3.02 to 41.43) Specificity: 97% (94.22 to 100) PPV: 67% (28.95 to 100) NPV: 87% (77.91 to 92.30) LR+: 9.11 (1.80 to 45.99) LR-: 0.79 (0.62 to 1.02) **FHR >160/min as predictor of histologic**	Predictive values are reported for white blood cell count, data not extracted as cut-off not clearly defined Maternal temperature ≥ 38°C - unclear from study report that this was the definition of a positive preductive test; however, this was the cut-off used to induce labour and so have assumed this to be the definition of a positive predictive test Method of fetal heart rate monitoring not reported

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
			of polymorphs in the intervillous space immediately below the chorionic plate; 3. leukocyte infiltration of the chorionic plate; 4. angiitis of umbilical vessels.	**chorioamnionitis** Prevalence of histologic chorioamnionitis: 63/100 (63%) Predictive values as reported by study authors in Table IV *95% CI, LR+, LR- and 2x2 table calculated by NCC techincal team using reported sensitivity and specificity, and reported prevalence of histologic chorioamnionitis. Calculated PPV and NPV differ from those reported in the original study. Sensitivity: 8% (1.26 to 14.61) Specificity: 97% (92.07 to 100) PPV: 83% (53.51 to 100) NPV: 38% (28.47 to 48.13) LR+: 2.94 (0.36 to 24.18) LR-: 0.95 (0.86 to 1.04) **Maternal temperature ≥ 38°C as predictor of clincial chorioamnionitis** Prevalence of clinical chorioamnionitis: 18/100 (18%) Predictive values as reported by study authors in Table IV *95% CI, LR+, LR- and 2x2 table calculated by NCC techincal team using reported sensitivity and specificity, and reported prevalence of histologic chorioamnionitis. Calculated PPV and NPV differ from those reported in the original study Sensitivity: 56% (32.6 to 78.51) Specificity: 98% (94.22 to 100) PPV: 83% (62.25 to 100) NPV: 91% (84.90 to 96.92) LR+: 22.78 (5.45 to 95.17) LR-: 0.46 (0.27 to 0.76)	

<table>
<tr><th>Bibliographic details</th><th>Participants</th><th>Tests</th><th>Methods</th><th>Outcomes and results</th><th>Comments</th></tr>
<tr><td></td><td></td><td></td><td></td><td>

<u>Maternal temperature ≥ 38°C as predictor of histologic chorioamnionitis</u>
Prevalence of histologic chorioamnionitis: 63/100 (63%)

Predictive values as reported by study authors in Table IV *95% CI, LR+, LR- and 2x2 table calculated by NCC techincal team using reported sensitivity and specificity, and reported prevalence of histologic chorioamnionitis. Calculated PPV and NPV differ from those reported in the original study

Sensitivity: 17% (8.09 to 26.83)
Specificity: 97% (92.07 to 100)
PPV: 90% (76.03 to 100)
NPV: 41% (30.64 to 51.18)
LR+: 6.46 (0.87 to 1.03)
LR-: 0.85 (0.75 to 0.96)

C-reactive protein - clinical reference test

<table>
<tr><th></th><th>Reference Test +ve</th><th>Reference Test -ve</th></tr>
<tr><td>Predictive Test +ve</td><td>15</td><td>37</td></tr>
<tr><td>Predictive Test -ve</td><td>3</td><td>45</td></tr>
</table>

C-reactive protein - histological reference test

</td><td></td></tr>
</table>

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments

	Reference Test +ve	Reference Test -ve
Predictive Test +ve	42	7
Predictive Test -ve	21	30

Fetal heart rate - clinical reference test

	Reference Test +ve	Reference Test -ve
Predictive Test +ve	4	2
Predictive Test -ve	14	80

Fetal heart rate - histological reference test

	Reference Test +ve	Reference Test -ve
Predictive Test +ve	5	1
Predictive Test -ve	58	36

<table>
<tr><th>Bibliographic details</th><th>Participants</th><th>Tests</th><th>Methods</th><th>Outcomes and results</th><th>Comments</th></tr>
<tr><td></td><td></td><td></td><td></td><td>Maternal temperature - clinical reference test
<table>
<tr><th></th><th>Reference Test +ve</th><th>Reference Test -ve</th></tr>
<tr><td>Predictive Test +ve</td><td>10</td><td>2</td></tr>
<tr><td>Predictive Test -ve</td><td>7</td><td>80</td></tr>
</table>
Maternal temperature - histological reference test
<table>
<tr><th></th><th>Reference Test +ve</th><th>Reference Test -ve</th></tr>
<tr><td>Predictive Test +ve</td><td>11</td><td>1</td></tr>
<tr><td>Predictive Test -ve</td><td>52</td><td>36</td></tr>
</table></td><td></td></tr>
<tr><td>Full citation

Kurki,T., Teramo,K., Ylikorkala,O., Paavonen,J., C-reactive protein in preterm premature rupture of the membranes.[Erratum appears in Arch Gynecol Obstet 1990;247(2):106], Archives of Gynecology and Obstetrics, 247, 31-37, 1990</td><td>Sample size
N = 147

Characteristics
<u>Maternal age (mean ± SD)</u>
Women with chorioamnionitis: 31.0 ± 6.4 weeks
Women without</td><td>Tests
Serum C-reactive protein</td><td>Methods
165 women with preterm PROM, admitted consecutively to University Central Hospital, Helsinki during the study period were included in the study. Preterm PROM was defined as visible leakage of amniotic fluid before 37 weeks. Gestational age was confirmed by reliable data from the last menstrual</td><td>Results
<u>CRP > 12 mg/l as predictor of clinical chorioamnionitis</u>
Prevalence of clinical chorioamnionits: 33/147 (22%)

Predictive values and 2x2 table as reported in the Erratum by study authors in Table 3 *95% CI, LR+, LR- calculated by NCC technical team

Sensitivity: 94% (85.8 to 100)</td><td>Limitations
Time sample analysed was taken unclear

Unclear whether index test and reference test results were interpreted independently

Unclear whether histology performed on placenta, umbilical cord or fetal</td></tr>
</table>

<table>
<tr><th>Bibliographic details</th><th>Participants</th><th>Tests</th><th>Methods</th><th>Outcomes and results</th><th>Comments</th></tr>
<tr>
<td>Ref Id

258742

Country/ies where the study was carried out

Finland

Study type

Case-series

Aim of the study
To assess the value of C-reactive protein (CRP) in the diagnosis of chorioamnionitis, puerperal endometriosis and neonatal infectious morbidity among women with preterm PROM

Study dates
1987-1988

Source of funding
Not reported</td>
<td>chorioamnionitis: 28.5 ± 5.6 weeks

<u>Multiple pregnancy (n/N, %)</u>
15/147 (10%)

<u>Gestational age at PROM (mean ± SD)</u>
Women with chorioamnionitis: 26.7 ± 0.8 weeks
Women without chorioamnionitis: 31.8 ± 2.6 weeks

<u>Gestational age at delivery (mean ± SD)</u>
Women with chorioamnionitis: 28.5 ± 3.4 weeks
Women without chorioamnionitis: 32.4 ± 3.5 weeks

<u>Duration of PROM (mean ± SD)</u>
Women with chorioamnionitis: 12.0 ± 18.5 days
Women without chorioamnionitis: 3.5 ± 12.1 days

Inclusion Criteria
PROM before 37 weeks gestation</td>
<td></td>
<td>period and by first trimester ultrasound.

Clinical diagnosis of chorioamnionitis was based on the presence of all the following criteria: axillary temperature ≥ 38°C, uterine tenderness, fetal or maternal tachycardia and white blood cell count > 12 x 10^9/l. Diagnosis was confirmed in all cases by the presence of histopathological evidence of infection in the placenta, umbilical cord or fetal membranes.

Neonatal septicaemia was determined by clinical findings and either by a positive blood culture for bacteria or by low counts of peripheral blood platelets and white blood cells. Intrauterine pneumonia was determined by clinical findings, chest X-ray findings and positive bacterial aspirate from the trachea of the newborn infant during the first day of life.

CRP levels were measured by an immunoturbidimetric method. Values > 12 mg/l were considered positive. CRP was routinely measured every 4 to 12 hours and all women had 3 or more measurements. CRP results</td>
<td>Specificity: 50% (40.82 to 59.18)
PPV: 35% (25.25 to 45.21)
NPV: 97% (91.99 to 100)
LR+: 1.88 (1.53 to 2.30)
LR-: 0.12 (0.03 to 0.47)

<u>CRP >40 mg/l as predictor of clinical chorioamnionitis</u>
Prevalence of clinical chorioamnionits: 33/147 (22%)

Predictive values and 2x2 table as reported in the Erratum by study authors in Table 3 *95% CI, LR+, LR- calculated by NCC technical team

Sensitivity: 72% (57.53 to 87.92)
Specificity: 77% (69.49 to 84.90)
PPV: 48% (34.15 to 61.85)
NPV: 91% (84.95 to 96.50)
LR+: 3.19 (2.14 to 4.74)
LR-: 0.35 (0.20 to 0.62)

C-reactive protein
<table>
<tr><th></th><th>Reference Test +ve</th><th>Reference Test -ve</th></tr>
<tr><td>Predictive Test +ve</td><td>31</td><td>57</td></tr>
<tr><td>Predictive Test -ve</td><td>2</td><td>57</td></tr>
</table>
C-reactive protein</td>
<td>Other information
147 women analysed; 18/165 women were excluded: 12 had urinary tract infections, 3 had acute appendicitis, 1 had bacterial pneumonia, 1 had acute pancreatitis and 1 had Crohn's disease

Statistically significantly higher maternal age (P < 0.05), lower gestational age at PROM and at delivery (P < 0.001) and longer duration of PROM (P < 0.001) in women with chorioamnionitis compared with women without chorioamnionitis

NCC recalculated specifcity values for both CRP > 12 mg/l and > 40 mg/l agrees with recalculations reported in van de Laar 2009 (excluded systematic review)</td>
</tr>
</table>

<table>
<tr><th>Bibliographic details</th><th>Participants</th><th>Tests</th><th>Methods</th><th>Outcomes and results</th><th>Comments</th></tr>
<tr><td></td><td>Exclusion Criteria
Other sources of fever or leukocytosis</td><td></td><td>were made available to clinicians and could have influenced the clinical decision making.</td><td><table><tr><th></th><th>Reference Test +ve</th><th>Reference Test -ve</th></tr><tr><td>Predictive Test +ve</td><td>24</td><td>26</td></tr><tr><td>Predictive Test -ve</td><td>9</td><td>88</td></tr></table></td><td></td></tr>
<tr><td>Full citation

Lewis,D.F., Adair,C.D., Weeks,J.W., Barrilleaux,P.S., Edwards,M.S., Garite,T.J., A randomized clinical trial of daily nonstress testing versus biophysical profile in the management of preterm premature rupture of membranes, American Journal of Obstetrics and Gynecology, 181, 1495-1499, 1999

Ref Id

258689

Country/ies where the study was carried out

USA

Study type

Randomised controlled study</td><td>Sample size
N = 135

Nonstress test n = 69

Biophysical profile n = 66

Characteristics
<u>Maternal age (mean ± SD)</u>
24.2 ± 7.0 years

<u>Gestational age at admission (mean ± SD)</u>
29.7 ± 3.0 weeks

<u>Latency period (mean ± SD)</u>
13.6 ± 11.3 days

<u>History of preterm delivery (n/N, %)</u>
14/69 (20.3%)

<u>Delivery for maturity</u></td><td>Tests
- Nonstress test

- Biophysical profile</td><td>Methods
All women with preterm premature rupture of membranes admitted to Louisiana State University School of Medicine were eligible for inclusion. Premature rupture of membranes was diagnosed by history of fluid leakage with confirmation by either sterile speculum examination documenting ferning or positive Nitrazine results or both. Eligible women were randomised to undergo either a daily nonstress test or daily biophysical profiling.

A nonstress test was considered reactive if it resulted in 2 accelerations with 15 beats/min above the baseline that lasted for ≥ 15 seconds during a 20-minute period. The test was considered abnormal if these criteria were not met, a late deceleration occurred or a</td><td>Results
<u>Abnormal nonstress test predicting neonatal infection (sepsis, presumed sepsis and congenital pneumonia)</u>
Prevalence of neonatal infection: 14/69 (20.3%)

Predictive values as reported by study authors in Table V *95% confidence intervals, LR+ and LR-, 2x2 table calculated by NCC and specificity and NPV recalculated by NCC technical team using reported sensitivity, PPV, number of abnormal stress tests and number of correctly predicted neonatal infections reported in text of study report

Sensitivity: 42.9% (16.93 to 68.78)
Specificity: 80% (NCC calculated) (69.43 to 90.57); 83.3% (reported)
PPV: 35.3% (12.58 to 58.01)
NPV: 84.62% (NCC calculated) (74.81 to 94.42); 87.3% (reported)
LR+: 2.14 (0.96 to 4.78)
LR-: 0.71 (0.45 to 1.15)

Nonstress test</td><td>Limitations
Exclusion criteria not reported

Unclear whether index test results interpreted independently of reference test results

Definition of neonatal infection included culture-confirmed sepsis and clinically suspected sepsis

Other information
Data for biophysical profile wee not extracted as this was not a test of interest specified by the review protocol

Women who had undergone cerclage or digital vaginal examination before tertiary transfer were included in the trial

Data for maternal infection</td></tr>
</table>

<table>
<tr><th>Bibliographic details</th><th>Participants</th><th>Tests</th><th>Methods</th><th>Outcomes and results</th><th>Comments</th></tr>
<tr>
<td>Aim of the study
To compare the efficacy of both a daily nonstress test and a full biophysical profile in pregnancies complicated by preterm premature rupture of membranes, and the ability of each test to predict infectious morbidity of both mother and neonate

Study dates
36-month period - dates not reported (before 1999)

Source of funding
Not reported</td>
<td><u>(n/N, %)</u>
23/69 (33.3%)

Inclusion Criteria
- Preterm premature rupture of membranes at ≤ 34 weeks gestation
- No obvious clinical infection
- No condition requiring immediate delivery
- Stable condition for 24h before transfer to study antenatal ward

Exclusion Criteria
Not reported</td>
<td></td>
<td>significant variable deceleration (30 beats for 30 seconds) occurred. Women with abnormal results on a nonstress test had a complete biophysical profile as a backup confirmatory test.

Delivery was prompted by spontaneous labour, clinical evidence of intra-amniotic infection, a mature fetal lung profile, or abnormal antenatal fetal test results.

All women received antibiotics during the intrapartal period for prophylaxis against group B Streptococcus.

Intra-amniotic infection was diagnosed clinically, by analysis of amniotic fluid obtained from amniocentesis (positive Gram stain or culture) or by maternal temperature ≥ 100.4°F, foul-smelling fluid and uterine tenderness.

Neonatal sepsis was diagnosed by positive results on blood or spinal fluid culture, or the presence of congenital pneumonia (diagnosed by neonatal staff, requiring positive radiographic finding plus</td>
<td>
<table>
<tr><th></th><th>Reference Test +ve</th><th>Reference Test -ve</th></tr>
<tr><td>Predictive Test +ve</td><td>6</td><td>11</td></tr>
<tr><td>Predictive Test -ve</td><td>8</td><td>44</td></tr>
</table>
</td>
<td>not reported separately

Data from last test before delivery were analysed

Data used for calculation of 2x2 table as follows: 14 cases of sepsis or presumed sepsis (taken from Table IV and text); 17 women had abnormal stress test (taken from text); sensitivity 42.9% (taken from Table V) and PPV (taken from Table V)</td>
</tr>
</table>

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
			evidence of sepsis). Presumed sepsis was diagnosed by the attending neonatologist and included clinical signs of infection with negative culture results and an abnormal leukocyte count (leukopenia, ≤ 5000 cells/mm³; neutropenia, ≤ 1500 cells/mm³; or leukocytosis ≥28,000 cells/mm³ with a left shift). Clinical signs of presumed sepsis included shock, poor perfusion, temperature instability, respiratory distress, hypotonia, lethargy and feeding intolerance Data from the last test before delivery was used in the analysis		
Full citation Perrone,G., Anceschi,M.M., Capri,O., Galoppi,P., Pizzulo,S., Buccheri,M., Pascone,R., Nofroni,I., Brunelli,R., Maternal C-reactive protein at hospital admission is a simple predictor of funisitis in preterm premature rupture of membranes, Gynecologic and Obstetric Investigation, 74, 95-99, 2012	**Sample size** N = 66 **Characteristics** Maternal age (mean, range) 32 years (24 to 40) Gestational age at PROM (mean ± SD) 28.6 ± 4.4 weeks	**Tests** Serum C-reactive protein	**Methods** During the study period 320 women with suspected pPROM between 24 and 37 weeks gestation were admitted to the emergency room of the Dept of Obstetrics and Gynaecology. Women with confirmed pPROM and gestational age between 24 and 33 weeks were enrolled in the study. pPROM was diagnosed by sterile speculum examination of the	**Results** **C-reactive protein >12,000 µ/l as predictior of funisitis** Prevalence of funisitis: 24/66 (36%) Predictive values and confidence intervals as reported by study authors in Table 2 *LR+ and LR- and 2x2 table calculated by NCC **CRP at admission** Sensitivity: 41.7 % (24.5 to 61.2) Specificity: 83.3% (69.4 to 91.7) PPV: 58.8% (36.6 to 78.4)	**Limitations** Unclear whether consecutive women were included Prophylactic antibiotics were given to all women Time that samples used in analysis were taken is unclear **Other information**

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
Ref Id 258897 **Country/ies where the study was carried out** Italy **Study type** To be decided **Aim of the study** To analyse the value of maternal serum C-reactive protein (CRP) in predicting funisitis in women with pPROM and to assess the prognostic role of maternal CRP in samples obtained at admission, a few hours after rupture of membranes **Study dates** December 2005 to December 2007 **Source of funding** Not reported	<u>Gestational age at birth (mean ± SD)</u> 30.8 ± 4.1 weeks <u>Interval between pPROM and birth (mean ± SD)</u> 16 ± 12 days **Inclusion Criteria** - Confirmed pPROM between 24 and 33 weeks gestation - Singleton pregnancy - Non-anomalous fetus **Exclusion Criteria** - Time interval between pPROM and admission to hospital >12h - Twin pregnancy - Fetal malformation - Fetal growth restriction - Clinical evidence of chorioamnionitis - Maternal or neonatal follow-up not available		clear fluid of the vaginal fornix and by Actim PROM test. All women were referred to intensive care unit for bed rest, close monitoring of maternal heart rate and contractions, fever and fetal biophysical profile. All women received corticosteroid prophylaxis for fetal lung maturation and antibiotic prophylaxis against chorioamnionitis. Tocolytics were administered to delay delivery in order to complete cycles of steroids and antibiotics. From admission until delivery, maternal non-fasting blood samples were collected every 3 days for white blood cell count, platelet count, and CRP assessment. Serum CRP concentrations were measured by microparticle-enhanced turbimetric immunoassay (Roche Diagnostic, Mannheim, Germany). Placenta and umbilical cord were examined for histological chorioamnionitis and funisitis. Diagnosis of histological chorioamnionitis was based on the presence of acute inflammatory cells on a chorioamniotic membrane roll and/or a chorionic plate.	NPV: 71.4% (57.4 to 82.2) LR+: 2.5 (1.10 to 5.71) LR-: 0.70 (0.49 to 1.01) **CRP pre-partum** Sensitivity: 75.0% (55.1 to 88.0) Specificity: 69.0% (54.0 to 80.9) PPV: 58.1% (40.8 to 73.6) NPV: 82.9% (67.3 to 91.9) LR+: 2.42 (1.46 to 4.02) LR-: 0.36 (0.18 to 0.75) **<u>CRP >20,000 µ/l as predictior of funisitis</u>** Prevalence of funisitis: 24/66 (36%) Predictive values and confidence intervals as reported by study authors in Table 2 *LR+ and LR- and 2x2 table calculated by NCC **CRP at admission** Sensitivity: 37.5% (21.2 to 57.3) Specificity: 90.5% (77.9 to 96.2) PPV: 69.2% (42.4 to 87.3) NPV: 71.7% (58.4 to 82.0) LR+: 3.94 (1.36 to 11.43) LR-: 0.69 (0.50 to 0.96) **CRP pre-partum** Sensitivity: 54.2% (35.1 to 72.1) Specificity: 88.1% (75.0 to 94.8) PPV: 72.2% (49.1 to 87.5) NPV: 77.1% (63.5 to 86.7) LR+: 4.55 (1.85 to 11.21) LR-: 0.52 (0.33 to 0.82) **C-reactive protein**	

<table>
<tr><th>Bibliographic details</th><th>Participants</th><th>Tests</th><th>Methods</th><th>Outcomes and results</th><th>Comments</th></tr>
<tr><td></td><td></td><td></td><td>Acute funisitis was diagnosed by the presence of neutrophils in the umbilical vessel wall and/or in Wharton's jelly.</td><td>
<table>
<tr><th></th><th>Reference Test +ve</th><th>Reference Test -ve</th></tr>
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<tr><td>Predictive Test -ve</td><td>14</td><td>35</td></tr>
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C-reactive protein
<table>
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<tr><td>Predictive Test +ve</td><td>18</td><td>13</td></tr>
<tr><td>Predictive Test -ve</td><td>6</td><td>29</td></tr>
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C-reactive protein
<table>
<tr><th></th><th>Reference Test +ve</th><th>Reference Test -ve</th></tr>
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<tr><td>Predictive Test -ve</td><td>15</td><td>38</td></tr>
</table>
</td><td></td></tr>
<tr><td>Full citation</td><td>Sample size
N = 51</td><td>Tests
- Serum C-</td><td>Methods
Women with PROM admitted</td><td>Results
<u>C-reactive protein ≥ 2mg/dl as predictor</u></td><td>Limitations
Unclear whether consecutive</td></tr>
</table>

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
Romem,Y., Artal,R., C-reactive protein as a predictor for chorioamnionitis in cases of premature rupture of the membranes, American Journal of Obstetrics and Gynecology, 150, 546-550, 1984 **Ref Id** 258734 **Country/ies where the study was carried out** USA **Study type** Case-series **Aim of the study** To evaluate the usefulness of C-reactive protein (CRP) determinations in the diagnostic process of clinical chorioamnionitis in women with premature rupture of the membranes at the time of admission and during follow-up **Study dates** September 1982 to August 1983	**Characteristics** <u>Maternal age (mean ± standard error of the mean [SEM])</u> 25.2 ± 0.7 years <u>Gestational age at admission (mean ± SEM)</u> 30.4 ± 0.4 weeks **Inclusion Criteria** - Women with premature rupture of membranes at ≤ 34 weeks gestation - Clinical manifestations of infection were ruled out - Expectant management attempted **Exclusion Criteria** Not reported	reactive protein - White blood cell count	to the Los Angeles County/University of Southern California Women's Hospital during the study period were included. Rupture of membranes was confirmed by positive Nitrazine test, pooling of fluid in the posterior vaginal fornix and positive ferning. All women were confined to bed-rest in hospital and monitored daily by white blood cell (WBC) count (with differential count) and four times for body temperature, pulse and fetal heart rate (at 06:00, 10:00, 14:00 and 22:00 hours). Betamethasone was given when fetal lung immaturity was suspected and/or at a gestational age < 32 weeks. On admission serum for CRP determination was obtained (25 tested daily, early am, until delivery; 6 tested early afternoon as well as at least 2h postprandially). Sera were stored at −20°C and analysed after discharge so that results would not influence management. CRP levels were determined by rate nephelometry immunoassay, utilising a Beckman Immunochemistry Analyser and a reagent kit for CRP (Beckman Instruments Inc., Fullerton, CA, USA).	**<u>for clinical chorioamnionitis</u>** Prevalence of clinical chorioamnionitis: 7/51 (13.7%) Predictive values as reported by study authors in Table V *95% CI, LR+, LR- and 2x2 table calculated by NCC technical team Sensitivity: 86% (59.79 to 100) Specificity: 82% (70.42 to 93.21) PPV: 43% (16.93 to 68.78) NPV: 97% (92.07 to 100) LR+: 4.71 (2.35 to 9.46) LR-: 0.17 (0.03 to 1.08) **<u>WBC ≥ 12.5 x 10^3 for predicting clinical chorioamnionitis</u>** Prevalence of clinical chorioamnionitis: 13.7% Values as reported by authors in Table V *95% CI, LR+, LR- and 2x2 table calculated by NCC technical team and NPV recalculated by NCC. Note that 2x2 table adds up to 49 rather than 51 Sensitivity: 43% (6.20 to 79.52) Specificity: 82% (70.42 to 93.21) PPV: 27% (0.95 to 53.59) NPV: 90% (NCC calculated) (80.70 to 99.30); 84% (reported) LR+: 2.36 (0.82 to 6.81) LR-: 0.70 (0.36 to 1.35) **<u>WBC ≥ 16.00 x 10^3 for predicting clinical chorioamnionitis</u>** Prevalence of clinical chorioamnionitis: 13.7%	women were included NCC calculate a slightly different NPV than is reported in the original paper **Other information** CRP levels were considered abnormal when values exceeded 1.78 to 1.89 mg/dl Analysed CRP levels on admission were analysed, timing of WBC analysed unclear

<table>
<tr><th>Bibliographic details</th><th>Participants</th><th>Tests</th><th>Methods</th><th>Outcomes and results</th><th>Comments</th></tr>
<tr>
<td>Source of funding
Sponsored by the Society for Gynecologic Investigation</td>
<td></td>
<td></td>
<td>Criteria used to diagnose clinical chorioamnionitis were as established by Gibbs 1980, Koh 1979 and Garite 1982, and include maternal fever > 38°C in the absence of other causes for such fever. CRP was considered abnormal when values exceeded 1.78 to 1.89 mg/dl</td>
<td>Values as reported by authors in Table V
*95% CI, LR+, LR- and 2x2 table calculated by NCC technical team

Sensitivity: 29% (0 to 62.04)
Specificity: 95% (89.30 to 100)
PPV: 50% (1.00 to 99.00)
NPV: 89% (80.55 to 98.18)
LR+: 6.29 (1.05 to 37.66)
LR-: 0.75 (0.47 to 1.20)

C-reactive protein
<table>
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<table>
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<tr><td>Predictive Test +ve</td><td>3</td><td>8</td></tr>
<tr><td>Predictive Test -ve</td><td>4</td><td>36</td></tr>
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White blood cell count</td>
<td></td>
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</table>

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<tr><th>Bibliographic details</th><th>Participants</th><th>Tests</th><th>Methods</th><th>Outcomes and results</th><th>Comments</th></tr>
<tr><td></td><td></td><td></td><td></td><td>
<table>
<tr><th></th><th>Reference Test +ve</th><th>Reference Test -ve</th></tr>
<tr><td>Predictive Test +ve</td><td>2</td><td>2</td></tr>
<tr><td>Predictive Test -ve</td><td>5</td><td>42</td></tr>
</table>
</td><td></td></tr>
<tr><td>Full citation

Smith,E.J., Muller,C.L., Sartorius,J.A., White,D.R., Maslow,A.S., C-reactive protein as a predictor of chorioamnionitis, Journal of the American Osteopathic Association, 112, 660-664, 2012

Ref Id

258739

Country/ies where the study was carried out

USA

Study type

Case-series

Aim of the study
To determine if C-reactive protein (CRP) is an effective early marker of chorioamnionitis in women with preterm premature</td><td>Sample size
N = 73

Characteristics
<u>Maternal age (mean ± SD)</u>
28.0 ± 5.9 years

<u>Gestational age at delivery (mean ± SD)</u>
31.0 ± 4.0 weeks

<u>Latency (median, interquartile range)</u>
4 (1 to 10) days

<u>Multiple pregnancy (n/N, %)</u>
16/73 (22%)

Inclusion Criteria
Women with clinical chorioamnionitis, histological chorioamnionitis or</td><td>Tests
Serum C-reactive protein</td><td>Methods
The medical records of women meeting the inclusion criteria who had received prenatal care at Geisinger Medical Centre (Danville, Pennsylvania, USA) were retrospectively reviewed.

Records were reviewed for the following variable: maternal age, race, gestational age, maternal smoking status, Gram stain and culture results, steroid administration, administration of antibiotics for latency, white blood cell count closest to delivery date, CRP before delivery, temperature at onset of labour and days of latency from time of premature rupture of membranes to delivery.

The final CRP level recorded before delivery was analysed.</td><td>Results
<u>C-reactive protein >5mg/dL as predictor of histological chorioamnionitis</u>
Prevalence of histological chorioamnionitis: 26/73 (36%)

Values reported in text of results section * LR+ and LR- and all 95% confidence intervals calculated by NCC using data reported in text of results
Sensitivity: 76.9% (60.73 to 93.12)
Specificity: 31.9% (18.59 to 45.24)
PPV: 38.5% (25.24 to 51.68)
NPV: 71.4% (52.11 to 90.75)
LR+: 1.13 (0.85 to 1.51)
LR-: 0.72 (0.32 to 1.64)

C-reactive protein
<table>
<tr><th></th><th>Reference Test +ve</th><th>Reference Test -ve</th></tr>
<tr><td>Predictive Test +ve</td><td>20</td><td>32</td></tr>
<tr><td>Predictive Test -ve</td><td>6</td><td>15</td></tr>
</table>
</td><td>Limitations
Retrospective case series

Unclear whether consecutive women were included

22% of women had a multiple pregnancy

Other information
Predictive values reported in results section of original study are for women with histologically confirmed chorioamnionitis

Final CRP level recorded before delivery were analysed</td></tr>
</table>

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
rupture of membranes **Study dates** 1 January 2005 - 31 December 2008 **Source of funding** None reported	both, and preterm premature rupture of membranes Gestational age between 20 and 37 weeks **Exclusion Criteria** No CRP data in medical records Medical records contained data that overturned diagnosis of preterm premature rupture of membranes				
Full citation Yoon,B.H., Jun,J.K., Park,K.H., Syn,H.C., Gomez,R., Romero,R., Serum C-reactive protein, white blood cell count, and amniotic fluid white blood cell count in women with preterm premature rupture of membranes, Obstetrics and Gynecology, 88, 1034-1040, 1996 **Ref Id** 259030	**Sample size** N = 91 (only 63 women analysed - see limitations) **Characteristics** Maternal age (mean ± SD) Negative amniotic fluid culture: 28.4 ± 3.9 years Positive amniotic fluid culture: 29.4 ± 5.1 years	**Tests** - Serum C-reactive protein - White blood cell count - Amniotic fluid white blood cell count	**Methods** Women admitted to the Seoul National University Hospital with a diagnosis of pPROM and who met the inclusion criteria were enrolled in the study. Amniotic fluid obtained by amniocentesis was cultured for aerobic and anaerobic bacteria, as well as for mycoplasmas (Ureaplasma urealyticum and Mycoplasma hominis). An aliquot was examined in a haemocytometer chamber to determine amniotic fluid white	**Results** **C-reactive protein ≥0.7 mg/dl as a predictor of histologic chorioamnionitis** Prevalence of histologic chorioamnionitis: 35/63 (56%) Predictive values as reported by study authors in Table 2 *95% confidence intervals, LR+ and LR- calculated by NCC technical team Sensitivity: 54% (37.78 to 70.79) Specificity: 86% (72.75 to 98.68) PPV: 83% (67.12 to 98.10) NPV: 60% (44.82 to 75.18) LR+: 3.8 (1.46 to 9.89) LR-: 0.53 (0.36 to 0.79)	**Limitations** Only women who had delivered within 72 hours of amniocentesis were included in the analysis (63/91; 69%) Some women (number unknown) with a negative amniotic fluid culture delivered at term During the study period 83% of women with pPROM and a singleton pregnancy also had amniocentesis and were therefore eligible for study inclusion; unclear whether

<table>
<tr><th>Bibliographic details</th><th>Participants</th><th>Tests</th><th>Methods</th><th>Outcomes and results</th><th>Comments</th></tr>
<tr>
<td>Country/ies where the study was carried out

Korea

Study type

Case-series

Aim of the study
To compare the diagnostic performance of maternal serum C-reactive protein (CRP) and white blood cell (WBC) count with that of amniotic fluid WBC count in the identification of positive amniotic fluid culture, acute histologic chorioamnionits, clinical chorioamnionitis and neonatal complications in women with preterm PROM

Study dates
April 1993 to April 1995

Source of funding
Grant #HMP-96-M-2-0020 of the '96 Good Health R&D Project, Ministry of Health and Welfare, Republic of Korea</td>
<td><u>Gestational age at admission (median, range)</u>
Negative amniotic fluid culture: 34.3 weeks (20 to 36.7)
Positive amniotic fluid culture: 32.7 weeks (23.1 to 36.4)

<u>Gestational age at delivery (median, range)</u>
Negative amniotic fluid culture: 35.3 weeks (24.3 to 41.4)
Positive amniotic fluid culture: 32.7 weeks (23.1 to 36.3)

Inclusion Criteria
- Singleton gestation
- Transabdominal amniocentesis performed for microbiological assessment of the amniotic cavity
- Maternal blood drawn for determination of WBC and CRP concentration at time of amniocentesis
- Rupture of membranes diagnosed by examination with</td>
<td></td>
<td>blood cell count. White blood cell count was determined with a Coulter counter (Coulter STKS, Hialeah, FL, USA). Blood not used for WBC was centrifuged at 700 x g for 10 min at 4°C and supernatant stored at −70°C until C-reactive protein was determined.

Acute histologic chorioamnionitis was defined as the presence of acute inflammatory changes in any of the tissue samples (amnion, chorion-decidua, umbilical cord or chorionic plate). Clinical chorioamnionitis was diagnosed by the criteria according to Gibbs et al., 1982</td>
<td><u>White blood cell count ≥ 13,000 cells per mm³ as a predictor of histologic chorioamnionitis</u>
Prevalence of histologic chorioamnionitis: 35/63 (56%)

Predictive values as reported by study authors in Table 2 *95% confidence intervals, LR+ and LR- calculated by NCC technical team

Sensitivity: 40% (23.77 to 56.23)
Specificity: 82% (67.96 to 96.35)
PPV: 74% (53.88 to 93.48)
NPV: 52% (37.51 to 67.03)
LR+: 2.24 (0.92 to 5.47)
LR-: 0.73 (0.53 to 1.01)

C-reactive protein
<table>
<tr><th></th><th>Reference Test +ve</th><th>Reference Test -ve</th></tr>
<tr><td>Predictive Test +ve</td><td>19</td><td>4</td></tr>
<tr><td>Predictive Test -ve</td><td>16</td><td>24</td></tr>
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White blood cell count
<table>
<tr><th></th><th>Reference Test +ve</th><th>Reference Test -ve</th></tr>
</table>
</td>
<td>consecutive women were included

Unclear whether results of index test were interpreted without knowledge of reference test results

Other information
One woman with a bloody tap with AF WBC of 101 cells per mm³ was excluded from the analysis

Values for amniotic blood cell count not extracted as this was not a test of interest specified in review protocol</td>
</tr>
</table>

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
	sterile speculum confirming pooling of amniotic fluid in the vagina, positive nitrazine paper test result and a positive ferning test result **Exclusion Criteria** Not reported			**Predictive Test +ve** 14 5 **Predictive Test -ve** 21 23	

16

H16 'Rescue' cervical cerclage

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Aoki,S., Ohnuma,E., Kurasawa,K., Okuda,M., Takahashi,T., Hirahara,F., Emergency cerclage versus expectant management for prolapsed fetal membranes: a retrospective, comparative study, Journal of Obstetrics and Gynaecology Research, 40, 381-386, 2014 **Ref Id** 325174	**Sample size** N=35 women **Characteristics** Age (years, median, range):Emergency cerclage [33 (27-42)] vs. Bedrest: [35.5(30-42)] **Weeks gestation on admission (median (range))** Emergency cerclage: 22.4 (15.7–26.1) Bedrest: 23.4 (21.1–26.4) **Inclusion criteria** Women who had been treated	**Interventions** Emergency Cerclage (N=15) McDonald cerclage (N=12) Shirodkar (N=2), both (N=1) Tocolysis 24hr post-op Expectant management (N=20) Bed rest Tocolytic administered.	**Details** Data were retrospectively analysed using the medical records of women who had been treated for prolapsed fetal membranes between January 2000 and December 2012 at the Perinatal Center for Maternity and Neonate, Yokohoma. Prolapsed fetal membranes were diagnosed to be present when an amniotic sac was identified under speculum exam, with cervical internal os dilation (defined as 1-4 cm). Cerclage was performed on women with prolapsed fetal membranes.	**Results** Premature delivery Emergency cerclage [N=12 (80.0%)] vs. Bedrest: [N=20 (100.0%)] p=0.07 Extremely premature delivery (22 wks 0 days-27 wks 6 days) Emergency cerclage [N=3 (20.0%)] vs. Bedrest: [N=16	**Limitations** Method of allocation unrelated to potential confounding factors: No Attempts made in design or analysis to balance comparison groups for confounding factors: No Comparison groups received same care apart from intervention studied: Unclear Participants blinded to treatment allocation: N/A Individuals administering care blinded to treatment allocation: N/A

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Country/ies where the study was carried out Japan **Study type** Retrospective cohort **Aim of the study** To compare outcomes after emergency cerclage vs. expectant management for prolapsed fetal membranes in women with cervical incompetency. **Study dates** Jan 2000-December 2012. **Source of funding** None	for prolapsed fetal membranes i) a singleton viable pregnancies between 15 + 0 and 26 + 6 gestational weeks ii) no premature rupture of membranes iii) No clinically discernible chorioamnionitis iv) no obvious fetal malformations v) no heavy bleeding vi) no treatment resistant uterine contractions **Exclusion criteria** Not reported		Expectant management consisted of bedrest. Data presented as medians or frequencies.	(80.0%)] p=<0.01 Days prolongation of pregnancy (median, (range)) Emergency cerclage:44 (4–165) Bedrest: 12.5 (2-93) p=<.01	All groups followed up for equal length of time: Unclear How many participants did not complete treatment: None Groups comparable for treatment completion: No statistically significant differences. Groups comparable with respect to availability of outcome data: Yes Appropriate length of follow up: Yes Precise definition of outcome: No Valid and reliable method of outcome measurement: Yes Investigators blinded to intervention: No Investigators blinded to other important confounding and prognostic factors: No Indirectness: No
Full citation Althuisius,S.M., Dekker,G.A., Hummel,P., van Geijn,H.P., Cervical inc, Cervical incompetence prevention randomized cerclage trial: emergency cerclage with bed rest versus bed rest alone, American Journal of Obstetrics and Gynecology, 189, 907-910, 2003 **Ref Id**	**Sample size** N = 23 **Characteristics** **Weeks of gestation at randomisation (mean ± SD)** Emergency cerclage: 22.2 ± 3.3 Bed rest: 23.0 ± 2.1 **Twin gestation (n (%))** Emergency cerclage: 3 (23.1) Bed rest: 4 (40%)	**Interventions** Emergency cerclage (n = 13 mothers, n = 16 babies) Bed rest (n = 10 mothers, n = 14 babies)	**Details** **Recruitment and randomisation** Eligible women were admitted to hospital immediately and randomised to either the cerclage group or bed rest group. Randomisation was organised in balanced blocks and assigned by telephone. **Care protocol** All women received amoxicillin/clavulanic acid 1g intravenously every 6 h and	**Results** **Neonatal survival (n/N (%))** Emergency cerclage: 9/16 (56.3) Bed rest: 4/14 (28.6) **Preterm birth < 34 weeks (n/N (%))** Emergency	**Limitations** **Appropriate randomisation:** Yes **Allocation concealment:**Yes **Groups comparable at baseline:** Yes **Groups received same care (apart from intervention):** not all women received tocolysis or corticosteroids but numbers were balanced across the groups **Blinding of participants:** No **Blinding of staff providing**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
246614 **Country/ies where the study was carried out** The Netherlands **Study type** Randomised controlled trial **Aim of the study** To compare pregnancy outcome following emergency cerclage, bed rest, antibiotics and indomethacin with bed rest only in women diagnosed with cervical incompetence with prolapsed membranes at or beyond a dilated external cervical os **Study dates** July 1995 – July 2000 **Source of funding** Supported by grant no. 28-2615 of the Health Research Development Council, The Hague, The Netherlands	**Received tocolysis - oral nifedipine (n (%))** Emergency cerclage: 11 (84.6) Bed rest: 8 (80) **Indication for steroid administration (n (%))** Emergency cerclage: 3 (23.1) Bed rest: 3 (30) **Inclusion criteria** Imminent preterm delivery because of cervical incompetence with membranes at or beyond a dilated external cervical os before 27 weeks of gestation. (Women with symptoms of cervical incompetence — loss of cervical mucus, sensation of downward pressure in the abdomen, feeling of a lump in the vagina — underwent transvaginal ultrasonography. In women with a cervical length < 25mm a speculum examination was performed to assess possible dilation of the external cervical os and prolapse of membranes.) **Exclusion criteria** Premature rupture of membranes Preterm labour (determined by detailed history and clinical observation)		metranidazole 500mg intravenously every 8 h for 1 week. Hospitalisation was maintained and women were restricted to bed until 30 weeks gestation. During bed rest period women received a low molecular weight heparin as thrombosis prophylaxis. At 30 weeks gestation women were allowed to start mobilisation. Discharge from hospital depended on home situation, when necessary home care was arranged. **Cerclage procedure** Women allocated to cerclage received an indomethacin 100mg suppository 2 h before and 6 h after the operation to inhibit possible contractions caused by the operation. Cerclage was performed under general anaesthetic with the woman in the lithotomy position with steep Trenelenburg tilt. Prolapsed membranes were gently pushed back into the uterine cavity with an inflated Foley catheter (Charrière 16). A single purse-string suture with a braided polyester thread (metric 8/USP 6) was performed, similar to the technique of McDonald. Cerclages were removed on maternal or fetal indication or electively at 37 weeks gestation.	cerclage: 7/13 (53.8) Bed rest: 10/10 (100) **Interval between randomisation and delivery - days (mean ± SD)** Emergency cerclage: 54 ± 47 Bed rest: 20 ± 28 **Gestational age at delivery - weeks (mean ± SD)** Emergency cerclage: 29.9 ± 8.4 Bed rest: 25.9 ± 4.3 **Compound neontal morbidity (n (%))** - defined as admission to NICU and/or neonatal death Emergency cerclage: 10/16 (62.5) Bed rest: 14/14 (100)	**care:** No **Blinding of outcome assessors:** Unclear **Missing data/loss to follow-up:** None **Precise definition of outcomes:** Neonatal morbidity includes neonatal death **Valid and reliable method of outcome assessment:** Yes **Intention-to-treat analysis performed:** Yes **Indirectness:** 3 women in the cerclage group and 4 women in the bed rest only group had a multiple pregnancy (30.4% of the study population) **Other information** **Cerclage removal** 8/23 removed on fetal and/or maternal indication at a mean of 24.74 weeks (95% CI, 19.14 to 30.28), and all delivered the same day 5/23 removed electively at a mean of 36.0 weeks: mean interval between removal and delivery 15 days (95% CI, 8 to 22)

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Curti,A., Simonazzi,G., Farina,A., Mehmeti,H., Facchinetti,F., Rizzo,N., Exam-indicated cerclage in patients with fetal membranes at or beyond external os: a retrospective evaluation, Journal of Obstetrics and Gynaecology Research, 38, 1352-1357, 2012 **Ref Id** 246677 **Country/ies where the study was carried out** Italy **Study type** Retrospective cohort study **Aim of the study** To compare the outcomes of operative and conservative treatment of pregnancies complicated by amniotic sac prolapse in the second trimester **Study dates** January 2001 – April 2009 **Source of funding** None reported	**Sample size** N = 52 **Characteristics** **Maternal age - years (mean ± SD)** Emergency cerclage: 30 ± 5 Conservative management: 32 ± 5 **Gestational age at diagnosis - weeks (median (min - max))** Emergency cerclage: 21 (17–28) Conservative management: 23 (19–26) **Cervical dilation - cm (median min - max))** Emergency cerclage: 2 (1–4) Conservative management: 4 (2–6) **Bulging beyond external os - %** Emergency cerclage: 75 Conservative management: 53 **Inclusion criteria** 1. Vital pregnancy between 17 and 27 weeks 2. Bulging fetal membranes, defined as hernia-like protrusion of the unopened amniotic sac through the	**Interventions** Exam-indicated cerclage (n = 37) Conservative management (n = 15)	**Details** **Recruitment** 52 women with bulging fetal membranes at or beyond the external orifice of the uterus requiring hospital admission at one of two hospitals were included in the study. Women were allocated to receive either cerclage or conservative management. **Care protocol and cerclage procedure** Cerclage was performed under general or spinal anaesthesia, at least 24 hours after admission. A moist swab on sponge-holding forceps was used to push the membranes back into the uterine cavity. Cerclage was performed using the Shirodkar technique in all cases but one, where the McDonald technique was used. Mersilene was always used as the suture material. All women in the cerclage group received a 7-day course of prophylactic antibiotics (erythromycin or ampicillin i.v.). Tocolytic drugs were administered on a case-by-case basis according to clinical findings. Conservative management consisted of bed rest during hospitalisation, antibiotics and clinical surveillance in all cases and tocolysis on a case-by-case	**Results** **Miscarriage - n/N (%)** Emergency cerclage: 5/37 (13%) Conservative management: 3/15 (20%) **Prolongation of pregnancy - days (median (min - max))** Emergency cerclage: 43 (12–83) Conservative management: 3 (1–7) **Gestational age at delivery - weeks (median (min - max))** Emergency cerclage: 29 (22–40) Conservative management: 24 (22–27) **Birth weight - grams (median (min - max))** Emergency cerclage: 1410 (590–3550)	**Limitations** **Method of allocation unrelated to potential confounding factors:** study states women were allocated to treatment but it is not clear how this allocation was made **Attempts made in design or analysis to balance comparison groups for confounding factors:** Yes **Groups comparable at baseline:** Yes **Comparison groups received same care apart from intervention studied:** 67% of women in cerclage group and 60% of women in conservative management group received tocolysis. Bed rest protocol for cerclage group unclear. **Participants blinded to treatment allocation:** N/A **Individuals administering care blinded to treatment allocation:** N/A **All groups followed up for equal length of time:** Yes **How many participants did not complete treatment:** None **Groups comparable for treatment completion:** Yes **Groups comparable with respect to availability of outcome data:** Yes **Appropriate length of follow up:** Yes **Precise definition of outcome:**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	cervical canal at or beyond the external orifice of the uterus, diagnosed digitally and by speculum examination **Exclusion criteria** 1. Multiple gestations 2. Preterm premature rupture of the membranes 3. Cervical dilation > 6cm 4. Symptoms of chorioamionitis (temperature > 38°C, uterine tenderness, fetal tachycardia) 5. Active labour (3 or more regular uterine contractions in 10 min associated with cervical changes) 6. Vaginal bleeding		basis.	Conservative management: 645 (437–3250) **Neonatal survival - n*/N (%)** Emergency cerclage: 30/37 (82) Conservative management: 8/15 (54) *n calculated by NCC-WCH from reported % **Admission to NICU - n*/N (%)** Emergency cerclage: 19/37 (51) Conservative management: 15/15 (100) *n calculated by NCC-WCH from reported %	Yes **Valid and reliable method of outcome measurement:** Yes **Investigators blinded to intervention:** No **Investigators blinded to other important confounding and prognostic factors:** No **Other information** Authors state that all women included in the study were at low risk of preterm birth. Cerclage procedure stopped in one woman due to amniorrhexis and moved to conservative management.
Full citation Daskalakis,G., Papantoniou,N., Mesogitis,S., Antsaklis,A., Management of cervical insufficiency and bulging fetal membranes, Obstetrics and Gynecology, 107, 221-226, 2006	**Sample size** N = 46 **Characteristics** **Maternal age - years (mean ± SD)** Emergency cerclage: 27.1 ± 3.6 Bed rest: 26.4 ± 3.4	**Interventions** Emergency McDonald cerclage (n = 29) Bed rest (n = 17)	**Details** **Recruitment** During the study period all pregnant women who had a second trimester scan anomaly between 18 and 23 weeks at the study hospital were offered the option of preterm labour screening, which involved	**Results** **Live birth (n/N (%)** Emergency cerclage: 25/29 (86.2) Bed rest: 7/17 (41.2)	**Limitations** **Method of allocation unrelated to potential confounding factors:** Unclear **Attempts made in design or analysis to balance comparison groups for confounding factors:** Unclear **Comparison groups received**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Ref Id 247115 **Country/ies where the study was carried out** Greece **Study type** Prospective cohort study **Aim of the study** To describe the treatment protocol for the management of women at high risk of preterm delivery and the experience with emergency cerclage in one hospital in Greece **Study dates** 1999 – 2005 **Source of funding** None reported	**Weeks gestation at diagnosis (mean ± SD)** Emergency cerclage: 22.4 ± 1.7 Bed rest: 22.6 ± 1.6 **Cervical dilation at diagnosis (mean ± SD)** Emergency cerclage: 4.1 ± 1.4 Bed rest: 4.0 ± 1.3 **Inclusion criteria** 1. Live intrauterine singleton pregnancy 2. Gestational age between 18 and 26 weeks 3. Cervical dilation more than 2cm and membrane prolapse 4. Intact membranes 5. Absence of uterine contractions 6. Absence of clinical evidence of chorioamnionitis 7. Absence of significant vaginal bleeding **Exclusion criteria** **Exclusion criteria before preterm delivery screening** 1. Previous spontaneous preterm delivery 2. Previous mid-trimester spontaneous abortion or termination of pregnancy 3. Multiple gestation 4. Oligohydramnios or hydramnios 5. Placenta praevia 6. Fetuses with congenital or		transvaginal ultrasonographic cervical assessment. Women with a short cervix (< 15 mm) were offered the option to have either a cervical cerclage or weekly transvaginal ultrasonographic scanning with the intention of treatment when further cervical changes were observed. Speculum examination was performed to assess possible dilation and membrane prolapse. When a woman was found to have cervical dilation with membranes at or beyond a dilated external cerival os at any time of screening before 26 weeks of gestation she was offered emergency cerclage and entered the study protocol. Those accepting cerclage formed the emergency cerclage group, those declining cerclage formed the bed rest group. **Care protocol** Women in the cerclage group were given cefuroxime and metronidazole intravenously in the operating room and continued for 48 h. Additionally they received erythromycin 1.5g orally daily for 10 days following cerclage. Following cerclage women received prophylactic tocolysis using 100mg indomethacin twice a day for 2 days and 5mg of ritodrine orally every 6 hours for 2 weeks.	**Neonatal survival (n/N (%)** Emergency cerclage: 24/25 (96) Bed rest: 4/7 (57.1) **Prolongation of pregnancy - weeks (mean ± SD)** Emergency cerclage: 8.8 ± 3.9 Bed rest: 3.1 ± 2.6 **Birth weight - grams (mean ± SD)** Emergency cerclage: 2101 (689.9) Bed rest: 739 (486.7) **Admission to NICU (n/N (%))** Emergency cerclage: 7/25 (28.0) Bed rest: 6/7 (85.7) **Preterm delivery < 32 weeks (n/N (%))** Emergency	**same care apart from intervention studied:** Unclear **Participants blinded to treatment allocation:** N/A **Individuals administering care blinded to treatment allocation:** N/A **All groups followed up for equal length of time:** Yes **How many participants did not complete treatment:** None **Groups comparable for treatment completion:** Yes **Groups comparable with respect to availability of outcome data:** Yes **Appropriate length of follow up:** Yes **Precise definition of outcome:** Yes **Valid and reliable method of outcome measurement:** Yes **Investigators blinded to intervention:** Unclear **Investigators blinded to other important confounding and prognostic factors:** Unclear **Indirectness:** None **Other information** All women were asymptomatic at the time of diagnosis of cervical dilation with membrane at or beyond a dilated external cervical os. Women were observed for 8–24 h to exclude preterm labour as the cause of

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	chromosomal abnormalities 7. Known congenital uterine malformation 8. Cervical insufficiency or cervical cerclage **Exclusion crieria following preterm delivery screening** 1. Premature rupture of membranes 2. Vaginal bleeding 3. Persistent contractions		Women were restricted to bed rest in the hospital for 7 days and discharged home with instruction for strict bed rest until 32 weeks. During the bed rest period women received low molecular weight heparin for thrombosis prophylaxis. Follow up included antenatal clinic assessment at 2-week intervals. After 32 weeks women were allowed to mobilise with plenty of rest. **Cerclage procedure** Emergency cerclage placement was performed under general anaesthesia. Women were placed in lithotomy position with steep Trendelenburg tilt. Vaginal walls and fornices were prepared with antiseptic solution. A moist swab on a sponge-holding forceps was used to push the membranes back into the uterine cavity. 5-mm polyester cerclage tape (Cervix-Set, Aesculap AG, Tuttlingen, Germany) with a large needle was placed, while the membranes were protected from perforation while being held away with a smaller moist swab. The knot was tied anteriorly and a long tail of tape left to facilitate removal before vaginal delivery. Ultrasound examination at 48-h postoperatively was used to confirm correct placement of cervical stitch. The suture was	cerclage: 9/29 (31.0) Bed rest: 16/17 (94.1) **Caesarean section (n/N (%))** Emergency cerclage: 7/29* (24.1) Bed rest: 2/17 (11.8) *Calculated by NCC from percentage reported in paper **Maternal adverse effects** **a. Cervical laceration** Emergency cerclage: 3/29 (10.3) Bed rest: 0/17 (0) **b. Cervical dystocia due to scar tissue, preventing cervical dilation** Emergency cerclage: 1/29 (3.4) Bed rest: 0/17 (0)	cervical dilation. Uterine activity was assessed with the woman's perceptions of contractions as well as abdominal palpation. Membrane rupture did not occur at the time of cerclage in any of the women. **Cerclage removal** The suture was removed in 3 women: in two of the three it was due to premature rupture of the membranes, 3 and 12 days following the procedure, respectively; in the third it was due to strong persistent contractions 2 weeks after cerclage placement. All three had histologic evidence of placental and chorioamniotic infection. None of the three neonates survived.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			removed at 37 weeks gestation or whenever labour was established.		
Full citation Olatunbosun,O.A., al-Nuaim,L., Turnell,R.W., Emergency cerclage compared with bed rest for advanced cervical dilatation in pregnancy, International Surgery, 80, 170-174, 1995 **Ref Id** 221859 **Country/ies where the study was carried out** Nigeria, Saudi Arabia and Canada **Study type** Prospective cohort study **Aim of the study** To compare the duration of pregnancy prolongation, maternal hospitalisation and perinatal outcomes in women who had emergency cerclage with women who had bed rest alone **Study dates** 1987 – 1993 **Source of funding** None reported	**Sample size** N = 37 **Characteristics** **Maternal age - years (mean ± SD)** Emergency cerclage: 28.7 ± 4.1 Bed rest: 28.0 ± 4.3 **Weeks gestation at diagnosis (mean ± SD)** Emergency cerclage: 22.4 ± 2.1 Bed rest: 23.2 ± 2.2 **Cervical dilatation - cm (mean ± SD)** Emergency cerclage: 6.0 ± 1.0 Bed rest: 6.0 ± 1.1 **Inclusion criteria** 1. Cervical effacement greater than 50% and dilatation at least 4 cm 2. Visibility or herniation of intact membranes through the open cervix 3. A live singleton intrauterine pregnancy 4. Absence of established labour 5. Absence of significant vaginal bleeding 6. Absence of clinical evidence of infection	**Interventions** Emergency cerclage (n = 22) Bed rest (n = 15)	**Details** **Recruitment** 43 consecutive women with widely dilated cervices at 20 – 27 weeks gestation were prospectively recruited by the first author during his time at three hospitals: Nigeria (1987–1989), Saudi Arabia (1989–1991) and Canada (1992–1993). Diagnosis of open cervix was made by speculum examination. **Care protocol** All women were admitted to the labour and delivery suite and monitored for uterine contractions for 4 h after fetal viability had been confirmed by transabdominal ultrasonography. If labour had not begun and there was no evidence of intra-amniotic infection, tocolysis with intravenous ritodrine or indomethacin suppositories was initiated in all women for an initial 48 h period and reinstituted only if uterine irritability developed. Corticosteroids were administered to women with significant contractions between 27 and 33 weeks gestation but were avoided when premature rupture of membranes occurred. Women diagnosed with intra-	**Results** **Neonatal survival (n/N (%))** Emergency cerclage: 17/22 (73.3%) Bed rest: 9/15 (66.7%) **Weeks gestation at delivery (mean ± SD)** Emergency cerclage: 33 ± 4.4 Bed rest: 28.8 ± 4.4 **Birth weight - kg (mean ± SD)** Emergency cerclage: 2.0 ± 0.8 Bed rest: 1.2 ± 0.7 **Caesarean section (n/N (%))** Emergency cerclage: 3/22 (13.6) Bed rest: 3/15 (20.0) **Prolonged**	**Limitations** **Method of allocation unrelated to potential confounding factors:** Unclear **Attempts made in design or analysis to balance comparison groups for confounding factors:** Yes **Comparison groups received same care apart from intervention studied:** All women received initial tocolysis which was continued in some women with uterine irritability. Not all women received corticosteroids or antibiotics **Participants blinded to treatment allocation:** N/A **Individuals administering care blinded to treatment allocation:** N/A **All groups followed up for equal length of time:** Yes **How many participants did not complete treatment:** None **Groups comparable for treatment completion:** Yes **Groups comparable with respect to availability of outcome data:** Yes **Appropriate length of follow up:** Yes **Precise definition of outcome:** Yes **Valid and reliable method of**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	Exclusion criteria 1. History of previous cervical cerclage 2. Habitual abortion (three last consecutive pregnancies terminating spontaneously before 20 weeks gestation) 3. A potential cause for mid-trimester abortion 4. Preterm labour		amniotic infection were treated with appropriate antibiotic therapy and labour was induced with oxytocin. Women with bed rest only were placed in the Trendelenburg position, transferred to the antepartum ward and remained in hospital until delivery. Women in both groups whose membranes ruptured were managed expectantly without tocolysis until spontaneous labour occurred or chorioamnionitis was identified. **Cerclage procedure** Emergency cerclage was performed within 6 hours of admission. Prolapsed fetal membranes were reduced either with an inflated Foley catheter with the tip cut, or by retrograde bladder filling with saline solution. All procedures were performed under general anaesthesia with women placed in steep Trendelenburg position. Postoperatively an indwelling Foley catheter was left in placed for 24-48 h and antibiotic therapy given for a total of 5 days. Tocolysis was continued for 24-48 h or until uterine irritability ceased. Absolute bed rest was required for the initial 48 h. Women were gradually ambulated and discharged on the 5th or 6th day and advised	**tocolysis (n/N (%))** Emergency cerclage: 5/22 (22.7) Bed rest: 11/15 (73.3) **Premature membrane rupture (n/N (%))** Emergency cerclage: 5/22 (22.7) Bed rest: 9/15 (60.0)	**outcome measurement:** Yes **Investigators blinded to intervention:** Unclear **Investigators blinded to other important confounding and prognostic factors:** Unclear **Indirectness:** None **Other information** 43 women met the inclusion criteria. Cerclage was successfully placed in 22/23 (96%) women. 5/20 (25%) women initially in the bed rest group elected to withdraw from the bed rest protocol to have operative treatment and were excluded from the analysis.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			against coitus. Following surgery women were reviewed weekly in an outpatient clinic. Women were hospitalised again if there was preterm labour or rupture of membranes. Sutures were removed at 38 weeks or whenever labour occurred.		
Full citation Stupin,J.H., David,M., Siedentopf,J.P., Dudenhausen,J.W., Emergency cerclage versus bed rest for amniotic sac prolapse before 27 gestational weeks. A retrospective, comparative study of 161 women, European Journal of Obstetrics, Gynecology, and Reproductive Biology, 139, 32-37, 2008 **Ref Id** 223248 **Country/ies where the study was carried out** Germany **Study type** Retrospective cohort study **Aim of the study**	**Sample size** N = 161 **Characteristics** **Maternal age on admission - years (median (range))** Emergency cerclage: 30 (20–41) Conservative treatment: 32 (18–41) **Weeks gestation on admission (median (range))** Emergency cerclage: 22 (18–26) Conservative treatment: 23 (18–26) **Multiple pregnancy (n/N (%))** Emergency cerclage: 18/89 (20) Conservative treatment: 13/72 (18) **Manually determined cervical dilatation - cm (median (range))** Emergency cerclage: 2.75 (0.5–5.0)	**Interventions** Emergency cerclage (n = 89 mothers) Convervative treatment (bed rest, tocolysis, and antibiotics) (n = 72 mothers) Study included women with multiple pregnancy but number of babies not reported	**Details** **Recruitment** Data were collected retrospectively from the medical files of 182 women who had been treated for amniotic sac prolapse during the study period at one hospital in Berlin. After applying the inclusion/exclusion criteria 161 women were included in the study. **Emergency cerclage group** In 93% of cases cerclage was performed on the day of admission or the following day. Methods used were the combination described by David and Farkic (double cerclage and complete closure of the uterus with fibrin adhesive in the cervical canal; n = 14), McDonald technique (n = 73) and closure of the uterus opening used by Saling (n = 2). 86/89 (96.6%) women received tocolysis with intravenous fenoterol/magnesium sulphate on	**Results** **Weeks gestation at delivery (median (range))** Emergency cerclage: 28 (18–42) Conservative treatment: 23 (18–39) **Birth weight < 500g (n/N (%))** Emergency cerclage: 20/89 (22) Conservative treatment: 40/72 (56) **Perinatal mortality* (n/N (%))** *any intrauterine fetal death or live-born neonates who died within 7-days	**Limitations** **Method of allocation unrelated to potential confounding factors:** No **Attempts made in design or analysis to balance comparison groups for confounding factors:** Unclear **Comparison groups received same care apart from intervention studied:** Unclear **Participants blinded to treatment allocation:** N/A **Individuals administering care blinded to treatment allocation:** N/A **All groups followed up for equal length of time:** Unclear **How many participants did not complete treatment:** None **Groups comparable for treatment completion:** Yes **Groups comparable with respect to availability of outcome data:** 17/182 women reviewed for inclusion were excluded due to incomplete data in their medical file

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
To compare the outcomes of operative and conservative treatment of amniotic sac prolapse in the second trimester **Study dates** December 1989–June 2005 **Source of funding** None reported	Conservative treatment: 2.0 (0.5–8.0) **Inclusion criteria** 1. A vital pregnancy between 17+0 and 26+0 gestational week 2. An amniotic sac prolapse, defined as a hernia-like protrusion of the unopened sac through the cervical canal and beyond the external orifice of the uterus (the extent of the internal and external opening of the uterus and remaining cervical length were not taken in to consideration) **Exclusion criteria** 1. Previous cervical operation in the same pregnancy 2. Symptoms of clinical chorioamnionitis (fever, uterine tenderness, fetal tachycardia, marked leukocytosis, and/or elevated C-reactive protein 3. Signs of preterm labour		admission. 3/89 women received tocolysis on the operating theatre. Tocolysis was discontinued after 48 h in women where the uterus remained free of contractions before and after the procedure. If no contractions occurred following suspension of tocolysis, and clinical and vaginal sonography showed a positive postoperative outcome, the initial protocol of absolute bed rest was relaxed then lifted. 54/89 (60.7%) women with signs of infection received antibiotic therapy peri- and post-operatively. Women in a stable condition were discharged home. **Convervative treatment** The decision to carry out intravenous tocolytic and/or antibiotic therapy was taken on a case-by-case basis. 65/72 (90.3%) women received tocolysis on admission, 7/72 (9.7%) women received tocolysis later during hospital stay. 50/72 (69.4%) women received antibiotic therapy. All women were required to observe bed rest, in some cases with an elevated pelvis.	postpartum Emergency cerclage: 5/89 (6) Conservative treatment: 13/72 (18) **Take-home baby rate (n/N (%))** Emergency cerclage: 64/89 (72) Conservative treatment: 18/72 (25)	**Appropriate length of follow up:** Yes **Precise definition of outcome:** Yes **Valid and reliable method of outcome measurement:** Yes **Investigators blinded to intervention:** No **Investigators blinded to other important confounding and prognostic factors:** No **Indirectness:** Yes - 31/161 (19%) women had a multiple pregnancy (emergency cerclage: 18/89 (20%); conservative treatment: 13/72 (18%)). **Other information** Allocation to emergency cerclage or conservative treatment was dependent on the equivalent preference of the physicans and/or the woman and was not significantly influenced by findings on admission or prognostic criteria, except for the amount of cervical dilatation. Denominator for all outcomes is the woman (NB 19% women had a multiple pregnancy) **Rupture of membranes during emergency cerlcage (n/N (%)** Total: 8/75 (10.7) McDonald technique: 7/73 (9.6) Saling technique: 1/2 (50)

H.17 Diagnosing preterm labour for women with intact membranes

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
Full citation van Baaren,G.J., Vis,J.Y., Wilms,F.F., Oudijk,M.A., Kwee,A., Porath,M.M., Oei,G., Scheepers,H.C., Spaanderman,M.E., Bloemenkamp,K.W., Haak,M.C., Bolte,A.C., Bax,C.J., Cornette,J.M., Duvekot,J.J., Nij Bijvanck,B.W., van,Eyck J., Franssen,M.T., Sollie,K.M., Vandenbussche,F.P., Woiski,M., Grobman,W.A., van der Post,J.A., Bossuyt,P.M., Opmeer,B.C., Mol,B.W., Predictive value of cervical length measurement and fibronectin testing in threatened preterm labor, Obstetrics and Gynecology, 123, 1185-1192, 2014 **Ref Id** 325288 **Country/ies where the study was carried out** The Netherlands **Study type** Prospective cohort study **Aim of the study** To examine combining cervical length measurement with fetal fibronectin testing in predicting delivery in women with symptoms of preterm labour **Study dates** December 2009 to August 2012	**Sample size** N=714 **Characteristics** **Mean maternal age, years ± SD** 29.7 ± 5.3 **Mean gestational age, weeks** 29 **Parity, n/N (%)** Nulliparous = 343/665 (52%) **Previous pre-term birth < 37 weeks, n (%)** Yes = 143 (22%) **Birth within 7 days after study entrance n (%)** 80 (12%) **Digital examination (N=510) n (%)** Cervical dilation 1 cm: 152 (30%) Cervical dilation 2 cm: 39 (7.6%) Cervical dilation 3 cm: 18 (3.6%)	**Tests** **Index test** Fetal fibronectin test with a cut-off of 0.05 microgram/ml (50 ng/ml) for a positive test result. Cervical length used 25 mm as a cut off at admission as determined by ultrasound. **Reference standard** Birth within 7 days of admission.	**Methods** **Details** Data were collected from 10 Dutch primary centres. Cervical length measurement by transvaginal ultrasound involved taking several measurements. Fibronectin specimen collected from the posterior fornix of the vagina before a vaginal examination or cervical length measurement performed. Primary outcomes were birth within 7 days using a 5% risk threshold. or pre-term birth ≤ 34 weeks' gestation. Definition of pre-term labour Painful and regular uterine contractions > 3/30 minutes alongside one of the following changes (bleeding, back or abdominal pain) Use of tocolysis Tocolytic medication was administered according to local management protocols. **Statistical analysis** Four logistic regression models were developed:	**Results** **Birth within 7 days** **Fibronectin test (cervical length <15 mm)** Likelihood ratio (positive) = 1.21 (1.01 to 1.45)* Likelihood ratio (negative) = 0.40 (0.18 to 1.01)* Sensitivity = 88.68 % (76.96 to 95.70)* Specificity = 26.67 % (16.08 to 39.66)* **Fibronectin test (cervical length 15 - 20 mm)** Likelihood ratio (positive) = 1.91 (1.56 to 2.34)* Likelihood ratio (negative) = 0.00* Sensitivity = 100 % (66.21 to 100)* Specificity = 47.67 % (36.79 to 58.73)* **Fibronectin test (cervical length 20-25 mm)** Likelihood ratio (positive) = 1.59	**Limitations** **QUADAS checklist** Was the spectrum of participants representative of the patients who will receive the test in practice? Yes Were selection criteria clearly described? Yes Was the reference standard likely to classify the target condition correctly? Yes Was the period between performance of the reference standard and the index test short enough to be reasonably sure that the target condition did not change between the two tests? Yes

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
Source of funding The Netherlands Organisation for Health Research and Development	**Inclusion Criteria** • Gestational age between 23 and 34 weeks • Painful and regular contractions (≥ 3 every 30 minutes), vaginal bleeding or abdominal or back pain • Intact membrance **Exclusion Criteria** • Received tocolysis within the previous 7 days • Premature rupture of membranes • Cervical dilation > 3cm • Suspected intrauterine infection • Lethal congenital abnormalities • Non reassuring fetal status • Placental abruption • Hypertensive disorder • A medically indicated pre-term birth		- A model with only cervical length as a predictor - A model with only fibronectin as a predictor - A model with both fibronectin and cervical length as predictors - A A combined model in that the increase of the risk associated with cervical length could differ from women with a positive fibronectin test result and for those with a negative result. Sensitivity and specificity were calculated for diagnosis of spontaneous pre-term birth within 7 days for different cervical lengths. Cervical length were analysed as a continuous variable. A test was considered positive when the predicted risk was equal to or > 5%. Positive and negative predictive values were calculated for prediction model. Data analysis were performed using R 2.10.0 and SPSS 20.0.	(1.05 to 2.40)* Likelihood ratio (negative) = 0.50 (0.19 to 1.34)* Sensitivity = 72.73 % (39.08 to 93.65)* Specificity = 54.13 % (44.32 % to 63.71)* **Fibronectin test (cervical length 25-30 mm)** Likelihood ratio (positive) = 1.93 (1.15 to 3.21)* Likelihood ratio (negative) = 0.34 (0.06 to 2.0)* Sensitivity = 80.0 % (28.81 to 96.70)* Specificity = 58.44 % (46.64 to 69.57)* **Fibronectin test (cervical length >=30 mm)** Likelihood ratio (positive) = 4.22 (3.38 to 5.26)* Likelihood ratio (negative) = 0.00* Sensitivity = 100 % (19.29 to 100)* Specificity = 76.28 % (70.55 to 81.39)* **Fibronectin test (all cervical**	Did the whole sample or a random selection of the sample receive verification using the reference standard? N/A Did participants receive the same reference standard regardless of the index test result? N/A Was the reference standard independent of the index test? (that is, the index test did not form part of the reference standard) Yes Was the execution of the index test described in sufficient detail to permit its replication? Yes Was the execution of the reference

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
				lengths) **Likelihood ratio** (positive) = 2.22 (1.95 to 2.52)* Likelihood ratio (negative) = 0.21 (0.12 to 0.37)* Sensitivity = 87.50 % (78.21 to 93.83)* Specificity = 60.51 % (56.42 to 64.50)* *Calculated by the NCC-WCH technical team.	standard described in sufficient detail to permit its replication? Yes Were the index test results interpreted without knowledge of the results of the reference standard? Unclear Were the reference standard results interpreted without knowledge of the results of the index test? N/A Were the same clinical data available when the test results were interpreted as would be available when the test is used in practice? Yes Were uninterpretable, indeterminate or intermediate test

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					results reported? N/A Were withdrawals from the study explained? Yes
Full citation Azlin,M.I., Bang,H.K., An,L.J., Mohamad,S.N., Mansor,N.A., Yee,B.S., Zulkifli,N.H., Tamil,A.M., Role of phIGFBP-1 and ultrasound cervical length in predicting pre-term labour, Journal of Obstetrics and Gynaecology, 30, 456-459, 2010 **Ref Id** 258526 **Country/ies where the study was carried out** Malaysia **Study type** Prospective cohort study **Aim of the study** To evaluate and compare the efficacy of pIGFBP-1 and cervical length measured by ultrasound, alone or in combination, in predicting pre-term labour. **Study dates** Not reported. **Source of funding** Financially supported by a UKMMC Fundamental Research Grant.	**Sample size** N = 51. **Characteristics** The following demographic data were collected: age, gravidity, parity, miscarriage, POA, income. These are presented by pIGFBP-1 testing status (+ve or -ve), cervical length <25mm, testing status (+ve or -ve) and both testing statuses (+ve or -ve). Demographic data were similar except for: **Gravidity ± SD** Cervical length < 25mm (Positive) = 1.94 ± 0.90 Cervical length ≥ 25mm (Negative) = 2.88 ± 1.70 **Miscarriage ± SD** Cervical length < 25mm (Positive) = 0.12 ± 0.33 Cervical length ≥ 25mm (Negative) = 0.91 ± 1.42 **Inclusion Criteria**	**Tests** **Index test** An pIGFBP-1 test with an unspecified threshold value for a positive result. **Index test** Cervical length < 25mm (positive) measured using transvaginal ultrasound (TV US). **Reference standard** Delivery < 1 week.	**Methods** **Details** pIGFBP-1 testing was performed before vaginal examination. A one step dipstick test kit was used for the detection of IGFBP-1 in cervical secretions. A cervical secretion specimen was obtained using a Dacron swab which was placed in extraction solution into which a dipstick was placed. One (positive) blue line on the dipstick confirmed that pIGFBP-1 concentration in the sample exceeded the threshold value for the test. A second blue line confirmed the test was performed correctly. If no lines appeared then the test was judged not to have performed properly. Clinicians were not blinded to results as this was a routine clinical test. Cervical length measurement was performed using TV US after the bladder was emptied. A standardised technique was used to identify the anatomical	**Results** **pIGFBP-1 test to diagnose birth within 7 days** Likelihood ratio (positive) = 12.27 (2.83 to 22.16)* Likelihood ratio (negative) = 0.21 (0.01 to 0.76)* Sensitivity = 80.0% (32.9 to 98.9)* Specificity = 93.5% (88.4 to 95.5)* **Cervical length <25 mm to diagnose birth within 7 days** Likelihood ratio (positive) = 2.83 (0.93 to 3.78)* Likelihood ratio (negative) = 0.28 (0.01 to 1.03)* Sensitivity = 80.0% (31.3 to 98.9)* Specificity = 71.7% (66.4 to 73.8)* **pIGFBP-1 test and**	**Limitations** **QUADAS checklist** Was the spectrum of participant's representative of the patients who will receive the test in practice? Yes Were selection criteria clearly described? Yes Was the reference standard likely to classify the target condition correctly? Yes Was the period between performance of the reference standard and the index test short enough to be reasonably sure that the target condition did not

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
	• Singleton pregnancies • Women with signs of pre-term labour • Gestational age between 24 and 36 weeks **Exclusion Criteria** • Pre-term premature rupture of membranes • Placenta previa or abruptio placenta • Multiple pregnancies • Cervical dilatation ≥ 3cm on vaginal examination • Cervical cerclage suture or cervical incompetence		position of the internal cervical os, cervical canal and external cervical os. The cervical length result was recorded as positive if < 25mm and negative if ≥ 25mm. Health care providers were blinded to the results of this test. Subsequent management of the woman was performed according to standard protocols of the hospital. <u>Definition of pre-term labour</u> Not reported. <u>Use of tocolysis</u> Tocolytic medication was administered at the discretion of the attending healthcare professionals who were blinded to ultrasound test results, but not IGFBP-1 test results. 12/51 (23.53%) of women received tocolysis and two of these women had positive results for both tests. 34/51 (66.67%) women were admitted for further management, 16/51 (31.37%) women were discharged and 1 woman (1.96%) was admitted twice for signs and symptoms of pre-term labour. **<u>Statistical analysis</u>** A sample size of 51 was required to achieve 80%	**<u>cervical length <25mm to diagnose birth within 7 days</u>** Likelihood ratio (positive) = 36.8 (4.83 to 508.35)* Likelihood ratio (negative) = 0.20 (0.02 to 0.71)* Sensitivity = 80.0% (34.4 to 98.2)* Specificity = 97.8% (92.9 to 99.8)* *Calculated by the NCC-WCH technical team	change between the two tests? Yes Did the whole sample or a random selection of the sample receive verification using the reference standard? The whole sample Did participants receive the same reference standard regardless of the index test result? Yes Was the reference standard independent of the index test? (that is, the index test did not form part of the reference standard) Yes Was the execution of the index test described in sufficient detail to permit its replication? Yes

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
			power and 95% confidence intervals, given an estimated 6% prevalence of pre-term labour. Demographic characteristics of the pregnancy, intervention during admission and timing of birth were analysed using the kappa estimate, ROC curve, central tendency, Student's t-tests and chi-squared tests. Statistical significance was taken at $p < 0.05$.		Were the index test results interpreted without knowledge of the results of the reference standard? Unclear Were the reference standard results interpreted without knowledge of the results of the index test? N/A
Full citation Bagga,R., Takhtani,M., Suri,V., Adhikari,K., Arora,S., Bhardwaj,S., Cervical length and cervicovaginal HCG for prediction of pre-term birth in women with signs and symptoms of pre-term labour, Journal of Obstetrics and Gynaecology, 30, 451-455, 2010 **Ref Id** 242576 **Country/ies where the study was carried out** India **Study type** Prospective cohort study	**Sample size** N = 100. **Characteristics** **Mean age, years ± SD** 25.49 ± 3.82 (range 20 to 36) **Mean gestational age at admission, weeks ± SD in days** 32+2 weeks ±17.80 days **Parity, n/N (%)** Nulliparous = 55/100 (55%) Multiparous = 45/100 (45%) **Previous pre-term birth, n/N (%)** 12/100 (12%) The number of women who	**Tests** **Index test** Cervical length < 25 mm as determined by transvaginal ultrasound at admission **Reference standard** Birth within 48 hours or 7 days of presentation	**Methods** **Details** Gestational age was determined using the last menstrual period and confirmed by ultrasound results from either the first or second trimester. Speculum examination was performed to determine HCG followed by digital cervical examination to assess dilation and effacement then transvaginal ultrasound. Primary outcomes were birth within 48 hours, 7 days, 7 to 14 days, after 14 days and under 37 weeks.	**Results** **Cervical length ≤ 25mm to diagnose birth within 48 hours** Likelihood ratio (positive) = 5.94 (2.75 to 12.60)* Likelihood ratio (negative) = 0.42 (0.25 to 0.66)* Sensitivity = 62.5% (44.6 to 76.6)* (15/24) Specificity = 89.5% (83.8 to 93.9)* (68/76) **Cervical length ≤ 25mm to diagnose**	**Limitations** **QUADAS checklist** Was the spectrum of participants representative of the patients who will receive the test in practice? Yes Were selection criteria clearly described? Yes Was the reference standard likely to classify the target condition correctly? Yes

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
Aim of the study To assess the role of cervicovaginal human chorionic gonadotoprin and cervical length measurement by transvaginal ultrasound to predict pre-term birth in women with signs and symptoms of pre-term labour. **Study dates** Not reported. **Source of funding** Not reported.	received tocolytic medication was not reported **Inclusion Criteria** • Singleton pregnancies • Gestational age > 26 and < 37 weeks • Presentation with signs and symptoms of threatened pre-term labour or actual pre-term labour **Exclusion Criteria** • Women with cervical dilation > 3cm • Antepartum haemorrhage • Rupture membranes • Congenitally malformed fetus • Uncertain gestational age		Definition of pre-term labour Threatened pre-term labour was defined as regular uterine contractions of 4 in 20 minutes or 8 in 60 minutes confirmed by palpation or tocodynamometry with no evidence of cervical change. Actual pre-term labour was defined as regular uterine contractions as for threatened pre-term labour plus cervical dilation ≥ 1cm or effacement ≥ 80%. Use of tocolysis Not reported. **Statistical analysis** No relevant statistical analyses were carried out in relation to the protocol for this review. Sensitivity, specificity, likelihood ratios and associated 95% confidence intervals were therefore calculated by the NCC-WCH technical team.	**birth within 7 days** Likelihood ratio (positive) = 19.50 (5.14 to 117.76)* Likelihood ratio (negative) = 0.41 (0.36 to 0.57)* Sensitivity = 60.0% (48.3 to 64.7)* (21/35) Specificity = 96.9% (91.6 to 99.5)* (63/65) *Calculated by the NCC-WCH technical team.	Was the period between performance of the reference standard and the index test short enough to be reasonably sure that the target condition did not change between the two tests? Yes Did the whole sample or a random selection of the sample receive verification using the reference standard? Yes Did participants receive the same reference standard regardless of the index test result? Yes Was the reference standard independent of the index test? (that is, the index test did not form part of the reference

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					standard) Yes Was the execution of the index test described in sufficient detail to permit its replication? Yes Was the execution of the reference standard described in sufficient detail to permit its replication? Yes Were the index test results interpreted without knowledge of the results of the reference standard? Unclear Were the reference standard results interpreted without knowledge of the results of the index test? N/A Were the same clinical data

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					available when the test results were interpreted as would be available when the test is used in practice? Yes Were uninterpretable, indeterminate or intermediate test results reported? N/A Were withdrawals from the study explained? N/A
Full citation Bartnicki,J., Casal,D., Kreaden,U.S., Saling,E., Vetter,K., Fetal fibronectin in vaginal specimens predicts preterm delivery and very-low-birth-weight infants, American Journal of Obstetrics and Gynecology, 174, 971-974, 1996 **Ref Id** 258252 **Country/ies where the study was carried out** Germany **Study type** Prospective cohort study	**Sample size** N = 112. **Characteristics** **Mean gestational age at admission, weeks ± SD** Pre-term birth (< 37 weeks' gestation) = 29.5 ± 3.2. Term birth = 30.8 ± 2.9. No other characteristics were reported. No data were provided for the number of women with previous pre-term births, the number who received tocolytic medication or parity.	**Tests** **Index test** Fetal fibronectin test with a cut-off of > 50ng/ml for a positive test result. **Reference standard** Birth within 7 days of admission.	**Methods** **Details** Eligible women were drawn from all 3254 births at the study hospital during 1991. A fetal fibronectin test was performed before all other tests at admission. A swab was taken from the posterior fornix of the vagina. A positive test result was defined as > 0.05µg/ml. A digital cervical examination was then performed. Uterine contractility was assessed using tocodynamometry or abdominal palpation.	**Results** **Fetal fibronectin to diagnose birth within 7 days** Likelihood ratio (positive) = 3.44 (2.57 to 4.60)* Likelihood ratio (negative) = 0.00 (0.00 to 1.15)* Sensitivity = 100.0% (19.2 to 100.0)* (2/2) Specificity = 70.9% (61.5 to 79.5)* (78/110) *Calculated by the NCC-WCH technical team.	**Limitations** **QUADAS checklist** Was the spectrum of participants representative of the patients who will receive the test in practice? Yes Were selection criteria clearly described? Yes Was the reference standard likely to classify the target condition

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
Aim of the study To evaluate the association of vaginal fetal fibronectin expression to risk of pre-term birth and birth of very-low-birth-weight infants. **Study dates** 1991. **Source of funding** Not reported.	**Inclusion Criteria** • Gestational age between 22 and 35 weeks • Intact amniotic membranes • Minimal cervical dilation (≤ 2cm) • Symptoms of pre-term labour **Exclusion Criteria** Not reported.		Definition of pre-term labour Symptoms of pre-term labour were defined as uterine contractions, change in vaginal discharge and abdominal discomfort. Use of tocolysis Tocolytic medication was administered at the discretion of the attending physician without knowledge of the fetal fibronectin test result. **Statistical analysis** No relevant statistical analyses were carried out in relation to the protocol for this review. Likelihood ratios, sensitivity, specificity and associated 95% confidence intervals were therefore calculated by the NCC-WCH technical team.		correctly? Yes Was the period between performance of the reference standard and the index test short enough to be reasonably sure that the target condition did not change between the two tests? Yes Did the whole sample or a random selection of the sample receive verification using the reference standard? Yes Did participants receive the same reference standard regardless of the index test result? Yes Was the reference standard independent of the index test? (that is, the index test did not form part of the

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					reference standard) Yes Was the execution of the index test described in sufficient detail to permit its replication? Yes Was the execution of the reference standard described in sufficient detail to permit its replication? Yes Were the index test results interpreted without knowledge of the results of the reference standard? Unclear Were the reference standard results interpreted without knowledge of the results of the index test? N/A Were the same

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					clinical data available when the test results were interpreted as would be available when the test is used in practice? Unclear - of relevant baseline characteristics only mean gestational age at admission is reported. Were uninterpretable, indeterminate or intermediate test results reported? N/A Were withdrawals from the study explained? N/A
Full citation Benattar,C., Taieb,J., Fernandez,H., Lindendaum,A., Frydman,R., Ville,Y., Rapid fetal fibronectin swab-test in preterm labor patients treated by betamimetics, European Journal of Obstetrics, Gynecology, and Reproductive Biology, 72, 131-135, 1997 **Ref Id** 270950	**Sample size** N = 114 **Characteristics** **Mean gestational age at sampling** Positive fibronectin test = 31.9 (SD 2.5) Negative fibronectin test = 31.3 (3.2)	**Tests** **Index test** Fetal fibronectin test with a cut-off of > 50ng/ml for a positive test result. **Reference test** Birth within 7 days.	**Methods** **Details** Out of 140 women presenting with symptoms of pre-term labour, 114 were included in the study. N = 110 singleton and 14 twin pregnancies, n = 19 women with raised temperature (38°C) and intact membranes.	**Results** Total N = 124 Positive fetal fibronectin n = 19 **Birth within 7 days n = 9** Sensitivity = 89% (55 to 100) Specificity = 90% (55 to 100)	**Limitations** **QUADAS checklist** Was the spectrum of participants representative of the patients who will receive the test in practice? Yes

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
Country/ies where the study was carried out France **Study type** Prospective cohort study **Aim of the study** To examine the value of a rapid fetal fibronectin swab test used as a bedside test in the prognosis of pre-term labour. **Study dates** Not reported. **Source of funding** Not reported.	**Mean Bishop score** Positive fibronectin test = 4.0 (SD 2.1) Negative fibronectin test = 4.9 (SD 2.1) **Mean duration of tocolysis (days)** Positive fibronectin test = 6 (SD 9.4) Negative fibronectin test = 6.6 (SD 12.2) **Inclusion Criteria** • 24 to 36 weeks' gestation • Symptoms of preterm labour **Exclusion Criteria** • Cervix ≥ 3cm dilated • Confirmed rupture of membranes • Vaginal bleeding		**Index test** Specimen was obtained from exocervix and posterior vaginal fornix by using a Dacron swab. The result was processed using ELISA rapid assay. The test was done at bedside and a result produced within 5 minutes. No cut-off was reported to determine a positive test result. Definition of pre-term labour Symptoms suggested of pre-term labour included regular contractions (> 5 per hour) associated with cervical changes since the last examination. Use of tocolysis All women received intravenous betamimetics on admission and treated with the same protocol of oral tocolytics after successful arrest of pre-term labour with parenteral drugs. **Statistical analysis** Continuous variables were analysed with Mann-Whitney U test. Categorical variables were analysed using Fisher's exact test using Statview SE Software.	No adequate data were reported to calculate positive and negative likelihood ratios. **Incidence of pre-term birth** Positive fibronectin test = 47% Negative fibronectin test = 15% P > 0.001	Were selection criteria clearly described? Yes Was the reference standard likely to classify the target condition correctly? Yes Was the period between performance of the reference standard and the index test short enough to be reasonably sure that the target condition did not change between the two tests? N/A Did the whole sample or a random selection of the sample receive verification using the reference standard? Yes Did participants receive the same reference standard regardless of the index test result? Yes

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					Was the reference standard independent of the index test? (that is, the index test did not form part of the reference standard) Yes Was the execution of the index test described in sufficient detail to permit its replication? Yes Was the execution of the reference standard described in sufficient detail to permit its replication? N/A Were the index test results interpreted without knowledge of the results of the reference standard? Yes Were the reference

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					standard results interpreted without knowledge of the results of the index test? Yes Were the same clinical data available when the test results were interpreted as would be available when the test is used in practice? Yes Were uninterpretable, indeterminate or intermediate test results reported? N/A Were withdrawals from the study explained? N/A **Other information** No cut-off to determine a positive test result was reported. Unclear if the vaginal examination was

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					performed before or after the fibronectin test. Unclear history of previous premature birth.
Full citation Botsis,D., Makrakis,E., Papagianni,V., Kouskouni,E., Grigoriou,O., Dendrinos,S., Creatsas,G., The value of cervical length and plasma proMMP-9 levels for the prediction of preterm delivery in pregnant women presenting with threatened preterm labor, European Journal of Obstetrics, Gynecology, and Reproductive Biology, 128, 108-112, 2006 **Ref Id** 271145 **Country/ies where the study was carried out** Greece **Study type** Prospective cohort study **Aim of the study** To determine the effectiveness of plasma proMMP-9 levels and cervical length as determined by transvaginal sonography in predicting birth within 7 days of presentation. **Study dates** June 2000 to February 2001.	**Sample size** N = 62 **Characteristics** **Median maternal age, years (range)** 28 (21 to 36) **Median gestational age at presentation, weeks (range)** 32 (24 to 36) **Nulliparity, %** Birth within 7 days = 45.4% No birth within 7 days = 35.3% **History of pre-term birth, %** Birth within 7 days = 18.1% No birth within 7 days = 7.8% **Use of tocolytics, %** Birth within 7 days = 45.4% No birth within 7 days = 31.3% **Inclusion Criteria** • Gestational age between 24 and 36 weeks	**Tests** **Index test** Cervical length < 15mm as determined by transvaginal sonography at admission. **Reference standard** Birth within 7 days of presentation.	**Methods** **Details** Recruitment was consecutive. A cut-off of 15mm was chosen for cervical length based on the results of previous published studies. Definition of pre-term labour Suspected pre-term labour was defined as the presence of ≥ 2 uterine contractions in a 10 minute period, confirmed by tocography. True pre-term labour was defined as regular uterine contractions at a minimum frequency of 2 every 10 minutes plus progressive cervical changes in effacement, dilation or both. Use of tocoloysis Administration of tocolytic medication was the decision of the attending obstetrician who was blinded to the results of the transvaginal ultrasound. **Statistical analysis**	**Results** **Cervical length < 15mm to diagnose birth within 7 days of presentation** Likelihood ratio (positive) = 10.43 (3.73 to 20.60)* Likelihood ratio (negative) = 0.20 (0.04 to 0.55)* Sensitivity = 81.8% (52.7 to 96.5)* (9/11) Specificity = 92.2% (85.9 to 95.3)* (47/51) *Calculated by the NCC-WCH technical team.	**Limitations** **QUADAS checklist** Was the spectrum of participants representative of the patients who will receive the test in practice? Yes Were selection criteria clearly described? Yes Was the reference standard likely to classify the target condition correctly? Yes Was the period between performance of the reference standard and the index test short enough to be reasonably sure that the target

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
Source of funding Not reported.	• Singleton pregnancies with a detectable fetal heart beat • Absence of any complication up until presentation • Absence of any pathological condition e.g. cardiovascular disease, connective tissue disease, gingival disease • Presence of ≥ 2 uterine contractions in a 10 minute period, confirmed by tocography • Absence of cervical dilation • No evidence of rupture of membranes • Absence of chorioamionitis • Availability of transvaginal ultrasound scan by the same sonographer **Exclusion Criteria** Not reported.		Sensitivity and specificity were calculated however these values are not quoted in this review as they were incorrect due to rounding errors. Sensitivity, specificity, likelihood ratios and associated 95% confidence intervals were therefore calculated by the NCC-WCH technical team.		condition did not change between the two tests? Yes Did the whole sample or a random selection of the sample receive verification using the reference standard? Yes Did participants receive the same reference standard regardless of the index test result? Yes Was the reference standard independent of the index test? (that is, the index test did not form part of the reference standard) Yes Was the execution of the index test described in sufficient detail to permit its replication? Yes

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					Was the execution of the reference standard described in sufficient detail to permit its replication? Yes Were the index test results interpreted without knowledge of the results of the reference standard? Yes / No / Unclear / N/A Were the reference standard results interpreted without knowledge of the results of the index test? N/A Were the same clinical data available when the test results were interpreted as would be available when the test is used in practice? Yes Were

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					uninterpretable, indeterminate or intermediate test results reported? N/A Were withdrawals from the study explained? N/A
Full citation Brik,M., Hernandez,A.I., Pedraz,C.C., Perales,A., Phosphorylated insulin-like growth factor binding protein-1 and cervical measurement in women with threatening preterm birth, Acta Obstetricia et Gynecologica Scandinavica, 89, 268-274, 2010 **Ref Id** 258409 **Country/ies where the study was carried out** Spain **Study type** Prospective cohort study **Aim of the study** To determine the use of cervical pIGFBP-1 in predicting pre-term birth and to assess its association with cervical length measured by transvaginal ultrasound. **Study dates** June 2004 to July 2008. **Source of funding**	**Sample size** N = 276 **Characteristics** **Symptoms of threatened labour** Abdominal pain 59%, contractions 7%, leaking of fluid 3%, lumbar pain 3%, other 3%. **Mean maternal age, years ± SD (range)** 29.4 ± 5.9 (15-46) **Parity, n/N (%)** Nulliparous = 161/276 (58.3%) Multiparous = 115/276 (41.6%) **Previous pre-term birth, n/N (%)** 26/276 (9.4%) **Mean gestational age at examination, weeks ± SD (range)** 29.9 ± 2.8 (23-34) **Inclusion Criteria**	**Tests** **Index test** A pIGFBP-1 test with a minimal detectable concentration of 10µg and a threshold concentration of 30µg for a positive result. **Reference standard** Birth within 48 hours or within 7 days.	**Methods** **Details** pIGFBP-1 testing was performed before TV US. Lastly a digital cervical examination was performed to estimate Bishop scores. Uterine contractions were considered significant if there were > 3 contractions in 30 minutes as determined by cardiotocography. Urine analysis was performed to exclude a UTI. A rapid strip test (Actim Partis test) for the detection of pIGFBP-1 in cervical secretions was used. A cervical fluid specimen from the external os was obtained using a Dacron swab. The swab was placed in extraction solution and shaken. A dipstick was placed in the solution. A concentration of > 30µg was required for a positive result apparent as two	**Results** **pIGFBP-1 test to diagnose birth within 48 hours** N = 276 Likelihood ratio (positive) = 2.10 (1.52 to 2.91) Likelihood ratio (negative) = 0.41 (0.19 to 0.87) Sensitivity = 73.7% Specificity = 64.9% **pIGFBP-1 test to diagnose birth within 7 days** N = 276 Likelihood ratio (positive) = 2.16 (1.60 to 2.92) Likelihood ratio (negative) = 0.41 (0.21 to 0.78) Sensitivity = 73.1% Specificity = 66.2%	**Limitations** **QUADAS checklist** Was the spectrum of participant's representative of the patients who will receive the test in practice? Yes Were selection criteria clearly described? Yes Was the reference standard likely to classify the target condition correctly? Yes Was the period between performance of the reference standard and the index test short enough to be

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
Supported by a grant from the Agencia Valenciana de Salud.	• Singleton pregnancies • Intact membranes • Threatened pre-term labour (symptoms of abdominal pain) • Gestational age between 24 and 34 weeks **Exclusion Criteria** • Premature rupture of membranes (nitrazine test or pIGFBP-1 at bedside) • Moderate to intense vaginal bleeding • Placental abruption • Active labour • Cervical cerclage • Fetal anomalies • Fetal distress leading to induction of labour or cord prolapse		blue lines. A negative result appeared as a single blue line. Definition of active labour Cervix 100% effaced with > 3cm dilation. Use of tocolysis Tocolytic medication was administered to women with established pre-term labour in accordance with local clinical protocols and steroids were administered as appropriate. **Statistical analysis** SPSS was used for analysis. Sensitivity, specificity, positive and negative likelihood ratios were calculated according to the Centre for Evidence Based Medicine.		reasonably sure that the target condition did not change between the two tests? Yes Did the whole sample or a random selection of the sample receive verification using the reference standard? The whole sample Did participants receive the same reference standard regardless of the index test result? Yes Was the reference standard independent of the index test? (that is, the index test did not form part of the reference standard) Yes Was the execution of the index test described in sufficient detail to

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					permit its replication? Yes Were the index test results interpreted without knowledge of the results of the reference standard? Unclear Were the reference standard results interpreted without knowledge of the results of the index test? N/A
Full citation Burwick,R.M., Zork,N.M., Lee,G.T., Ross,M.G., Kjos,S.L., Cervilenz assessment of cervical length compared to fetal fibronectin in the prediction of preterm delivery in women with threatened preterm labor, Journal of Maternal-Fetal and Neonatal Medicine, 24, 127-131, 2011 **Ref Id** 258105 **Country/ies where the study was carried out** USA **Study type**	**Sample size** N = 52. **Characteristics** **Mean maternal age, years ± SD** 27.9 ± 7.27 **Nulliparous** 38.5% **Previous pre-term birth** 28.9% **Mean gestational age at admission, weeks ± SD** 30.4 ± 2.85	**Tests** **Index test** Fetal fibronectin test with a cut-off of > 50ng/mL for a positive test result. **Reference standard** Birth within 7 days.	**Methods** **Details** Women with suspected pre-term labour were included in the study. Women were enrolled as a part of randomised control trial evaluating management algorithms for threatened preterm labour. At the entry women underwent two step evaluations. First, specimens were collected during the speculum examination from posterior fornix and then cervical length was measured with the Cervilenz device [as	**Results** Total N = 49 Positive fetal fibronectin n = 12 (24.5%) **Birth within 7 days** Sensitivity = 66.7% (53.5 to 79.9) Specificity = 78.3% (66.7 to 89.8) No adequate data were reported to calculate other diagnostic accuracy features.	**Limitations** **QUADAS checklist** Was the spectrum of participants representative of the patients who will receive the test in practice? Yes Were selection criteria clearly described? No Was the reference standard likely to

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
Prospective cohort study **Aim of the study** To determine whether cervical length (CL) measured by the Cervilenz measuring device is an effective screening tool for the prediction of pre-term delivery (PTD) compared to fetal fibronectin (fFN) **Study dates** Not reported. **Source of funding** Not reported.	**Inclusion Criteria** • Between 24 and 34 weeks' gestation • Intact membranes • Singleton • Cervix < 3 cm dilated • Presence of uterine contractions **Exclusion Criteria** • Vaginal bleeding • Presence of cervical cerclage • Recent intercourse		the Cervilenz device is not our interest for this review, details and result from this will not be reported here]. Definition of pre-term labour Not reported. Use of tocoloysis Not reported. **Statistical analysis** Receiver operator characteristic (ROC) analysis was utilised to compare significant area under curve. All analyses performed with Stata v 10.0.		classify the target condition correctly? Yes Was the period between performance of the reference standard and the index test short enough to be reasonably sure that the target condition did not change between the two tests? N/A Did the whole sample or a random selection of the sample receive verification using the reference standard? Yes Did participants receive the same reference standard regardless of the index test result? Yes Was the reference standard independent of the index test? (that is, the index

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					test did not form part of the reference standard) Yes Was the execution of the index test described in sufficient detail to permit its replication? No Was the execution of the reference standard described in sufficient detail to permit its replication? N/A Were the index test results interpreted without knowledge of the results of the reference standard? Unclear Were the reference standard results interpreted without knowledge of the results of the index test? N/A

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					Were the same clinical data available when the test results were interpreted as would be available when the test is used in practice? Unclear Were uninterpretable, indeterminate or intermediate test results reported? N/A Were withdrawals from the study explained? N/A **Other information** No more details about the fibronectin test were reported in the paper. Unclear what test was used and how was analysed (what cut-off was used).

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					Unclear if the test was done before or after the vaginal examination. Unclear if the clinicians were blinded to the result of the test.
Full citation Danti,L., Prefumo,F., Lojacono,A., Corini,S., Testori,A., Frusca,T., The combination of short cervical length and phIGFBP-1 in the prediction of preterm delivery in symptomatic women, Journal of Maternal-Fetal and Neonatal Medicine, 24, 1262-1266, 2011 **Ref Id** 258567 **Country/ies where the study was carried out** Italy **Study type** Prospective cohort study **Aim of the study** To evaluate the combined use of cervical length and phosphorylated IGFBP-1 measurement to predict pre-term delivery in symptomatic women. **Study dates** December 2004 to December 2006.	**Sample size** N = 102 **Characteristics** Cervical length ≤ 30mm N = 60 Cervical length > 30mm N = 42 **Median maternal age (IQR)** Cervical length ≤ 30mm = 31 (28 to 34) Cervical length > 30mm = 34 (30 to 37) **Nulliparious (%)** Cervical length ≤ 30mm = 38 (63%) Cervical length > 30mm = 26 (62%) **Median gestational age (wks) at assessment (IQR)** Cervical length ≤ 30mm = 30.0 (28.7 to 31.4) Cervical length > 30mm = 28.9 (26.6 to 30.9) **Corticosteroid use (%)** Cervical length ≤ 30mm = 28	**Tests** **Index test** Cervical length ≤ 30mm (positive) measured using transvaginal ultrasound (TV US). **Index test** An pIGFBP-1 test with an threshold value of > 10µg for a positive result. **Reference standard** Birth within 7 days of presentation.	**Methods** **Details** Cervical length measurement was performed using TV US after the bladder was emptied. Women were placed in the dorsal lithotomy position. An ultrasound probe was inserted into the vagina, with gel applied beteen the probe and probe cover only and not on the external probe cover surface. The probe was placed in the anterior fornix and the cervical length was measured. The managing clinician was not blinded to results. Women were admitted to hospital if cervical length ≤ 30mm (n=60) and offered a pIGFBP-1 test. pIGFBP-1 testing was performed before vaginal examination. A rapid strip test (Actim Partis test) for the detection of pIGFBP-1 in	**Results** **Cervical length ≤30mm to diagnose birth within 7 days** N= 102 TP: 4 FP: 56 FN: 0 TN: 42* Likelihood ratio (positive) = 1.58 (0.64 to 1.77)*† Likelihood ratio (negative) = 0.23 (0.00 to 1.53)*† Sensitivity = 90.0% (47.8 to 99.5)*† Specificity = 42.9% (40.3 to 43.4)*† **In women with cervical length ≤30mm, pIGFBP-1 test to diagnose birth within 7 days** N= 60 TP: 2 FP: 17 FN: 2 TN:39* Likelihood ratio (positive) = 1.65	**Limitations** **QUADAS checklist** Was the spectrum of participant's representative of the patients who will receive the test in practice? Yes Were selection criteria clearly described? Yes Was the reference standard likely to classify the target condition correctly? Yes Was the period between performance of the reference standard and the index test short

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
Source of funding Not reported.	(47%) Cervical length > 30mm = 4 (10%) **<u>Use of tocolysis (%)</u>** Cervical length ≤ 30mm = 22 (37%) Cervical length > 30mm = 5 (12%) **Inclusion Criteria** • Singleton pregnancies • Gestational age between 24+0 and 32+6 weeks • Women presenting with complaint of uterine contractions and in whom at least 4 contractions in 20 mins were measured with a cardiotocograpy **Exclusion Criteria** • Ruptured membranes • Known uterine abnormalities • Fetal abnormalities • Vaginal bleeding • Cervical dilatation ≥ 3cm • Cervical cerclage • Other pregnancy		cervical secretions was used. Following sterile speculum insertion, a cervical secretion specimen from the external os was obtained using a Dacron swab. The swab was placed in extraction solution, shaken and withdrawn. The bottom of a reagent strip was placed in the solution. After 20 seconds the strip was removed and placed horizontally. A positive result (pIGFBP-1 concentration > 10µg) appeared as 2 blue lines on the strip and a negative result was a single blue line. The managing clinician was blinded to results as was the study data collector. <u>Definition of pre-term labour</u> Not reported. <u>Use of tocolysis</u> Tocolytic medication was administered at the discretion of the attending healthcare professionals who were blinded to pIGFBP-1 test results, but not ultrasound test results. Decisions to use corticosteroids or tocolytics were recorded in the clinical notes. 22/60 (37%) of women with cervical length ≤ 30mm and 5/42 (12%) women with cervical length > 30mm received tocolysis.	(0.57 to 4.74) Likelihood ratio (negative) = 0.72 (0.27 to 1.94) Sensitivity = 50% (7 to 93) Specificity = 70% (56 to 81) **<u>In women with cervical length 20-30mm, pIGFBP-1 test to diagnose birth within 7 days</u>** N=41 Likelihood ratio (positive) = 61.5 (3.5 to 1083)*† Likelihood ratio (negative) = 0.25 (0.02 to 2.79)*† Sensitivity = 75% (15 to 100)*† Specificity = 98.8% (95 to 100)*† **<u>In women with cervical length <20mm and pIGFBP-1 test to diagnose birth within 7 days</u>** N= 19 Likelihood ratio (positive) = 0.89 (0.16 to 4.97) Likelihood ratio (negative) = 1.07 (0.44 to 2.59)	enough to be reasonably sure that the target condition did not change between the two tests? Yes Did the whole sample or a random selection of the sample receive verification using the reference standard? The whole sample Did participants receive the same reference standard regardless of the index test result? Yes Was the reference standard independent of the index test? (that is, the index test did not form part of the reference standard) Yes Was the execution of the index test described in

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
	complications (placenta previa, abruptio placentae, fetal growth restriction and pre-eclampsia)		**Statistical analysis** For inter-group comparisons the Mann Whitney test, chi-squared test, and Fisher's exact test were used. A sample size of 58 was required to estimate sensitivity and specificity with a 95% confidence interval no larger than 20%, but it was planned that 97 participants would enrol.	Sensitivity = 33% (1 to 91) Specificity = 63% (35 to 85) *Calculated by the NCC-WCH technical team. †0.5 has been added to each cell in the 2x2 contingency table.	sufficient detail to permit its replication? Yes Were the index test results interpreted without knowledge of the results of the reference standard? Unclear Were the reference standard results interpreted without knowledge of the results of the index test? N/A
Full citation Demirci,O., Unal,A., Demirci,E., Sozen,H., Akdemir,Y., Boybek,E., Ertekin,A., Sonographic measurement of cervical length and risk of preterm delivery, Journal of Obstetrics and Gynaecology Research, 37, 809-814, 2011 **Ref Id** 271042 **Country/ies where the study was carried out** Turkey **Study type**	**Sample size** N = 209 **Characteristics** **Mean maternal age, years ± SD** < 15mm = 25.9 ± 4.6 ≥ 15mm = 25.8 ± 5.4 **Mean gravidity ± SD** < 15mm = 2.1 ± 1.8 ≥ 15mm = 1.9 ± 1.2 **Mean parity ± SD** < 15mm = 0.5 ± 1.1 ≥ 15mm = 0.6 ± 0.8	**Tests** **Index test** Cervical length < 15mm as determined by transvaginal sonography. **Reference standard** Birth within 7 days of presentation.	**Methods** **Details** Sonographic measurement of cervical length was carried out at admission. Three measurements were taken and the shortest value in the absence of uterine contractions was used in analyses. A cervical length cut-off off 15mm was used based on the results of previous studies. The primary outcome	**Results** **Cervical length < 15mm to diagnose birth within 7 days of presentation** Likelihood ratio (positive) = 13.64 (7.15 to 20.89)* Likelihood ratio (negative) = 0.22 (0.08 to 0.47)* Sensitivity = 78.9% (57.0 to 92.5)* (15/19) Specificity = 94.2% (92.0 to 95.6)*	**Limitations** **QUADAS checklist** Was the spectrum of participants representative of the patients who will receive the test in practice? Yes Were selection criteria clearly described? Yes Was the reference

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
Prospective cohort study **Aim of the study** To examine the potential role of soongraphic measurement of cervical length in predicting birth within 7 days of presentation in women with threatened pre-term labour. **Study dates** July 2007 to February 2008. **Source of funding** Not reported.	**Mean gestational age, weeks ± SD** < 15mm = 31.0 ± 2.8 ≥ 15mm = 31.2 ± 2.4 **Tocolytic treatment, n/N (%)** < 15mm = 21/26 (81%) ≥ 15mm = 96/183 (52%) **Previous preterm delivery, n/N (%)** < 15mm = 3/26 (12%) ≥ 15mm = 11/183 (6%) **Inclusion Criteria** • Singleton pregnancies • Painful and regular contractions (≥ 2 contractions at intervals of 10 minutes for at least one hour) • Gestational age of 24 to 34 weeks **Exclusion Criteria** • Women with ruptured membranes • Prior or subsequent cervical cerclage • Pre-eclampsia • Polyhydramnios • Oligohydramnios • Placenta previa		was birth within 7 days of presentation to the labour ward. Definition of pre-term labour Threatened pre-term labour was defined as painful and regular contractions (≥ 2 contractions at intervals of 10 minutes for at least one hour). Active labour was defined by the presence of cervical dilation ≥ 3cm. Use of tocolysis Administration of tocolytic medication was determined by the attending obstetricians, who were blinded to the results of cervical length measurement. Some women received tocolytic medication (see characteristics). **Statistical analysis** No relevant statistical analyses were carried out in relation to the protocol for this review. Likelihood ratios, sensitivities and specificities were calculated by the NCC-WCH technical team.	(179/190) *Calculated by the NCC-WCH technical team.	standard likely to classify the target condition correctly? Yes Was the period between performance of the reference standard and the index test short enough to be reasonably sure that the target condition did not change between the two tests? Yes Did the whole sample or a random selection of the sample receive verification using the reference standard? Yes Did participants receive the same reference standard regardless of the index test result? Yes Was the reference standard independent of the index test?

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
	• Abruptio placenta • Pathological fetal heart rate pattern • Fetal anomalies				(that is, the index test did not form part of the reference standard) Yes Was the execution of the index test described in sufficient detail to permit its replication? No - a reference was provided without a description. Was the execution of the reference standard described in sufficient detail to permit its replication? Yes Were the index test results interpreted without knowledge of the results of the reference standard? Unclear Were the reference standard results interpreted

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					without knowledge of the results of the index test? N/A Were the same clinical data available when the test results were interpreted as would be available when the test is used in practice? Yes Were uninterpretable, indeterminate or intermediate test results reported? N/A Were withdrawals from the study explained? N/A
Full citation Diaz,J., Chedraui,P., Hidalgo,L., Medina,M., The clinical utility of fetal fibronectin in the prediction of pre-term birth in a low socio-economic setting hospital in Ecuador, Journal of Maternal-Fetal and Neonatal Medicine, 22, 89-93, 2009 **Ref Id** 258565 **Country/ies where the study was carried out**	**Sample size** N = 180 **Characteristics** **Mean gestational age at admission, weeks ± SD** Fetal fibronectin positive = 33.1 ± 2.25 Fetal fibronectin positive = 33.4 ± 2.1 P = 0.83 **Nulliparous**	**Tests** **Index test** Fetal fibronectin test with a cut-off of > 50ng/ml for a positive test result. **Reference standard** Birth within 7 days.	**Methods** **Details** Study conducted at high risk pregnancy unit of a teaching hospital. Women with suspected preterm labour were included in the study. At the entry, specimens were collected during the speculum examination from posterior fornix by fetal fibronectin quick check dipstick test. A cut-off of > 50ng/ml was used to	**Results** Total N = 180 Positive fetal fibronectin n = 52 **Birth within 7 days n = 22** Likelihood ratio (positive) = 3.44 (2.36 to 5.01)* Likelihood ratio (negative) = 0.32 (0.16 to 0.64)*	**Limitations** **QUADAS checklist** Was the spectrum of participants representative of the patients who will receive the test in practice? Yes Were selection criteria clearly

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
Ecuador **Study type** Prospective cohort study **Aim of the study** To examine the clinical utility of fFN in predicting pre-term birth in a low socio-economic, non-profit hospital setting. **Study dates** January 2006 to January 2007. **Source of funding** Not specified. Support and technical assistance of Adeza Biomedical was acknowledged.	Fetal fibronectin positive = 22 (42.3%) Fetal fibronectin positive = 62 (48.4%) P = 0.45 **<u>Previous pre-term birth</u>** Fetal fibronectin positive = 12 (23.1%) Fetal fibronectin positive = 18 (14.1%) P = 0.14 **Inclusion Criteria** • Nulliparous • Between 24 and 36 weeks + 6 days gestation • Intact membranes • Singleton • Presence of uterine contractions and cervical changes **Exclusion Criteria** • Confirmed rupture of membranes • Acute fetal distress • Abnormal vaginal bleeding • History of cervical cerclage • Fetal congenital abnormality		determine a positive test result. Women with a positive result were admitted to the antenatal high risk unit and eventually discharged with the treatment. Those with a negative test result were observed for 24 hours and then discharged. Women with the positive and negative result were followed two weeks later. Women with positive test result who become symptomatic again were retested with fetal fibronectin and readmitted if positive. <u>Definition of pre-term labour</u> Not reported. <u>Use of tocoloysis</u> Symptomatic treatment included intravenous antibiotics, tocolysis and corticosteroids. **<u>Statistical analysis</u>** Analysis performed using the EPI-INFO 2000 statistical program. Categorical and continuous data were analysed with the X^2 and non-paired Student's t tests. Fisher extract test was used when the sample size was small.	Sensitivity = 75% (52.9 to 89.4) Specificity = 78.2% (70.7 to 84.2) *Calculated by NCC technical team.	described? Yes Was the reference standard likely to classify the target condition correctly? Yes Was the period between performance of the reference standard and the index test short enough to be reasonably sure that the target condition did not change between the two tests? N/A Did the whole sample or a random selection of the sample receive verification using the reference standard? Yes Did participants receive the same reference standard regardless of the index test result? Yes Was the reference

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
	• Multiple gestation • Having coitus or digitally examination within 24 hours • Cervix dilated > 3 cm				standard independent of the index test? (that is, the index test did not form part of the reference standard) Yes Was the execution of the index test described in sufficient detail to permit its replication? Yes Was the execution of the reference standard described in sufficient detail to permit its replication? Yes Were the index test results interpreted without knowledge of the results of the reference standard? Unclear Were the reference standard results interpreted

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					without knowledge of the results of the index test? N/A Were the same clinical data available when the test results were interpreted as would be available when the test is used in practice? Yes Were uninterpretable, indeterminate or intermediate test results reported? N/A Were withdrawals from the study explained? N/A
Full citation Eroglu,D., Yanik,F., Oktem,M., Zeyneloglu,H.B., Kuscu,E., Prediction of preterm delivery among women with threatened preterm labor, Gynecologic and Obstetric Investigation, 64, 109-116, 2007 **Ref Id** 258436 **Country/ies where the study was carried out**	**Sample size** N = 51 **Characteristics** **Mean age (yrs) ± SD** 27.6 ± 3.5 **Mean parity ± SD** 0.4 ± 0.6 **Spontaneous abortion (≥2)** 2/51 (3.9%)	**Tests** **Index test** A fFN test with an unknown threshold value for a positive result. **Index test** An pIGFBP-1 test with a threshold value	**Methods** **Details** Women with documented contraction frequency > 10/hr were admitted and external tocodynamometry and fetal heart monitoring were performed. A low vaginal culture was taken, then samples for fFN and pIGFBP-1 tests, then ultrasound was performed and lastly a digital	**Results** **fFN test to diagnose birth within 7 days** N = 51 TP: 5 FP: 9 FN: 1 TN: 36 Likelihood ratio (positive) = 4.17 (1.50 to 5.54)* Likelihood ratio (negative) = 0.21 (0.01 to 0.82)*	**Limitations** **QUADAS checklist** Was the spectrum of participant's representative of the patients who will receive the test in practice? Yes Were selection

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
Turkey **Study type** Prospective cohort study **Aim of the study** To estimate the predictive values of fFN, pIFBP-1 in cervicovaginal secretions and cervical length measurement using ultrasound for birth < 35 weeks' gestation in women with uterine contractions. **Study dates** February 2004 to February 2006. **Source of funding** Not reported.	**History of spontaneous pre-term delivery** 2/51 (3.9%) **Mean BMI (kg/m2) ± SD** 22.6 ± 2.9 **Inclusion Criteria** • Singleton pregnancies • Regular uterine contractions (> 10/hr) • Gestational age of 24 to 35 weeks **Exclusion Criteria** • Confirmed ruptured membranes (2 of 3 present of vaginal pooling, positive nitrazine paper, positive ferning) • Uterine abnormalities • Congenital fetal abnormalities • Vaginal bleeding • Sexual intercourse in previous 24hrs • Multiple pregnancy • Placenta previa • Abruptio placentae • Intrauterine growth restriction	of >10µg for a positive result. **Index test** Cervical length ≤ 30mm (Positive) measured using transvaginal ultrasound (TV US). **Reference standard** Delivery within 7 days.	cervical examination was performed. A test kit (Adeza Fetal Fibronectin QuickCheck) for the detection of fFN in vaginal fluid was used. Following sterile speculum insertion, a vaginal fluid specimen from the posterior fornix was obtained using a Dacron swab. A rapid fFN assay was used to analyse the sample for presence of fFN. The primary physician was blinded to results until delivery. A one step dipstick test (Actim Partus test) for the detection of pIGFBP-1 in cervical secretions was used. Following sterile speculum insertion, a cervical secretion specimen from the external os was obtained using a Dacron swab. The specimen was analysed using the dipstick test. The primary physician was blinded to results until delivery. Cervical length measurement was performed using TV US in accordance with a described technique and after the bladder was emptied. An ultrasound probe was placed on the cervix and a proper sagittal image was obtained	Sensitivity = 83.3% (38.9 to 99.1)* Specificity = 80.0% (74.1 to 82.1)* **pIGFBP-1 test to diagnose birth within 7 days** N = 51 TP: 5 FP: 7 FN: 1 TN: 38 Likelihood ratio (positive) = 5.38 (1.83 to 7.37)* Likelihood ratio (negative) = 0.20 (0.01 to 0.77)* Sensitivity = 83.3% (39.2 to 99.1)* Specificity = 84.4% (78.6 to 86.5)* **Cervical length <20mm to diagnose birth within 7 days** N = 51 TP: 4 FP: 2 FN: 2 TN: 43 Likelihood ratio (positive) = 15.00 (2.79 to 78.49)* Likelihood ratio (negative) = 0.35 (0.09 to 0.81)* Sensitivity = 66.7% (27.1 to 91.3)* Specificity = 95.6% (90.3 to 98.8)* Data are also	criteria clearly described? Yes Was the reference standard likely to classify the target condition correctly? Yes Was the period between performance of the reference standard and the index test short enough to be reasonably sure that the target condition did not change between the two tests? Yes Did the whole sample or a random selection of the sample receive verification using the reference standard? The whole sample Did participants receive the same reference standard regardless of the index test result? Yes

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
	• Pre-eclampsia		with the internal os, the cervical canal and the external os being identified. After the image was obtained, the probe was withdrawn slightly to avoid an artificial increase of cervical length as a result of pressure of the transducer against the cervix. A total of three measurements were taken for each woman and the shortest best image was used. The primary physician was blinded to results until delivery. Women were admitted to hospital according to the frequency of contractions or the findings of digital examination of the cervix. On admission women were recommended bed rest and hydrated with 500ml Ringer solution. <u>Definition of pre-term labour</u> Not reported. <u>Use of tocolysis</u> Tocolytic therapy (first line treatment with calcium channel blockers) was started if there was a progressive cervical change documented by the same examiner or if persistent contractions ar least 2 hours after hydration were present. Maternal	presented for diagnosing birth within 7 days using fFN or pIGFBP-1 in women with a cervical length < 20mm and < 25mm. These results are not presented due to the small sample sizes (N = 6 and N = 9 respectively). *Calculated by the NCC-WCH technical team.	Was the reference standard independent of the index test? (that is, the index test did not form part of the reference standard) Yes Was the execution of the index test described in sufficient detail to permit its replication? Yes Were the index test results interpreted without knowledge of the results of the reference standard? Unclear Were the reference standard results interpreted without knowledge of the results of the index test? N/A

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
			corticosteroids were given. No tocolytics or maternal steroids were used after 34 weeks gestation. **Statistical analysis** The Student t test, X^2 test, and Fisher exact test were used to determine whether a statistically significant difference ($p < 0.05$) had occurred between groups.		
Full citation Giles,W., Bisits,A., Knox,M., Madsen,G., Smith,R., The effect of fetal fibronectin testing on admissions to a tertiary maternal-fetal medicine unit and cost savings, American Journal of Obstetrics and Gynecology, 182, 439-442, 2000 **Ref Id** 271080 **Country/ies where the study was carried out** Australia **Study type** Prospective cohort study **Aim of the study** To evaluate whether the introduction of routine fetal fibronecting testing affected costs, transfer rates and direct admissions to a tertiary referral centre.	**Sample size** N = 151 **Characteristics** No characteristics were reported. **Inclusion Criteria** • Women in threatened pre-term labour • Intact membranes **Exclusion Criteria** • Multiple pregnancies • Women with vaginal bleeding • History of sexual intercourse or vaginal examination in the preceding 24 hours	**Tests** **Index test** A positive fetal fibronectin test result defined as > 50ng/ml. **Reference standard** Birth within 7 days of admission.	**Methods** **Details** Women included in the study were also under consideration for inclusion in a randomised controlled trial of nitric oxide tocolysis. The inclusion criteria for this trial were painful uterine contractions, a positive fetal fibronectin result and cervical dilation < 5cm. At initial assessment a sterile vaginal speculum was inserted and a swab for fetal fibronectin was obtained using a Dacron swab from the test kit (Adeza Biomedical) before digital cervical examination. Fetal fibronectin values > 50ng/ml were considered positive. Definition of pre-term labour Not reported.	**Results** Fetal fibronectin positive = 43/45 (95.6%) Fetal fibronectin negative = 49/106 (46.2%) **Fetal fibronectin to diagnose birth within 7 days of admission** Likelihood ratio (positive) = 2.73 (1.75 to 4.23)* Likelihood ratio (negative) = 0.41 (0.20 to 0.87)* Sensitivity = 68.7% (46.0 to 91.5)* (11/16) Specificity = 74.8% (67.5 to 82.1)* (101/135)	**Limitations** **QUADAS checklist** Was the spectrum of participants representative of the patients who will receive the test in practice? Yes Were selection criteria clearly described? Yes Was the reference standard likely to classify the target condition correctly? Yes Was the period between performance of the reference

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
Study dates June 1996 to January 1998. **Source of funding** Supported by the the Australian Commonwealth Government Targeted Institutional Links Grant and the Government Employees Medical Research Fund.	• Cervical dilation < 5cm		<u>Use of tocolysis</u> Administration of tocolytic management was standard practice at the main study centre however not all women were transferred to this centre and not all women at the centre received tocolysis. Blinding of clinicians to fFN results is not reported. **<u>Statistical analysis</u>** No relevant statistical analyses were performed in relation to the protocol for this review. Likelihood ratios, sensitivity, specificity and associated 95% confidence intervals were therefore calculated by the NCC-WCH technical team.	*Calculated by the NCC-WCH technical team.	standard and the index test short enough to be reasonably sure that the target condition did not change between the two tests? Yes Did the whole sample or a random selection of the sample receive verification using the reference standard? Yes Did participants receive the same reference standard regardless of the index test result? Yes Was the reference standard independent of the index test? (that is, the index test did not form part of the reference standard) Yes Was the execution of the index test

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					described in sufficient detail to permit its replication? Yes Was the execution of the reference standard described in sufficient detail to permit its replication? Yes Were the index test results interpreted without knowledge of the results of the reference standard? Unclear Were the reference standard results interpreted without knowledge of the results of the index test? N/A Were the same clinical data available when the test results were interpreted as would be available when

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					the test is used in practice? Unclear - no characteristics except use of tocolysis were reported. Were uninterpretable, indeterminate or intermediate test results reported? N/A Were withdrawals from the study explained? N/A
Full citation Gomez,R., Romero,R., Medina,L., Nien,J.K., Chaiworapongsa,T., Carstens,M., Gonzalez,R., Espinoza,J., Iams,J.D., Edwin,S., Rojas,I., Cervicovaginal fibronectin improves the prediction of preterm delivery based on sonographic cervical length in patients with preterm uterine contractions and intact membranes.[Erratum appears in Am J Obstet Gynecol. 2005 Jul;193(1):308-9], American Journal of Obstetrics and Gynecology, 192, 350-359, 2005 **Ref Id** 258100 **Country/ies where the study was carried out**	**Sample size** N = 215 **Characteristics** **Mean maternal age, years ± SD** 24.7 ± 8.2 **Parity, n/N (%)** Nulliparous = 97/215 (45%) **Previous pre-term delivery, n/N (%)** 28/215 (13%) **Mean gestational age at admission, weeks ± SD** 31.7 ± 2.8	**Tests** **Index test** Cervical length < 15mm or < 30mm or positive fetal fibronectin test result (> 50ng/ml). **Reference standard** Birth within 48 hours or 7 days of presentation.	**Methods** **Details** On admission digital cervical examination was performed to determine dilation and effacement. Endovaginal sonography was performed shortly after admission using a transvaginal probe. Three images were obtained and the shortest value was used in analayses. For fetal fibronectin fluid was collected from the posterior fornix of the vagina before digital and sonographic	**Results** **Cervical length < 15mm to diagnose birth within 48 hours** Likelihood ratio (positive) = 6.74 (3.47 to 10.55)* Likelihood ratio (negative) = 0.39 (0.18 to 0.67)* Sensitivity = 64.7% (40.5 to 83.9)* (11/17) Specificity = 90.4% (88.3 to 92.1)* (179/198) **Cervical length <**	**Limitations** **QUADAS checklist** Was the spectrum of participants representative of the patients who will receive the test in practice? Yes Were selection criteria clearly described? Yes Was the reference standard likely to classify the target condition

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
Chile **Study type** Prospective cohort study **Aim of the study** To determine whether the combined use od fetal fibronectin and transvaginal sonography of cervical length improves prediction of spontaenous pre-term birth in women presenting with uterine contractions and intact membranes. **Study dates** July 1998 to October 2002. **Source of funding** Not reported.	The number of women who received tocolytic medication was not reported. **Inclusion Criteria** • Increased pre-term uterine contractility (3 contractions in 30 minutes) • Intact membranes • Singleton pregnancy • Gestational age between 22 and 35 weeks • Cervical dilation ≤ 3cm determined by digital examination **Exclusion Criteria** Not reported.		examinations. Fetal fibronectin > 50ng/ml was considered to represent a positive test result. Primary outcomes were birth within 48 hours, 7 days, 14 days, ≤ 32 weeks' gestation and ≤ 35 weeks' gestation. Definition of pre-term birth Threatened pre-term labour was defined as 3 uterine contractions in 30 minutes. Actual labour was not formally defined however women with cervical dilation > 3cm were excluded from the study. Use of tocolysis Tocolytic medication was administered to women with persistent uterine contractility for at least 2 hours after intravenous hydration. **Statistical analysis** Likelihood ratios were calculated however no confidence intervals were provided. Sensitivity and specificity were not calculated by study authors therefore these values, their associated 95% confidence intervals and confidence intervals for likelihood ratios were calculated by the NCC-WCH technical team.	**15mm to diagnose birth within 7 days** Likelihood ratio (positive) = 8.73 (4.58 to 15.66)* Likelihood ratio (negative) = 0.42 (0.26 to 0.62)* Sensitivity = 60.7% (43.6 to 75.1)* (17/28) Specificity = 93.0% (90.5 to 95.2)* (174/187) **Cervical length < 30mm to diagnose birth within 48 hours** Likelihood ratio (positive) = 1.88 (1.29 to 2.12)* Likelihood ratio (negative) = 0.22 (0.04to 0.72)* Sensitivity = 88.2% (63.2 to 97.9)* (15/17) Specificity = 53.0% (50.9 to 53.9)* (105/198) **Cervical length < 30mm to diagnose birth within 7 days** Likelihood ratio (positive) = 2.01 (1.53 to 2.25)* Likelihood ratio	correctly? Yes Was the period between performance of the reference standard and the index test short enough to be reasonably sure that the target condition did not change between the two tests? Yes Did the whole sample or a random selection of the sample receive verification using the reference standard? Yes Did participants receive the same reference standard regardless of the index test result? Yes Was the reference standard independent of the index test? (that is, the index test did not form part of the

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
				(negative) = 0.19 (0.05 to 0.53)* Sensitivity = 89.3% (71.8 to 97.2)* (25/28) Specificity = 55.6% (53.0 to 56.8)* (104/187) **Fetal fibronectin > 50ng/ml to diagnose birth within 48 hours** Likelihood ratio (positive) = 2.77 (1.48 to 4.13)* Likelihood ratio (negative) = 0.52 (0.25 to 0.86)* Sensitivity = 58.8% (34.4 to 80.0)* (10/17) Specificity = 78.8% (76.7 to 80.6)* (156/198) **Fetal fibronectin > 50ng/ml to diagnose birth within 7 days** Likelihood ratio (positive) = 3.54 (2.19 to 5.03)* Likelihood ratio (negative) = 0.44 (0.24 to 0.69)* Sensitivity = 64.3% (45.8 to 79.8)* (18/28)	reference standard) Yes Was the execution of the index test described in sufficient detail to permit its replication? Yes Was the execution of the reference standard described in sufficient detail to permit its replication? Yes Were the index test results interpreted without knowledge of the results of the reference standard? Unclear Were the reference standard results interpreted without knowledge of the results of the index test? N/A Were the same

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
				Specificity = 81.8% (79.1 to 84.1)* (153/187) **<u>Cervical length < 15mm plus positive fetal fibronectin to diagnose birth within 48 hours</u>** Likelihood ratio (positive) = 9.06 (3.32 to 22.07)* Likelihood ratio (negative) = 0.62 (0.40 to 0.84)* Sensitivity = 41.2% (20.9 to 61.6)* (7/17) Specificity = 95.5% (93.7 to 97.2)* (189/198) **<u>Cervical length < 15mm plus positive fetal fibronectin to diagnose birth within 7 days</u>** Likelihood ratio (positive) = 20.04 (6.60 to 69.99)* Likelihood ratio (negative) = 0.58 (0.48 to 0.75)* Sensitivity = 42.9% (28.4 to 52.2)* (12/28) Specificity = 97.7%	clinical data available when the test results were interpreted as would be available when the test is used in practice? Yes Were uninterpretable, indeterminate or intermediate test results reported? N/A Were withdrawals from the study explained? N/A **Other information** None.

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
				(95.7 to 99.3)* (183/187) **<u>Cervical length < 30mm plus positive fetal fibronectin to diagnose birth within 48 hours</u>** Likelihood ratio (positive) = 4.16 (2.14 to 6.46)* Likelihood ratio (negative) = 0.48 (0.23 to 0.78)* Sensitivity = 58.8% (34.7 to 79.8)* (10/17) Specificity = 85.9% (83.8 to 87.7)* (170/198) **<u>Cervical length < 30mm plus positive fetal fibronectin to diagnose birth within 7 days</u>** Likelihood ratio (positive) = 5.41 (3.09 to 8.54)* Likelihood ratio (negative) = 0.44 (0.26 to 0.66)* Sensitivity = 60.7% (42.9 to 76.2)* (17/28) Specificity = 88.8% (86.1 to 91.1)*	

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
				(166/187) *Calculated by the NCC-WCH technical team.	
Full citation Gramellini,D., Fieni,S., Kaihura,C., Modena,A.B., Cervical length as a predictor of preterm delivery: gestational age-related percentiles vs fixed cut-offs, Acta Bio-Medica de l Ateneo Parmense, 78, 220-224, 2007 **Ref Id** 270307 **Country/ies where the study was carried out** Italy **Study type** Prospective cohort study **Aim of the study** To assess whether pre-term birth is better predicted by cervical length assessed by sonography using fixed cut-offs or gestational age-specific percentiles. **Study dates** January 2002 to May 2004 **Source of funding** Not reported.	**Sample size** N = 108 **Characteristics** **Median maternal age, years (range)** 32 (17 to 41) **Median gestational age at admission, weeks (range)** 29 (20 to 33) **Nulliparous, n/N (%)** 41/108 (37.9%) **Ethnic origin, n/N (%)** Caucasian = 100/108 (92.5%) African = 5/108 (4.6%) Other = 3/108 (2.7%) **Use of tocolysis, n/N (%)** 70/108 (64.8%) The number of women with previous pre-term birth was not reported. **Inclusion Criteria** • Suspected pre-term labour (≥ 4 painful uterine contractions	**Tests** **Index test** Cervical length < 15mm or < 25mm as determined by transvaginal sonography at admission. **Reference standard** Birth within 7 days of presentation.	**Methods** **Details** All women hospitalised during the study period with suspected pre-term labour were given transvaginal sonography to determine cervical length. Three consecutive measurements were obtained and an average taken for use in analysis. Cut-offs of 15mm and 25mm were chosen for cervical length based on the results of two previous systematic reviews. Definition of pre-term labour Suspected pre-term labour was defined as ≥ 4 painful uterine contractions every 20 minutes. Actual pre-term labour was defined as cervical dilation ≥ 3cm. Use of tocolysis Administration of tocolytic medication was based on the results of digital cervical examination. Medical staff were blinded to the results of	**Results** **Cervical length < 15mm to diagnose birth within 7 days of presentation** Likelihood ratio (positive) = 5.86 (1.46 to 24.29)* Likelihood ratio (negative) = 0.77 (0.61 to 0.96)* Sensitivity = 26.3% (11.2 to 39.7)* (5/19) Specificity = 95.5% (92.3 to 98.4)* (85/89) **Cervical length < 25mm to diagnose birth within 7 days of presentation** Likelihood ratio (positive) = 3.22 (1.77 to 5.00)* Likelihood ratio (negative) = 0.42 (0.20 to 0.73)* Sensitivity = 66.6% (45.7 to 83.3)* (14/21) Specificity = 79.3%	**Limitations** **QUADAS checklist** Was the spectrum of participants representative of the patients who will receive the test in practice? Yes Were selection criteria clearly described? Yes Was the reference standard likely to classify the target condition correctly? Yes Was the period between performance of the reference standard and the index test short enough to be reasonably sure that the target condition did not change between

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
	every 20 minutes) **Exclusion Criteria** • Twin pregnancies • Pregnancies in which gestational age could not be determined using sonography before 22 weeks' gestation • Premature rupture of membranes • Cervical dilation ≥ 3cm at digital examination • Active vaginal bleeding • Placenta previa • Cervical cerclage • Maternal or fetal indications of pre-term birth		transvaginal sonography. Women who did not receive tocolysis were put to bed rest. **<u>Statistical analysis</u>** Sensitivity and specificity were calculated for cervical length < 15mm to diagnose birth within 7 days. Confidence intervals for sensitivity and specificity and likelihood ratios were not provided therefore were calculated by the NCC-WCH technical team.	(74.2 to 83.3)* (69/87) *Calculated by the NCC-WCH technical team.	the two tests? Yes Did the whole sample or a random selection of the sample receive verification using the reference standard? Yes Did participants receive the same reference standard regardless of the index test result? Yes Was the reference standard independent of the index test? (that is, the index test did not form part of the reference standard) Yes Was the execution of the index test described in sufficient detail to permit its replication? Yes Was the execution of the

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					reference standard described in sufficient detail to permit its replication? Yes Were the index test results interpreted without knowledge of the results of the reference standard? Unclear Were the reference standard results interpreted without knowledge of the results of the index test? N/A Were the same clinical data available when the test results were interpreted as would be available when the test is used in practice? No - history of previous pre-term birth was not reported. Were

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					uninterpretable, indeterminate or intermediate test results reported? N/A Were withdrawals from the study explained? N/A
Full citation Holst,R.M., Jacobsson,B., Hagberg,H., Wennerholm,U.B., Cervical length in women in preterm labor with intact membranes: relationship to intra-amniotic inflammation/microbial invasion, cervical inflammation and preterm delivery, Ultrasound in Obstetrics and Gynecology, 28, 768-774, 2006 **Ref Id** 270320 **Country/ies where the study was carried out** Sweden **Study type** Prospective cohort study **Aim of the study** To investigate the relationship between cervical length determined by transvaginal sonography and spontaneous pre-term birth within 7 days of sampling or ≤ 34 weeks' gestation. **Study dates**	**Sample size** N = 55 **Characteristics** Data reported are based on all 87 women enrolled in the study. The final population used in analyses was only 55 women. **Median maternal age, years (range)** 29 (19 to 43) **Nulliparous, n/N (%)** 53/87 (61%) **Previous pre-term birth, n/N (%)** 17/87 (20%) **Median gestational age at admission, weeks (range)** 30+6 (23+1 to 33+5) The number of women who received tocolytic medication and the number of multiple births was not reported.	**Tests** Index test Cervical length ≤ 15mm determined by transvaginal sonography. Reference standard Birth within 7 days of presentation.	**Methods** **Details** Gestational age was determined by routine ultrasound during the second trimester (16 to 19 weeks' gestation). Three women had gestational age determined using menstrual history. Cervical length measurement by transvaginal ultrasound involved taking three measurements with the shortest value recorded. Primary outcomes were birth within 7 days or pre-term birth ≤ 34 weeks' gestation. Definition of pre-term labour Painful and regular uterine contractions every 10 minutes for at least 30 minutes alongside one of the following cervical changes (assessed by digital cervical examination) and/or cervical length ≤ 30mm	**Results** **Cervical length < 15mm to diagnose birth within 7 days** Likelihood ratio (positive) = 4.32 (1.88 to 11.04)* Likelihood ratio (negative) = 0.34 (0.18 to 0.63)* Sensitivity = 72% (56 to 63) (18/25) Specificity = 83% (70 to 93) (25/30) *Calculated by the NCC-WCH technical team.	**Limitations** **QUADAS checklist** Was the spectrum of participants representative of the patients who will receive the test in practice? Yes Were selection criteria clearly described? Yes Was the reference standard likely to classify the target condition correctly? Yes Was the period between performance of the reference standard and the index test short enough to be

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
1996 to 2001. **Source of funding** Supported by the Swedish Medical Research Council, The Göteborg Medical Society, The Frimurare Barnhus Foundation and by Swedish government grants.	**Inclusion Criteria** • Women who presented at a gestational age of 22 and 33+6 weeks • Intact membranes **Exclusion Criteria** • Pre-term rupture of membranes • Known uterine malformations • Fetal malformations • Significant vaginal bleeding • Imminent birth • Cervical cerclage • Fetal distress		measured by transvaginal ultrasound: • ≤ 2cm length + ≥ 1cm dilation • ≤ 2cm length + cervical softening • ≥ 1cm dilation + cervical softening Use of tocolysis Tocolytic medication was administered according to local management protocols. **Statistical analysis** Sensitivity and specificity were calculated for diagnosis of spontaneous pre-term birth within 7 days for different cervical lengths. Positive and negative likelihood ratios were not provided therefore were calculated by the NCC-WCH technical team. ROC curves were used to define the best cut-off for cervical length (15mm) in relation to birth within 7 days.		reasonably sure that the target condition did not change between the two tests? Yes Did the whole sample or a random selection of the sample receive verification using the reference standard? Yes Did participants receive the same reference standard regardless of the index test result? Yes Was the reference standard independent of the index test? (that is, the index test did not form part of the reference standard) Yes Was the execution of the index test described in sufficient detail to permit its

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					replication? Yes Was the execution of the reference standard described in sufficient detail to permit its replication? Yes Were the index test results interpreted without knowledge of the results of the reference standard? Unclear Were the reference standard results interpreted without knowledge of the results of the index test? N/A Were the same clinical data available when the test results were interpreted as would be available when the test is used in practice? Yes

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					Were uninterpretable, indeterminate or intermediate test results reported? N/A Were withdrawals from the study explained? Yes
Full citation Iams,J.D., Casal,D., McGregor,J.A., Goodwin,T.M., Kreaden,U.S., Lowensohn,R., Lockitch,G., Fetal fibronectin improves the accuracy of diagnosis of preterm labor, American Journal of Obstetrics and Gynecology, 173, 141-145, 1995 **Ref Id** 258249 **Country/ies where the study was carried out** Canada **Study type** Prospective cohort study **Aim of the study** To assess the utility of cervicovaginal expression of fetal fibronectin in the diagnosis of pre-term labour. **Study dates** Not reported.	**Sample size** N = 192 **Characteristics** **Race** White = 48% Black = 16% Hispanic = 31% Asian = 5% **Parity** Multiparous 71% **Mean age** 25 (SD 6 years) **Inclusion Criteria** • Between 24 and 34 weeks gestation • Symptoms of pre-term labour **Exclusion Criteria**	**Tests** **Index test** Fetal fibronectin test with a cut-off of > 50ng/ml for a positive test result. **Reference standard** Birth within 7 days.	**Methods** **Details** Study was conducted in five tertiary care university hospitals. Women with confirmed rupture of membranes were excluded from the study. The diagnosis of ruptured membranes was made by presence of two of three standard test; finding of pH ≥ 7, fern pattern of dried fluid, and vaginal pooling of amniotic fluid. Two vaginal specimens were collected for the fetal fibronectin assay, one from external os and the second form posterior fornix of vagina, using Dacron swab. The probe was analysed by an enzyme-linked immunosorbent that uses the murine monoclonal antibody FDC-6. Result reported as either positive (≥ 50ng/mL) or negative (< 50ng/mL). Adherence to the clinical	**Results** Total N = 194 Positive fetal fibronectin n = 45 **Birth within 7 days n = 14** Likelihood ratio (positive) = 5.17 (3.66 to 7.30)* Likelihood ratio (negative) = 0.09 (0.01 to 0.58)* Sensitivity = 93% (66 t0 99.8)* Specificity = 82% (75.5 to 87.3)* *Calculated by the NCC-WCH technical team.	**Limitations** **QUADAS checklist** Was the spectrum of participants representative of the patients who will receive the test in practice? Yes Were selection criteria clearly described? Yes Was the reference standard likely to classify the target condition correctly? Yes Was the period between performance of the reference standard and the index test short

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
Source of funding Not reported.	• Confirmed rupture of membranes • Cervical dilation ≥ 3cm • Presence of cervical cerclage • placenta previa • Uterine abnormalities		pathway was at the discretion of the practitioner. <u>Definition of pre-term labour</u> Suspected pre-term labour was defined as the presence uterine activity, abdominal discomfort, change in vaginal discharge, bleeding, cramping and suspected amniorrhexis. <u>Use of tocoloysis</u> Rate of tocolysis rate was 55.6 % in fetal fibronectin positive group and 40.8% in fetal fibronectin negative group. **<u>Statistical analysis</u>** Multivariate statistical analyses with stepwise logistic regression were performed.		enough to be reasonably sure that the target condition did not change between the two tests? N/A Did the whole sample or a random selection of the sample receive verification using the reference standard? Yes Did participants receive the same reference standard regardless of the index test result? Yes Was the reference standard independent of the index test? (that is, the index test did not form part of the reference standard) Yes Was the execution of the index test described in sufficient detail to

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					permit its replication? Yes Was the execution of the reference standard described in sufficient detail to permit its replication? Yes Were the index test results interpreted without knowledge of the results of the reference standard? Unclear Were the reference standard results interpreted without knowledge of the results of the index test? N/A Were the same clinical data available when the test results were interpreted as would be available when the test is used in practice? Yes

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					Were uninterpretable, indeterminate or intermediate test results reported? N/A Were withdrawals from the study explained? N/A **Other information** None.
Full citation Kwek,K., Khi,C., Ting,H.S., Yeo,G.S., Evaluation of a bedside test for phosphorylated insulin-like growth factor binding protein-1 in preterm labour, Annals of the Academy of Medicine, Singapore, 33, 780-783, 2004 **Ref Id** 258208 **Country/ies where the study was carried out** Singapore **Study type** Prospective cohort study **Aim of the study** To evaluate the efficacy of a bedside pIGFBP-1 test kit in predicting premature birth in	**Sample size** N = 42 (5 women were lost to follow up for the specified outcomes out of the full cohort of 47). **Characteristics** pIGFBP-1 positive group n=18 pIGFBP-1 negative group n=29 **Median maternal age (years) (range)** pIGFBP-1 positive group = 25.5 (17-39) pIGFBP-1 negative group = 29.0 (20-40) **Median gestation at admission (weeks) (range)** pIGFBP-1 positive group = 31.5 (23-33) pIGFBP-1 negative group =	**Tests** **Index test** A pIGFBP-1 test with an unknown theshold value for a positive result. **Reference standard** Birth within 2 days or within 7 days.	**Methods** **Index test** A bedside test kit (Actim) for the detection of pIGFBP-1 in cervical secretions was used. A cervical secretion specimen was obtained by applying a Dacron swab gently to the cervix. The swab was placed in extraction solution, mixed and removed. The test strip was placed in the solution. After 3 minutes, a negative result appeared as a single blue line and a positive result was apparent as two blue lines. The cut off values for the test are not reported. A single operator conducted all the tests. Definition of pre-term labour	**Results** **pIGFBP-1 test to diagnose birth within 2 days** N = 42 TP: 4 FP: 14 FN: 2 TN: 22 Likelihood ratio (positive) = 1.71 (0.56 to 2.73)* Likelihood ratio (negative) = 0.54 (0.09 to 1.37)* Sensitivity = 66.7% (25.5 to 93.8)* Specificity = 61.1% (54.2 to 65.6)* **pIGFBP-1 test to diagnose birth within 7 days** N = 42 TP: 10 FP: 8 FN: 2 TN: 22	**Limitations** **QUADAS checklist** Was the spectrum of participant's representative of the patients who will receive the test in practice? Yes Were selection criteria clearly described? Yes Was the reference standard likely to classify the target condition correctly? Yes Was the period

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
symptomatic women. **Study dates** Not reported. **Source of funding** Not reported.	31.0 (24-33) **<u>Nulliparous</u>** pIGFBP-1 positive group = 9/18 (50%) pIGFBP-1 negative group = 18/29 (62.1%) **Inclusion Criteria** • Suspected pre-term labour requiring tocolysis • Between 23 and 33 weeks amenorrhoea **Exclusion Criteria** • Ruptured membranes • Antepartum haemorrhage • Multiple pregnancies • Cervical dilatation ≥ 3cm • Cervical cerclage • Any contraindication to tocolysis		Complaints of regular intermittent painful contractions occuring at least 1 per 10 mins with regular uterine activity on cardiotocographic monitoring in women with 23 to 33 weeks' amenorrhoea. <u>Use of tocolysis</u> All women received tocolysis and antenatal steroids according to existing protocols and the decision to treat was mae prior to pIGFBP-1 testing. 46 women received tocolysis with IV salbutamol. **<u>Statistical analysis</u>** Continuous variables were compared using the Mann Whitney U test and prorportions using the X^2 test. $P < 0.05$ was considered statistically significant.	Likelihood ratio (positive) = 3.12 (1.476 to 4.56)* Likelihood ratio (negative) = 0.23 (0.04 to 0.71)* Sensitivity = 83.3% (55.6 to 96.9)* Specificity = 73.3% (62.2 to 78.8)* *Calculated by NCC-WCH technical team.	between performance of the reference standard and the index test short enough to be reasonably sure that the target condition did not change between the two tests? Yes Did the whole sample or a random selection of the sample receive verification using the reference standard? The whole sample Did participants receive the same reference standard regardless of the index test result? Yes Was the reference standard independent of the index test? (that is, the index test did not form part of the reference standard) Yes

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					Was the execution of the index test described in sufficient detail to permit its replication? Yes Were the index test results interpreted without knowledge of the results of the reference standard? Unclear Were the reference standard results interpreted without knowledge of the results of the index test? N/A
Full citation LaShay,N., Gilson,G., Joffe,G., Qualls,C., Curet,L., Will cervicovaginal interleukin-6 combined with fetal fibronectin testing improve the prediction of preterm delivery?, Journal of Maternal-Fetal Medicine, 9, 336-341, 2000 **Ref Id** 258676	**Sample size** N = 135 **Characteristics** **Mean gestational age at admission, weeks ± SD** 30.5 ± 3.0 No significant differences observed between study sites in maternal age, parity, prior	**Tests** **Index test** Fetal fibronectin test with a cut-off of > 50ng/ml for a positive test result. **Reference standard** Birth within 7	**Methods** **Details** Study was conducted in two tertiary medical centres in New Mexico. A sterile speculum examination was performed for all women who met the inclusion criteria. Specimen was obtained using Dacron swab. Two vaginal swabs were placed in the	**Results** Total N = 48 Total positive fetal fibronectin n = not reported **Birth within ≤ 48 hours n = 4** Sensitivity = 75% Specificity = 88% OR = 17.86 (95% CI	**Limitations** **QUADAS checklist** Was the spectrum of participants representative of the patients who will receive the test in practice? Yes

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
Country/ies where the study was carried out United States of America **Study type** Prospective cohort study **Aim of the study** To investigate if determination of cervicovaginal interleukin-6 (IL-6) levels would enhance the positive predictive value of fetal fibronectin (fFN) for pre-term birth. **Study dates** Not reported. **Source of funding** Not reported.	preterm birth and mode of birth. No further details were reported. **Inclusion Criteria** • Between 24 and 34 weeks • Intact membranes **Exclusion Criteria** • Confirmed rupture of membranes • Multiple gestations • Vaginal bleeding of unknown cause • A major fetal anomaly • Cervical dilation ≥ 3cm • Presence of cervical cerclage • Hypertention • Placenta previa • Polyhydraminous • Cervical manipulation within the previous 24 hours (intercourse, vaginal examination, vaginal ultrasonic scan)	days of presentation.	endo-cervix/posterior fornix of vagina for 15 seconds to achieve saturation,. The probe was analysed by an enzyme-linked immunosorbent assay (fetal fibronectin enzyme immunoassay, Adeza Sunnyvale, CA). Result reported as either positive (≥ 50ng/mL) or negative (< 50ng/mL). Definition of pre-term labour Suspected pre-term labour was defined as the presence uterine contraction (at least 4 per 20 min interval or 8 times per hour) dilatation of cervix at least 1 cm with 50% effacement on initial examination and cervical changes of effacement and dilatation 2 hours later. Use of tocoloysis Used at the discretion of the practitioner. **Statistical analysis** Receiver operator characteristic (ROC) analysis was utilised to compare the significant area under the curve.	1.97 to 166) p = 0.009 **Birth within 7 days n = 5** Sensitivity = 67% Specificity = not reported OR = 11.9 (95% CI 2.36 to 58.82) p = 0.004 No adequate data were reported to calculate other diagnostic accuracy features.	Were selection criteria clearly described? Yes Was the reference standard likely to classify the target condition correctly? Yes Was the period between performance of the reference standard and the index test short enough to be reasonably sure that the target condition did not change between the two tests? N/A Did the whole sample or a random selection of the sample receive verification using the reference standard? Yes Did participants receive the same reference standard regardless of the index test result? Yes

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					Was the reference standard independent of the index test? (that is, the index test did not form part of the reference standard) Yes Was the execution of the index test described in sufficient detail to permit its replication? Yes Was the execution of the reference standard described in sufficient detail to permit its replication? Yes Were the index test results interpreted without knowledge of the results of the reference standard? Unclear Were the reference

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					standard results interpreted without knowledge of the results of the index test? N/A Were the same clinical data available when the test results were interpreted as would be available when the test is used in practice? Yes Were uninterpretable, indeterminate or intermediate test results reported? N/A Were withdrawals from the study explained? N/A **Other information** Unclear if clinicians were blinded to the result of the test.
Full citation Lembet,A., Eroglu,D., Ergin,T., Kuscu,E.,	**Sample size** N = 36	**Tests** **Index test** A pIGFBP-1 test	**Methods** **Details** Women with documented	**Results** **pIGFBP-1 test to diagnose birth**	**Limitations** **QUADAS checklist**

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
Zeyneloglu,H., Batioglu,S., Haberal,A., New rapid bed-side test to predict preterm delivery: phosphorylated insulin-like growth factor binding protein-1 in cervical secretions, Acta Obstetricia et Gynecologica Scandinavica, 81, 706-712, 2002 **Ref Id** 258386 **Country/ies where the study was carried out** Turkey **Study type** Prospective cohort study **Aim of the study** To assess whether detection of pIGFBP-1 using a bedside test could be used to predict pre-term birth in patients with regular uterine contractions. **Study dates** July 2000 to July 2001. **Source of funding** Not reported.	**Characteristics** pIGFBP-1 positive group n=18 pIGFBP-1 negative group n=18 **Mean maternal age (years) ± SD** pIGFBP-1 positive group = 26.9 ± 6.8 pIGFBP-1 negative group = 29.9 ± 4.1 **Mean gestation at admission (weeks) ± SD** pIGFBP-1 positive group = 32.4 ± 3.5 pIGFBP-1 negative group = 29.8 ± 2.5 **Mean gravidity ± SD** pIGFBP-1 positive group = 2.0 ± 1.5 pIGFBP-1 negative group = 2.4 ± 1.7 **BMI >26kg/m^2** pIGFBP-1 positive group = 14/18 (77.8%) pIGFBP-1 negative group = 15/18 (83.3%) **Previous preterm birth** pIGFBP-1 positive group = 5/18 (25%) pIGFBP-1 negative group = 2/18 (9.1%) **Inclusion Criteria**	with a threshold value of 30-50 µgrams/l for a positive result. **Reference standard** Birth within 48 hours or within 7 days.	contraction frequency >10/hr were admitted and external tocodynamometry and fetal heart monitoring were performed. A low vaginal culture was taken, then a sample for pIGFBP-1 testing was obtained, followed by a digital cervical examination. A one step dipstick test (Actim Partus test) for the detection of pIGFBP-1 in cervical secretions was used. Following sterile speculum insertion, a cervical secretion specimen from the external os was obtained using a Dacron swab. The swab was placed in extraction solution, mixed and removed. The bottom of the dipstick was placed in the solution, then removed after 20s. The dipstick was placed horizontally. A negative result appeared as a single blue line and a positive result was apparent as two blue lines. If there were no visible lines then then test was judged not to have worked properly.The test was performed by a member of staff not directly related to the patient's care. The primary physician was blinded to results until delivery. On admission women were recommended bed rest and	**within 48 hours** N = 36 TP: 14 FP: 4 FN: 1 TN: 17 Likelihood ratio (positive) = 4.90 (2.12 to 6.85)* Likelihood ratio (negative) = 0.08 (0.004 to 0.42)* Sensitivity = 93.3% (72.3 to 99.6)* Specificity = 81.0% (65.9 to 85.5)* **pIGFBP-1 test to diagnose birth within 7 days** N = 36 TP: 15 FP: 3 FN: 1 TN: 17 Likelihood ratio (positive) = 6.25 (2.43 to 9.71)* Likelihood ratio (negative) = 0.07 (0.004 to 0.37)* Sensitivity = 93.8% (74.3 to 99.7)* Specificity = 85.0% (69.4 to 87.9)* *Calculated by the NCC-WCH technical team.	Was the spectrum of participant's representative of the patients who will receive the test in practice? Yes Were selection criteria clearly described? Yes, although it is unclear if any or how many women did not have intact membranes Was the reference standard likely to classify the target condition correctly? Yes Was the period between performance of the reference standard and the index test short enough to be reasonably sure that the target condition did not change between the two tests? Yes Did the whole sample or a random selection

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
	• Symptoms suggestive of pre-term labour (regular uterine contractions > 10/hour) • Gestational ages between 20 and 36 weeks Intact membranes are not specified in the inclusion criteria. **Exclusion Criteria** • Multiple gestations • Uterine anomalies • Congenital fetal abnormalities • Vaginal bleeding • Sexual intercourse in previous 24hrs • Intrauterine growth retardation • Pre-eclampsia Rupture of membranes is not specified in the exclusion criteria.		hydrated with 500ml Ringer solution. Definition of pre-term labour Not reported. Use of tocolysis Tocolytic therapy (first line treatment with magnesium sulphate) was started if there was a progressive cervical change documented by the same examiner and contractions persisted. Maternal corticosteroids were given as necessary over 24 weeks gestation. **Statistical analysis** The Student's t test, X^2 test, and Fisher exact test were used to determine whether a statistically significant difference ($p < 0.05$) had occurred between groups.		of the sample receive verification using the reference standard? The whole sample Did participants receive the same reference standard regardless of the index test result? Yes Was the reference standard independent of the index test? (that is, the index test did not form part of the reference standard) Yes Was the execution of the index test described in sufficient detail to permit its replication? Yes Were the index test results interpreted without knowledge of the results of the

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					reference standard? Unclear Were the reference standard results interpreted without knowledge of the results of the index test? N/
Full citation Lukes,A.S., Thorp,J.M.,Jr., Eucker,B., Pahel-Short,L., Predictors of positivity for fetal fibronectin in patients with symptoms of preterm labor, American Journal of Obstetrics and Gynecology, 176, 639-641, 1997 **Ref Id** 258447 **Country/ies where the study was carried out** United States of America **Study type** Prospective cohort study **Aim of the study** To examine diagnostic accuracy of fetal fibronectin immunoassays at identifying patients at risk for pre-term birth. **Study dates** Not reported.	**Sample size** N = 763 **Characteristics** **Mean maternal age** 24.2 years **Race** 40% white **Gravidity** 29% primigravid **History of previous premature infants** 15% **Sexual activity within 24 hours of sample collection** n = 66/763 (9%) **Cervical examination within 24 hours of sample collection** n = 107/763 (14%) **Vaginal bleeding**	**Tests** **Index test** Fetal fibronectin test with a cut-off of > 50ng/ml for a positive test result. **Reference standard** Birth within 7 days of presentation.	**Methods** **Details** The study conducted in 11 hospitals across the United States. A specimen was obtained using speculum examination by using a Dacron swab. Speculum examination performed before the digital examination. The result was processed using ELISA rapid assay. A cut-off of > 50ng/mL was used to determine a positive test result. Definition of pre-term labour Symptoms suggested of pre-term labour were including regular contractions, low abdominal cramping, low back pain, vaginal bleeding, or increased vaginal discharge. Use of tocolytics 10/11 participating hospitals	**Results** Total N = 763 Positive fetal fibronectin n = 150 (19.6%) **Birth within 7 days, n = 22** Likelihood ratio (positive) = 4.89 (3.89 to 6.18)* Likelihood ratio (negative) = 0.17 (0.06 to 0.47)* Sensitivity = 82.3% (79.3 to 97)* Specificity = 82.31% (79.3 to 85) *Calculated by the NCC-WCH technical team. Result from logistic regression analysis indicates that five variables (uterine	**Limitations** **QUADAS checklist** Was the spectrum of participants representative of the patients who will receive the test in practice? Yes Were selection criteria clearly described? Yes Was the reference standard likely to classify the target condition correctly? Yes Was the period between performance of the reference standard and the

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
Source of funding Not reported.	n = 118/759 (16%) **<u>Uterine contractions</u>** n = 192/750 (26% with three or more in 1 hour) **<u>Cervical dilatation</u>** n = 94/763 (12% with dilatation between 1 and 3 cm) **<u>Estimated gestational age at sampling</u>** Mean = 30 weeks 2 days **Inclusion Criteria** • Between 24 and 34 weeks 6 days' gestation • Intact membranes • Symptoms of pre-term labour • Cervical dilation < 3cm **Exclusion Criteria** Not reported.		used tocolytic therapy. **<u>Statistical analysis</u>** A logistic regression model was used to detect the simultaneous effects of multiple variables on predicting positive fetal fibronectin immunoassay. Independent variables included were women age, race, gravidity, history of previous premature infants, sexual activity within 24 hours of sample collection, cervical examination within 24 hours of sample collection, vaginal bleeding, uterine contractions, cervical dilatation (< 1cm or between 1 and 3cm), estimated gestational age. Uterine contractions were measured by external tocodynometry. Two variables, tocolysis and investigational site, were tested for the potential confounders.	contraction, cervical dilatation, intercourse, cervical examination, vaginal bleeding) were found to be significantly predictive of positive fetal fibronectin.	index test short enough to be reasonably sure that the target condition did not change between the two tests? N/A Did the whole sample or a random selection of the sample receive verification using the reference standard? Yes Did participants receive the same reference standard regardless of the index test result? Yes Was the reference standard independent of the index test? (that is, the index test did not form part of the reference standard) Yes Was the execution of the index test described in

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					sufficient detail to permit its replication? Yes Was the execution of the reference standard described in sufficient detail to permit its replication? Yes Were the index test results interpreted without knowledge of the results of the reference standard? Unclear Were the reference standard results interpreted without knowledge of the results of the index test? N/A Were the same clinical data available when the test results were interpreted as would be available when the test is used in

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					practice? Yes Were uninterpretable, indeterminate or intermediate test results reported? N/A Were withdrawals from the study explained? N/A
Full citation Malak,T.M., Sizmur,F., Bell,S.C., Taylor,D.J., Fetal fibronectin in cervicovaginal secretions as a predictor of preterm birth, British Journal of Obstetrics and Gynaecology, 103, 648-653, 1996 **Ref Id** 258253 **Country/ies where the study was carried out** United Kingdom **Study type** Prospective cohort study **Aim of the study** To investigate the reliability of fetal fibronectin detection as a predictor of pre-term birth (< 37 weeks' gestation) in women with symptoms suggestive of pre-term labour. **Study dates**	**Sample size** N = 141 **Characteristics** **Mean maternal age, years ± SE** Positive fetal fibronectin = 23.7 ± 1.5 Negative fetal fibronectin = 24.9 ± 0.6 **Primiparity, %** Positive fetal fibronectin = 42.8% Negative fetal fibronectin = 37.9% **Mean gestational age at sampling, days ± SE** Positive fetal fibronectin = 218.4 ± 3.7 Negative fetal fibronectin = 210.1 ± 2.1 Previous pre-term births were	**Tests** **Index test** Fetal fibronectin test with a cut-off of > 50ng/ml for a positive test result. **Reference standard** Birth within 7 days of admission.	**Methods** **Details** Upon admission a speculum examination was performed to assess cervical dilation and rupture of membranes. During this examination a swab was taken from the ectocervix and posterior fornix to determine fetal fibronectin. Women were followed up until birth. Clinicians were blinded to the results of the fetal fibronectin test. Definition of pre-term labour Definition included the following symptoms: painful uterine contractions or abdominal cramps and pelvic pressure with back ache. Use of tocolysis	**Results** **Birth within 7 days n = 10** Likelihood ratio (positive) = 8.16 (4.2 to 15.9)* Likelihood ratio (negative) = 0.22 (0.06 to 0.77)* Sensitivity = 80% (44.4 to 96.9)* (8/10) Specificity = 90.2% (82.7 to 95.2)* (92/102) *Calculated by the NCC-WCH technical team	**Limitations** **QUADAS checklist** Was the spectrum of participants representative of the patients who will receive the test in practice? Yes Were selection criteria clearly described? Yes Was the reference standard likely to classify the target condition correctly? Yes Was the period between performance of

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
Not reported. **Source of funding** Supported by Wellbeing. Fetal fibronectin tests were supplied as a gift by Mast Diagnostic.	not reported nor was the number of women who received tocolytic medication. **Inclusion Criteria** • Singleton pregnancies • Gestational age between 24 and 37 weeks • Symptoms of pre-term labour • No history of ruptured membranes **Exclusion Criteria** • Placenta previa • The presence of any blood on speculum examination • Sexual intercourse in the preceding 24 hours		The use of tocolytic medication was determined by the attending physician. **Statistical analysis** Sensitivity and specificity were calculated by the study authors however no confidence intervals were provided. Likelihood ratios, sensitivity, specificity and their associated 95% confidence intervals were therefore calculated by the NCC-WCH technical team.		the reference standard and the index test short enough to be reasonably sure that the target condition did not change between the two tests? Yes Did the whole sample or a random selection of the sample receive verification using the reference standard? Yes Did participants receive the same reference standard regardless of the index test result? Yes Was the reference standard independent of the index test? (that is, the index test did not form part of the reference standard) Yes Was the execution of the

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					index test described in sufficient detail to permit its replication? Yes Was the execution of the reference standard described in sufficient detail to permit its replication? Yes Were the index test results interpreted without knowledge of the results of the reference standard? Unclear Were the reference standard results interpreted without knowledge of the results of the index test? N/A Were the same clinical data available when the test results were interpreted as would be

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					available when the test is used in practice? Yes Were uninterpretable, indeterminate or intermediate test results reported? N/A Were withdrawals from the study explained? N/A
Full citation McKenna,D.S., Chung,K., Iams,J.D., Effect of digital cervical examination on the expression of fetal fibronectin, Journal of Reproductive Medicine, 44, 796-800, 1999 **Ref Id** 270472 **Country/ies where the study was carried out** United States of America **Study type** Prospective cohort study **Aim of the study** To determine the effect of a single digital cervical examination on the results of fetal fibronectin (fFN) expression in women symptomatic of pre-term labour.	**Sample size** N = 50 **Characteristics** **History of previous spontaneous pre-term birth** Frequency = 30% (15/50) **Mean gestational age, weeks ± SD** Sampling = 29.3 ± 2.0 At birth = 36.3 ± 0.8 **Ethnicity** Caucasian = 62% African American = 38% Parity, the proportion of women having multiple births and the number of women who received tocolytic medication were not reported.	**Tests** **Index test** A fetal fibronectin test with a cut-off of > 50ng/ml for a positive test result. **Reference test** Birth ≤ 7 days.	**Methods** **Protocol** fFN samples were routinely collected from all women who present to the study centre with signs or symptoms of pre-term labour. Samples were obtained using speculum examination and a swab of the posterior fornix of the vagina and external cervical os. Following the initial fFN test a digital cervical examination was performed. Consent was then obtained to perform a repeat fFN test. The repeat test was performed within 1 to 3 hours of the initial fFN test. If women remained hospitalised, did not give birth and did not have an	**Results** **Birth ≤ 7 days (fFN before cervical examination)** Likelihood ratio (positive) = 3.83 (1.32 to 3.83)* Likelihood ratio (negative) = 0.00 (0.00 to 0.85)* Sensitivity = 100.0% (41.1 to 100.0)* (4/4) Specificity = 73.9% (68.8 to 73.9)* (34/46) **Birth ≤ 7 days (fFN after cervical examination)** Likelihood ratio (positive) = 2.16	**Limitations** **QUADAS checklist** Was the spectrum of participants representative of the patients who will receive the test in practice? Yes Were selection criteria clearly described? Yes Was the reference standard likely to classify the target condition correctly? Yes Was the period between

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
Study dates February to December 1997. **Source of funding** Supported by Adeza Biomedical.	**Inclusion Criteria** • Women aged between 18 and 45 years • Gestational ages between 22 and 34 weeks • Symptoms of pre-term labour (undefined) **Exclusion Criteria** • Women who had digital cervical examination, endovaginal ultrasound or coitus within the previous 24 hours • Confirmed rupture of membranes • Known untreated cervical infection • Cervical dilation ≥ 3cm • Presence of cervical cerclage • Uterine abnormalities • Placenta previa or abruptio placentae		additional cervical examination a third fFN test was performed approximately 24 hours after the initial test. Assays for fFN were performed using ELISA. A cut-off of > 50ng/ml was used to determine a positive test result. Characteristics were obtained using patient charts and telephone interviews. <u>Definition of pre-term labour</u> Not reported. <u>Use of tocolysis</u> Not reported. **<u>Statistical analysis</u>** Sensitivity, specificity, positive predictive value and negative predictive value were calculated for birth ≤ 7 days for fFN test results before and after cervical examination.	(0.58 to 3.02)* Likelihood ratio (negative) = 0.38 (0.02 to 1.27)* Sensitivity = 75.0% (22.7 to 98.7)* (3/4) Specificity = 65.2% (60.7 to 67.3)* (30/46) **<u>Change in fFN result following cervical examination</u>** Negative → positive = 5/34 Positive → negative = 2/16 *Calculated by the NCC-WCH technical team.	performance of the reference standard and the index test short enough to be reasonably sure that the target condition did not change between the two tests? N/A Did the whole sample or a random selection of the sample receive verification using the reference standard? Yes Did participants receive the same reference standard regardless of the index test result? Yes Was the reference standard independent of the index test? (that is, the index test did not form part of the reference standard) Yes Was the

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					execution of the index test described in sufficient detail to permit its replication? Yes Was the execution of the reference standard described in sufficient detail to permit its replication? Yes Were the index test results interpreted without knowledge of the results of the reference standard? Unclear Were the reference standard results interpreted without knowledge of the results of the index test? N/A Were the same clinical data available when the test results were interpreted

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					as would be available when the test is used in practice? Yes Were uninterpretable, indeterminate or intermediate test results reported? N/A Were withdrawals from the study explained? N/A
Full citation Palacio,M., Sanin-Blair,J., Sanchez,M., Crispi,F., Gomez,O., Carreras,E., Coll,O., Cararach,V., Gratacos,E., The use of a variable cut-off value of cervical length in women admitted for preterm labor before and after 32 weeks, Ultrasound in Obstetrics and Gynecology, 29, 421-426, 2007 **Ref Id** 271139 **Country/ies where the study was carried out** Spain **Study type** Prospective cohort study **Aim of the study** To evaluate the use of different cut-offs for	**Sample size** N = 333 **Characteristics** **Mean maternal age, years ± SD** 29.4 ± 5.8 **Parity, n/N (%)** Nulliparous = 146/333 (43.8%) **Previous pre-term birth, n/N (%)** Yes = 45/333 (13.5%) **Mean gestational age at admission, weeks ± SD** 31.9 ± 2.6 **Mean Bishop score ± SD** 2.9 ± 1.3	**Tests** **Index test** Cervical length < 15mm or < 25mm as determined by transvaginal ultrasound between 24 and 48 hours after admission. **Reference standard** Birth within 7 days of admission.	**Methods** **Details** Gestational age was calculated based on the date of the last menstrual period or by ultrasound during early pregnancy. Ultrasound examination was performed 24 to 48 hours after admission. At least three images were taken and the shortest value was recorded and used in analysis. Clinicians were blinded to the results of the transvaginal ultrasound therefore these results were not used in the clinical management of each woman.	**Results** **Cervical length < 15mm to diagnose birth within 7 days in the whole cohort** Likelihood ratio (positive) = 8.10 (2.83 to 20.65)* Likelihood ratio (negative) = 0.74 (0.54 to 0.91)* Sensitivity = 28.6% (12.9 to 47.1)* (6/21) Specificity = 96.5% (95.4 to 97.7)* (301/312) **Cervical length < 25mm to diagnose birth within 7 days**	**Limitations** **QUADAS checklist** Was the spectrum of participants representative of the patients who will receive the test in practice? Yes Were selection criteria clearly described? Yes Was the reference standard likely to classify the target condition correctly? Yes Was the period

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
cervical length depending on gestational age as measured at admission to identify women with symptomatic contractions who are at low risk of pre-term birth. **Study dates** January 2001 to December 2003. **Source of funding** Supported by grants from Fondo de Investigaciones Sanitarias of the Spanish government.	All women received tocolytic medication. **Inclusion Criteria** • Singleton pregnancies • Intact membranes • Women that presented with pre-term labour (at least 2 regular, painful contractions within 10 minutes that persisted after one hour of rest) • Gestational age between 24 and < 36 weeks **Exclusion Criteria** • Bishop score ≥ 6 • Rupture of membranes on admission • Women who gave birth within 24 hours following admission • Women who gave birth due to iatrogenic intervention for reasons other than active labour e.g. maternal disease, placental abruption or pathological fetal heart		Primary outcomes were birth within 7 days of admission and birth at < 34 weeks' gestation. Definition of pre-term labour Pre-term labour was defined as at least 2 regular, painful contractions within 10 minutes that persisted after one hour of rest. Use of tocolysis Tocolytic medication was administered to all women. **Statistical analysis** Sensitivity, specificity and likelihood ratios were calculated for different cut-offs of cervical length. No confidence intervals were provided therefore these were calculated by the NCC-WCH technical team. Not all relevant data were presented for cervical length < 20mm therefore it was not possible to calculate confidence intervals for this cut-off and as a result these results were discarded.	**in the whole cohort** Likelihood ratio (positive) = 3.43 (2.17 to 4.44)* Likelihood ratio (negative) = 0.36 (0.16 to 0.66)* Sensitivity = 71.4% (48.6 to 87.6)* (15/21) Specificity = 79.2% (77.6 to 80.3)* (247/312) **Cervical length < 15mm to diagnose birth within 7 days in women admitted before 32 weeks' gestation** Likelihood ratio (positive) = 3.23 (0.00 to 41.52)* Likelihood ratio (negative) = 0.93 (0.49 to 1.04)* Sensitivity = 10.0% (0.00 to 51.8)* (0/4)# Specificity = 96.9% (96.5 to 98.8)* (109/112) **Cervical length < 25mm to diagnose birth within 7 days in women admitted before 32 weeks'**	between performance of the reference standard and the index test short enough to be reasonably sure that the target condition did not change between the two tests? Yes Did the whole sample or a random selection of the sample receive verification using the reference standard? Yes Did participants receive the same reference standard regardless of the index test result? Yes Was the reference standard independent of the index test? (that is, the index test did not form part of the reference standard) Yes

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
	pattern Women with subsequent rupture of membranes whose labour was induced were not excluded.			**gestation** Likelihood ratio (positive) = 5.25 (1.39 to 7.34)* Likelihood ratio (negative) = 0.29 (0.02 to 0.92)* Sensitivity = 75.0% (22.5 to 98.7)* (3/4) Specificity = 85.7% (83.8 to 86.6)* (96/112) **Cervical length < 15mm to diagnose birth within 7 days in women admitted at or later than 32 weeks' gestation** Likelihood ratio (positive) = 8.82 (2.93 to 23.96)* Likelihood ratio (negative) = 0.67 (0.46 to 0.89)* Sensitivity = 35.3% (16.4 to 55.2)* (6/17) Specificity = 96.0% (94.4 to 97.7)* (192/200) **Cervical length < 25mm to diagnose birth within 7 days in women admitted at or later than 32 weeks' gestation** Likelihood ratio	Was the execution of the index test described in sufficient detail to permit its replication? Yes Was the execution of the reference standard described in sufficient detail to permit its replication? Yes Were the index test results interpreted without knowledge of the results of the reference standard? Unclear Were the reference standard results interpreted without knowledge of the results of the index test? N/A Were the same clinical data available when the test results

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
				(positive) = 2.88 (1.69 to 3.85)* Likelihood ratio (negative) = 0.39 (0.15 to 0.75)* Sensitivity = 70.6% (45.2 to 88.4)* (12/17) Specificity = 75.5% (73.3 to 77.0)* (151/200) *Calculated by the NCC-WCH technical team. #0.5 was added to each cell in the 2x2 table to allow sensitivity to be calculated.	were interpreted as would be available when the test is used in practice? Yes Were uninterpretable, indeterminate or intermediate test results reported? N/A Were withdrawals from the study explained? N/A
Full citation Sakai,M., Sasaki,Y., Yamagishi,N., Tanebe,K., Yoneda,S., Saito,S., The preterm labor index and fetal fibronectin for prediction of preterm delivery with intact membranes, Obstetrics and Gynecology, 101, 123-128, 2003 **Ref Id** 258593 **Country/ies where the study was carried out** Japan **Study type**	**Sample size** N = 185 fFN positive n = 89 fFN negative n = 96 **Characteristics** **Maternal Age (y)** fFN positive = 25.4 ± 5.7 fFN negative = 25.3 ± 5.2 **Primiparous** fFN positive = 46.6% fFN negative = 47.1% **Previous preterm delivery** fFN positive = 9.3% fFN negative = 9.0% **Education <12y** fFN positive = 1.1%	**Tests** **Index test** Fetal fibronectin with a positive test being defined at concentrations of 50ng/ml or more in cervicovaginal secretions **Reference standard** Birth within 7 days	**Methods** **Details** Fetal fibronectin testing was performed before vaginal examination. A specimen was obtained using a high vaginal Dacron swab and tested using an immunoassay (Adeza Biomedical) **Definition of preterm labour** Preterm labour defined (according to the Canadian Preterm Labour Investigatos Group) as presence of regular uterine contractions (6/60mins) or any uterine	**Results** **Fetal fibronectin test to diagnose birth within 7 days** Likelihood ratio (positive) = 2.86* Likelihood ratio (negative) = 0.35* Sensitivity = 73.8% Specificity = 74.2% * Calculated by NCC-WCH technical team	**Limitations** **QUADAS checklist** Was the spectrum of participant's representative of the patients who will receive the test in practice? Yes Were selection criteria clearly described? Yes Was the reference standard likely to classify the target

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
Prospective cohort study **Aim of the study** To evaluate the value of the preterm labour index (not reported here) and fetal fibronectin to predict preterm birth in women in preterm labour with intact membranes **Study dates** 1997 - 2001 **Source of funding** Not stated	fFN negative = 1.1% **Smoker** fFN positive = 2.2% fFN negative = 3.1% **Gestational age at hospitalisation (wk)** fFN positive = 29.6 ± 8.9 fFN negative = 28.9 ± 8.2 **Inclusion Criteria** Pregnant women brought to hospital because of preterm labour **Exclusion Criteria** • Pre-term PROM • Multiple pregnancy • Early delivery due to fetal asphyxia • Pre-eclampsia • Placenta previa • Abruptio placentae • Meternal medical complications (such as diabetes mellitus, hyperthyroidism and asthma)		activity associated with a cervix effaced by at least 50% or dilated by 2cms or more **Use of tocolysis** Women in preterm labour were treated with an initial dose of ritodrine hydrochloride IV infusion (33 micrograms/minute). When the maximum dose was exceeded (100micrograms/minute), magnesium sulphate was added at 4g/30 minutes, then continued at 1 to 2 g/hr **Statistical analysis** A sample size of 180 patients was required to demonstrate a significant association between fetal fibronectin and outcome with a positive predicitive value of 50% and a negative predicive value of 80% Demographic characteristics were analysed using Student's t-tests and chi-squared tests. Statistical significance was taken at $p < 0.05$		condition correctly? Yes Was the period between performance of the reference standard and the index test short enough to be reasonably sure that the target condition did not change between the two tests? Yes Did the whole sample or a random selection of the sample receive verification using the reference standard? The whole sample Did participants receive the same reference standard regardless of the index test result? Yes Was the reference standard independent of the index test? (that is, the index test did not form part of the reference

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					standard) Yes Was the execution of the index test described in sufficient detail to permit its replication? Yes Were the index test results interpreted without knowledge of the results of the reference standard? Unclear Were the reference standard results interpreted without knowledge of the results of the index test? N/A
Full citation Schmitz,T., Maillard,F., Bessard-Bacquaert,S., Kayem,G., Fulla,Y., Cabrol,D., Goffinet,F., Selective use of fetal fibronectin detection after cervical length measurement to predict spontaneous preterm delivery in women with preterm labor, American Journal of Obstetrics and Gynecology, 194, 138-143, 2006 **Ref Id** 258534	**Sample size** N = 359 **Characteristics** **Mean maternal age, years ± SD** 31.1 ± 5.1 **Ethnic origin, n (%)** France = 235 (65.8%) North Africa = 34 (9.5%) Central and West Africa = 22	**Tests** **Index test** Fetal fibronectin test with a cut-off of > 50ng/ml for a positive test result. **Reference standard** Birth within 7 days of	**Methods** **Details** Gestational age was determined by the date of the last menstrual period and confirmed by sonography performed during the first trimester. If gestational age by menstrual history was unreliable or discordant by > 5 days, sonography results alone were used.	**Results** **Cervical length ≤ 25 mm to diagnose birth within 7 days** Likelihood ratio (positive) = 2.25 (1.83 to 2.77) Likelihood ratio (negative) = 0.21 (0.07 to 0.61) Sensitivity = 87% (66 to 97)	**Limitations** **QUADAS checklist** Was the spectrum of participants representative of the patients who will receive the test in practice? Yes Were selection

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
Country/ies where the study was carried out France **Study type** Prospective cohort study **Aim of the study** To determine whether selective use of fetal fibronectin detection after ultrasound measurement of cervical length predicts pre-term delivery in symptomatic patients better than either indicator alone. **Study dates** January 1997 to May 2000. **Source of funding** Not reported.	(6.2%) French Caribbean = 22 (6.2%) Other = 44 (11.7%) **Parity, n (%)** Nulliparous = 191 (53.2%) **Previous pre-term birth, n (%)** ≤ 28 weeks' gestation = 23 (6.5%) > 28 weeks' gestation = 37 (10.5%) **Mean gestational age at inclusion, weeks ± SD** 29 ± 3.7 The number of women who received tocolytic medication was not reported. **Inclusion Criteria** • Women hospitalised for pre-term labour between 18 and 34 weeks' gestation **Exclusion Criteria** • Cervical dilation ≥ 3cm • Confirmed rupture of membranes • Women who had cervical manipulation or sexual intercourse in the preceding 24	admission.	Fetal fibronectin was performed first at admission by swabbing the posterior fornix of the vagina. Also at admission, after fetal fibronectin testing, transvaginal sonography was used to determine cervical length. Clinicians were blinded to the results of both the fetal fibronectin test and cervical length measurement to prevent this knowledge affecting subsequent patient management. The secondary outcome was birth within 7 days of admission. Definition of pre-term labour Pre-term labour was defined as at least 4 regular uterine contractions of 30 seconds in duration in 30 minutes confirmed by tocodynamometry and cervical dilation of 0 to 3cm (nulliparous women) or 1 to 3cm (primiparous/multiparous women) and 50% cervical effacement. Use of tocolysis Tocolytic medication was administered at the discretion	Specificity = 61% (56 to 67) **Fetal fibronectin ≥ 50 ng/mL to diagnose birth within 7 days** Likelihood ratio (positive) = 3.91 (2.69 to 5.17) Likelihood ratio (negative) = 0.22 (0.09 to 0.54) Sensitivity = 83%* (61 to 95) Specificity = 79%** (74 to 83) *P = 0.1 vs cervical length **p < 0.001	criteria clearly described? Yes Was the reference standard likely to classify the target condition correctly? Yes Was the period between performance of the reference standard and the index test short enough to be reasonably sure that the target condition did not change between the two tests? Yes Did the whole sample or a random selection of the sample receive verification using the reference standard? Yes Did participants receive the same reference standard regardless of the index test result? Yes

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
	hours • Cervical cerclage • Uterine abnormalities • Vaginal bleeding • Placenta previa • Abruptio placentae • Intrauterine growth restriction • Pre-eclampsia • Medically indicated pre-term birth before 35 weeks' gestation		of the attending physician. **Statistical analysis** Sensitivity, specificity, likelihood ratios and associated 95% confidence intervals were calculated.		Was the reference standard independent of the index test? (that is, the index test did not form part of the reference standard) Yes Was the execution of the index test described in sufficient detail to permit its replication? Yes Was the execution of the reference standard described in sufficient detail to permit its replication? Yes Were the index test results interpreted without knowledge of the results of the reference standard? Unclear Were the reference standard results

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					interpreted without knowledge of the results of the index test? N/A Were the same clinical data available when the test results were interpreted as would be available when the test is used in practice? Yes Were uninterpretable, indeterminate or intermediate test results reported? N/A Were withdrawals from the study explained? N/A
Full citation Schmitz,T., Kayem,G., Maillard,F., Lebret,M.T., Cabrol,D., Goffinet,F., Selective use of sonographic cervical length measurement for predicting imminent preterm delivery in women with preterm labor and intact membranes, Ultrasound in Obstetrics and Gynecology, 31, 421-426, 2008 **Ref Id**	**Sample size** N = 395 **Characteristics** **Mean maternal age, years ± SD** 30.9 ± 5.1 **Parity, n/N (%)**	**Tests** Index test Digital cervical examination with Bishop score assigned followed by ultrasound assessment of the cervix.	**Methods** **Detail** Gestational age of eligible women was determined using the date of the last menstrual period. If mentrual data were unreliable or discordant by more than 5 days gestational age was determined by ultrasound.	**Results** **Bishop score ≥ 4 to diagnose birth within 48 hours** Likelihood ratio (positive) = 1.66 (1.20 to 1.76)* Likelihood ratio (negative) = 0.14 (0.01 to 0.72)* Sensitivity = 94%	**Limitations** **QUADAS checklist** Was the spectrum of participants representative of the patients who will receive the test in practice? Yes

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
222058 **Country/ies where the study was carried out** France **Study type** Prospective cohort study **Aim of the study** To evaluate the diagnostic performance of sonographic cervical length measurement in women selected based on the results of digital cervical examination. **Study dates** January 1997 to May 2000. **Source of funding** Not reported.	Nulliparous = 211/395 (53.4%) **Previous pre-term birth, n (%)** ≤ 28 weeks' gestation = 24 (6.1%) > 28 weeks' gestation = 37 (9.4%) **Ethnic origin, n (%)** France = 262 (67.2%) North Africa = 20 (5.1%) Central and West Africa = 35 (9.0%) French Caribbean = 19 (4.9%) Other = 54 (13.9%) The number of women who received tocolytic medication was not reported. **Inclusion Criteria** • Hospitalised for pre-term labour • Gestational age between 24 and 34+6 week **Exclusion Criteria** • Multiple pregnancies • Premature rupture of membranes • Cervical dilation > 3cm • Cervical cerclage • Uterine abnormalities • Placenta previa	Reference standard Birth ≤ 48 hours or ≤ 7 days.	Women had a digital cervical examination followed by recording of uterine contractions then cervical length measurement using ultrasound. All examinations were made at admission. Ultrasound took place no more than 30 minutes after digital examination. A Bishop score was assigned after digital cervical examination. At least two measurements of cervical length were made using ultrasound with the shortest measurement being used in analysis. Hospitalisation was based on digital cervical examination or uterine contractions. Primary outcomes were birth within either 48 hours or 7 days based on the duration of efficient tocolysis and fetal lung maturation following administration of corticosteroids. Definition of pre-term labour Regular uterine contractions of 30 seconds in duration at a rate of four contractions per 30 minutes, confirmed by external uterine tocodynamometry and cervical changes.	(71 to 100) Specificity = 43% (38 to 48) **Bishop score ≥ 4 to diagnose birth within 7 days** Likelihood ratio (positive) = 1.76 (1.46 to 1.82)* Likelihood ratio (negative) = 0.07 (0.004 to 0.40)* Sensitivity = 97% (84 to 100) Specificity = 45% (39 to 50) **Bishop score ≥ 8 to diagnose birth within 48 hours** Likelihood ratio (positive) = 12.13 (4.29 to 29.42)* Likelihood ratio (negative) = 0.67 (0.44 to 0.87)* Sensitivity = 35% (14 to 62) Specificity = 97% (94 to 98) **Bishop score ≥ 8 to diagnose birth within 7 days** Likelihood ratio (positive) = 17.83 (6.87 to 47.57)* Likelihood ratio	Were selection criteria clearly described? Yes Was the reference standard likely to classify the target condition correctly? Yes Was the period between performance of the reference standard and the index test short enough to be reasonably sure that the target condition did not change between the two tests? Yes Did the whole sample or a random selection of the sample receive verification using the reference standard? Yes Did participants receive the same reference standard regardless of the index test result? Yes

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
	• Placental abruption • Intrauterine growth restriction • Pre-eclampsia • A medically indicated pre-term birth		Use of tocolysis Administered at the discretion of the attending physician. If administered tocolysis was maintained until contractions stopped and ceased 24 to 48 hours after contractions ended. **Statistical analysis** Members of the obstetric team were blinded to the results of ultrasound cervical length measurement but not the Bishop score. Optimal cut-offs for the Bishop score and cervical length were determined by ROC curves using STATA. Bishop score cut-offs were chosen to maximise both sensitivity and specificity. Cervical length cut-offs were chosen to maximise sensitivity regardless of specificity, considering the consequences of missed diagnosis. Likelihood ratios and 95% confidence intervals were calculated for each test separately then for ultrasound length on the selected population (based on cut-offs for the Bishop score).	(negative) = 0.67 (0.55 to 0.81)* Sensitivity = 34% (19 to 53) Specificity = 98% (96 to 99) **Cervical length ≤ 20mm to diagnose birth within 48 hours in women with a Bishop score of 4 to 7** n = 213 Likelihood ratio (positive) = 1.66 (0.75 to 2.43)* Likelihood ratio (negative) = 0.63 (0.21 to 1.15)* Sensitivity = 60% (26 to 88) Specificity = 64% (57 to 71) **Cervical length ≤ 25mm to diagnose birth within 48 hours in women with a Bishop score of 4 to 7** n = 213 Likelihood ratio (positive) = 1.48 (0.81 to 1.80)* Likelihood ratio (negative) = 0.44 (0.08 to 1.23)* Sensitivity = 80%	Was the reference standard independent of the index test? (that is, the index test did not form part of the reference standard) Yes Was the execution of the index test described in sufficient detail to permit its replication? Yes for cervical ultrasound, no for Bishop score (reference provided but not described). Was the execution of the reference standard described in sufficient detail to permit its replication? Yes Were the index test results interpreted without knowledge of the

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
				(44 to 97) Specificity = 46% (39 to 53) **<u>Cervical length ≤ 30mm to diagnose birth within 48 hours in women with a Bishop score of 4 to 7</u>** n = 213 Likelihood ratio (positive) = 1.25 (0.75 to 1.39)* Likelihood ratio (negative) = 0.36 (0.02 to 1.67)* Sensitivity = 90% (55 to 100) Specificity = 28% (22 to 34) **<u>Cervical length ≤ 20mm to diagnose birth within 7 days in women with a Bishop score of 4 to 7</u>** n = 213 Likelihood ratio (positive) = 1.57 (0.90 to 2.24)* Likelihood ratio (negative) = 0.69 (0.37 to 1.06)* Sensitivity = 55% (31 to 77) Specificity = 65% (58 to 71)	results of the reference standard? Unclear - Were the reference standard results interpreted without knowledge of the results of the index test? N/A Were the same clinical data available when the test results were interpreted as would be available when the test is used in practice? Yes Were uninterpretable, indeterminate or intermediate test results reported? Yes Were withdrawals from the study explained? Yes

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
				Cervical length ≤ 25mm to diagnose birth within 7 days in women with a Bishop score of 4 to 7 n = 213 Likelihood ratio (positive) = 1.64 (1.16 to 1.87)* Likelihood ratio (negative) = 0.31 (0.08 to 0.82)* Sensitivity = 85% (62 to 97) Specificity = 48% (41 to 55) **Cervical length ≤ 30mm to diagnose birth within 7 days in women with a Bishop score of 4 to 7** n = 213 Likelihood ratio (positive) = 1.34 (1.02 to 1.41)* Likelihood ratio (negative) = 0.17 (0.01 to 0.94)* Sensitivity = 95% (75 to 100) Specificity = 29% (22 to 36) **Cervical length ≤ 30mm to diagnose**	

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
				birth within 48 hours in the entire cohort Likelihood ratio (positive) = 1.48 (1.22 to 1.80) Likelihood ratio (negative) = 0.29 (0.08 to 1.07) Sensitivity = 88% (64 to 98) Specificity = 40% (35 to 46) **Cervical length ≤ 30mm to diagnose birth within 7 days in the entire cohort** Likelihood ratio (positive) = 1.63 (1.43 to 1.84) Likelihood ratio (negative) = 0.15 (0.04 to 0.57) Sensitivity = 94% (79 to 99) Specificity = 42% (37 to 47) **Selective test to diagnose birth within 48 hours in a clinically selected population** n = 213 Likelihood ratio (positive) = 2.08 (1.74 to 2.63)	

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
				Likelihood ratio (negative) = 0.20 (0.06 to 0.75) Sensitivity = 88% (64 to 99) Specificity = 58% (54 to 64) **Selective test to diagnose birth within 7 days in a clinically selected population** n = 213 Likelihood ratio (positive) = 2.35 (2.01 to 2.74) Likelihood ratio (negative) = 0.10 (0.03 to 0.40) Sensitivity = 94% (79 to 99) Specificity = 60% (55 to 65) *Calculated by the NCC-WCH technical team.	
Full citation Schreyer,P., Caspi,E., Bar,NatanN, Tal,E., Weinraub,Z., The predictive value of fetal breathing movement and Bishop score in the diagnosis of 'true' preterm labor, American Journal of Obstetrics and Gynecology, 161, 886-889, 1989 **Ref Id**	**Sample size** N = 70 **Characteristics** **Mean age, years ± SD** Fetal breathing present = 26.2 ± 2.4 Fetal breathing absent = 24.7 ± 3.1	**Tests** **Test** Cervical length, consistency, position, dilation and station of the head scored according to Bishop score.	**Methods** **Protocol** All women admitted to the study centre during the study period who met inclusion and exclusion criteria were eligible. Gestational age was based on the date of the last menstrual	**Results** **Bishop score of 0 to 3 versus 4 to 6 to diagnose birth ≤ 48 hours** Likelihood ratio (positive) = 2.63 (1.27 to 4.09) Likelihood ratio	**Limitations** **QUADAS checklist** Was the spectrum of participants representative of the patients who will receive the test in practice?

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
271098 **Country/ies where the study was carried out** Israel **Study type** Prospective cohort study **Aim of the study** To assess the validity of fetal breathing movement and Bishop score in apparent signs of pre-term labour in women between 32 and 36 weeks' gestation with intact membranes. **Study dates** January 1986 to January 1987. **Source of funding** Not reported.	**Parity** Primiparous = 27/70 Multiparous = 43/70 **Mean weeks' gestation at admission ± SD** Fetal breathing present = 33.4 ± 1.6 Fetal breathing absent = 33.8 ± 1.2 The proportion of women with previous pre-term births and the number of women who received tocolytic medication were not reported. **Inclusion Criteria** • Complaints of painful uterine contractions • Gestational age between 32 and 36 weeks • Uncomplicated pregnancies **Exclusion Criteria** • Multiple pregnancies • Women with pre-term rupture of membranes • Bleeding in the third trimester • Women with hyperpyrexia • Women who did not	**Reference/gold standard** Birth ≤ 48 hours or ≤ 7 days.	period. This was confirmed by ≥ 1 ultrasonography examination in the first two trimesters. Women underwent vaginal examination according to the Bishop score. Definition of pre-term labour Not reported, although women with painful uterine contractions were included in the study. Use of tocolysis Women received no medication except pre-natal vitamins and iron however women with cervical scores that did not increase significantly were discharged after 48 hours and did not receive tocolytic treatment until labour occurred. **Statistical analysis** No specific statistical analyses were performed. Frequencies of women who gave birth within ≤ 48 hours or ≤ 7 days were reported according to their Bishop score.	(negative) = 0.42 (0.14 to 0.87) Sensitivity = 69.2% (41.4 to 89.0) (9/13) Specificity = 73.7% (67.3 to 78.2) (42/57) **Bishop score of 0 to 3 versus 4 to 6 to diagnose birth ≤ 7 days** Likelihood ratio (positive) = 2.85 (1.43 to 4.64) Likelihood ratio (negative) = 0.41 (0.16 to 0.81) Sensitivity = 68.8% (44.6 to 86.9) (11/16) Specificity = 75.9% (68.8 to 81.3) (41/54)	Yes Were selection criteria clearly described? Yes Was the reference standard likely to classify the target condition correctly? Yes Was the period between performance of the reference standard and the index test short enough to be reasonably sure that the target condition did not change between the two tests? N/A Did the whole sample or a random selection of the sample receive verification using the reference standard? Yes Did participants receive the same reference standard regardless of the

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
	exhibit ≥ 1 uterine contraction every 10 minutes • Women with unborn babies with a non-reactive heart rate (< 2 accelerations of 15 beats/minute in ≥ 15 seconds)				index test result? Yes Was the reference standard independent of the index test (that is, the index test did not form part of the reference standard)? Yes Was the execution of the index test described in sufficient detail to permit its replication? No Was the execution of the reference standard described in sufficient detail to permit its replication? Yes Were the index test results interpreted without knowledge of the results of the reference standard? Unclear

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					Were the reference standard results interpreted without knowledge of the results of the index test? N/A Were the same clinical data available when the test results were interpreted as would be available when the test is used in practice? Yes Were uninterpretable, indeterminate or intermediate test results reported? N/A Were withdrawals from the study explained? N/A
Full citation Senden,I.P., Owen,P., Comparison of cervical assessment, fetal fibronectin and fetal breathing in the diagnosis of preterm labour, Clinical and Experimental Obstetrics and Gynecology, 23, 5-9, 1996 **Ref Id**	**Sample size** N = 2 **Characteristics** Mean maternal age = 25 years (range 16 to 40) Primiparous = 12/25 (48%) Mean gestational age at presentation = 31 ± 4 weeks	**Tests** **Index test** Bishop's score >2 **Index test** Fetal fibronectin test with no threshold	**Methods** **Details** A Bishop's score was recorded that was based on vaginal examination performed in all women by one investigator. Attending staff were aware of the	**Results** **Bishop's score >2 to diagnose birth within 7 days** TP:3 FP:6 FN:0 TN:16* Likelihood ratio (positive) = 3.10	**Limitations** **QUADAS checklist** Was the spectrum of participants representative of the patients who will receive the

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
209118 **Country/ies where the study was carried out** Scotland, UK **Study type** Prospective cohort study **Aim of the study** To evaluate the value of the cervical scoring (using Bishop's scores), fetal breathing monitoring and fetal fibronectin testing in the diagnosis of false and true pre-term labour in women with pre-term uterine activit **Study dates** A six month period in 1994 **Source of funding** Not stated	(range 25 ± 4 to 34 ± 4 weeks) Mean number of contractions/hour at presentation = 13 **Inclusion Criteria** Women attendng the delivery unit with a singleton pregnancy at 25-35 wks gestation (ultrasound determined at 18 wks) with regular uterine activity of >5 contractions per hour **Exclusion Criteria** • Ruptured membranes • Vaginal bleeding • Clinical chorioamnionitis • Maternal diabetes mellitus • History suggestive of cervical incompetence or cervical dilatation >4cm	specified for a positive result **Reference standard** Birth within 7 days	Bishop's score It was not specified if the fetal fibronectin test was performed before vaginal examination. A specimen was obtained using a swab applied to the posterior vaginal fornix and tested using a testing kit (Adeza Biomedical). Attending staff were not made aware of the test result. **Definition of preterm labour** Preterm labour was not defined **Use of tocolysis** 7/25 (28%) women received ritodrine, 8/25 (32%) women received antibiotic therapy and 19/25 (76%) received corticosteroids. Treatment was according to the established practice of administration when considered appropriate **Statistical analysis** Not stated	(95% CI 0.86 to 3.83)** Likelihood ratio (negative) = 0.17 (95% CI 0.000 to 1.09)** Sensitivity = 100% Specificity = 73% **Fetal fibronectin test to diagnose birth within 7 days** TP:3 FP:3 FN:0 TN:19* Likelihood ratio (positive) = 5.75 (95% CI 1.34 to 7.67)** Likelihood ratio (negative) = 0.15 (95% CI 0.000 to 0.89)** Sensitivity = 100% Specificity = 86% **Bishop's score >2 and fetal fibronectin test to diagnose birth within 7 days** TP:3 FP:1 FN:0 TN:21* Likelihood ratio (positive) = 13.42 (95% CI 2.16 to 23.0)** Likelihood ratio (negative) = 0.13 (95% CI 0.000 to 0.78)** Sensitivity = 100%	test in practice? Yes Were selection criteria clearly described? Yes Was the reference standard likely to classify the target condition correctly? Yes Was the period between performance of the reference standard and the index test short enough to be reasonably sure that the target condition did not change between the two tests? Yes Did the whole sample or a random selection of the sample receive verification using the reference standard? The whole sample Did participants receive the same reference standard regardless of the index test result? Yes

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
				Specificity = 95% * Calculated by NCC-WCH technical team. ** Calculated by NCC-WCH technical team. 0.5 added to each cell to allow calculation (as FN=0)	Was the reference standard independent of the index test? (that is, the index test did not form part of the reference standard) Yes Was the execution of the index test described in sufficient detail to permit its replication? Yes Were the index test results interpreted without knowledge of the results of the reference standard? Unclear Were the reference standard results interpreted without knowledge of the results of the index test? N/A
Full citation Skoll,A., St,Louis P., Amiri,N., Delisle,M.F., Lalji,S., The evaluation of the fetal fibronectin test for prediction of preterm delivery in symptomatic patients, Journal of Obstetrics and Gynaecology	**Sample size** N = 149 **Characteristics** **Singleton pregnancy:** n = 147/160 (91.9%)	**Tests** **Index test** Fetal fibronectin test with a cut-off of > 50ng/ml	**Methods** **Details** The study was conducted in two different hospitals in Montreal and Vancouver.	**Results** Total N = 149 Positive fetal fibronectin n = 32 (21.4%)	**Limitations** **QUADAS checklist** Was the spectrum of participants

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
Canada: JOGC, 28, 206-213, 2006 **Ref Id** 258579 **Country/ies where the study was carried out** Canada **Study type** Prospective cohort study **Aim of the study** The evaluation of the fetal fibronectin test for prediction of pre-term delivery in symptomatic women. **Study dates** Two-year period (dates not specified). **Source of funding** Not reported.	**<u>Reason for admission (n = 130)</u>** Contracting: n = 92 Bleeding: n = 10 Abdominal/back pain: n = 23 Cramps: n =29 Discharge: n = 8 Pressure; n = 5 Pregnancy induced hypertension: n = 1 **Inclusion Criteria** • Between 24 and 34 completed weeks gestation • Intact membranes • No indication of preterm birth including chorioamnionitis, severe maternal hypertention and fetal death • No moderate or severe vaginal bleedings **Exclusion Criteria** • Membrane rupture	for a positive test result. **<u>Reference test</u>** Birth within 7 days of presentation.	Women who met the inclusion criteria were included in the study. From 184 women eligible and included in the study 24 had no fetal fibronectin result available (for various reasons such as label detached, insufficient sample, sample leaked). From n = 160 women with available results, n = 11 women were lost to follow up, leaving 149 women for final analysis. Specimens were obtained using speculum examination and a swab of cervico-vaginal secretions from posterior fornix by the house officer physician. If the physician exclude the diagnosis of preterm labour on clinical assessment and vaginal examination and discharge the women home, then the swab was discard and women were excluded from final analysis. Specimens were stored in the laboratory at - 4°C, analysis performed using the rapid fetal fibronectin TLi System (Adeza Biomedical Corporation). A cut-off of > 50ng/mL was used to determine a positive test result. <u>Definition of pre-term labour</u> Not reported.	**<u>Birth within 7 days n = 20</u>** Likelihood ratio (positive) = 5.36 (3.32 to 8.63) Likelihood ratio (negative) = 0.23 (0.08 to 0.64) Sensitivity = 80% (51 to 94) Specificity = 87% (77 to 90)	representative of the patients who will receive the test in practice? Yes Were selection criteria clearly described? Yes Was the reference standard likely to classify the target condition correctly? Yes Was the period between performance of the reference standard and the index test short enough to be reasonably sure that the target condition did not change between the two tests? N/A Did the whole sample or a random selection of the sample receive verification using the reference standard? Yes Did participants

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
			Use of tocolysis Not reported. **Statistical analysis** Categorical values were calculated using descriptive analysis. To show a significant association (set at $p < 0.05$) between fFN levels and pre-term delivery, with a negative predictive value of 95% and a positive predictive value of 50%, they required at least 186 women.		receive the same reference standard regardless of the index test result? Yes Was the reference standard independent of the index test? (that is, the index test did not form part of the reference standard) Yes Was the execution of the index test described in sufficient detail to permit its replication? Yes Was the execution of the reference standard described in sufficient detail to permit its replication? Yes Were the index test results interpreted without knowledge of the

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					results of the reference standard? Unclear Were the reference standard results interpreted without knowledge of the results of the index test? N/A Were the same clinical data available when the test results were interpreted as would be available when the test is used in practice? Yes Were uninterpretable, indeterminate or intermediate test results reported? N/A Were withdrawals from the study explained? N/A
Full citation Sotiriadis,A., Kavvadias,A., Papatheodorou,S., Paraskevaidis,E., Makrydimas,G., The value of serial cervical length measurements for the prediction of threatened preterm labour,	**Sample size** N = 122 **Characteristics** No characteristics of the women included in the study were	**Tests** Index test Cervical length < 15mm or < 25mm at	**Methods** **Details** Cervical length was measured at admission and 24 hours later using transvaginal	**Results** **Cervical length < 15mm at admission to diagnose birth**	**Limitations** **QUADAS checklist** Was the spectrum of participants

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
European Journal of Obstetrics, Gynecology, and Reproductive Biology, 148, 17-20, 2010 **Ref Id** 271146 **Country/ies where the study was carried out** Greece **Study type** Prospective cohort study **Aim of the study** To explore whether a second measurement of cervical length 24 hours after admission provides better predictive ability to diagnose pre-term birth in women with symptoms of pre-term labour. **Study dates** Not reported. **Source of funding** Not reported.	reported. No data regarding the number of women with previous pre-term birth were provided. No women with multiple pregnancies or ruptured membranes were included in the study. All women received tocolytic medication. **Inclusion Criteria** • Singleton pregnancies • Gestational age between 23 and 33+6 weeks • Painful and regular contractions (≥ 1 every 10 minutes for at least one hour) **Exclusion Criteria** • Women in active labour (cervical dilation ≥ 3cm) • Women with evidence of pre-term rupture of membranes	admission and at 24 hours after admission as determined by transvaginal ultrasound. Reference standard Birth within 7 days of admission.	sonography by one of three investigators. The shortest measurement was recorded. Investigators were not blinded to the results of the first measurement of cervical length. If women presented twice during their pregnancy they were included in the study only at their first admission. Four women were excluded because of elective birth before 35 weeks' gestation due to complications. Primary outcomes were birth within 7 days, birth before 35 weeks or before 32 weeks' gestation. Definition of pre-term labour Symptoms of pre-term labour were defined as painful and regular contractions (≥ 1 every 10 minutes for at least one hour). Active labour was defined as cervical dilation ≥ 3cm. Use of tocolysis All women were given tocolytic medication until contractions ceased or side effects were reported. **Statistical analysis**	**within 7 days** Likelihood ratio (positive) = 20.0 (5.77 to 31.16)* Likelihood ratio (negative) = 0.17 (0.01 to 0.65)* Sensitivity = 83.3% (43.7 to 97.0) (5/6) Specificity = 95.8% (89.8 to 98.4) (92/96) **Cervical length < 25mm at admission to diagnose birth within 7 days** Likelihood ratio (positive) = 3.64 (1.46 to 16.61)* Likelihood ratio (negative) = 0.22 (0.01 to 0.84)* Sensitivity = 83.3% (43.7 to 97.0) (5/6) Specificity = 77.1% (67.7 to 84.3) (74/96) **Cervical length change > 20% after 24 hours to diagnose birth within 7 days** Likelihood ratio (positive) = 6.86 (1.54 to 16.61)* Likelihood ratio	representative of the patients who will receive the test in practice? Yes Were selection criteria clearly described? Yes Was the reference standard likely to classify the target condition correctly? Yes Was the period between performance of the reference standard and the index test short enough to be reasonably sure that the target condition did not change between the two tests? Yes Did the whole sample or a random selection of the sample receive verification using the reference standard? Yes Did participants

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
			Change in cervical length was expressed as per cent change (100 x the difference between the two measurements ÷ the first measurement). Sensitivities and specificities were calculated alongside 95% confidence intervals. Likelihood ratios were not reported and were calculated by the NCC-WCH technical team.	(negative) = 0.54 (0.16 to 0.94)* Sensitivity = 50.0% (18.8 to 81.2) (3/6) Specificity = 92.7% (85.7 to 96.4) (89/96) **Cervical length < 15mm plus change > 20% after 24 hours to diagnose birth within 7 days** Likelihood ratio (positive) = 48.00 (4.96 to 1171.37)* Likelihood ratio (negative) = 0.51 (0.34 to 0.87)* Sensitivity = 50.0% (18.8 to 81.2) (3/6) Specificity = 99.0% (94.3 to 99.8) (95/96) **Cervical length > 15mm plus change > 20% after 24 hours to diagnose birth within 7 days** Likelihood ratio (positive) = 3.57 (0.00 to 16.17)*# Likelihood ratio (negative) = 0.81 (0.10 to 1.08)*# Sensitivity = 25.0% (0.0 to 90.3)* (0/1)# Specificity = 93.0%	receive the same reference standard regardless of the index test result? Yes Was the reference standard independent of the index test? (that is, the index test did not form part of the reference standard) Yes Was the execution of the index test described in sufficient detail to permit its replication? Yes Was the execution of the reference standard described in sufficient detail to permit its replication? Yes Were the index test results interpreted without knowledge of the

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
				(92.5 to 94.4)* (86/92)# **<u>Cervical length < 25mm plus change > 20% after 24 hours to diagnose birth within 7 days</u>** Likelihood ratio (positive) = 24.00 (3.61 to 173.72)* Likelihood ratio (negative) = 0.51 (0.24 to 0.88)* Sensitivity = 50.0% (18.8 to 81.2) (3/6) Specificity = 97.2% (92.7 to 99.4) (94/96) *Calculated by the NCC-WCH technical team. #A value of 0.5 was added to each cell in order to calculate the relevant values. The study authors did not use this approach for sensitivity and specificity therefore these values were re-calculated by the NCC-WCH technical team.	results of the reference standard? No - investigators were not blinded to the results of the first cervical length measurements. Were the reference standard results interpreted without knowledge of the results of the index test? N/A Were the same clinical data available when the test results were interpreted as would be available when the test is used in practice? Unclear - no characteristics were reported. Were uninterpretable, indeterminate or intermediate test results reported? N/A Were withdrawals

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					from the study explained? Yes
Full citation Swamy,G.K., Simhan,H.N., Gammill,H.S., Heine,R.P., Clinical utility of fetal fibronectin for predicting preterm birth, Journal of Reproductive Medicine, 50, 851-856, 2005 **Ref Id** 258121 **Country/ies where the study was carried out** United States of America **Study type** Prospective cohort study **Aim of the study** To determine if fetal fibronectin can be used in a clinical setting to predict pre-term birth and guide clinical management. **Study dates** December 1999 to December 2000. **Source of funding** No funding, however the first author of the paper was partly funded by Azeda Biochemical Corporation (manufacture of the fetal fibronectin collection kit) to attend the 23rd annual Meeting of the Society of Maternal- Fetal Medicine. She was also served once as a guest speaker for Adeza and received a $300 honorarium.	**Sample size** N = 404 **Characteristics** 68% of the study population were Caucasian (the rest were African American except for 1 Hispanic). 40% were nulliparous, 55% married, 93% had their first antenatal visit at < 12 weeks, 20% used tobacco and 43% had some college education. **Mean gestational age** Fetal fibronectin positive = 34 weeks Fetal fibronectin negative = 38 weeks p < 0.05 **Symptomatic treatment** Fetal fibronectin positive = 44% Fetal fibronectin negative = 37% OR = 1.4 (0.7 to 2.6) p = 0.33 **Inclusion Criteria** • Between 24 and 34 weeks gestation • Intact membranes • Symptoms of pre-term	**Tests** **Index test** Fetal fibronectin test. **Reference standard** Birth within 7 days of presentation.	**Methods** **Details** A clinical protocol developed for use of the rapid fetal fibronectin test for women presenting with symptoms of pre-term labour. Women who met the inclusion criteria were divided into 2 groups based on the fetal fibronectin result. The study investigators were blinded to the fetal fibronectin result abstracted from women hospital notes and electronic database. Specimens were collected during the speculum examination before the digital examination. The fetal fibronectin test was carried out using fibronectin specemen collection kit (adeza biochemical corporation) contains a swab and a buffer filled collection tube. The swab was used to collect a sample from crevico-vaginal secretions from posterior fornix. All samples were immediately transport to the hospital laboratory and processed using ELISA rapid assay (Adeza) with results available within 30 to 60	**Results** N = 404 Positive fetal fibronectin n = 46 (11%) **Birth within 7 days** Sensitivity = 67% Specificity = 92% Time until birth and gestational age at delivery were lower in women with a positive test, while the frequency of therapeutic interventions was higher (p < 0.01).	**Limitations** **QUADAS checklist** Was the spectrum of participants representative of the patients who will receive the test in practice? Yes Were selection criteria clearly described? Yes Was the reference standard likely to classify the target condition correctly? Yes Was the period between performance of the reference standard and the index test short enough to be reasonably sure that the target condition did not change between the two tests? N/A Did the whole

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
	labour • Last vaginal digital examination and intercourse before 24 hours • Cervix < 2cm dilated and > 1cm long **Exclusion Criteria** Not reported.		minutes. A cut-off of ≥ 50ng/ml was used to determine a positive test result. <u>Definition of pre-term labour</u> Not reported. <u>Use of tocoloysis</u> Intravenous magnesium, intravenous terbutaline, continuous oral nifedipine or oral indocin. Symptomatic treatment included subcutaneous or oral turbutaline and narcotics give at the time of the presentation. Fetal fibronectin positive = 38%, fetal fibronectin negative = 9%, OR = 6.5 (3.2 to 13.2), p < 0.001. **<u>Statistical analysis</u>** Statistical analysis performed using Stata 7.0 for Windows. Univariate associations between the categorical variables were analysed using Fisher's exact test and logistic regression. Continuous variables were analysed with Mann-Whitney U test.		sample or a random selection of the sample receive verification using the reference standard? Yes Did participants receive the same reference standard regardless of the index test result? Yes Was the reference standard independent of the index test? (that is, the index test did not form part of the reference standard) Yes Was the execution of the index test described in sufficient detail to permit its replication? Yes Was the execution of the reference standard described in

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					sufficient detail to permit its replication? Yes Were the index test results interpreted without knowledge of the results of the reference standard? Yes Were the reference standard results interpreted without knowledge of the results of the index test? N/A Were the same clinical data available when the test results were interpreted as would be available when the test is used in practice? Yes Were uninterpretable, indeterminate or intermediate test results reported? N/A

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					Were withdrawals from the study explained? N/A
Full citation Tanir,H.M., Sener,T., Yildiz,Z., Cervicovaginal fetal fibronectin (FFN) for prediction of preterm delivery in symptomatic cases: a prospective study, Clinical and Experimental Obstetrics and Gynecology, 35, 61-64, 2008 **Ref Id** 222185 **Country/ies where the study was carried out** Turkey **Study type** Prospective cohort study **Aim of the study** To assess the clinical value of cervicovaginal fetal fibronectin (FFN) in the prediction of pre-term delivery in women with signs and symptoms of pre-term labour. **Study dates** January 2004 to July 2006. **Source of funding** Not reported.	**Sample size** N = 65 **Characteristics** **Mean maternal age, years ± SD** Fetal fibronectin positive = 28.5 ± 3.5 Fetal fibronectin negative = 28.3 ± 2.3 P = NS **Mean gestational age at admission, weeks ± SD** Fetal fibronectin positive = 31.1 ± 2.5 Fetal fibronectin negative = 30.6 ± 2.3 P = NS **Parity** Fetal fibronectin positive = 0.69 ± 0.7 Fetal fibronectin negative = 0.69 ± 0.2 P = NS **Inclusion Criteria** • Between 24 and 37 weeks' gestation • Intact membranes	**Tests** **Index test** Fetal fibronectin test with a cut-off of > 50ng/ml for a positive test result. **Reference test** Birth within 7 days.	**Methods** **Details** Women with suspected preterm labour were included in the study. At entry, a sterile speculum examination was performed for all women who met the inclusion criteria. Specimen was obtained by specimen collection kit (Quick check fFN, AdezaBiochemical Cooperation) using a Dacron swab. All samples were sent to the hospital laboratory and fFN test processed by monoclonal antibody ELISA rapid assay. The results were available within 30 minutes. A digital examination was performed after the test was carried out. Managing obstetricians were blinded to the result of fibronectin test. Results were reported as either positive (≥ 50ng/mL) or negative (< 50ng/mL). Definition of pre-term labour Suspected pre-term labour was defined as the presence uterine contractions (at least 4 per 20 minute interval or 8 times per hour) dilatation of	**Results** Total N = 65 Positive fetal fibronectin n = 36 **Birth within 7 days n = 10** Likelihood ratio (positive) = 4.3 (2.1 to 9.8 Likelihood ratio (negative) = 0.3 (0.2 to 0.5) Sensitivity = 68.6% Specificity = 84.4% RR = 14.6 (95% CI 4.3 to 49.9) p < 0.001 No adequate data reported to calculate confidence intervals for all diagnostic accuracy features.	**Limitations** **QUADAS checklist** Was the spectrum of participants representative of the patients who will receive the test in practice? Yes Were selection criteria clearly described? Yes Was the reference standard likely to classify the target condition correctly? Yes Was the period between performance of the reference standard and the index test short enough to be reasonably sure that the target condition did not change between the two tests? N/A

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
	• Cervix < 3 m dilated **Exclusion Criteria** • Cervial manipulation within the previous 24 hours (intercourse, vaginal examination, vaginal ultrasonic scan) • Presence of cervical cerclage • Pre-eclampsia • Hyperthyroidism • Asthma • Diabetes • Massive vaginal bleedings		cervix at least 1cm with 50% effacement on initial examination and cervical changes of effacement and dilatation 2 hours later. <u>Use of tocoloysis</u> Used at the discretion of the practitioner. Fetal fibronectin positive = 34, fetal fibronectin negative = 29, p = NS **<u>Statistical analysis</u>** All analyses performed using SPSS 10.0 statistical package.		Did the whole sample or a random selection of the sample receive verification using the reference standard? Yes Did participants receive the same reference standard regardless of the index test result? Yes Was the reference standard independent of the index test? (that is, the index test did not form part of the reference standard) Yes Was the execution of the index test described in sufficient detail to permit its replication? Yes Was the execution of the reference standard

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					described in sufficient detail to permit its replication? Yes Were the index test results interpreted without knowledge of the results of the reference standard? Unclear Were the reference standard results interpreted without knowledge of the results of the index test? N/A Were the same clinical data available when the test results were interpreted as would be available when the test is used in practice? Yes Were uninterpretable, indeterminate or intermediate test results reported? N/A

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					Were withdrawals from the study explained? N/A
Full citation Tanir,H.M., Sener,T., Yildiz,Z., Cervical phosphorylated insulin-like growth factor binding protein-1 for the prediction of preterm delivery in symptomatic cases with intact membranes, Journal of Obstetrics and Gynaecology Research, 35, 66-72, 2009 **Ref Id** 258096 **Country/ies where the study was carried out** Turkey **Study type** Prospective cohort study **Aim of the study** To assess the efficacy of a pIGFBP-1 test at first admission in symptomatic women with intact members for predicting impending pre-term birth **Study dates** January 2004 to June 2006. **Source of funding** Not reported.	**Sample size** N = 68 **Characteristics** pIGFBP-1 positive group n=52 pIGFBP-1 negative group n=43 **Mean maternal age (years) ± SD** pIGFBP-1 positive group = 28.4 ± 4.6 pIGFBP-1 negative group = 28.4 ± 5.3 **Mean gestation at admission (weeks) ± SD** pIGFBP-1 positive group = 30.6 ± 3.5 pIGFBP-1 negative group = 29.6 ± 2.3 **Mean BMI (kg/m2) ± SD** pIGFBP-1 positive group = 25.1 ± 3.5 pIGFBP-1 negative group = 26.9 ± 4.4 **Mean gravidity ± SD** pIGFBP-1 positive group = 2.1 ± 1.3 pIGFBP-1 negative group = 2.2 ± 1. **Inclusion Criteria**	**Tests** **Index test** A pIGFBP-1 test with an unknown theshold value for a positive result **Reference standard** Birth within 7 days.	**Methods** **Details** A rapid bedside test kit (Actim Partus test) for the detection of pIGFBP-1 in cervical secretions was used. Following sterile speculum insertion, and a check for signs of infection, a cervical secretion specimen was obtained using a Dacron swab. The swab was placed in extraction solution, mixed and removed. The bottom of the dipstick was placed in the solution, then removed after 20 to 40 seconds. The dipstick was placed horizontally. A negative result appeared as a single blue line and a positive result was apparent as two blue lines. The cut off values for the test are not reported. In two cases there were no visible lines and these patients were assigned as test positive. The managing obstetrician was blinded to the results of the test. Definition of pre-term labour	**Results** **pIGFBP-1 test positive to diagnose birth within 7 days** N = 68 TP: 14 FP: 11 FN: 1 TN: 42 Likelihood ratio (positive) = 4.50 (2.53 to 5.25)* Likelihood ratio (negative) = 0.08 (0.004 to 0.42* Sensitivity = 93.3% (69.6 to 99.6)* Specificity = 79.2% (72.5 to 81.0)* *Calculated by the NCC-WCH technical team.	**Limitations** **QUADAS checklist** Was the spectrum of participant's representative of the patients who will receive the test in practice? Yes Were selection criteria clearly described? Yes Was the reference standard likely to classify the target condition correctly? Yes Was the period between performance of the reference standard and the index test short enough to be reasonably sure that the target condition did not change between the two tests? Yes

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
	• Symptoms suggestive of pre-term labour (regular uterine contractions at 10/hour, low back pain, minimal vaginal bleeding, increased vaginal discharge) • Gestational ages between 24 and 37 weeks • < 3cm cervical dilation • Intact membranes **Exclusion Criteria** • Cervical cerclage • Massive vaginal bleeding • Tocolysis at admission • Cervical manipulation (vaginal douche, intercourse or digitalexmination within the previous 24h) • Pre-eclampsia • Multiple pregnancy • diabetes mellitus • Hyperthyroidism • Asthma		A diagnosis of pre-term labour was made when 1) there were painful contractions, that were palpable, lasted longer than 30s and occurred at least 4 times in 20minutes 2) evidence of a change in the position, consistency, length and/or dilation of the cervix. Use of tocolysis Decisions regarding tocolytic and steroid use were made by the managing physicians. Symptomatic treatment included IV ritodrine hydrochloride or magnesium sulphate. Betamethasone was given twice daily to enhance fetal lung maturation where indicated. pIGFBP-1 positive group = 23/52, pIGFBP-1 negative group = 40/43. **Statistical analysis** SPSS was used for data analysis. It was caculated that 66 participants would be needed to yield a significant association between pIGFBP-1 and birth < 34 weeks or dirth within 7 days of admission. This assumed a pre-term birth rate of 7% in the low risk group (testing negative) and 30% in the high risk group (testing positive).		Did the whole sample or a random selection of the sample receive verification using the reference standard? The whole sample Did participants receive the same reference standard regardless of the index test result? Yes Was the reference standard independent of the index test? (that is, the index test did not form part of the reference standard) Yes Was the execution of the index test described in sufficient detail to permit its replication? Yes Were the index test results

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					interpreted without knowledge of the results of the reference standard? Unclear Were the reference standard results interpreted without knowledge of the results of the index test? N/A **Other information** An unknown number of women had a multiple pregnancy although this was an exclusion criterion. Women could be recruited up to gestation of 37 weeks. It is not known how many were over 36 weeks' gestation, therefore an unknown number of births within 7

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					days were at term rather than being pre-term.
Full citation Tekesin,I., Marek,S., Hellmeyer,L., Reitz,D., Schmidt,S., Assessment of rapid fetal fibronectin in predicting preterm delivery, Obstetrics and Gynecology, 105, 280-284, 2005 **Ref Id** 235257 **Country/ies where the study was carried out** Germany **Study type** Prospective cohort study **Aim of the study** To estimate the effectiveness of cervical fetal fibronectin assayed by the rapid fetal fibronectin assay in predicting preterm delivery in patients with signs or symptoms of pre-term labour. **Study dates** November 2001 to January 2004. **Source of funding** Not reported.	**Sample size** N = 170 **Characteristics** Women with fibronectin positive and negative result were similar with respect to: • Mean maternal age • Mean parity • Nulliparity • Multiparity • Mean gravidity • Gestational age at enrolment Women with a positive fibronectin test had significantly fewer previous pre-term births, a lower gestational age at birth and shorter admission to birth interval. **Gestational age** Fetal fibronectin negative (n = 124) = 38.6 ± 2.5 weeks Fetal fibronectin positive results (n = 46) = 35.71 ± 3 weeks P < 0.001 **Admission-to-delivery interval** Fetal fibronectin negative (n =	**Tests** **Index test** Fetal fibronectin test with a cut-off of > 50ng/ml for a positive test result. **Reference test** Birth within 7 days.	**Methods** **Details** Women with preterm labor that meet the inclusion criteria were included. Samples were obtained using speculum examination and a swab of the cervix by placing a dry Dacron swab against the area for 10 seconds. The probe was analysed using the rapid fetal fibronectin TLi System qualitative method, with result reported as either positive (≥ 50ng/mL) or negative (< 50ng/mL)). Digital examination performed after the fibronectin test, to estimate cervical dilatation and effacement. Gestational age of eligible women was determined using the date of the last menstrual period. If menstrual data were unreliable or discordant by more than 10 days gestational age was determined by ultrasound. Managing obstetricians were blinded to fetal fibronectin results. Outcome data were collected after birth.	**Results** **Time of birth within 7 days** Sensitivity = 81.8% (48.2 to 97.7) Specificity = 76.7% (69.4 to 83.1)	**Limitations** **QUADAS checklist** Was the spectrum of participant's representative of the patients who will receive the test in practice? Yes Were selection criteria clearly described? Yes Was the reference standard likely to classify the target condition correctly? Yes Was the reference standard likely to classify the target condition correctly? Yes Was the period between performance of the reference standard and the index test short enough to be reasonably sure

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
	124)= 36.1 ± 29.9 weeks Fetal fibronectin positive results (n = 46) = 63.4 ± 29.2 weeks P < 0.001 **Inclusion Criteria** • Between 24 and 34 weeks + 6 days of gestation • Singleton pregnancies • Intact membranes • Women with the symptoms of pre-term labour **Exclusion Criteria** • Confirmed rupture of membranes • Multiple gestations • Placenta previa • Vaginal bleeding of unknown cause • Intrauterine growth restriction of fetus • Pre-eclampsia • Known untreated cervical infection • Suspected fetal asphyxia • A major fetal anomaly • Cervical dilation ≥ 3cm • Presence of cervical cerclage		Definition of preterm labour Preterm labour was defined as the presence of uterine contractions happening at the frequency of 4 in 20 minutes or 8 at 1 hour or any uterine activity associated with the changes of cervical effacement up to 50% or more and dilatation of at least 2cm. Use of tocolysis Based on the hospital policy all pre-term labour between 24 weeks to 34 weeks' gestation were either given magnesium sulfate or β-mimetics as a tocolytic agent. **Statistical analysis** Continuous variables were analysed with Mann-Whitney U test and nominal data were analysed with the X^2 test. Data were analysed carried out using SPSS 11.0 for Windows.		that the target condition did not change between the two tests? N/A Did the whole sample or a random selection of the sample receive verification using the reference standard? Yes Did participants receive the same reference standard regardless of the index test result? Yes Was the reference standard independent of the index test? (that is, the index test did not form part of the reference standard) Yes Was the execution of the index test described in sufficient detail to permit its replication? Yes

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
	• Uterine abnormalities • Cervical manipulation within the previous 24 hours (intercourse, vaginal examination, vaginal ultrasonic scan)				Were the index test results interpreted without knowledge of the results of the reference standard? Unclear Were the reference standard results interpreted without knowledge of the results of the index test? N/A Were the same clinical data available when the test results were interpreted as would be available when the test is used in practice? Yes Were uninterpretable, indeterminate or intermediate test results reported? N/A Were withdrawals from the study explained? N/A

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
Full citation Ting,H.S., Chin,P.S., Yeo,G.S., Kwek,K., Comparison of bedside test kits for prediction of preterm delivery: phosphorylated insulin-like growth factor binding protein-1 (pIGFBP-1) test and fetal fibronectin test, Annals of the Academy of Medicine, Singapore, 36, 399-402, 2007 **Ref Id** 235346 **Country/ies where the study was carried out** Singapore **Study type** Prospective cohort study **Aim of the study** To compare the effectiveness of pIGFBP-1 and fFN bedside test kits in predicting pre-term delivery **Study dates** January 2003 to January 2005 **Source of funding** Funded through a Singhealth Research Grant	**Sample size** N=94 **Characteristics** The following demographic data were collected: maternal age, gestational age at admission, gravidity, parity and mean cervical dilation. These are presented by for pIGFBP-1 testing status (+ve or -ve), and fFN testing status (+ve or -ve). Demographic data were similar within testing groups except for mean cervical dilation in both testing groups **Inclusion Criteria** • Singleton pregnancies • Women with symptoms suggestive of pre-term labour • Gestational age between 24 and 34 weeks • Intact membranes **Exclusion Criteria** • Pre-term rupture of membranes • Placenta previa • Multiple pregnancy • Cervical dilatation ≥ 3cm • Cervical cerclage suture • Chorioamnionitis	**Tests** Index test A pIGFBP-1 test with a threshold value of >10micrograms for a positive result Index test A fFN test with an unknown theshold value for a positive result Reference standard Delivery within 48 hours Delivery within 7 days	**Methods** Index test Test: A rapid strip test (Actim Partus test) for the detection of pIGFBP-1 in cervical secretions was used Procedure: Following sterile speculum insertion, a cervical secretion specimen was obtained using a Dacron swab. The swab was placed in extraction solution, shaken and removed. The test strip was placed in the solution. After waiting 5 minutes, a negative result appeared as a single blue line and a positive result was apparent as two blue lines. The cut off values for the test are not reported. The managing obstetrician was blinded to the results of the test. Index test Test: A test kit (Actim Partus test) for the detection of fFN in cervico-vaginal secretions was used Procedure: Following sterile speculum insertion, a cervical secretion specimen was obtained using a Dacron swab. The swab was placed in extraction solution, shaken and removed. The test strip was placed in the solution. After waiting 5 minutes, a negative result appeared as a single blue line and a positive result was apparent as two	**Results** pIGFBP-1 test positive to diagnose birth within 48 hours N= 94 Sensitivity = 100% Specificity = 74% Positive LR = 3.85* Negative LR = NC* pIGFBP-1 test positive to diagnose birth within 7 days N= 94 Sensitivity = 69% Specificity = 78% Positive LR = 3.13* Negative LR =0.40* fFN test positive to diagnose birth within 48 hours N= 94 Sensitivity = 60% Specificity = 72% Positive LR = 2.14* Negative LR =0.56* fFN test positive to diagnose birth within 7 days N= 94 Sensitivity = 56% Specificity = 76% Positive LR = 2.33* Negative LR =0.73* *Calculated by NCC-WCH team	**Limitations** **QUADAS checklist** Was the spectrum of participant's representative of the patients who will receive the test in practice? Yes Were selection criteria clearly described? Yes Was the reference standard likely to classify the target condition correctly? Yes Was the period between performance of the reference standard and the index test short enough to be reasonably sure that the target condition did not change between the two tests? Yes Did the whole sample or a random selection of the sample receive verification using the reference standard? The

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
	• Intrauterine fetal growt restriction • Preeclampsia • Suspected fetal asphyxia • Major fetal anomaly		blue lines. The cut off values for the test are not reported. The managing obstetrician was blinded to the results of the test. Clinical care was offered to women in accordance with hospital guidelines for the management of pre-term labour. <u>Definition of pre-term labour</u> Not reported <u>Use of tocolysis</u> Management of preterm labour consisted of admission the delivery suite and tocolysis (oral nifedipine as first line treatment). Corticosteroid therapy (dexamethasone) was administered for fetal pulmonary maturation. **<u>Statistical analysis</u>** SPSS was used for data analysis. Levene's test for equality of variances and t test for equality of means were carried out.		whole sample Did participants receive the same reference standard regardless of the index test result? Yes Was the reference standard independent of the index test? (that is, the index test did not form part of the reference standard) Yes Was the execution of the index test described in sufficient detail to permit its replication? Yes Were the index test results interpreted without knowledge of the results of the reference standard? Unclear Were the reference standard results interpreted without knowledge of the results of the

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					index test? N/A
Full citation Tsoi,E., Fuchs,I.B., Rane,S., Geerts,L., Nicolaides,K.H., Sonographic measurement of cervical length in threatened preterm labor in singleton pregnancies with intact membranes, Ultrasound in Obstetrics and Gynecology, 25, 353-356, 2005 **Ref Id** 222229 **Country/ies where the study was carried out** Germany, South Africa and the United Kingdom **Study type** Prospective cohort study **Aim of the study** To examine the relationship between cervical length and birth within 48 hours or 7 days of presentation and before 35 weeks' gestation in women with threatened pre-term labour. **Study dates** Not reported. **Source of funding** Funded by the Fetal Medicine Foundation.	**Sample size** N = 510 **Characteristics** **Median maternal age, years (range)** 26 (16 to 41) **Parity, n (%)** Nulliparous = 232 (45.5%) Multiparous = 278 (54.5%) **Median gestational age, weeks (range)** 30.2 (24 to 33.9) **Use of tocolysis, n (%)** Yes = 265 (52.0%) **Ethnic origin, n (%)** Caucasian = 396 (77.6%) African = 83 (16.3%) Asian = 31 (6.1%) The number of women with previous pre-term delivery was not reported. **Inclusion Criteria** • Singleton pregnancies • Painful and regular contractions • Gestational age of 24 to 33+6 weeks	**Tests** **Index test** Cervical length ≤ 5mm, ≤ 10mm or ≤ 15mm as determined by transvaginal sonography at admission. **Reference standard** Birth within 48 hours or 7 days of presentation.	**Methods** **Details** This was a multicentre study involving 7 hospitals. Women who presented to the labour ward and met inclusion criteria were included in the study. Definition of pre-term labour Pre-term labour was not defined other than painful and regular uterine contractions. Active labour was defined as cervical dilation ≥ 3cm. Use of tocolysis Administration of tocolytic medication was determined by the attending obstetrician without consideration of ultrasound findings. **Statistical analysis** No relevant statistical analyses were carried out in relation to the protocol for this review. Sensitivity, specificity, likelihood ratios and associated confidence intervals were therefore calculated by the NCC-WCH technical team.	**Results** **Cervical length ≤ 5mm to diagnose birth within 48 hours of presentation** Likelihood ratio (positive) = 19.05 (7.93 to 41.84)* Likelihood ratio (negative) = 0.59 (0.39 to 0.78)* Sensitivity = 42.9% (24.2 to 61.2)* (9/21) Specificity = 97.8% (96.9 to 98.5)* (478/489) **Cervical length ≤ 5mm to diagnose birth within 7 days of presentation** Likelihood ratio (positive) = 43.44 (14.65 to 149.45)* Likelihood ratio (negative) = 0.63 (0.57 to 0.75)* Sensitivity = 37.2% (26.7 to 43.4)* (16/43) Specificity = 99.1% (98.2 to 99.7)* (463/467)	**Limitations** **QUADAS checklist** Was the spectrum of participants representative of the patients who will receive the test in practice? Yes Were selection criteria clearly described? Yes Was the reference standard likely to classify the target condition correctly? Yes Was the period between performance of the reference standard and the index test short enough to be reasonably sure that the target condition did not change between the two tests? Yes Did the whole sample or a

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
	Exclusion Criteria • Women with ruptured membranes • Active labour (cervical dilation ≥ 3cm)			**Cervical length ≤ 10mm to diagnose birth within 48 hours of presentation** Likelihood ratio (positive) = 12.77 (8.10 to 16.14)* Likelihood ratio (negative) = 0.20 (0.07 to 0.44)* Sensitivity = 81.0% (59.0 to 93.6)* (17/21) Specificity = 93.7% (92.7 to 94.2)* (458/489) **Cervical length ≤ 10mm to diagnose birth within 7 days of presentation** Likelihood ratio (positive) = 15.21 (9.30 to 23.68)* Likelihood ratio (negative) = 0.36 (0.24 to 0.51)* Sensitivity = 65.1% (51.5 to 76.5)* (28/43) Specificity = 95.7% (94.5 to 96.8)* (447/467) **Cervical length ≤ 15mm to diagnose birth within 48 hours of**	random selection of the sample receive verification using the reference standard? Yes Did participants receive the same reference standard regardless of the index test result? Yes Was the reference standard independent of the index test? (that is, the index test did not form part of the reference standard) Yes Was the execution of the index test described in sufficient detail to permit its replication? No Was the execution of the reference standard described in sufficient detail to

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
				<u>presentation</u> Likelihood ratio (positive) = 6.43 (4.91 to 6.62)* Likelihood ratio (negative) = 0.03 (0.00 to 0.25)* Sensitivity = 97.7% (78.8 to 100.0)* (21/21) Specificity = 84.8% (83.9 to 84.9)* (415/489) **<u>Cervical length ≤ 15mm to diagnose birth within 7 days of presentation</u>** Likelihood ratio (positive) = 8.61 (7.04 to 8.96)* Likelihood ratio (negative) = 0.03 (0.001 to 0.15)* Sensitivity = 97.7% (86.9 to 99.9)* (42/43) Specificity = 88.7% (87.7 to 88.9)* (414/467) *Calculated by the NCC-WCH technical team. #0.5 was added to each cell in the 2x2 table due to the presence of a zero	permit its replication? Yes Were the index test results interpreted without knowledge of the results of the reference standard? Unclear Were the reference standard results interpreted without knowledge of the results of the index test? N/A Were the same clinical data available when the test results were interpreted as would be available when the test is used in practice? No - history of previous pre-term labour was not reported. Were uninterpretable, indeterminate or intermediate test results

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
				value in one cell.	reported? N/A Were withdrawals from the study explained? N/A
Full citation Tsoi,E., Akmal,S., Geerts,L., Jeffery,B., Nicolaides,K.H., Sonographic measurement of cervical length and fetal fibronectin testing in threatened preterm labor, Ultrasound in Obstetrics and Gynecology, 27, 368-372, 2006 **Ref Id** 243476 **Country/ies where the study was carried out** United Kingdom and South Africa **Study type** Prospective cohort study **Aim of the study** To determine whether the combination of testing positive for a short cervix and fetal fibronectin provides a better prediction of birth within 7 days than each test alone in women with threatened pre-term labour. **Study dates** February 2002 to June 2003. **Source of funding** The Fetal Medicine Foundation (registered	**Sample size** N = 195 **Characteristics** **Median maternal age, years (range)** 27 (16 to 41) **Parity, n (%)** Nulliparous = 74 (37.9%) Parous = 121 (62.1%) **Previous pre-term delivery, n/N (%)** Yes = 24/195 (12.3%) **Ethnic origin, n (%)** Caucasian = 111 (56.9%) Afro-Caribbean = 63 (32.3%) Asian = 21 (10.8%) **Number of women administered tocolytic medication, n (%)** Yes = 42 (21.5%) **Inclusion Criteria** • Singleton pregnancies • Gestational age of 24 to 36 weeks	**Tests** Index test Fetal fibronectin as determined by speculum examination at presentation followed by transvaginal ultrasound. Reference standard Birth ≤ 7 days of presentation.	**Methods** **Details** The study was carried out at four hospitals (two in the UK , two in South Africa). Gestational age was calculated based on menstrual history and ultrasound in early pregnancy. A fetal fibronectin test was performed at presentation via speculum examination; specimens were collected from the posterior fornix or endo-cervix. No cut-off for a positive test is provided. Digital examination was then performed and women with cervical dilation > 3cm excluded. Transvaginal sonography was then carried out. The primary outcome was birth within 7 days of presentation. Definition of pre-term labour Women with cervical dilation >	**Results** **Fetal fibronectin to diagnose birth ≤ 7 days** Likelihood ratio (positive) = 2.49 (1.81 to 2.66)* Likelihood ratio (negative) = 0.09 (0.004 to 0.45)* Sensitivity = 94.7% (73.0 to 99.7)* (18/19) Specificity = 61.9% (59.6 to 62.5)* (109/176) *Calculated by the NCC-WCH technical team.	**Limitations** **QUADAS checklist** Was the spectrum of participants representative of the patients who will receive the test in practice? Yes Were selection criteria clearly described? Yes Was the reference standard likely to classify the target condition correctly? Yes Was the period between performance of the reference standard and the index test short enough to be reasonably sure that the target condition did not change between

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
charity).	• Presenting with painful and regular uterine contractions **Exclusion Criteria** • Women in active labour (cervical dilation ≥ 3 cm) • Women with ruptured membranes		3cm were excluded as they were deemed to be in active labour. Women included in the study were in suspected pre-term labour defined by painful and regular uterine contractions. Use of tocolysis Tocolytic medication was administered at the discretion of the attending obstetrician who was blinded to both ultrasound and fetal fibronectin test results. **Statistical analysis** ROC curves were used to compare the performance of the two index tests. No statistical analyses relevant for this review (likelihood ratios, sensitivity and specificity) were undertaken.		the two tests? Yes Did the whole sample or a random selection of the sample receive verification using the reference standard? Yes Did participants receive the same reference standard regardless of the index test result? Yes Was the reference standard independent of the index test? (that is, the index test did not form part of the reference standard) Yes Was the execution of the index test described in sufficient detail to permit its replication? Yes / No / Unclear / N/A Was the

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					execution of the reference standard described in sufficient detail to permit its replication? Yes Were the index test results interpreted without knowledge of the results of the reference standard? Yes / No / Unclear / N/A Were the reference standard results interpreted without knowledge of the results of the index test? N/A Were the same clinical data available when the test results were interpreted as would be available when the test is used in practice? Yes Were uninterpretable,

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					indeterminate or intermediate test results reported? Yes / No / Unclear / N/A Were withdrawals from the study explained? Yes / No / Unclear / N/A

H.8 Maternal corticosteroids

H.8.1 Different gestations

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Roberts,D., Dalziel,S., Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth. [69 refs], Cochrane Database of Systematic Reviews, CD004454-, 2013 **Ref Id** 247457	**Sample size** N = 21 trials N = 3885 women N = 4269 babies **Characteristics** *additional information which had to be accessed from the full text of the trials because it was not reported in the systematic review **<u>Amorim 1999</u>** **Inclusion criteria:** women with severe pre-eclampsia, singleton pregnancy with a live fetus and	**Interventions** A corticosteroid capable of crossing the placenta (betamethasone, dexmethsone, hydrocortisone) compared with placebo or with no treatment.	**Details** The Cochrane Pregnancy and Childbirth Group's Trials Register was searched in October 2005. The trial register contains trials identified from: - quartlerly searches of the Cochrane Central Register of Controlled Trials (CENTRAL) - weekly searches of MEDLINE - handsearches of 30 journals and the proceedings of major conferences	**Results** **<u>1. Maternal deaths</u>** Corticosteroids: 1/188 Control: 1/177 RR 0.98 (95% CI 0.06 to 15.50) I^2 = 0% [Fixed effect; 3 trials: Amorim 1999; Dexiprom 1999, Schutte 1980] **<u>2. Chorioamnionitis</u>** **All women** Corticosteroids: 91/1234 Control: 100/1251 RR 0.91 (95% CI 0.70 to 1.18) I^2 = 0%	**Limitations** **<u>Risk of bias of included studies, as assessed by the review authors and indirectness assessed by NCC-WCH technical team</u>** Additional notes from NCC-WCH technical team are marked with † **Amorim 1999** - Adequate method of randomisation and allocation concealment - 1% of women in the placebo group withdrew from the study following randomisation - No intention-to-treat analysis

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Country/ies where the study was carried out Various **Study type** Systematic review of randomised controlled trials **Aim of the study** To assess the effects of antenatal corticosteroids on fetal and neonatal morbidity and mortality, on maternal morbidity and mortality and on the child in later life **Study dates** The search was performed in October 2005; review content was assessed as up-to-date by the authors in May 2006. An updated search was performed in April 2010 and the results were added to the studies awaiting assessment section **Source of funding** Trinity College Dublin, Ireland;	gestational age between 26 and 34 weeks. **Exclusion criteria:** indication for immediate delivery, diabetes, premature rupture of membranes (PROM), maternal disease, congenital malformations, perinatal haemolytic disease, Group B strep infection **Sample size:** N = 220 women **Intervention:** 12mg betamethasone intramuscularly (IM), repeated after 24h and weekly thereafter if delivery had not occurred **Comparator:** Identical placebo **Other details of care:** delivery was at 34 weeks or in the presence of maternal or fetal compromise in both groups. **Gestational age at intervention:** *[at admission] mean ± SD: experiemental = 29.3 weeks ± 2.9; control = 29.6 weeks ± 2.7 **Gestational age at delivery:** *mean ± SD: experimental = 31.8 weeks ± 2.0; control = 32.0 weeks ± 2.0 **Term deliveries:** *not reported **Interval between drug administration and delivery:** *not clearly reported **Block 1977** **Inclusion criteria:** women with preterm labour and PROM. Gestational age range not reported		- weekly current awareness of alerts for a further 44 journals plus monthly BioMed Central email alterts No language restrictions were applied **Data collection and analysis** Two review authors assessed trials for eligibility and methodological quality without consideration of results. Two review authors extracted data and checked for discrepancies, and contacted trialists for further information. Disagreements were resolved through discussion. Allocation concealment was assessed using criteria described in Cochrane Handbook (2005) as adequate, unclear, inadequate, or not used. Outcomes were analysed on an intention-to-treat basis. Statistical analysis was performed using Review Manager 4.1. **Subgroup analysis** The following subgroup analyses were done: - gestational age at delivery (< 28 weeks, < 30 weeks, < 32 weeks, < 34 weeks, < 36 weeks, at least 34 weeks, at least 36 weeks)	[Fixed effect; 12 trials: Amorim 1999; Carlan 1991; Dexiprom 1999; Fekih 2002; Garite 1992; Kari 1994; Lewis 1996; Liggins 1972; Morales 1989; Qublan 2001; Schutte 1980; Silver 1996] **Women with PROM at first dose** Corticosteroids: 52/460 Control: 52/459 RR 1.00 (95% CI 0.70 to 1.43) I^2 = 0% [Fixed effect; 6 trials: Carlan 1991; Dexiprom 1999; Lewis 1996; Liggins 1972; Morales 1989; Qublan 2001] **First dose < 26 weeks gestation** Corticosteroids: 6/22 Control: 3/24 RR 2.18 (95% CI 0.62 to 7.69) I^2 = NC [Fixed effect; 1 trial: Liggins 1972] **First dose between 26 and < 30 weeks gestation** Corticosteroids: 17/129 Control: 14/113 RR 1.06 (95% CI 0.55 to 2.06) I^2 = NC [Fixed effect; 1 trial: Liggins 1972] **First dose between 30 and < 33 weeks gestation** Corticosteroids: 2/150	- Unclear whether any women received tocolysis (not described as component of care protocol) - Unclear how many women received the full dose (2 injections) Indirectness: All women had pre-eclampsia. Unclear how many women received more than a single course of corticosteroids **Block 1977** - Adequate method of randomisation and allocation concealment - 10% of women delivered elsewhere and were lost to follow up; losses were balanced across groups. One woman in experimental and three women in control group excluded from analysis as they failed to complete the protocol - No intention-to-treat anaylsis - Unclear how many women received alcohol to delay labour - 70% of women received the maximum of 2 doses Indirectness: Unclear whether women with a multiple pregnancy included. **Cararach 1991** - Abstract only; no further data supplied by study authors - Unclear allocation concealment and method of randomisation - No losses to follow up - Intention-to-treat analysis Indirectness: All women had

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
University of Liverpool, UK; Liverpool Women's NHS Foundation Trust, UK; University of Auckland, New Zealand	**Exclusion criteria:** not stated **Sample size:** N = 167 women **Intervention:** 12 mg betamethasone IM repeated after 24h if delivery had not occurred (max 2 doses) **Comparator:** 1ml normal saline IM repeated after 24h if delivery had not occurred (max 2 doses) **Other details of care:** if there was evidence of progressive cervical dilatation an alcohol infusion was given to delay deliver for 48h (numbers not reported). In women with PROM delivery was induced if serial white blood cell counts or temperatures became elevated regardless of time elapsed since drug administration **Gestational age at intervention:** *not reported **Gestational age at delivery:** *not reported **Term deliveries:** *not reported **Interval between drug administration and delivery:** not clearly reported **<u>Cararach 1991</u>** **Inclusion criteria:** women with PROM and gestational age between 28 and 30 weeks **Exclusion criteria:** not stated **Sample size:** N = 18 women **Intervention:** type and dose of corticosteroid not reported **Comparator:** expectant management **Other details of care:** none		- entry to delivery interval (< 24 hours, < 48 hours, 1–7 days, > 7 days) - prelabour rupture of membranes (at trial entry, > 24 hours before delivery, > 48 hours before delivery - pregnancy-induced hypertension syndromes - type of glucocorticoid (betamethasone, dexamethasone, hydrocortisone) Post hoc subgroup analysis was performed for gestational age at entry to trial (< 26 weeks, between 26 and 29+6 weeks, between 30 and 32+6 weeks, between 33 and 34+6 weeks, between 35 and 36+6 weeks, > 37 weeks)	Control: 10/144 RR 0.19 (95% CI 0.04 to 0.86) I^2 = NC [Fixed effect; 1 trial: Liggins 1972] **First dose between 33 and < 35 weeks gestation** Corticosteroids: 3/158 Control: 7/175 RR 0.47 (95% CI 0.12 to 1.80) I^2 = NC [Fixed effect; 1 trial: Liggins 1972] **First dose 35 and < 37 weeks gestation** Corticosteroids: 0/81 Control: 3/100 RR 0.18 (95% CI 0.01 to 3.36) I^2 = NC [Fixed effect; 1 trial: Liggins 1972] **First dose > 37 weeks gestation** Corticosteroids: 0/16 Control: 0/24 RR 0.00 (95% CI 0.00 to 0.00) I^2 = NC [Fixed effect; 1 trial: Liggins 1972] **<u>3. Puerperal sepsis</u>** **All women** Corticosteroids: 57/496 Control: 44/507 RR 1.35 (95% CI 0.93 to 1.95) I^2 = 36%	PROM. Details of intervention not reported. **Carlan 1991** - Unclear allocation concealment and method of randomisation - 2/24 (8%) infants with documented pulmonary maturity and 5/24 (17%) women with subsequent sealed membranes were not analysed - No intention-to-treat analysis Indirectness: All women had PROM. Unclear how many women received more than a single course of corticosteroid **Collaborative 1981** - Inadequate method of allocation concealment and unclear method of randomisation - 37% of children were lost to follow up at age 3 (balanced across groups) - No intention-to-treat anaylsis - † Significant difference in gestational age distribution between the groups when split into age groups (< 30 wks, 30 and 31 wks, 32 and 33 wks, ≥ 34 wks) which the authors state was adjusted for in the analysis - † 54% of women in corticosteroid group and 51% of women in placebo group received a tocolytic - † Nearly 70% of women received the full course of corticosteroids (4 injections), 79% received three or more, almost

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	reported **Interval between drug administration and delivery:** data not available (full text of paper not accessed by NCC-WCH techincal team) **<u>Carlan 1991</u>** **Inclusion criteria:** women with ruptured membranes and gestational age between 24 and 34 weeks **Exclusion criteria:** not stated **Sample size:** N = 24 women **Intervention:** 12mg betamethasone IM repeated after 24h and weekly thereafter until delivery at 34 weeks **Comparator:** expectant managment **Other details of care:** none reported **Gestational age at intervention:** *[at rupture of memranes] mean (SD not reported): experimental = 31 weeks; control = 30 weeks **Gestational age at delivery:** *not reported **Term deliveries:** *not reported **Interval between drug administration and delivery:** *[rupture of membranes to delivery] mean (SD not reported): experimental = 191.7 hours; control = 312.7 hours **<u>Collaborative 1981</u>** **Inclusion criteria:** women at high risk of preterm delivery and			[Fixed effect; 8 trials: Amorim 1999; Dexiprom 1999; Garite 1992; Lewis 1996; Qublan 2001; Schutte 1980; Silver 1996; Taeusch 1979] **Women with PROM at first dose** Corticosteroids: 16/242 Control: 14/235 RR 1.11 (95% CI 0.55 to 2.25) I^2 = 41% [Fixed effect; 4 trials: Dexiprom 1999; Lewis 1996; Qublan 2001; Schutte 1980] **<u>4. Fever in women after trial entry requiring antibiotics</u>** Corticosteroids: 37/234 Control: 37/247 RR 1.11 (95% CI 0.74 to 1.67) I^2 = 61% [Fixed effect; 4 trials: Amorim 1999; Nelson 1985; Schutte 1980; Taeusch 1979] **Women with PROM at first dose** Corticosteroids: 11/110 Control: 14/108 RR 0.77 (95%CI 0.37 to 1.62) I^2 = 0% [Fixed effect; 1 trial: Amorim 1999] **<u>5. Intrapartum fever in women requiring antibiotics</u>** Corticosteroids: 3/160 Control: 5/159 RR 0.60 (95% CI 0.15 to 2.49)	90% received at least 2 doses Indirectness: 8% of women had a multiple pregnancy **Dexiprom 1999** - Adequate allocation concealment and method of randomisation - 3% of women were excluded from analysis - No intention-to-treat analysis - † 20% of women in corticosteroid group and 16% of women in placebo group received a tocolytic - † 77% of women received the full course of corticosteroids (2 injections) Indirectness: All women had PROM. 2% of women had a multiple pregnancy **Doran 1980** - Unclear allocation concealment and method of randomisation - Gestational age was significantly lower in the control group at both entry to the study (1.2 weeks) and at delivery (1.8 weeks) - No losses to follow up - Intention-to-treat analysis - † 12% of women in corticosteroid group and 35% of women in placebo group received a tocolytic - † 67% of women received the full course of corticosteroids (4 injections) Indirectness: 5% of women had a

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	gestational age between 26 and 37 weeks **Exclusion criteria:** > 5 cm cervical dilatation, anticipated delivery < 24 or > 7 days, intrauterine infection, previous glucocorticoid treatment, history of peptic ulcer disease, active tuberculosis, viral keratitis, severe fetal Rh sensitisation, infant unlikely to be available for follow up **Sample size:** N = 696 women, N = 757 babies **Intervention:** 5mg dexamethasone IM, 4 doses 12h apart **Comparator:** Placebo **Other details of care:** in some cases labour was arrested for at least 48h with tocolytic agents (53.9% in the corticosteroid group and 50.7% in the placebo group received at least one tocolytic drug); tocolysis was halted if labour continued to progress to a cervical dilatation of 5cm or if complications arose **Gestational age at intervention:** *[at trial entry] mean ± SD: experimental = 31.1 weeks ± 0.12; control = 31.4 weeks ± 0.12 **Gestational age at birth:** *not reported **Term deliveries:** *not reported **Interval between drug administration and delivery:** mean (SEM): experimental = 252 (29) hours; control = 239			I^2 = 36% [Fixed effect; 2 trials: Amorim 1999; Schutte 1980] **6. Postnatal fever in women** Corticosteroids: 50/663 Control:54/660 RR 0.92 (95% CI 0.64 to 1.33) I^2 = 0% [Fixed effect; 5 trials: Amorim 1999; Collaborative 1981; Dexiprom 1999; Fekih 2002; Schutte 1980] **7. Side-effects of therapy in women** Corticosteroids: 0/50 Control: 0/51 RR 0.00 (95% CI 0.0 to 0.0) I^2 = NC [Fixed effect; 1 trial: Schutte 1980] **8. Fetal and neonatal deaths** **All women** Corticosteroids: 261/1813 Control: 341/1814 RR 0.77 (95% CI 0.67 to 0.89) I^2 = 38% [Fixed effect; 13 trials: Amorim 1999; Block 1977; Collaborative 1981; Dexiprom 1999; Doran 1980; Gamsu 1989; Garite 1992; Kari 1994; Liggins 1972; Parsons 1988; Qublan 2001; Schutte 1980; Taeusch 1979] **Women with PROM** Corticosteroid: 55/368	multiple pregnancy. **Fekih 2002** - Unclear allocation concealment and method of randomisation - Numbers lost to follow up not reported - No intention-to-treat analysis Indirectness: Included women with multiple pregnancy but percentage cannot be calculated by NCC-WCH techincal team from data reported in Cochrane review **Gamsu 1989** - Unclear allocation concealment and method of randomisation - No losses to follow up - Intention-to-treat analysis Indirectness: 6% of women had a multiple pregnancy **Garite 1992** - Adequate allocation concealment and method of randomisation - 7% delivered elsewhere and were lost to follow up - No intention-to-treat analysis Indirectness: 8% of women had a multiple pregnancy. Unclear how many women received more than a single course of corticosteroid **Kari 1994** - Unclear allocation concealment and method of randomisation - 11% of infants were lost to follow up †at 2 years

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	(29) hours. No significant difference between groups **Dexiprom 1999** **Inclusion criteria:** women with PROM and gestational age between 28 and 34 weeks or estimated fetal weight between 1000g and 2000g if gestational age unknown **Exclusion criteria:** cervical dilatation > 4cm, evidence of infection, evidence of antepartum haemorrhage, < 19 years old **Sample size:** N = 204 women, N = 208 babies **Intervention:** 12mg dexamethsone IM, 2 doses 24h apart **Comparator:** Placebo **Other details of care:** All women received ampicillin and metronidazole. Hexaprenaline was used if the woman was in labour on admission or went into labour within 24h of admission (20% of women in corticosteroid group and 16% of women in placebo group, no P value reported). 77% of women received both injections of corticosteroid **Gestational age at intervention:** *[at trial entry] mean ± SD: experiental = 31.02 weeks ± 2.27; control = 30.57 weeks ± 2.14 **Gestational age at delivery:** *not reported			Control: 88/365 RR 0.62 (95% CI 0.46 to 0.82) I^2 = 34% [Fixed effect; 4 trials: Dexiprom 1999; Liggins 1972; Parsons 1988; Qublan 2001] **First dose < 26 weeks gestation** Corticosteroids: 15/23 Control: 17/26 RR 1.00 (95% CI 0.66 to 1.50) I^2 = NC [Fixed effect; 1 trial: Liggins 1972] **First dose between 26 and < 30 weeks gestation** Corticosteroids: 50/140 Control: 54/121 RR 0.89 (95% CI 0.59 to 1.08) I^2 = NC [Fixed effect; 1 trial: Liggins 1972] **First dose between 30 and < 33 weeks gestation** Corticosteroids: 19/165 Control: 30/154 RR 0.59 (95% CI 0.35 to 1.01) I^2 = NC [Fixed effect; 1 trial: Liggins 1972] **First dose between 33 and < 35 weeks gestation** Corticosteroids: 18/168 Control: 18/185 RR 1.10 (95% CI 0.59 to 2.05) I^2 = NC	- Intention-to-treat analysis Indirectness: 20% of women had a multiple pregnancy. **Lewis 1996** - Adequate allocation concealment and method of randomisation - 2% of women left hospital after randomisation and were lost to follow up - No intention-to-treat analysis Indirectness: All women had PROM. Unclear how many women received more than a single course of corticosteroid **Liggins 1972** - Adequate allocation concealment and method of randomisation - 18% of infants were lost to follow up in the study at 4 to 6 years of age; 44% of adults were lost to follow up in the study at 30 years of age - Intention-to-treat analysis Indirectness: 6% of women had a multiple pregnancy **Morales 1989** - Unclear method of randomisation and allocation concealment - No losses to follow up - No intention-to-treat analysis Indirectness: Unclear how many women received more than a single course of corticosteroid

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	Term deliveries: *not reported **Interval between drug administration and delivery:** Deliveries > 24h: experimental group = 74 women (73%); control group = 84 women (82%) **<u>Doran 1980</u>** **Inclusion criteria:** women with PROM, spontaneous preterm labour or planned elective preterm delivery, and gestational age between 24 and 34 weeks **Exclusion criteria:** women with pre-eclampsia, or in whom steroids were contraindicated on medical grounds **Sample size:** N = 137 women, N = 144 babies **Intervention:** 3mg betamethasone acetate and 3mg betamethsone sodium phosphate IM, 4 doses 12h apart **Comparator:** Placebo **Other details of care:** Alcohol or isoxsuprine were used to supress labour, at the discretion of the individual obstetrician: 12% of women in corticosteroid group and 35% of women in placebo group received a tocolytic. 67% received 4 injections, 10% received 3 injections, 8% received 2 injections and 15% received one injection (four injection course)			[Fixed effect; 1 trial: Liggins 1972] **First dose 35 and <37 weeks gestation** Corticosteroids: 3/87 Control: 3/107 RR 1.23 (95% CI 0.25 to 5.94) I^2 = NC [Fixed effect; 1 trial: Liggins 1972] **First dose > 37 weeks gestation** Corticosteroids: 3/18 Control: 0/24 RR 9.21 (95% CI 0.51 to 167.82) I^2 = NC [Fixed effect; 1 trial: Liggins 1972] **<u>9. Chronic lung disease</u>** **All women** Corticosteroids: 48/413 Control: 59/405 RR 0.86 (95% CI 0.61 to 1.22) I^2 = 65% [Fixed effect; 6 trials: Amorim 1999; Garite 1992; Kari 1994; Morales 1989; Silver 1996; Taeusch 1979] **Women with PROM at first dose** Corticosteroids: 23/87 Control: 41/78 RR 0.50 (95% CI 0.33 to 0.76) I^2 = NC	**Nelson 1985** - Adequate allocation concealment and method of randomisation - No losses to follow up - Intention-to-treat analysis - Study contained 3 arms. Group 1: betamethasone plus tocolysis with delivery instituted between 24 and 48h after initial PROM and 24h after corticosteroids; group 2: tocolysis with delivery insituted between 24 and 48h after initial PROM and 24 after corticosteroids; group 3: expectant management. Group 3 was excluded from anaylsis in the review Indirectness: All women had PROM **Parson 1988** - Unclear method of randomisation and allocation concealment - No losses to follow up - Intention-to-treat analysis Indirectness: Unclear how many women received more than a single course of corticosteroid **Qublan 2001** - Adequate method of randomisation, unclear allocation concealment - No losses to follow up - Intention-to-treat analysis Indirectness: Unclear how many women received more than a single course of corticosteroid

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	Gestational age at intervention: *mean ± SD: experimental = 30.3 weeks ± 2.9; control = 29.1 weeks ± 2.9 **Gestational age at delivery:** *mean ± SD: experimental = 33.6 weeks ± 4.6; control = 31.8 weeks ± 4.6 **Term deliveries:** *not reported **Interval between drug administration and delivery:** *not reported **<u>Fekih 2002</u>** **Inclusion criteria:** women in preterm labour and gestational age between 26 and 34 weeks **Exclusion criteria:** gestational diabetes, > 4cm cervical dilatation, fetal abnormalities, contraindication to corticosteroids, delivery elsewhere or after 34 weeks (post-randomisation exclusions) **Sample size:** N = 118 women, N = 131 babies **Intervention:** 12mg betamethasone IM, 2 doses 24h apart **Comparator:** Expectant management **Other details of care:** not reported **Gestational age at intervention:** data not available (full text of paper not accessed by NCC-WCH technical team) **Gestational age at delivery:** data not available (full text of paper not accessed by NCC-			[Fixed effect; 1 trial: Morales 1989] **<u>10. Cerebroventricular haemorrhage</u>** **All women** Corticosteroids: 88/1445 Control: 155/1427 RR 0.54 (95% CI 0.43 to 0.69) I^2 = 32% [Fixed effect; 13 trials: Amorim 1999; Dexiprom 1999; Doran 1980; Fekih 2002; Gamsu 1989; Garite 1992; Kari 1994; Lewis 1996; Liggins 1972; Morales 1989; Qublan 2001; Silver 1996; Taeusch 1979] **Women with PROM at first dose** Corticosteroids: 19/454 Control: 38/441 RR 0.47 (95% CI 0.28 to 0.79) I^2 = 0% [Fixed effect; 5 trials: Dexiprom 1999; Lewis 1996; Liggins 1972; Morales 1989; Qublan 2001] **First dose < 26 weeks gestation** Corticosteroids: 3/15 Control: 2/15 RR 1.20 (95% CI 0.24 to 6.06) I^2 = NC [Fixed effect; 1 trial: Liggins 1972] **First dose between 26 and < 30 weeks gestation**	**Schutte 1980** - Unclear method of randomisation and allocation concealment - 12% of infants were lost to follow up in the study at 10 to 12 years of age (twice as many in the control arm than in the experimental arm); 21% of adults were lost to follow up in the study at 20 years of age (losses to follow up balanced across groups) - No intention-to-treat analysis Indirectness: 16% of women had a multiple pregnancy **Silver 1996** - Adequate allocation concealment and method of randomisation - 40% of the 124 initially recruited women remained undelivered at 29 weeks and were excluded from analysis - No intention-to-treat analysis Indirectness: 14% of women had a multiple pregnancy. Unclear how many women received more than a single course of corticosteroid. All neonates included in analysis recevied prophylactic surfactant at birth **Taeusch 1979** - Unclear method of randomisation and allocation concealment - Maternal outcomes were not

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	WCH technical team) **Term deliveries:** *not reported **Interval between drug administration and delivery:** data not available (full text of paper not accessed by NCC-WCH technical team) **<u>Gamsu 1989</u>** **Inclusion criteria:** women with spontaneous or planned preterm delivery and gestational age < 34 weeks **Exclusion criteria:** contraindication to corticosteroids, contraindication to postponing delivery, diabetes, suspected intrauterine infection **Sample size:** N = 251 women, N = 268 babies **Intervention:** 4mg betamethsone IM, 6 doses 8h apart **Comparator:** Placebo **Other details of care:** All women with spontaneous labour received IV salbutamol **Gestational age at intervention:** *not reported **Gestational age at delivery:** *not reported **Term deliveries:** *not reported **Interval between drug administration and delivery:** < 24h = 61 women; 24 to 47h = 23 women; 48 to 95h = 23 women; 96 to 143h = 13 women; 144 to 168h = 5 women; > 168h = 126 women			Corticosteroids: 9/121 Control: 18/108 RR 0.45 (95% CI 0.21 to 0.95) I^2 = NC [Fixed effect; 1 trial: Liggins 1972] **First dose between 30 and < 33 weeks gestation** Corticosteroids: 1/155 Control: 4/140 RR 0.23 (95% CI 0.03 to 2.00) I^2 = NC [Fixed effect; 1 trial: Liggins 1972] **First dose between 33 and < 35 weeks gestation** Corticosteroids: 3/161 Control: 3/178 RR 1.11 (95% CI 0.23 to 5.40) I^2 = NC [Fixed effect; 1 trial: Liggins 1972] **First dose 35 and < 37 weeks gestation** Corticosteroids: 0/85 Control: 0/106 RR 0.00 (95% CI 0.0 to 0.0) I^2 = NC [Fixed effect; 1 trial: Liggins 1972] **First dose > 37 weeks gestation** Corticosteroids: 0/18 Control: 0/24 RR 0.00 (95% CI 0.0 to 0.0) I^2 = NC	available for 3% of women - No intention-to-treat analysis Indirectness: 10% of women had a multiple pregnancy **Teramo 1980** - Unclear method of randomisation and allocation concealment - No losses to follow up - Intention-to-treat analysis Indirectness: 8% of women had a multiple pregnancy **Other information** Data from trials involving the use of methyl-prednisolone (Block 1977; Schmidt 1984) were discarded as it has not been shown to induce lung maturation in animal models and is known to have altered placental transfer Some included trials had a protocol of weekly repeat doses if the mother remained undelivered. None of the trials reported outcomes separately for those exposed to repeat doses. Additional data were supplied by the study authors for the following trials: Amorim 1999, Dexiprom 1999, Liggins 1972 (individual patient data), Nelson 1985 **<u>Long-term follow-up of childhood outcomes</u>**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	Garite 1992 **Inclusion criteria:** women likely to deliver between 24h and 7 days with spontaneous preterm labour or planned preterm delivery **Exclusion criteria:** PROM, clinical or laboratory evidence of infection, contraindication to or previously given corticosteroids, diabetes **Sample size:** N = 76 women (N = 82 babies) **Intervention:** 6mg betamethasone acetate and 6mg betamethasone phosphate IM, 2 doses 24h apart and weekly thereafter if still < 28 weeks and thought likely to deliver within the next week **Comparator:** Placebo **Other details of care:** women undelivered after 28 weeks and 1 week past their last dose of study mediction were allowed glucocorticoids at the discretion of their physician **Gestational age at intervention:** *[at admission] mean ± SD: experimental = 25.5 weeks ± 1.2; control = 25.8 weeks ± 1.3 **Gestational age at delivery:** *not reported **Term deliveries:** *not reported **Interval between drug administration and delivery:** 0 to 1 days = 17 neonates; 2 to 7 days = 30 neonates; ≥ 8 days = 26 neonates			[Fixed effect; 1 trial: Liggins 1972] **11. Need for mechanical ventilation/CPAP** **All women** Corticosteroids: 62/286 Control: 92/283 RR 0.69 (95% CI 0.53 to 0.90) I^2 = 17% [Fixed effect; 4 trials: Amorim 1999; Block 1977; Dexiprom 1999; Garite 1992] **Women with PROM** Corticosteroids: 15/105 Control: 16/101 RR 0.90 (95% CI 0.47 to 1.73) I^2 = NA [Fixed effect; 1 trials: Dexiprom 1999] **12. Sepsis in the first 48h of life** **All women** Corticosteroids: 32/665 Control: 56/654 RR 0.56 (95% CI 0.38 to 0.85) I^2 = 0% [Fixed effect; 5 trials: Amorim 1999; Collaborative 1981; Dexiprom 1999; Gamsu 1989; Parsons 1988] **Women with PROM at first dose** Corticosteroids: 11/128 Control: 11/123 RR 0.96 (95% CI 0.44 to 2.12)	Amorim 1999: additional data supplied by author, no details reported in study report Collaborative 1981: Follow up performed before 1984; losses to follow up by 18 months of age = 45.2% Kari 1994: Follow up performed 1991 to 1994; losses to follow up = 54% Liggins 1972: Follow up performed before 1981; losses to follow up by 4 years of age = 74% Schutte 1980: Follow up performed between 1984 and 1987; losses to follow up at 10-12 years of age = 27% **Measurement of developmental childhood outcomes** **Neurodevelopmental delay** Kari 1994: "Severe disability" defined as tetraplegic cerebral palsy and/or a score < 70 on Bayley Scales for 2-year children. **Developmental delay** Collaborative 1981: Psychomotor Developmental Index of the Bayley Scales at 18 months of age (50 ≤ Index ≤ 67). Amorim 1999: not reported **Intellectual impairment** Collaborative 1981: Mental Developmental Index of the Bayley Scales at 18 months of age (50 ≤ Index ≤ 67) Liggins 1972: ≤ 70 on Stanford-

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	Kari 1994 **Inclusion criteria:** women with preterm labour or threatened preterm labour due to pre-eclampsia and gestational age 24 to 31.9 weeks **Exclusion criteria:** rupture of membranes, chorioamnionitis, congenital abnormalities, proven lung maturity, insulin-treated diabetes, previously treated with corticosteroids **Sample size:** N = 157 women (N = 189 babies) **Intervention:** 6mg dexamethasone sodium phosphate IM, 4 doses 12h apart **Comparator:** Placebo **Other details of care:** Rescue treatment with exogenous human surfactant was given to neonates born 24 to 33 weeks who at 2 to 24h of age required mechanical ventilation with > 40% oxygen for respiratory distress syndrome (RDS) **Gestational age at intervention:** *[at trial entry] mean ± SD: experimental = 28.9 weeks ± 2.1; control = 28.9 weeks ± 2.3 **Gestational age at delivery:** *mean ± SD: experimental = 31.5 weeks ± 3.6; control = 32.4 weeks ± 3.9 **Term deliveries:** *not reported **Interval between drug administration and delivery:**			I^2 = 0% [Fixed effect; 2 trials: Dexiprom 1999; Parsons 1988] **13. Cerebral palsy in childhood** Corticosteroids: 20/490 Control: 28/414 RR 0.60 (95% CI 0.34 to 1.03) I^2 = 0% [Fixed effect; 5 trials: Amorim 1999; Collaborative 1981; Kari 1994; Liggin 1972; Schutte 1980] **14. Visual impairment in childhood** Corticosteroids: 9/100 Control: 11/66 RR 0.55 (95% CI 0.24 to 1.23) I^2 = 0% [Fixed effect; 2 trials: Kari 1994; Schutte 1980] **15. Hearing impairment in childhood** Corticosteroids: 1/100 Control: 1/66 RR 0.64 (95% CI 0.04 to 9.87) I^2 = 0% [Fixed effect; 2 trials: Kari 1994; Schutte 1980] **16.Neurodevelopmental delay in childhood** Corticosteroids: 3/50 Control: 3/32 RR 0.64 (95% CI 0.14 to 2.98) I^2 = 0% [Fixed effect; 1 trial: Kari 1994]	Binet Intelligence Scale Schutte 1980: < 70 on Weschler Intelligence Scale for Children-Revised full-scale IQ **Behavioural/learning difficulties** Scutte 1980: children who had to repeated a class or required special education **Definitions of cerebroventricular haemorrhage in original papers (experimental n/N; control n/N)** Amorim 1999 - intraventricular haemorrhage Dexiprom 1999 - intraventricular haemorrhage Doran 1980 - cause of death was intraventricular haemorrhage - 1/80; 4/60 (unclear whether there were any other cases of IVH which did not result in death) Feikh - could not access original paper Gamsu 1989 - cause of death was intraventricular haemorrhage - 2/130; 4/132 (unclear whether there were any other cases of IVH which did not result in death) Garite 1992 - total cases of intraventricular haemorrhage - 10/33; 19/40: cases of grade 3 or 4 IVH - 1/33; 9/40 Kari 1994 - intraventricular haemorrhage Lewis 1996 - grade 3 or 4 intraventricular haemorrhage - 0/38; 3/39

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	*not reported **Lewis 1996** **Inclusion criteria:** women with singleton pregnancies with PROM, and gestational age between 24 and 34 weeks **Exclusion criteria:** evidence of infection, vaginal examination, cerclage, allergic to penicillin, contraindication to expectant management, lung maturity confirmed by L/S ratio if 32 weeks or more **Sample size:** N = 79 **Intervention:** 12g betamethasone IM, 2 doses 24h apart and repeated weekly if the women had not delivered **Comparator:** Expectant management **Other details of care:** all women received 3g ampicillin-sulbactam every 6h for 7 days **Gestational age at intervention:** [at rupture of membranes] mean ± SD: experimental = 29.3 weeks ± 3.0; control = 29.7 weeks ± 3.1 **Gestational age at delivery:** *not reported **Term deliveries:** *not reported **Interval between drug administration and delivery:** Latency period (mean ± SD): experimental group = 353.2 hours ± 230; control group = 378.4 hours ± 385			**17. Development delay in childhood** Corticosteroids: 11/266 Control: 19/252 RR 0.49 (95% CI 0.24 to 1.00) I^2 = 0% [Fixed effect; 2 trials: Amorim 1999; Collaborative 1981] **18. Intellectual impairment in childhood** Corticosteroids: 16/409 Control: 17/369 RR 0.86 (95% CI 0.44 to 1.69) I^2 = 0% [Fixed effect; 3 trials: Collaborative 1981; Liggins 1972; Schutte 1980] **19. Behavioural difficulties in childhood** Corticosteroids: 9/54 Control: 7/36 RR 0.86 (95% CI 0.35 to 2.09) I^2 = NA [Fixed effect; 1 trial: Schutte 1980] *Additional data extracted from original papers and analysed by NCC-WCH technical team ***20. Intraventricular haemorrhage grades 3 or 4** RR 0.22 (95% CI 0.10 to 0.49) I^2 = 0% [Fixed effect; Garite 1992; Lewis 1996; Morales 1989; Silver 1996]	Liggins 1972 - not defined in original paper - possibly additional data supplied to review authors Morales 1989 - intraventricular haemorrhage - 13/87; 20/78: cases of grade 3 or 4 IVH - 3/87; 12/78 Qublan 2001 - intraventricular haemorrhage Silver 1996 - total cases of intraventricular haemorrhage - 12/28; 10/30: cases of grade 3 or 4 IVH - 2/28; 6/30 Taeusch 1979 - intracranial haemorrhage

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	Liggins 1972 **Inclusion criteria:** women with threatened or planned preterm delivery and gestational age between 24 and 36 weeks **Exclusion criteria:** imminent delivery, contraindication to corticosteroids **Sample size:** N = 1142 women (N = 1218 babies) **Intervention:** 6mg betamethasone phosphate and 6mg betamethasone acetate IM, 2 doses 24h apart. After the first 717 women had enrolled the treatment intervention was doubled to 2 doses of 12mg betamethasone phosphate and 12mg betamethasone acetate IM 24h apart **Comparator:** 6mg cortisone acetate (1/70th the corticosteroid potency of betamethasone) **Other details of care:** ethanol or salbutamol IV were used to delay delivery by 48h to 72h. Women with spontaneous PROM on admission recieved antiobtics and period of attempted suppression of labour limited to 48h. In planned preterm delivery, first injection given 3 days before elective induction **Gestational age at intervention:** *[at trial entry] mean ± SD: experimental = 221 days ± 21; control = 225 days ± 20				

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	Gestational age at delivery: *mean ± SD: experimental = 249 days ± 31; control = 244 days ± 29 **Term deliveries:** *[≥ 37 weeks] 33%: experimental = 33/93; control = 23/75 **Interval between drug administration and delivery:** < 24h = 50 women; ≥ 24h, < 7 days = 87 women; ≥ 7 days, < 21 days = 10 women; ≥ 21 days = 66 women **Morales 1989** **Inclusion criteria:** women with singleton pregnancies with PROM and gestational age between 26 and 34 weeks **Exclusion criteria:** PROM < 12h before onset of labour, uterine tenderness, foul smelling lochia, fetal tachycardia, allergy to penicillin, congenital abnormalities, L/S ratio 2 or more, unable to obtain an L/S ratio, Dubowitz assigned gestational age different from obstetric assessment by 3 weeks (postrandomisation exclusion) **Sample size:** N = 165 women **Intervention:** 12mg betamethasone IM, 2 doses 24h apart repeated weekly if the woman remained undelivered **Comparator:** Expectant management **Other details of care:** four arm trial: group 1 expectant				

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	management, group 2 betamethasone, group 3 expectant management plus 2g ampicillin IV every 6h until cervical cultures were negative, group 4 betamethsone and ampicillin. [for the review groups 2 and 4 formed the experimental group; groups 1 and 3 formed the control group] **Gestational age at intervention:** *not clearly reported **Getstational age at delivery:** *not reported **Term deliveries:** *not reported **Interval between drug administration and delivery:** *not reported **Nelson 1985** **Inclusion criteria:** women with PROM and gestational age between 28 and 34 weeks **Exclusion criteria:** fetal distress, active labour, cervical dilatation > 3 cm, sensitivity to tocolytics, PROM > 24h, existing infection **Sample size:** N = 44 women **Intervention:** 6mg or 12mg betamethasone IM, 2 doses 12h apart and delivery 24 to 48h after PROM, 24h after corticosteroid **Comparator:** Delivery 24 to 48h after PROM **Other details of care:** ritodrine or terbutaline was used to delay labour a minimum of 24h				

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	provided there was no evidence of sepsis. 43% of women received tocolysis **Gestational age at intervention:** *[at rupture of membranes] mean ± SD: experimental = 31.8 weeks ± 3.0; control = 32.0 weeks ± 3.2 **Gestational age at delivery:** *not reported **Term deliveries:** *not reported **Interval between drug administration and delivery:** 24h in all women **<u>Parsons 1988</u>** **Inclusion criteria:** women with PROM and < 4cm of cervical dilatation **Exclusion criteria:** infection, fetal distress, fetal anomalies, contraindication to tocolysis **Sample size:** N = 45 women **Intervention:** 12mg betamethasone IM, 2 doses 12h apart and repeated weekly until 32 weeks **Comparator:** expectant management **Other details of care:** none stated in Cochrane review **Gestational age at intervention:** *data not available (full text of paper not accessed by NCC-WCH technical team) **Gestational age at delivery:** *data not available (full text of paper not accessed by NCC-WCH technical team)				

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	Term deliveries: *data not available (full text of paper not accessed by NCC-WCH technical team) **Interval between drug administration and delivery:** data not available (full text of paper not accessed by NCC-WCH techincal team) **<u>Qublan 2001</u>** **Inclusion criteria:** women with singleton pregnancies and PROM, and gestational age between 27 and 34 weeks **Exclusion criteria:** lethal congenital anomaly, fetal death, infection, expected delivery within 12h **Sample size:** N = 137 women **Intervention:** 6mg betamethasone IM, 4 doses 12h apart and repeated if woman had not delivered after 1 week **Comparator:** expectant management **Other details of care:** infection and non-reactive non-stress test were reasons to stop treatment, start antibiotics and induce labour or perform Caesarean section **Gestational age at intervention:** *not reported **Gestational age at birth:** *not reported **Term deliveries:** *not reported **Interval between drug administration and delivery:** not reported				

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	Schutte 1980 **Inclusion criteria:** women with preterm labour in whom it was possible to delay delivery for at least 12h and gestational age between 26 and 32 weeks **Exclusion criteria:** insulin-treated diabetes, hyperthyroidism, infection, severe hypertension, cardiac disease, marked fetal growth retardation or fetal distress **Sample size:** N = 101 women (N = 123 babies) **Intervention:** 8mg betamethasone phosphate and 6mg betamethasone acetate IM, 2 doses 24h apart **Comparator:** placebo **Other details of care:** all women received ociprenaline infusion and bed-rest until 32 weeks **Gestational age at intervention:** *not reported **Gestational age at birth:** *not reported **Term deliveries:** *not reported **Interval between drug administration and delivery:** <12h = 22 women; 12h to 7 days = 47 women; 8 days to 21 days = 14 women; >21 days = 11 women **Silver 1996** **Inclusion criteria:** women at risk of delivery between 24 and				

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	29 weeks **Exlcusion criteria:** infection, maternal or fetal indications for urgent delivery **Sample size:** N = 75 women, N = 96 babies **Intervention:** 5mg dexamethasone IM, 4 doses 12h apart, repeated weekly if the woman remained undelivered **Comparator:** placebo **Other details of care:** all infants born < 30 weeks received prophylactic surfactant at birth. Tocolytic therapy (magnesium sulphate first-line, followed by terbutaline) used in 80% of women **Gestational age at intervention:** *[on admission] mean ± SD: experimental = 25.1 weeks ± 1.4; control = 25.6 weeks ± 1.3 **Gestational age at birth:** *****mean ± SD: experimental = 26.9 weeks ± 1.5; control = 26.6 weeks ± 1.3 **Interval between drug administration and delivery:** *not reported **Taeusch 1979** **Inclusion criteria:** women with preterm labour, PROM or with cervical dilatation < 5 cm at ≤ 33 weeks and women with an L/S ratio < 2 if > 33 weeks or who had a previous infant with RDS **Exclusion criteria:** indication				

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	for immediate delivery, obstetrician objection, preeclampsia, previously received corticosteroids **Sample size:** N = 122 women, N = 127 babies **Intervention:** 4mg dexamethasone phosphate IM, 6 doses 8h apart **Comparator:** placebo **Other details of care:** none stated **Gestational age at intervention:** *not reported **Gestational age at birth:** *not reported for full study population **Term deliveries:** *[≥ 36 weeks] 27%: experimental = 16/57; control = 18/71 **Interval betwen drug administration and delivery:** *not reported **Teramo 1980** **Inclusion criteria:** women with preterm labour and cervical dilatation < 4 cm without progression of labour upon initial observation of up to 12h **Exclusion criteria:** preeclampsia, diabetes **Sample size:** N = 74 women, N = 80 babies **Intervention:** 12mg betamethasone IM, 2 doses 24h apart **Comparator:** placebo **Other details of care:** all women received either nylidrine or ritodrine to suppress uterine				

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	activity **Gestational age at intervention:** *not reported **Gestational age at birth:** *not reported **Term deliveries:** *not reported **Interval between drug administration and delivery:** < 1 day = 17 women; 1 to 7 days = 39 women; > 7 days = 18 women **Inclusion criteria** Randomised trials comparing antenatal corticosteroids (betamethasone, dexamethasone, or hydrocortisone) with placebo, or with no treatment given to women prior to anticipated preterm delivery (planned or spontaneous), regardless of other comorbidity. **Exclusion criteria** Quasi-randomised trials Trials which tested the effect of corticosteroids along with other co-interventions Trials with greater than 20% loss to follow up				
Full citation Porto,A.M., Coutinho,I.C., Correia,J.B., Amorim,M.M.,	**Sample size** N = 320 women **Characteristics** **Maternal age (years) - mean ± SD**	**Interventions** 12mg betamethasone (6mg acetate and 7.8mg disodium phosphate)	**Details** **Recruitment and randomisation** Physicians in the obstetrics department identified potentially eligible women.	**Results** **1. Fetal and neonatal deaths - n/N (%)** Corticosteroids: 1/144 (0.7) Control: 3/131 (2.3)	**Limitations** **Appropriate randomisation:** Yes **Allocation concealement:** Yes **Groups comparable at baseline:** Yes

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Effectiveness of antenatal corticosteroids in reducing respiratory disorders in late preterm infants: randomised clinical trial, BMJ (Clinical research ed.), Vol.342, pp.d1696, 2011., - **Ref Id** 254025 **Country/ies where the study was carried out** Brazil **Study type** Randomised controlled trial **Aim of the study** To determine the effectiveness of antenatal treatment with corticosteroids at 34-36 weeks of pregnancy in reducing the incidence of neonatal respiratory disorders **Study dates** April 2008 - June 2010	Corticosteroids: 23.2 ± 6.1 Control: 22.9 ± 5.5 **Gestational age at admission (weeks) - mean ± SD** Corticosteroids: 35.0 ± 0.7 Control: 35.0 ± 0.7 **Gestational age at delivery (weeks) - mean ± SD** Corticosteroids: 35.6 ± 1.17 Control: 35.5 ± 1.08 **Term deliveries (≥ 37 weeks) - n/N (%)** Corticosteroids: 16/143 (11%) Control: 11/130 (8%) **PROM - n/N (%)** Corticosteroids: 54/143 (38) Control: 54/130 (42) **Received tocolysis (nifedipine) - n/N (%)** Corticosteroids: 88/143 (62) Control: 79/130 (61) **Inclusion criteria** 34 to 36+6 weeks gestation and at risk of imminent premature delivery, either spontaneous or planned **Exclusion criteria** Multiple pregnancy Major congenital malformations Haemorrhagic syndromes with active bleeding Clinical evidence of chorioamnionitis	intramuscularly; 2 doses 24h apart (n = 163) Placebo (0.9% saline solution) (n = 157)	Having given consent to participate women were randomised by the investigators. A statistician not involved in the study prepared a table of random numbers in a single block (random allocation software, version 1.0). The hospital pharmacy (Clinics Hospital, University of San Paulo) prepared 320 sealed cardboard boxes, containing betamethasone or placebo, identical in appearance, volume and colour and numbered in accordance with the table of random numbers. The investigators, physicians who cared for the women, statistician and women themselves were unaware of the contents of the boxes. **Care protocol** The study investigators were not involved in the prepartum or postpartum management of women or in neonatal management. Women in premature labour recevied tocolysis (nifedipine) in accordance with routine hospital practice, in an attempt to allow the full course of medication to be administered.	**2. Need for mechanical ventilation - n/N (%)** Corticosteroids: 2/144 (1.2) Control: 1/131 (0.8) **3. Neonatal sepsis - n/N (%)** Corticosteroids: 6/144 (4) Control: 9/130 (7)	**Groups received same care (apart from intervention):**Yes **Blinding of participants:** Yes **Blinding of staff providing care:** Yes **Blinding of outcome assessors:** Yes **Missing data/loss to follow up:** 15% of the randomised population were excluded (see other information) **Precise definition of outcomes:** Yes **Valid and reliable method of outcome assessment:** Yes **Indirectness:** none identified **Other information** The study was powered to detect a 50% reduction in respiratory disorders with the use of corticosteroids. Women who delivered before she received a second dose of medication were analysed on an intention-to-treat basis. 43/320 (13%) women were excluded after randomisation as they were discharged from hospital while still pregnant and went on to deliver elsewhere (experimental = 19/163 (12%), control = 24/157 (15%)). Two further post-randomisation exclusions were in the placebo group - one due to detection of

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Source of funding Instituto de Medicina Integral Prof Fernando Figueira-IMP, a private, not-for-profit healthcare organisation based in Recife, Pernambuco, Brazil where the study was carried out	Previous use of corticosteroids Need for immediate delivery for maternal or fetal reasons				twin pregnancy after randomisation and one was found to have reached term. There was one stillbirth in each group. Authors therefore used following denominators: 143 babies in experimental group and 130 babies in control group. NCC-WCH technical team have included stillbirth in fetal and neonatal outcome and so denominators used by NCC for all outcomes are 144 and 131, respectively. 212/275 (77%) women followed up received the full course of medication (experimental = 111/144 (77%), control = 101/131 (77%). Interval between administration of the last dose and delivery was a median of 2 days in both groups (interquartile range 1 to 4). Outcomes for women with PROM not reported separately. No local or systemic side effects occurred and there were no unexpected effects or adverse reactions to corticosteroid treatment.

H.8.2.1 Health economics

Bibliographic details	Interventions and comparisons	Data Sources	Time horizon & Method	Results	Reviewer comment
Full citation	**Study dates**	**Source of effectiveness**	**Time horizon and**	**Cost per patient per**	**Limitations**

Bibliographic details	Interventions and comparisons	Data Sources	Time horizon & Method	Results	Reviewer comment
Mugford,M., Piercy,J., Chalmers,I., Cost implications of different approaches to the prevention of respiratory distress syndrome, Archives of Disease in Childhood, 66, 757-764, 1991 **Ref Id** 324912 **Economic study type** Cost effectiveness analysis **Country(ies) where the study was done** UK **Perspective & Cost Year** Perspective: Hospital Cost Year: 1989 **Source of funding** Department of Health	January 1989 to June 1989 **Intervention** Antenatal corticosteroids **Comparison(s)** No treatment	**data** Effectiveness of corticosteriods derived from an analysis of 12 trials of prenatal corticosteroids incorporated in the overview reported by Crowley 1990 **Source of cost data** Costs were based on a costing study of resource use in John Radcliffe Maternity Hospital, Oxford in 1989. Costs of corticosteriods were obtained from discussion with pharmacists. Costs include Staff (Nursing, Medical, Physiotherapy), Depreciation and running costs of equipment, including ultrasound, Pathology (Biochemistry, Haematology, Microbiology), Radiology (including staff and equipment), Disposable supplies, Oxygen, Pharmacy (including blood products and total parenteral nutrition), Overheads (including all	**discount rate** Time Horizon: NA Discount Rate: NA **Method of eliciting health valuations (if applicable)** Data was collected about babies' survival from John Radcliffe Maternity Hospital, Oxford from January 1989 to June 1989 **Modelling approach** A Decision Tree model was used to simulate the outcomes of preterm birth of <31 weeks and <35 weeks.	**alternative** Per baby (<31 weeks) With antenatal corticosteroids: 6,542 No treatment: GBP 6,120 Per baby (<35 weeks) With antenatal corticosteroids: 3,450 No treatment: GBP 3,844 **Effectiveness per patient per alternative** <31 weeks gestation Survived without respiratory distress syndrome With antenatal corticosteroids: 25.83% No treatment: 16.67% Survived With antenatal corticosteroids: 73.33% No treatment: 62.5% <35 weeks gestation Survived without respiratory distress syndrome With antenatal corticosteroids: 69.57% No treatment: 57.14% Survived With antenatal corticosteroids: 87.86% No treatment: 84.29%	Specific resource use and Unit costs not provided. Total costs have no confidence intervals; only mean cost provided. There was no sensitivity analysis. **Other information**

Bibliographic details	Interventions and comparisons	Data Sources	Time horizon & Method	Results	Reviewer comment
		ancillary and support services) **Other data sources e.g. transition probabilities**		**Incremental cost-effectiveness** <31 weeks survived without respirator distress syndrome: antenatal corticosteroids dominates Survived: antenatal corticosteroids dominates <35 weeks survived without respirator distress syndrome: antenatal corticosteroids dominates Survived: antenatal corticosteroids dominates **Other reporting of results** **Uncertainty** None	

H.8.2 Repeat courses

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Crowther,Caroline A., McKinlay,JD Christopher, Middleton,Philippa, Harding,Jane E., Repeat doses of prenatal corticosteroids for women at risk of preterm birth for improving neonatal health outcomes, Cochrane Database of Systematic Reviews, -, 2013 **Ref Id** 239375 **Country/ies where the study was carried out** Various **Study type** Systematic review of randomised controlled trials **Aim of the study** To assess the effectiveness and safety of a repeat dose(s) of prenatal corticosteroids, given to women who remain at risk of preterm birth 7 or more days after an initial course of prenatal corticosteroids **Study dates** The search was performed in March 2011; review content was assessed as up-to-date by the authors in April 2011 **Source of funding** Discipline of Obstetrics and	**Sample size** N = 10 trials N = 4733 women N = 5700 babies **Characteristics** *additional information which had to be accessed from the full text of the trials because it was not reported in the systematic review **Aghajafari 2002** **Inclusion criteria:** women at 24-30 weeks gestation at continued increased risk of preterm birth who remained undelivered 7 or more days following a single course of antenatal corticosteroids (12 mg/dose betamethsone IM, two doses at 12- or 24-h apart or 5-6mg betamethsone IM, four doses at 12-h apart **Exclusion criteria:** chronic doses of corticosteroids secondary to medical conditions, contraindication to corticosteroids, clinical evidence of chorioaminonitis, known lethal congenital anomaly **Sample size:** N = 12 **Intervention:** weekly course of 12mg betamethasone IM, two	**Interventions** Corticosteroids (intravenously, intramuscularly, or orally) in women who have already received a single course of prenatal corticosteroid ≥ 7 days previously compared with either placebo or no placebo	**Details** The Cochrane Pregnancy and Childbirth Group's Trials Register was searched in March 2011. This trial register contains trials identified from: - quarterly searches of the Cochrane Central Register of Controlled Trials (CENTRAL) - weekly searches of MEDLINE - weekly searches of EMBASE - handsearches of 30 journals and the proceedings of major conferences - weekly current awareness alerts for a further 44 journals plus monthly BioMed Central email alerts No language restrictions were applied **Data collection and analysis** Review authors independently evaluated trials under consideration for inclusion without consideration of their results. Two review authors independently extracted study data, using a predesigned data	**Results** **1. Fetal and neonatal mortality** Corticosteroids: 96/2791 Control: 102/2763 RR 0.94 (95% CI 0.71 to 1.23) I^2 = 0% [Fixed effect; 9 trials: Aghajafari 2002; Crowther 2006; Garite 2009; Guinn 2002; Mazumder 2008; McEvoy 2010; Murphy 2008; Peltoniemi 2007; Wapner 2006] **Women with pPROM** Corticosteroids: 3/81 Control: 6/79 RR 0.49 (95% CI 0.13 to 1.88) I^2 = NA [Fixed effect; 1 trial: Guinn 2002] **Babies exposed to one repeat course of corticosteroids (exposed to two courses in total**) Corticosteroids: 14/504 Control: 10/511 RR 1.41 (95% CI 0.64 to 3.08) I^2 = 25% [Fixed effect; 3 trials: Garite 2009; McEvoy 2010; Peltoniemi 2007] **2. Chronic lung disease**	**Limitations** **Risk of bias of included studies. as assessed by the review authors and indirectness assessed by NCC-WCH technical team** Additional notes from NCC-WCH technical team are marked with † **Aghajafari 2002** - Adequate allocation concealment and method of randomisation - No losses to follow up - Intention-to-treat analysis Indirectness: none detected **Crowther 2006** - Adequate allocation concealment and method of randomisation - Losses to follow up at 2-year corrected age assessment: 4% had no paediatric assessment, 8% had no psychological assessment - Intention-to-treat analysis Indirectness: 16% of women had a multiple pregnancy **Garite 2009**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Gynaecology, The University of Adelaide, Australia Liggins Institute, University of Auckland, New Zealand Australian Department of Health and Ageing, Australia National Institute for Health Research, UK [NIHR Programme of centrally managed pregnancy and childbirth systematic reviews of priority to the NHS and users of the NHS: 10/4001/02]	doses 24h apart, until 33 weeks or delivery if the woman remained at increased risk of preterm birth **Comparator:** weekly course of placebo, normal saline IM, two doses 24h apart, until 33 weeks or delivery if the woman remained at increased risk of preterm birth **Other details of care provided: ***aspects of medical care for each woman and neontate were determined by treating physician, according to hospital local hospital policies **Gestational age at intervention:** NR **Gestational age at birth:** *mean ± SD: experimental = 31 ± 4 weeks; control = 35 ± 5 weeks **Term deliveries:** *NR **Interval between corticosteroid administration and delivery:** *median (interquartile range): experimental = 23 (5,96) days; control = 57 (1,89) days **Completed repeat course(s): ***one course = 4/12 (33%); two course = 3/12 (25%); more than two courses = 5/12 (42%) **<u>Crowther 2006</u>** **Inclusion criteria:** women with singleton or multiple pregnancy < 32 weeks gestation who had received an initial treatment of		extraction form. Discrepancies were resolved through discussion. Risk of bias was assessed by two review authors independently according to the following criteria, which were judged to be high, low or unclear risk of bias: - sequence generation (selection bias) - allocation concealment (selection bias) - blinding (performance bias) - incomplete outcome data (attrition bias) - selective reporting bias - other sources of bias As far as possible, analyses were done on an intention-to-treat basis. The denominator for each outcome in each trial was taken as the number randomised minus any participants whose outcomes were known to be missing ('available case' analysis). Heterogeneity was assessed using T^2, I^2 and Chi^2 statistics. Heterogeneity was regarded as substantial if T^2 was greater than zero	Corticosteroids: 181/2709 Control: 170/2684 RR 1.06 (95% CI 0.87 to 1.30) I^2 = 0% [Fixed effect; 8 trials: Aghajafari 2002; Crowther 2006; Garite 2009; Guinn 2002; Mazumder 2008; Murphy 2008; Peltoniemi 2007; Wapner 2006] **Women with pPROM** Corticosteroids: 15/81 Control: 19/79 RR 0.77 (95% CI 0.42 to 1.41) I^2 = NA [Fixed effect; 1 trial: Guinn 2002] **Babies exposed to one repeat course of corticosteroids (exposed to two courses in total**) Corticosteroids: 42/432 Control: 34/445 RR 1.27 (95% CI 0.83 to 1.96) I^2 = 0% [Fixed effect; 2 trials: Garite 2009; Peltoniemi 2007] **<u>3. Intraventricular haemorrhage</u>** Corticosteroids: 129/1533 Control: 137/1532 RR 0.94 (95% CI 0.75 to 1.18)	- *Women received some form of additional care; it was unclear what additional care women received and whether this was balanced across the two groups - Adequate allocation concealment and method of randomisation - No data available for 13 babies in the experimental group and 6 babies in the control group - Intention-to-treat analysis Indirectness: 32% of women had a multiple pregnancy. **Guinn 2002** - Recruitment stopped early due to safety concerns: †planned to recruit 1000 women to have 90% power to detect one-third reduction in composite morbidity but interim analysis found probability of detecting a significant difference was less than 2% and increasing reports at time of interim analysis of potential for long-term neurological complications with weekly courses of

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	corticosteroid 7 or more days previously and were judged to be at continued risk of preterm birth **Exclusion criteria:** contraindication to corticosteroids, in second stage of labour, chorioamnionitis needing urgent delivery, further corticosteroid therapy was judged to be essential **Sample size:** N = 982 women, N = 1146 babies **Intervention:** weekly course of 11.4mg Celestone Chronodose (7.8mg betamethasone sodium phosphate and 6mg betamethasone acetate) if woman remained underlivered, at risk of preterm birth and < 32 weeks gestation **Comparator:** weekly saline IM **Other details of care provided:** *all other care was according to standard practice at each participating centre **Gestational age at intervention:** *[initial steroids] median (interquartile range): experimental = 26.7 weeks (24.7 to 28.7); control = 26.7 weeks (24.7 to 28.7) **Gestational age at birth:** mean ± SD: experimental = 32.5 weeks ± 3.9; control = 32.4 weeks ± 3.9 **Term deliveries:** [≥ 37 weeks] 18%: experimental = 109/567 (19%); control = 94/577 (16%)		and either I^2 was greater than 30% or there was a low P value (less than 0.10) in the Chi^2 for heterogeneity. A fixed-effect model was used for combining data in the absence of significant heterogeneity as the trials were sufficiently similar. A random-effects model was used where there was clinical or substantial statistical heterogeneity. RevMan software (version 5.0) was used for statistical analyses. **Subgroup analyses** The following subgroup analyses were done: - the reasons the woman was considered to be at risk of preterm birth - the number of babies in utero - the type of corticosteroid given - the planned interval between corticosteroid treatments - the planned number of repeat courses of corticosteroids to be given - the number of repeat course of corticosteroids actually given postrandomisation	I^2 = 0% [Fixed effect; 6 trials: Crowther 2006; Garite 2009; Guinn 2002; Mazumder 2008; Peltoniemi 2007; Wapner 2006] **Babies exposed to one repeat course of corticosteroids (exposed to two courses in total)** Corticosteroids: 50/431 Control: 52/441 RR 0.99 (95% CI 0.69 to 1.42) I^2 = 31% [Fixed effect; 2 trials: Garite 2009; Peltoniemi 2007] **4. Intraventricular haemorrhage grade 3/4** Corticosteroids: 32/2419 Control: 28/2400 RR 1.13 (95% CI 0.69 to 1.86) I^2 = 22% [Fixed effect; 6 trials: Aghajafari 2002; Crowther 2006; Garite 2009; Guinn 2002; Murphy 2008; Peltoniemi 2007] **5. Periventricular leucomalacia** Corticosteroids: 20/2453 Control: 26/2435 RR 0.77 (95% CI 0.43 to 1.37)	antenatal corticosteroids - Adequate allocation concealment and method of randomisation - Interval between first corticosteroid course (before randomisation) and birth significantly shorter in corticosteroid group, therefore more women in corticosteroid group received fewer study courses - 16 women were lost to follow up - Details of additional care were not reported - Indirectness: 15% of women had a multiple pregnancy; in cases of multiple gestation one of the infants was randomly selected for analysis **Mazumder 2008** - Adequate allocation concealment and method of randomisation - Neither participants or staff were blinded to treatment allocation - no treatment acted as control rather than placebo - One loss to follow up before delivery - Details of additional care were not reported - Indirectness: 9% of

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	Interval between corticosteroid administration and delivery: *not reported **Completed repeat course(s):** *****one course = 408/982 (42%), two courses = 227/982 (23%), three courses = 117/982 (12%), four or more courses = 215/982 (22%) **<u>Garite 2009</u>** **Inclusion criteria:** women with singleton or twin pregnancy, > 25 weeks and < 33 weeks who had received a course of betamethasone ≥ 14 days previously and who were judged to have recurrent or continued risk of preterm birth **Exclusion criteria:** major fetal anomaly, cervical dilatation 5cm or more, triplet or higher order multiples, ruptured membranes, clinical chorioamnionitis, documented lung maturity, receiving corticosteroids for other indications, HIV or active tuberculosis **Sample size:** N = 437 women, N = 577 babies **Intervention:** single course of 12mg betamethasone IM, two doses 24h apart (women had received a course of betamethsone ≥ 14 days previously). In some centre betamethasone became unavailable and was replaced with dexamethasone 6mg IM,		- the planned dosage of corticosteroid given per treatment - the planned dose of repeat dose of corticosteroid drug exposure/week - the method of treatment administration - the gestational age at which the first repeat treatment was given	I^2 = 0% [Fixed effect; 7 trials: Aghajafari 2002; Crowther 2006; Garite 2009; Guinn 2002; Mazumder 2008; Murphy 2008; Peltoniemi 2007] **<u>6. Use of mechanical ventilation</u>** Corticosteroids: 556/2463 Control: 668/2455 RR 0.84 (95% CI 0.71 to 0.99) I^2 = 61% [Fixed effect; 6 trials: Crowther 2006; Garite 2009; McEvoy 2010; Murphy 2008; Peltoniemi 2007; Wapner 2006] **<u>7. Birthweight Z scores</u>** Corticosteroids: mean ± SD: Crowther 2006 -0.4 ± 1.05; McEvoy 2010 -0.14 ± 0.86 Control: Crowther 2006 -0.27 ± 1.14; McEvoy 2010 -0.14 ± 0.98 Mean difference -0.11 (95% CI -0.23 to 0.00) I^2 = 0% [Fixed effect; 2 trials: Crowther 2006; McEvoy 2010] **Babies exposed to one repeat course of corticosteroids (exposed to two courses in total**)	women had a multiple pregnancy; in cases of multiple gestation one of the infants was randomly selected for analysis **McEvoy 2002** - Adequate allocation concealment and method of randomisation - No losses to follow up - Intention-to-treat analysis - Indirectness: none detected **McEvoy 2010** - Adequate allocation concealment and method of randomisation - All participants, investigators and care providers were blinded to treatment allocation - One baby in placebo group lost to follow up - Intention-to-treat anaylsis - Indirectness: 16% of women had a multiple pregnancy **Murphy 2008** - Method of randomisation not clearly described but assessed to be adequate, adequate allocation concealment

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	4 doses, every 12h. 31 women received dexamethasone and 30 women received equivalent placebo **Comparator:** weekly saline IM **Other details of care provided:** *Each clinician determined the remainder of clinical care **Gestational age at intervention:** *not reported **Gestational age at birth:** delivery at < 34 weeks: experimental = 56%; control = 55% **Term deliveries:** *not reported **Interval between corticosteroid administration and delivery:** *mean ± SD: experimental = 24.5 days ± SD not reported; control = 25.1 days ± SD not reported **Completed repeat course(s)**: *all women received the single course of corticosteroid treatment **Guinn 2002** **Inclusion criteria:** women between 24 and 33 weeks' gestation at high risk of preterm birth who remained undelivered 1 week following an initial course of antenatal corticosteroids **Exclusion criteria:** requiring immediate delivery, fetal anomalies incompatible with life, documented fetal lung maturity, maternal active			Corticosteroids: -0.14 ± 0.86 Control: -0.14 ± 0.98 Mean difference -0.0 (95% CI -0.34 to 0.34) I^2 = NA [Fixed effect; 1 trial: McEvoy 2010] **8. Chorioamnionitis** Corticosteroids: 140/2152 Control: 118/2109 RR 1.16 (95% CI 0.92 to 1.46) I^2 = 0% [Fixed effect; 6 trials: Aghajafari 2002; Crowther 2006; Garite 2009; Guinn 2002; Murphy 2008; Wapner 2006] **Women with pPROM** Corticosteroids: 40/81 Control: 25/79 RR 1.56 (95% CI 1.05 to 2.31) I^2 = NA [Fixed effect; 1 trial: Guinn 2002] **Babies exposed to one repeat course of corticosteroids (exposed to two courses in total**) Corticosteroids: 6/223 Control: 9/214 RR 0.64 (95% CI 0.23 to 1.77) I^2 = NA [Fixed effect; 1 trial: Garite	- Blinding of participants and care providers - 5 women (0.3%) were lost to follow up (balanced across groups) - Intention-to-treat analysis - Indirectness: 20% of women had a multiple pregnancy **Peltoniemi 2007** - Method of randomisation not clearly described but assessed to be adequate, adequate allocation concealment - Blinding of participants, investigators and care providers - Losses to follow up at 2-year corrected age assessment: 83% of survivors completed 2-year follow up - Recruitment was terminated early, primarily due to a decrease in intact surivival in the experimental group and additional concerns about long-term adverse effects of glucocorticoids - Imbalance in multiple pregnancies between groups not addressed in analysis

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	tuberculosis, HIV **Sample size:** N = 502 women **Intervention:** weekly course of 12mg betamethasone IM, two doses 24h apart, until 34 weeks or birth, whichever came first **Comparator:** similarly administered placebo **Other details of care provided: ***not reported **Gestational age at intervention:** *[at randomisation] mean ± SD: experimental = 29.2 weeks ± 2.7; control = 28.8 weeks ± 2.7 **Gestational age at birth:** mean ± SD: experimental=33.1 weeks ± 4.0; control=33.5 weeks ± 4.0 **Term deliveries:** *not reported **Interval between corticosteroid administration and delivery:** mean ± SD: experimental = 5.0 weeks ± 3.7; control = 5.8 weeks ± 3.8 **Completed repeat course(s):** *Details reported for experimental arm only: two courses = 88/256, three courses = 55/256, four courses = 34/256, five courses = 20/256, six or more courses = 48/256 **Mazumder 2008** **Inclusion criteria:** women between 26 and 33 weeks' gestation at risk of preterm birth who had received a			2009] **9. Puerperal sepsis** Corticosteroids: 72/1565 Control: 61/1526 RR 1.15 (95% CI 0.83 to 1.60) I^2 = 13% [Fixed effect; 5 trials: Aghajafari 2002; Guinn 2002; Murphy 2008; Peltoniemi 2007; Wapner 2006] **Women with pPROM** Corticosteroids: 4/81 Control: 6/79 RR 0.65 (95% CI 0.19 to 2.22) I^2 = NA [Fixed effect; 1 trial: Guinn 2002] **Babies exposed to one repeat course of corticosteroids (exposed to two courses in total**) Corticosteroids: 19/125 Control: 12/124 RR 1.57 (95% CI 0.80 to 3.10) I^2 = NA [Fixed effect; 1 trial: Peltoniemi 2007] **10. Postpartum haemorrhage** Corticosteroids: 17/249 Control: 27/236 RR 0.60 (95% CI 0.33 to	- Indirectness: 16% of women had a multiple pregnancy **Wapner 2006** - Recruitment stopped after 495 women (planned 2400) based on concerns about reduced birthweight in repeat corticosteroids group with no evidence of reduced morbidity - Adequate method of randomisation and allocation concealment - Adequate blinding, including blinding of follow-up assessors - <1% loss to follow up at primary hospital discharge, 16.5% loss to follow-up at 2-year assessment - Intention-to-treat analysis - Indirectness: 22% of women had a multiple pregnancy **Other information** **Maternal side effects** **Crowther 2006** Any of the following: pain/discomfort, maternal distress, haematoma, rash, sleeplessness, lethargy,

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	course of betamethasone 7 or more days previously **Exclusion criteria:** unreliable gestational age, frank chorioamnionitis, major fetal malformation **Sample size:** N = 76 women, N = 83 babies **Intervention:** weekly course of 12mg betamethasone IM, two doses 24h apart, until delivery or end of 33rd week of gestation **Comparator:** no intervention **Other details of care provided:** *not reported **Gestational age at intervention:** *[at baseline] mean ± SD: experimental = 30.2 weeks ± 4.0; control = 30.0 weeks ± 1.7 **Gestational age at birth:***not reported **Term deliveries:** *not reported **Interval betwen corticosteroid administration and delivery:** *not reported **Completed repeat course(s):** *one course = 3/38, two courses = 15/38, three courses = 7/38, four courses = 8/38, five courses = 3/38, six courses = 2/38 **McEvoy 2002** **Inclusion criteria:** women between 25 and 33 weeks' gestation who were at increased risk of preterm birth and remained undelivered 1			1.07) I^2 = NA [Fixed effect; 1 trial: Guinn 2002] **11. Postnatal pyrexia** Corticosteroids: 32/489 Control: 37/493 RR 0.87 (95% CI 0.55 to 1.38) I^2 = NA [Fixed effect; 1 trial: Crowther 2006] **12. Any maternal side effects** Corticosteroids: 115/739 Control: 159/735 RR 0.97 (95% CI 0.24 to 3.90) I^2 = 96% [Fixed effect; 2 trials: Crowther 2006; Wapner 2006] **13. Major neurosensory disability at early childhood follow-up** Corticosteroids: 56/613 Control: 71/643 RR 1.08 (95% CI 0.31 to 3.76) I^2 = 42% [Fixed effect; 2 trials: Crowther 2006; Peltoniemi 2007] **Babies exposed to one repeat course of corticosteroids (exposed**	'other' **Wapner 2006** The following trials were ended early due to safety concerns: Guinn 2002 aimed to recruit 1000 women and stopped recruitment at 502 Peltoniemi 2007 aimed to recruit 440 women and stopped recruitment at 249 Wapner 2006 aimed to recruit 2400 women and stopped recruitment at 495 No additional data from trialists was included in the analysis Outcomes of interest were not reported for subgroups receiving more than one repeat course of corticosteroids (more than two courses of corticosteroids in total) Trials where a single repeat course was administered (after a qualifying single course of cortiocsteroids): Garite 2009, McEvoy 2010, Peltoniemi 2007

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	week after a single course of antenatal corticosteroids **Exclusion criteria:** insulin-dependent diabetes, drug addiction, known lethal congenital anomaly **Sample size:** N = 37 **Intervention:** weekly course of 12mg betamethasone IM, two doses, timing not reported, until delivery or 34 weeks' gestation **Comparator:** weekly doses of IM placebo until delivery or 34 weeks's gestation **Other details of care provided:** *not reported **Gestational age at intervention:** *[at randomisation] mean ± SD: experimental = 29.8 weeks ± 2.9; control = 30.2 weeks ± 2.1 **Gestational age at birth:** *mean ± SD: experimental = 32.2 weeks ± 3.3; control = 32.8 weeks ± 2.7 **Term deliveries:** *[>36 weeks] 5%: experimental = 1/18; control = 1/19 **Interval between corticosteroid administration and delivery:** *mean (range): experimental = not reported; control = 24 days (7.5 to 55 days) **Completed repeat course(s):** two courses = 8/18, three courses = 5/18, four courses = 4/18, 5 courses = 1/18			**to two courses in total**) Corticosteroids: 3/118 Control: 1/139 RR 3.53 (95% CI 0.37 to 33.52) I^2 = NA [Fixed effect; 1 trial: Peltoniemi 2007] **14. Developmental delay at early childhood follow-up** Corticosteroids: 260/1603 Control: 269/1599 RR 0.97 (95% CI 0.84 to 1.13) I^2 = 0% [Fixed effect; 3 trials: Crowther 2006; Murphy 2008; Peltoniemi 2007] **15. Cerebral palsy at early childhood follow-up** Corticosteroids:254/1909 Control: 52/1891 RR 1.03 (95% CI 0.71 to 1.50) I^2 = 12% [Fixed effect; 4 trials: Crowther 2006; Murphy 2008; Peltoniemi 2007; Wapner 2006]	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	McEvoy 2010 **Inclusion criteria:** women between 26 and 34 weeks' gestation who had received one course of antenatal corticosteroids at least 14 days previously and were at continued risk of preterm birth **Exclusion criteria:** insulin-dependent diabetes, major fetal or chromosomal abnormality, multiple pregnancy greater than twins, clinical chorioamnionitis, first course of corticosteroids given < 24 weeks' gestation, chronic steroid use during pregnancy for clinical care **Sample size:** N = 85 women, N = 113 babies **Intervention:** one course of 12mg betamethasone IM, 2 doses 24h apart **Comparator:** one course of 25mg cortisone acetate - an inactive steroid - 2 doses 24h apart **Other details of care provided:** *surfactant therapy, when required (pulmonary function was measured before administration) **Gestational age at intervention:** *both groups received first course of corticosteroids at about 27 weeks and study dose at 30 weeks **Gestational age at birth:** *83/113 (73.5%) were				

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	delivered at ≤34 weeks **Term deliveries:** *not reported **Interval between corticosteroid administration and delivery:** *not reported **Completed repeat course(s):** all women received the single course of corticosteroid treatment **Murphy 2008** **Inclusion criteria:** women with single, twin or triplet pregnancy between 25 and 32 weeks' gestation who had received an initial course of antenatal corticosteroids (either betamethasone or dexamethasone) 14-21 days previously and who remained undelivered and at continued high risk of preterm birth **Exclusion criteria:** contraindication to corticosteroid use, need for chronic doses of corticosteroids, evidence of chorioamnionitis, known lethal congenital abnormality, initial course of corticosteroids before 23 weeks' gestation, previously participated in the MACS study, women with a multiple pregnancy with fetal death after 13 weeks' gestation **Sample size:** N = 1858 women, N = 2304 babies **Intervention:** fortnightly course of 12mg betamethasone IM, 2 doses				

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	24h apart until 33 weeks' gestation or birth, whichever happened first. For women with PROM the recommendation was to stop the study medication at 32 weeks' gestation **Comparator:** similarly appearing IM injection of dilute concentration of aluminium monostearate **Other details of care provided:** *at baseline 49% of women had received a tocolytic during the previous 2 weeks **Gestational age at intervention:** *[at randomisation] mean ± SD: experimental = 29.3 weeks ± 2.0; control = 29.4 weeks ± 2.0 **Gestational age at birth:** *mean ± SD: experimental = 34.5 weeks ± 3.6; control = 34.9 weeks ± 3.6 **Term deliveries:** *[≥ 37 weeks] 32%: experimental = 278/935 (30%); control = 318/918 (35%) **Interval between corticosteroid administration and delivery:** *"time of delivery after repeated drug exposures": <48h = 183/1853 (10%); 48h to < 7 days = 284/1853 (15%); ≥ 7 days = 1374/1853 (75%) **Completed repeat course(s):** "number of courses of study drug": zero courses =				

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	10/1853 (0.5%), one course = 750/1853 (40.5%), two courses = 578/1853 (31%), three courses = 319/1853 (17%), four courses = 194/1853 (10.5%) **<u>Peltoniemi 2007</u>** **Inclusion criteria:** women at < 34 weeks' gestation who had received a single course of betamethasone > 7 days previously and were to have elective delivery within 48h or were at very high risk of spontaneous preterm birth within 48h (cervical opening ≥ 3cm and regular contractions at 5 to 10 min intervals) **Exclusion criteria:** long-term maternal corticosteroid use, clinical chorioamnionitis, lethal disease of the fetus **Sample size:** N = 249 women, N = 326 babies **Intervention:** single dose of 12mg betamethasone IM **Comparator:** isotonic saline IM **Other details of care provided:** *not reported **Gestational age at intervention:** mean ± SD: experimental = 30.3 weeks ± 2.6, control = 30.7 weeks ± 2.5 **Gestational age at birth:** *24-27 weeks = 51/326 (16%), 28-30 weeks = 89/326 (27%), 31-34 weeks = 159/326 (49%), ≥ 34 weeks = 27/326 (8%)				

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	Term deliveries: not reported [see above line for reported gestational age categories] **Interval between corticosteroid administration and delivery:** *median (interquartile range): experimental = 9 hours (3 to 23), control = 7 hours (3 to 23) **Completed repeat course(s):** all women received the single course of corticosteroids **<u>Wapner 2006</u>** **Inclusion criteria:** women with intact membranes between 23+0 weeks and 31+6 weeks who had received a single full course of betamethasone or dexamethasone between 7 and 10 days previously and were at high risk of preterm birth, or had the placenta praevia or chronic abruption **Exclusion criteria:** pPROM, confirmed fetal lung maturity, chorioamnionitis, major fetal anomaly, non-reassuring fetal status, systemic corticosteroid use during current pregnancy, insulin-dependent diabetes **Sample size:** N = 495 women (planned for 2400), N=591 babies **Intervention:** 12mg betamethasone IM, 2 doses 24 h apart, repeated weekly until 33+6 weeks or birth, whichever				

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	came first. After 67 women had been recruited the number of courses (including the qualifying course) was limited to 4 because of difficulty in recruitment and interim analysis showed a tendency towards decreased birthweight in the experimental group **Comparator:** "matching" placebo **Other details of care reported:** *not reported **Gestational age at intervention:** *[at randomisation] mean ± SD: experimental = 28.0 weeks ± 2.4; control = 28.1 weeks ± 2.3 **Gestational age at birth:** *Mean ± SD: experimental = 34.8 weeks ± 3.8; control = 34.8 weeks ± 3.9 **Term deliveries:** *[≥ 37 weeks] 36%: experimental = 93/157; control = 85/157 **Interval between corticosteroid administration and delivery:** *Mean ± SD: experimental = 47.4 days ± 28.9; control = 47.0 days ± 27.1 **Completed repeat course(s):** 63.4% of women received 4 or more study courses of corticosteroids **Inclusion criteria** Randomised controlled trials				

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	(published, unpublished or ongoing) comparing repeat dose(s) of prenatal corticosteroids with a single dose of corticosteroid in women at risk of preterm birth **Exclusion criteria** Quasi-randomised and crossover trials Trials where the fetus received corticosteroids directly				
Full citation Asztalos, E. V., Murphy, K. E., Willan, A. R., Matthews, S. G., Ohlsson, A., Saigal, S., Armson, B. A., Kelly, E. N., Delisle, M. F., Gafni, A., Lee, S. K., Sananes, R., Rovet, J., Guselle, P., Amankwah, K., Saleem, M., Sanchez, J., Macs- Collaborative Group, Multiple courses of antenatal corticosteroids for preterm birth study: outcomes in children at 5 years of age (MACS-5), JAMA Pediatrics, 167, 1102-10, 2013 **Ref Id** 336098 **Country/ies where the study was carried out** Canada **Study type** Cohort follow-up study	**Sample size** N=1724 eligible women N=2141 eligible children N=1728 children followed-up N=873 multiple-courses group children N=855 single-course group children **Characteristics** **Sample size:** N=1376 women followed-up at 5 years N=1728 children followed-up at 5 years N=873 multiple-courses group children N=855 single-course group children **Gestational age at intervention:** [at randomisation] mean ± SD: experimental = 29.3 weeks ± 1.9; control = 29.4 weeks ± 2.0 **Term deliveries:** [≥37 weeks]: experimental =	**Interventions** Fortnightly course of 12mg betamethasone IM, 2 doses 24h apart until 33 weeks' gestation or birth, whichever happened first. For women with PROM the recommendation was to stop the study medication at 32 weeks' gestation **Comparator:** Similarly appearing IM injection of dilute concentration of aluminium monostearate in single-course arm	**Details** Cohort follow-up study of children seen between June 2006 and May 2012 at 55 centres. In total, 1724 women (2141 children) were eligible for the study, of whom 1728 children (80.7% of the 2141 eligible children) participated. **Data collection and analysis** All children alive at 5 years of age underwent the 5-year assessment, which included a neurologic assessment to determine the presence of cerebral palsy and any hearing/visual difficulties and the completion of 2 parent questionnaires. The institutions were encouraged to contact	**Results** **1. Child mortality up to 5 years of age (n=93)** Multiple-courses: 46/873 Control: 47/855 OR 0.94 (95% CI 0.61 to 1.46) P=.79 **2. Neuromotor disability (nonambulatory cerebral palsy) at 5 years of age** Multiple-courses: 4/827 Control: 11/808 OR 0.35 (95% CI 0.11 to 1.10) P=.06 **3. Neurosensory disability (blindness, deafness, visual aids, hearing aids) at 5 years of age** Multiple-courses: 70/827 Control: 61/808 OR 1.12 (95% CI 0.77 to 1.63) P=.55 -Blindness Multiple-	**Limitations** **Risk of bias of included studies. as assessed by the review authors and indirectness assessed by NCC-WCH technical team** - Method of randomisation not clearly described but assessed to be adequate, adequate allocation concealment - Blinding of participants and care providers - 19.3% children were lost to follow up (calculated from 80.7% of eligible children who participated) -Intention-to-treat analysis - Indirectness: 22.3% of women had a multiple pregnancy -Low risk of selection,

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Aim of the study To determine the effects of single vs multiple courses of antenatal corticosteroid therapy on death or neurodevelopmental disability (neuromotor, neurosensory, or neurocognitive/neurobehavioral function) at 5 years of age in children whose mothers participated in MACS **Study dates** Children were seen between June 2006 and May 2012 **Source of funding** Canadian Institutes of Health Research grant	201/689 (29.2%); control = 236/687 (34.4%) **Completed repeat course(s):** "number of courses of study drug": zero courses = 6/1376, one course = 549/1376, two courses = 437/1376, three courses = 237/1376, four courses = 146/1376 **Women with P-PROM at randomisation** Experimental: 106/689 (15.4%) Control: 117/687 (17%) **Inclusion criteria** women with single, twin or triplet pregnancy between 25 and 32 weeks' gestation who had received an initial course of antenatal corticosteroids (either betamethasone or dexamethasone) 14-21 days previously and who remained undelivered and at continued high risk of preterm birth - All children alive at 5 years of age **Exclusion criteria** contraindication to corticosteroid use, need for chronic doses of corticosteroids, evidence of chorioamnionitis, known lethal congenital abnormality, initial course of corticosteroids before 23 weeks' gestation,		the families of all surviving children even if no contact had been made at 18 to 24 months of age. The target date for the visit was the child's fifth chronological birthday; completing the assessments within 4 months of the target date was encouraged, but efforts to locate and assess the children continued beyond this age when necessary. The analysis was based on an "intention-to-treat" approach. Descriptive statistics were used to check for dissimilarity in the 2 groups.	courses: 1/827 Control: 2/808 -Needing visual aids Multiple-courses: 61/827 Control: 52/808 -Deafness Multiple-courses: 11/827 Control: 6/808 -Needing amplification/hearing aids Multiple-courses: 4/827 Control: 5/808 **3. Neurocognitive/ neurobehavioural disability (abnormal attention, memory or behaviour) at 5 years of age** Multiple-courses: 108/822 Control: 109/793 OR .98 (95% CI 0.73 to 1.33) P=.91	detection and performance bias -Moderate risk of attrition bias

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	previously participated in the MACS study, women with a multiple pregnancy with fetal death after 13 weeks' gestation				
Full citation Atarod,Z., Taghipour,M., Roohanizadeh,H., Fadavi,S., Taghavipour,M., Effects of single course and multicourse betamethasone prior to birth in the prognosis of the preterm neonates: A randomized, double-blind placebo-control clinical trial study, Journal of Research in Medical Sciences, 19, 715-719, 2014 **Ref Id** 346285 **Country/ies where the study was carried out** Iran **Study type** Randomised control trial **Aim of the study** To examine the effect of single and multiple betamethasone administration on neonatal outcomes **Study dates** Not specified **Source of funding**	**Sample size** N = 1348 women n = 674 women in each group (intervention and placebo) **Characteristics** **Mean age (yr)** -Multiple course group: 23.4 -placebo group: 23.5 p>0.05 **Preterm birth n(%)** -Multiple course group: 271 (46.5%) -placebo group: 316 (53.8%) p: not reported **Caesarean birth (%)** -Multiple course group: 65.5% -placebo group: 67.5% p: not reported **Vaginal birth (%)** -Multiple course group: 33.5% -placebo group: 23.5% p: not reported **Mean duration of hospitalisation (days)** -Multiple course group: 2.03 -placebo group: 3.31 p: 0.01 **Inclusion criteria** • Women with risk of	**Interventions** 12mg betamethasone IM (3cc), and repeated 24h after the first injection. 3cc placebo were injected in the same manner	**Details** n = 1348 women were recruited for the study from a hospital at north of Iran. All received the first course of betamethasone and then randomly divided to placebo and multi course of betamethasone groups using the table of random numbers. Injection of placebo in placebo and betamethasone in the multiple course group repeated every 10 days up to two courses. These were carried out by a trained nurse at the research centre. Both women and the nurse were blinded to the group allocations. a weekly contact were maintained with all participants. <u>Statistical analysis</u> Data analysis carried out using statistical analysis package (SPSS version 18). Categorical data analysed by means of Chi-square and the	**Results** The total number of participants for each outcome and subgroup not reported **Neonatal death (%)** -Multiple course group: 21.4% -placebo group: 29.4% p> 0.05 <u>28-30 weeks gestation</u> -Multiple course group: 33% -placebo group: 52% p=0.04 <u>31-32 weeks gestation</u> -Multiple course group: 30.5% -placebo group: 50% p> 0.05 <u>33-35 weeks gestation</u> -Multiple course group: 16.3% -placebo group: 20.2% p> 0.05 **RDS** -Multiple course group: 38.7% -placebo group: 49.4% p=0.01 <u>28-30 weeks gestation</u> -Multiple course group: 61%	**Limitations** -Indirect to our review protocol: a total of 42 women had twin pregnancy -48/674 women in placebo group and 56/674 women in multi-course group were excluded, the reason not specified -No intention to treat analysis performed -The total number of participants for each neonatal outcome and the subgroup (based on the gestational age) not reported **Other information** n=138 women received two courses and n=149 women received three courses of betamethasone in the intervention group

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Not specified	preterm labour (gestational age 28-35 weeks, painful or painless uterine contractions, lower abdominal pain and cervical dilatation <3cm) and birth or preterm birth history • Placenta previa • Chronic detachment and cerclage history **Exclusion criteria** • Premature rupture of membranes before entering the trial • Major fetal anomalies • IUGR • Insulin-dependent diabetes • Chorioamnionitis • Taking systemic corticosteroids during pregnancy		differences between sample means in the two groups examined using t-test.	-placebo group: 65% p=0.04 <u>31-32 weeks gestation</u> -Multiple course group: 53.8% -placebo group: 75.9% p=0.02 <u>33-35 weeks gestation</u> -Multiple course group: 30% -placebo group: 40% p=0.03 **Need for ventilation** -Multiple course group: 27.7% -placebo group: 39.6% p=0.002 <u>28-30 weeks gestation</u> -Multiple course group: 50% -placebo group: 60% p=0.04 <u>31-32 weeks gestation</u> -Multiple course group: 34% -placebo group: 61% p=0.007 <u>33-35 weeks gestation</u> -Multiple course group: 21.3% -placebo group: 30.6% p=0.04	

H29 Magnesium sulfate for neuroprotection

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Doyle,L.W., Anderson,P.J., Haslam,R., Lee,K.J., Crowther,C., Australasian Collaborative Trial of Magnesium Sulphate (ACTOMgSO, School-age outcomes of very preterm infants after antenatal treatment with magnesium sulfate vs placebo, JAMA, 312, 1105-1113, 2014 **Ref Id** 323873 **Country/ies where the study was carried out** Australia and New Zealand **Study type** Randomised controlled trial **Aim of the study** To determine the association between exposure to antenatal magnesium sulphate and neurological, cognitive, academic and behavioural outcomes at school age. **Study dates** February 1996 to September 2000	**Sample size** N = 1062 women randomized (1262 fetuses alive at entry) **Characteristics** <u>Gestational age at birth (mean [SD])</u> Magnesium sulphate: 27.3 (2.2) Placebo: 27.4 (2) <u>Multiple pregnancy (n (%))</u> Magnesium sulphate: 124 (28) Placebo: 128 (30) **Inclusion criteria** Singleton, twin, triplet or quadruplet pregnancy Less than 30 weeks gestation (judged by menstrual history and early ultrasound) Birth planned or expected within 24 hours **Exclusion criteria** Second stage of labour Received magnesium sulphate in current pregnancy Contraindications to magnesium sulphate (respiratory rate < 16/minute, absent patellar	**Interventions** Magnesium sulphate (n = 535 women; n = 633 babies; n = 629 live babies) Placebo (n = 527 women; n = 629 babies; n = 626 live babies)	**Details** RCT Conducted in 16 centres in Australia and New Zealand comparing MgSo4 vs placebo given to pregnant women (n=535 magnesium; n=527 placebo) for who imminent birth was planned or expected < 30 weeks gestation. Children who survived from the 14/16 centres who participated in the school age f/u (n=443 MgSO4; n=424 placebo) were invited for assessment at 6-11 years of age. 334 children were f/u in MgSO4 arm. Multiple imputation used to impute missing outcomes in the sites participating in the f/u. No conclusions were altered in the complete case analysis (eTable 4 in Supplement 2 of article). 335 children were f/u in placebo arm.	**Results** MgSo4 vs Placebo Cerebral palsy (Analysis with multiple imputation, adjusted for study centre and clustering) 23/295 (8%) vs. 21/314 (7%) p=0.27 OR= 1.26 (0.84-1.91) Severity of cerebral palsy (no imputation, no adjustment for study center or clustering): None: 272/292 (92%) vs. 293/314 (93%) Mild: 16/295 (5%) vs. 14/314 (4%) Moderate: 5/295 (2%) vs. 5/314 (1%) Severe: 2/295 (1%) vs. 2/314 (1%) p-value=0.60 Gross motor function classification system (no imputation, no adjustment for study center or clustering):	**Limitations** Appropriate randomisation: Yes Allocation concealment: Yes Groups comparable at baseline: Yes. There are no statistically significant differences in perinatal, 2-yr and demographic characteristics of children available for f/u. Groups received same care (apart from intervention): Yes Blinding of participants: Yes Blinding of staff providing care: Yes Blinding of outcome assessors: Yes Missing data/loss to follow-up: From 2 yr f/u 3 died before school age f/u and 190 were from centers that did not participate in school age f/u leaving 867 (443 MgSo4 and 424 placebo). Precise definition of outcomes: Yes Valid and reliable method of outcome assessment: Yes Intention-to-treat analysis performed: No

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
(recruitment) 2005-2011 (outcomes measurement) **Source of funding** National Health and Medical Research Council Australia and Victorian Government's Operational Infrastructure Support Program.	reflexes, urine output < 100 ml in previous 4 hours, renal failure, or hypocalcemia)			Level 0: 264/304(87%) vs. 277/314 (88%) Level 1: 28/304 (9%) vs. 26/314 (8%) Level 2: 7/304 (2%) vs. 7/314 (2%) Level 3: 1/304 (<1%) vs. 2/314 (1%) Level 4: 3/304 (1%) vs. 1/314 (<1%) Level 5: 1/304 (<1%) vs. 1/314 (<1%) p=0.60 Movement Assessment Battery for Children Centile Analysis with multiple imputation, adjusted for study centre and clustering- *Median (IQR) 29 (6-60) vs. 32 (6-65) Mean difference (95% CI): -2.8 (-9.1 to 3.5); p=0.38 No imputation, no adjustment for study center or clustering)- Normal: 187/297 (63%) vs. 191/301 (63%)	Indirectness: 28% of the MgS04 arm and 30% of placebo arm had multiple pregnancies

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				Suspect: 36/297 (12%) vs. 35/301 (63%) Abnormal: 74/297 (25%) vs. 75/301 (25%) p=0.93 Definite motor dysfunction (<5th centile or cerebral palsy) 80/297 (27%) vs. 80/300 (27%) OR=1.16 (0.88-1.52); p=0.28 **N Mean (SD); Mean Difference (95% CI)** General cognitive function Full scale IQ: 93.8 (15.8) vs. 94.9 (15.0); −1.4 (−4.2 to 1.4) Verbal comprehension index: 94.2 (15.1) vs. 94.9 (13.6); −0.9 (−3.6 to 1.9) Perceptual reasoning index: 96.1 (15.4) vs. 7.6 (15.2) ; −2.1 (−4.8 to 0.7) Working memory index: 95.1 (14.9) vs. 96.4 (14.7); −1.2 (−4.0 to 1.6) Processing speed index:94.9 (15.1) vs. 94.5 (14.1); 0.2 (−2.4 to 2.8) Academic skills Reading: 99.4 (17.0) vs. 98.9 (16.9) ; 1.0 (−2.4 to 4.4)	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				Spelling: 98.3 (15.7) vs. 97.1 (15.2); 1.2 (−2.0 to 4.4) Arithmetic: 89.8 (16.6) vs. 89.5 (16.1) ; 0.5 (−2.6 to 3.7) Attention Selective-Sky Search: 9.8 (3.3) vs. 9.8 (3.4) ; −0.3 (−0.9 to 0.4) Sustained-Score 8.8 (3.6) vs. 8.5 (3.8); 0.1 (−0.7 to 0.9) Divided-Sky Search Dual Task: 79.1 (16.9) vs.77.6 (17.4); 0.3 (−3.1 to 3.7) Shifting-Creature Counting: 9.1 (3.8) vs.8.7 (3.8); 0.2 (−0.6 to 1.0) Executive function Rey complex figure copy score: 17.4 (7.1) vs. 18.1 (7.4); −1.1 (−2.4 to 0.3) Rey complex figure recall score: 8.4 (5.4) vs. 8.8 (5.6); −0.6 (−1.8 to 0.6) BRIEF parent T scores Global executive composite: 53.1 (12.5) vs. 52.6 (12.1); 0.8 (−1.6 to 3.2) Metacognition index: 53.4 (12.9) vs. 52.8 (12.5); 1.2 (−1.2 to 3.6)	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				Behavioural regulation index: 51.7 (12.5) vs. 51.7 (11.6); −0.0 (−2.4 to 2.4) BRIEF teacher T scores Global executive composite: 54.0(12.4) vs. 53.1 (10.9); 1.5 (−0.7 to 3.8) Metacognition index: 54.5 (12.6) vs. 54.0 (11.1); 1.4 (−0.8 to 3.7) Behavioural regulation index: 52.0 (11.9) vs. 51.5 (10.7); 1.3 (−0.9 to 3.5) Behaviour CADS parent T scores ADHD index: 57.3 (11.5) vs. 56.3 (10.7); 1.3 (−0.7 to 3.3) DSM-IV inattentive: 56.1 (11.6) vs. 55.4 (10.7) DSM_IV hyperactive-impulsive: 56.1 (12.3) vs. 55.9 (12.0); 0.3 (−2.0 to 2.6) DSM-IV: 56.6 (11.7) vs. 56.0(11.2); 0.9 (−1.2 to 3.0) CADS teacher T scores ADHD index: 54.3 (11.3) vs. 53.8 (10.5); 1.4 (−0.8 to 3.5) DSM-IV inattentive: 50.0 (8.6) vs. 49.4 (8.4); 1.0 (−0.6 to 2.7) DSM-IV hyperactive-impulsive: 51.9 (10.4) vs. 51.2 (9.4); 1.5 (−0.3 to 3.3) DSM-IV: 52.8 (10.2) vs. 52.0 (9.1); 1.6 (−0.2 to 3.5) SDQ total difficulties	

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				Parent scores: 11 (6 to 17) vs. 10 (6 to 15); 0.9 (−0.3 to 2.1) Teacher scores: 8 (4 to 14) vs. 8 (4 to 13); 0.5 (−0.9 to 1.8) Growth Mean (SD scores) Ht: −0.25 (1.24) vs. −0.09 (1.20) ; −0.11 (−0.35 to 0.14) Wt: −0.18 (1.43) vs. 0.05 (1.33); −0.22 (−0.48 to 0.04) BMI: −0.04 (1.43) vs. 0.15 (1.37); −0.22 (−0.46 to 0.03) Head circumference: −1.07 (1.13) vs. −0.86 (1.26) ; −0.18 (−0.39 to 0.03) Functional outcomes Median (25th-75th Centile) Health utility index: 1 (1 to 1) vs. 1 (1 to 1) ; −0.00 (−0.03 to 0.02) Child Health questionnaire summary scores Median (25th-75th Centile) Physical: 361 (326 to 379) vs. 355 (324 to 375) ; −2.2 (−12.8 to 8.4) Psychosocial: 501 (412 to 542) vs. 89 (423 to 544); −8.1 (−24.7 to 8.4 Other neurosensory outcomes No./Total No. (%) Blindness: 1/269 (0.4) vs.0/285 Deafness: 6/280 (2) vs. 7/304 (2); 0.93 (0.31 to 2.81)	

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				Neurosensory disability None: 174/257 (68) vs. 171/254 (67) Mild: 50/257 (19) vs. 56/254 (22) Moderate: 24/257 (9) vs. 20/254 (8) Severe: 9/257 (4) vs. 7/254 (3)	
Full citation Crowther,C.A., Hiller,J.E., Doyle,L.W., Haslam,R.R., Australasian Collaborative Trial of Magnesium Sulphate (ACTOMg SO, Effect of magnesium sulfate given for neuroprotection before preterm birth: a randomized controlled trial, JAMA, 290, 2669-2676, 2003 **Ref Id** 222551 **Country/ies where the study was carried out** Australia and New Zealand **Study type** Randomised controlled trial **Aim of the study** To evaluate the	**Sample size** N = 1062 women randomised **Characteristics** **Gestational age at trial entry/weeks (median [IQR])** Magnesium sulphate: 27^{+3} (25^{+5} to 28^{+5}) Placebo: 27^{+2} (25^{+5} to 28^{+5}) **Multiple pregnancy (n (%))** Magnesium sulphate: 88 (16.4) Placebo: 89 (16.9) **Reason for preterm birth (n (%))** a. Preterm labour Magnesium sulphate: 335 (62.6) Placebo: 330 (62.6) b. Pre-	**Interventions** Magnesium sulphate (n = 535 women; n = 633 babies; n = 629 live babies) Placebo (n = 527 women; n = 629 babies; n = 626 live babies) [Note: There were 7 babies who were part of multiple gestations and had already died prior to randomisation (they are not included in the analysis)]	**Details** **Recruitment and randomisation** This study was conducted in 16 tertiary hospitals (13 Australia; 3 New Zealand). Randomisation was stratified by centre and by order of pregnancy (singleton, twin, higher order). Randomisation sequence was generated by computer in varying block sizes and managed by nonclinical staff in the Clinical Trials Unit. Study numbers were placed on masked treatment packs which were sent to each centre ready to use. When women gave consent, they were enrolled by taking the next treatment pack (they both looked identical) from the drug supplies at the centre. When it was opened, this was considered the point of randomisation regardless of whether the infusion was ever started. **Care protocol**	**Results** **Death of the baby (n/total (%))** a. Total Magnesium sulphate: 87/629 (13.8) Placebo: 107/626 (17.1) RR 0.83 (95% CI 0.64 to 1.09); p = 0.19 [Note: the RR was similar in singleton pregnancies (RR 0.82 {0.60 to 1.12}) and in multiple pregnancies (RR 0.80 {0.46 to 1.39})] b. Stillbirth following randomisation Magnesium sulphate: 9/629 (1.4) Placebo: 11/626 (1.8) RR 0.81 (95% CI 0.34 to 1.95) c. Death after birth before	**Limitations** **Appropriate randomisation:** Yes **Allocation concealment**: Yes **Groups comparable at baseline:** Generally yes, although the authors report that there was an imbalance in race, hospital, public patient status, and either antepartum haemorrhage or preterm prelabour rupture of membranes. They report that these things were only associated with mortality (not with cerebral palsy) and therefore they performed an adjusted analysis. **Groups received same care (apart from intervention):** Yes **Blinding of participants:** Yes **Blinding of staff providing care:** Yes

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
effectiveness of magnesium sulphate in preventing paediatric mortality and cerebral palsy when given to women at risk of preterm birth before 30 weeks gestation **Study dates** February 1996 to September 2000 (recruitment) **Source of funding** 5 year grant from the National Health and Medical Research Council Australia, the Channel 7 Research Foundation of South Australia Inc, and the Queen Victoria Hospital Research Foundation, Adelaide. It was also supported by the Department of Obstetrics and Gynaecology at the University of Adelaide.	eclampsia/eclampsia Magnesium sulphate: 86 (16.1) Placebo: 75 (14.2) c. Chorioamnionitis Magnesium sulphate: 73 (13.6) Placebo: 72 (13.7) d. Antepartum haemorrhage Magnesium sulphate: 70 (13.1) Placebo: 81 (15.4) e. Severe intrauterine growth restriction (IUGR) Magnesium sulphate: 50 (9.3) Placebo: 43 (8.2) f. Premature rupture of membranes (PROM) Magnesium sulphate: 43 (8.0) Placebo: 54 (10.2) g. Fetal distress Magnesium sulphate: 20 (3.7) Placebo: 13 (2.5) h. Other Magnesium sulphate: 29 (5.4) Placebo: 30 (5.7) **Previous obstetric history (n (%))**		- Magnesium sulphate Women were given a loading infusion of 8 ml (4g) of magnesium suphate for 20 minutes, followed by a maintenance infusion of 2 ml/hour until birth (if birth occurred within 24 hours) or up to 24 hours. Of the 535 women assigned to magnesium sulphate, 13 women did not receive the intervention at all. Of the 522 women in whom the loading dose was started, 484 completed it. 451 started the maintenance dose and 70 completed the maintenance dose. The median volume of medication received was 13 ml (IQR 9 - 28). - Placebo Women were given a loading infusion of 8 ml of isotonic 0.9% sodium chloride solution, followed by a maintenance infusion of 2 ml/hour until birth (if birth occurred within 24 hours) or up to 24 hours. Of the 527 women assigned to placebo, 18 women did not receive it at all. Of the 509 women in whom the loading dose was started, 495 completed it. 459 started the maintenance dose and 77 completed the maintenance dose. The median volume of placebo received was 13 ml (IQR 10 - 29) Magnesium sulphate was not given for tocolysis. 4 (0.7%)	discharge* Magnesium sulphate: 76/629 (12.1) - ≤ 28 days: 61 - > 28 days: 15 Placebo: 92/626 (14.7) - ≤ 28 days: 75 - > 28 days: 17 d. Death after discharge, up to a corrected age of 2 years Magnesium sulphate: 2/629 (0.3) Placebo: 4/626 (0.6) * The authors appear to have excluded the stillbirths from the denominators; therefore, their calculated percentages are 12.3% and 15.0% **Cerebral palsy at 2 years among those babies who were alive and available for follow-up† (n/total (%))** a. Any cerebral palsy Magnesium sulphate: 36/533 (6.8) Placebo: 42/514 (8.2) b. Mild cerebral palsy Magnesium sulphate: 21/533 (3.9) Placebo: 21/513 (4.1)	**Blinding of outcome assessors:** Yes **Missing data/loss to follow-up:** 9 babies from the magnesium sulphate arm and 5 from the placebo arm did not have the two year follow-up; up to 10% babies had missing data for other outcomes at 2-year follow-up in addition to those who died (e.g. 8.4% of babies who survived do not have data for developmental delay) **Precise definition of outcomes:** Yes **Valid and reliable method of outcome assessment:** Yes **Intention-to-treat analysis performed:** Yes **Indirectness:** 16% of the magnesium sulphate arm and 17% of the placebo arm had multiple pregnancy **Other information** **Time from randomisation to birth/hours (median (IQR))** Magnesium sulphate: 3.7 (1.4 to 13.8) Placebo: 3.1 (1.3 to 12.9) **Gestational age at**

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	a. Very preterm birth (< 32 weeks) Magnesium sulphate: 71 (27.7) Placebo: 75 (26.0) b. Preterm birth at 32-36 weeks Magnesium sulphate: 57 (22.3) Placebo: 58 (20.1) c. Perinatal death at or after 20 weeks Magnesium sulphate: 47 (18.4) Placebo: 58 (20.1) **Maternal age/years (mean ± SD)** Magnesium sulphate: 28.4 ± 5.8 Placebo: 28.7 ± 5.8 **Nulliparous (n (%))** Magnesium sulphate: 279 (52.1) Placebo: 239 (45.4) **Blood pressure/mmHg (median (IQR))** a. Systolic Magnesium sulphate: 114 (110 - 124) Placebo: 115 (110 - 120)		women from the magnesium sulphate group and 11 (2.1%) women from the placebo group received magnesium for clinical reasons after enrollment. Women's pulse rate, blood pressure and respiratory rate were monitored throughout the infusion and any adverse effects were noted. The loading or maintenance infusions were stopped if respiratory rate decreased more than 4/minute or the diastolic BP dropped more than 15 mmHg below baseline. Infusion could be restarted if either of these returned to baseline levels. Attending clinicians were told not to measure magnesium levels, in order to maintain blinding. **Follow-up** All babies who survived had a cranial ultrasound performed within the first 7 days of life (to detect intraventricular haemorrhage) and then had a later ultrasound at at least 4 weeks of age and as close to discharge as possible to identify periventricular leukomalacia. Women and their babies were followed up until the child was 2 years (corrected for prematurity). Surviving babies were assessed by a development paediatrician and psychologist at 2 years of age (both were blinded).	RR 0.96 (95% CI 0.53 to 1.74) c. Moderate cerebral palsy Magnesium sulphate: 12/533 (2.3) Placebo: 15/513 (2.9) RR 0.77 (95% CI 0.36 to 1.62) d. Severe cerebral palsy Magnesium sulphate: 3/533 (0.6) Placebo: 6/513 (1.2) RR 0.48 (95% CI 0.12 to 1.92) † Note: Despite definitively reporting below the table that they are using the number of babies alive at randomisation as the denominator, in fact the reported % match the use of a denominator of those randomised minus those who died and those who were lost to follow-up. 1 further baby seems to have missing data on severity, judging by the reported denominator in table 5 of the paper **Gross motor dysfunction among those alive and available for follow-up (n/total (%))**	**birth/weeks (median (IQR))** Magnesium sulphate: 27^{+5} (26 to 29) Placebo: 27^{+3} (25^{+6} to 29)

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	b. Diastolic Magnesium sulphate: 70 (60 - 75) Placebo: 70 (60 - 75) 54% of the magnesium sulphate group and 55% of the placebo group gave birth by caesarean section. **Inclusion criteria** Singleton, twin, triplet or quadruplet pregnancy Less than 30 weeks gestation (judged by menstrual history and early ultrasound) Birth planned or expected within 24 hours **Exclusion criteria** Second stage of labour Received magnesium sulphate in current pregnancy Contraindications to magnesium sulphate (respiratory rate < 16/minute, absent patellar reflexes, urine output < 100 ml in previous 4 hours, renal failure, or hypocalcemia)		**Statistical analysis** Sample size calculation was based on detecting a 50% reduction in risk of cerebral palsy in survivors at 2 years (from 10% to 5%) with 80% probability and an alpha of 0.05. A sample size of 848 babies was needed but this was adjusted upwards to 1250 to account for predicted mortality of 20% and the effect of multiple births. Data were reviewed twice by an independent data monitoring committee. Analysis was done intention-to-treat. Variance estimation was used to account for clustering of babies within mothers. **Outcomes reported** **- Death:** All deaths were reviewed by an independent (blinded) committee to determine main cause of death **- Cerebral palsy:** Criteria included abnormalities of tone and loss of motor function; assessed at a corrected age of 2 years **- Composite of death and cerebral palsy**	a. Minimal Magnesium sulphate: 84/529 (15.9) Placebo: 73/513 (14.2) RR 1.12 (95% CI 0.82 to 1.51) b. Substantial Magnesium sulphate: 18/529 (3.4) Placebo: 34/513 (6.6) RR 0.51 (95% CI 0.29 to 0.91) **Bayley Scales of Infant Development (mean ± SD)** a. Psychomotor Development Index Magnesium sulphate: 88.9 ± 18.0 (n = 482) Placebo: 90.2 ± 19.0 (n = 461) b. Mental Development Index Magnesium sulphate: 89.0 ± 18.7 (n = 483) Placebo: 90.4 ± 18.6 (n = 466) **Delayed development (n/total (%))** a. Mild Magnesium sulphate: 97/494	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			- Gross motor function: Assessed at corrected age of 2 years. Children were classed as walking normally, walking with minimal limitations such as toe walking or asymmetrical gait, or not walking independently. The latter group were classed as having substantial gross motor dysfunction. - **Bayley Scales of Infant Development**: Psychomotor Developmental Index (PDI) and Mental Development Index (MDI) were used. Those unable to complete the scales due to severe delay were automatically assigned a score of 49 (a score which indicates severe disability). **- Developmental delay:** defined as mild (Mental Development Index - 2 SDs to less than - 1 SD), moderate (Mental Development Index - 3 SDs to - 2 SDs) or severe (Mental Development Index < 3 SDs) based on MDI scores **- Neurosensory disability (composite):** Assessed at a corrected age of 2 years. Severe neurosensory disability comprised any of severe cerebral palsy (permanently non-ambulant), severe development delay (Mental Development Index < 3 SDs) and blindness. Moderate disability comprised any of	(19.6) Placebo: 103/478 (21.5) RR 0.91 (95% CI 0.71 to 1.18) <u>b. Moderate</u> Magnesium sulphate: 47/494 (9.5) Placebo: 34/478 (7.1) RR 1.34 (95% CI 0.85 to 2.12) <u>c. Severe</u> Magnesium sulphate: 32/494 (6.5) Placebo: 33/478 (6.9) RR 0.94 (95% CI 0.57 to 1.55) **<u>Neurosensory disability (composite outcome) among those alive and available for follow-up (n/total (%))</u>** <u>a. Mild</u> Magnesium sulphate: 104/504 (20.6) Placebo: 109/483 (22.6) RR 0.91 (95% CI 0.72 to 1.16) <u>b. Moderate</u> Magnesium sulphate: 54/504 (10.7) Placebo: 44/483 (9.1) RR 1.18 (95% CI 0.79 to 1.76)	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			moderate cerebral palsy (non-ambulant at 2 years but likely to walk), moderate development delay (Mental Development Index - 3 SDs to - 2 SDs) and deafness. Mild disability was either mild cerebral palsy (walking at 2 years) or mild developmental delay (Mental Development Index - 2 SDs to less than - 1 SD). **- Vision and hearing:** Children were considered blind if their vision in both eyes was worse than 6/60. They were considered deaf if they required hearing aids. **- Intraventricular haemorrhage:** Assessed using a cranial ultrasound scan during first 7 days of life **- Periventricular leukomalacia:** Assessed using a cranial ultrasound scan after 4 weeks of age - **Maternal adverse effects:** Respiratory rate, blood pressure drop and PPH (> 600 ml and > 1000 ml) are reported, as well as clinical and self-assessed more minor effects	c. Severe Magnesium sulphate: 35/504 (6.9) Placebo: 34/483 (7.0) RR 0.99 (95% CI 0.61 to 1.61) **Vision and hearing (n/total (%))** a. Proportion of children who were blind (n/total (%)) Magnesium sulphate: 1/533 (0.2) Placebo: 1/514 (0.2) RR 0.96 (95% CI 0.06 to 15.3) b. Proportion of children who were deaf Magnesium sulphate: 8/533 (1.5) Placebo: 7/514 (1.4) RR 1.10 (95% CI 0.40 to 3.02) **Composite outcomes** a. Death or cerebral palsy (n/total (%)) Magnesium sulphate: 123/620 (19.8) Placebo: 149/621 (24.0)	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				[Note: Despite reporting that they are using those alive at randomisation as the sample, their calculated percentages make it clear that they excluded those lost to follow-up from the denominator] b. Death or substantial motor dysfunction (n/total (%)) Magnesium sulphate: 105/616 (17.0) Placebo: 141/620 (22.7) RR 0.75 (95% CI 0.59 to 0.96) **Intraventricular haemorrhage (n/total (%))** a. Any intraventricular haemorrhage Magnesium sulphate: 165/596 (27.7) Placebo: 148/586 (25.3) RR 1.10 (95% CI 0.90 to 1.33) b. Grade III or IV intraventricular haemorrhage Magnesium sulphate: 49/596 (8.2) Placebo: 50/586 (8.5) RR 0.96 (95% CI 0.65 to 1.43) Periventricular leukomalacia	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				(n/total (%)) Magnesium sulphate: 22/596 (3.7) Placebo: 21/586 (3.6) RR 1.03 (95% CI 0.57 to 1.87) **Maternal outcomes (n/total (%))** a. Respiratory rate < 16/minute Magnesium sulphate: 34/535 (6.4) Placebo: 28/527 (5.3) RR 1.20 (95% CI 0.74 to 1.94) b. Diastolic blood pressure decrease of more than 15 mmHg Magnesium sulphate: 77/535 (14.4) Placebo: 52/527 (9.9) RR 1.46 (95% CI 1.05 to 2.03) c. Postpartum haemorrhage > 600 ml Magnesium sulphate: 86/535 (16.1) Placebo: 99/527 (18.8) RR 0.86 (95% CI 0.66 to 1.11) d. Major postpartum	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				haemorrhage (> 1000 ml) Magnesium sulphate: 26/535 (4.9) Placebo: 25/527 (4.7) RR 1.02 (95% CI 0.60 to 1.75) **Clinical and self-assessed adverse effects (n/total (%))** a. Death Magnesium sulphate: 0/535 (0) Placebo: 0/527 (0) b. Cardiac or respiratory arrest Magnesium sulphate: 0/535 (0) Placebo: 0/527 (0) c. Infusion stopped due to adverse effects Magnesium sulphate: 78/535 (14.6) Placebo: 28/527 (5.3) RR 2.74 (95% CI 1.81 to 4.15) d. Any adverse effects Magnesium sulphate: 476/535 (89.0) Placebo: 199/527 (37.8) RR 2.36 (95% CI 2.10 to 2.64) e. Warmth over body	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				Magnesium sulphate: 393/535 (73.5) Placebo: 88/527 (16.7) RR 4.40 (95% CI 3.61 to 5.36) <u>f. Any discomfort with infusion</u> Magnesium sulphate: 355/535 (66.4) Placebo: 39/527 (7.4) RR 8.97 (95% CI 6.59 to 12.2) <u>g. Mouth dryness</u> Magnesium sulphate: 212/535 (39.6) Placebo: 99/527 (18.8) RR 2.11 (95% CI 1.72 to 2.59) <u>h. Nausea</u> Magnesium sulphate: 137/535 (25.6) Placebo: 55/527 (10.4) RR 2.45 (95% CI 1.84 to 3.28) <u>i. Sleepiness</u> Magnesium sulphate: 119/535 (22.2) Placebo: 47/527 (8.9) RR 2.49 (95% CI 1.82 to 3.42) <u>j. Sweating</u>	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				Magnesium sulphate: 104/535 (19.4) Placebo: 29/527 (5.5) RR 3.53 (95% CI 2.38 to 5.24) k. Dizziness Magnesium sulphate: 83/535 (15.5) Placebo: 37/527 (7.0) RR 2.21 (95% CI 1.53 to 3.19) l. Blurred vision Magnesium sulphate: 38/535 (7.1) Placebo: 16/527 (3.0) RR 2.34 (95% CI 1.32 to 4.14) m. Tachycardia (pulse rate of > 160 bpm or increase of 20/minute from baseline) Magnesium sulphate: 56/535 (10.5) Placebo: 36/527 (6.8) RR 1.53 (95% CI 1.03 to 2.29) n. Respiratory depression (decrease of more than 4/minute from baseline) Magnesium sulphate: 54/535 (10.1) Placebo: 51/527 (9.7)	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				RR 1.04 (95% CI 0.73 to 1.50)	
Full citation Marret,S., Marpeau,L., Zupan-Simunek,V., Eurin,D., Leveque,C., Hellot,M.F., Benichou,J., PREMAG trial group., Magnesium sulphate given before very-preterm birth to protect infant brain: the randomised controlled PREMAG trial*, BJOG: An International Journal of Obstetrics and Gynaecology, 114, 310-318, 2007 **Ref Id** 222947 **Country/ies where the study was carried out** France **Study type** Randomised controlled trial **Aim of the study** To evaluate if magnesium sulphate given to women at risk of preterm birth would provide neuroprotection to preterm babies and would prevent neonatal mortality and severe white-matter injury	**Sample size** N = 573 women randomised (Note: 573 women were initially randomised, but 2 of the participating centres enrolled 0 women and 3 enrolled less than 5 women. According to a predefined rule, the women were not retained, leaving 564 women in the analysis) **Characteristics** **Gestational age at entry/weeks (median (range))** Magnesium sulphate: 30 (24 - 32^{+6}) Placebo: 30 (23^{+4} - 32^{+6}) **Singleton pregnancy (n (%))** Magnesium sulphate: 222 (77.6) Placebo: 220 (79.1) **Maternal age/years (mean ± SD)** Magnesium sulphate: 29.3 ± 5.3 Placebo: 29.5 ± 5.1	**Interventions** Magnesium sulphate (n = 286 women; n = 354 babies; n = 352 live babies) Placebo (n = 278 women; n = 341 babies; n = 336 live babies) [Note: At the time of randomisation, 7 women with twin pregnancies had one baby that had not survived]	**Details** **Recruitment and randomisation** 18 tertiary hospitals with neonatal intensive care units (NICUs) agreed to participate in this trial. Randomisation was stratified by study centre, singleton/multiple pregnancy, and gestational age (< 27, 27-29, 30-32 weeks). The randomisation sequence was generated by computer and managed centrally. Once allocated, the next pack from the participating centres was used. Treatment packs were prepared by the coordinating centre and sent through to the participating centres. The time of assignment by phone was considered to be the point of randomisation, regardless of whether the infusion was later started. The women were blinded to what treatment they received (it is reported that the packs looked similar); however, the anaesthetists and obstetricians providing care were not. The authors report that this was a) so that they could take immediate action against the adverse effects of magnesium sulphate and b) because the treatment is associated with flushes and so	**Results** **Death of baby (n/total (%))** a. In utero Magnesium sulphate: 2/352 (0.6) Placebo: 3/336 (0.9) b. Postnatal (before discharge) Magnesium sulphate: 31/352 (8.8) Placebo: 32/336 (9.5) c. Total Magnesium sulphate: 33/352 (9.4) Placebo: 35/336 (10.4) Adjusted OR 0.79 (95% CI 0.44 to 1.44) [Note: 12 in the magnesium sulphate arm and 15 in the placebo arm are reported as being "neurological"] **Severe white matter injury (n/total (%))** Magnesium sulphate: 34/341 (10.0) Placebo: 38/324 (11.7) Adjusted OR 0.78 (95% CI 0.47	**Limitations** **Appropriate randomisation:** Yes **Allocation concealment:** Yes **Groups comparable at baseline:** Yes **Groups received same care (apart from intervention):** Yes **Blinding of participants:** Yes **Blinding of staff providing care:** No **Blinding of outcome assessors:** Assessment of cranial ultrasounds was done by a blinded neonatologist or radiologist **Missing data/loss to follow-up:** No **Precise definition of outcomes:** Yes, apart from the fact that no definition of hypotension is provided **Valid and reliable method of outcome assessment:** Yes **Intention-to-treat analysis performed:** Yes Recruitment was stopped before the study reached its sample size due to lack of motivation of some investigators and therefore a dramatically decreased

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Study dates July 1997 to July 2003 **Source of funding** Funded by a 3-year grant from the French Department of Health and a grant from Rouen University Hospital	**Reasons for preterm birth (n (%))** a. Preterm labour Magnesium sulphate: 236 (84.0) Placebo: 242 (88.3) b. Prelabour preterm rupture of membranes (PPROM) Magnesium sulphate: 187 (53.9) Placebo: 156 (46.6) c. Chorioamnionitis* Magnesium sulphate: 27 (9.5) Placebo: 34 (12.6) d. Antepartum haemorrhage (APH) Magnesium sulphate: 54 (19.0) Placebo: 54 (20.0) e. Other** Magnesium sulphate: 33 (9.8) Placebo: 43 (13.3) **Treatment received (n (%))** **a. Tocolysis** Magnesium sulphate: 190 (67.6) Placebo: 192 (70.8)		blinding would not be feasible. **Care protocol** - Magnesium sulphate Women received a single 40 ml infusion of 0.1 g/ml magnesium sulphate solution over 30 minutes (therefore corresponding to 4 grams or 16 mmol of magnesium sulphate). Of the 286 women assigned to this arm, 266 started the loading dose and 259 completed it. 20 women did not receive the allocated intervention. - Placebo Women received a single 40 ml infusion of isotonic 0.9% saline over 30 minutes. Of the 278 women assigned to this arm, 257 started the loading dose and 249 completed it. 21 women did not receive the allocated intervention. Apart from the intervention, women were cared for according to standard clinical practice. Pulse rate, blood pressure, respiratory rate, tendon reflexes and any maternal adverse effects were recorded throughout the infusion. It was stopped at the attending anaesthetist's discretion. Fetal heart rate was monitored throughout labour. No women received magnesium sulphate for clinical reasons after enrolment. **Follow-up**	to 1.31) [Note: 23 babies died too early to be included in the assessment of cranial ultrasound] **Intracranial haemorrhage (n/total (%))** a. Intraparenchymal haemorrhage Magnesium sulphate: 8/341 (2.4) Placebo: 11/324 (3.4) RR 0.42 (95% CI 0.14 to 1.21) b. Nonparenchymal haemorrhage Magnesium sulphate: 63/341 (18.5) Placebo: 71/324 (21.9) RR 0.75 (95% CI 0.50 to 1.11) **Maternal adverse effects (n/total (%))** a. Death Magnesium sulphate: 0/286 (0) Placebo: 1/278 (0.4) [Note: the woman had placenta accreta and died following a	rate of enrolment. **Indirectness:** 64 (22.4%) women from the magnesium sulphate group and 58 (20.9%) women from the placebo group had a multiple pregnancy **Other information** **Interval from infusion to birth/minutes (median (range))** Magnesium sulphate: 98 (5 to 1505 [25 hours 5 minutes]) Placebo: 90 (8 to 3690 [61 hours 30 minutes]) [p = 0.21] **Gestational age at birth/weeks (median (range))** Magnesium sulphate: 30^{+1} (24^{+1} to 32^{+6}) Placebo: 30^{+1} (23^{+4} to 32^{+6}) [p = 0.87]

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	b. Antibiotics Magnesium sulphate: 219 (77.1) Placebo: 207 (75.3) **c. Corticosteroids** Magnesium sulphate: 270 (95.1) Placebo: 261 (94.6) *Defined as the presence of at least 2 of: pyrexia > 38 degrees, fetal tachycardia, meconium stained amniotic fluid, bacteria in amniotic fluid, C-reactive protein level > 40 mg/l, or neutrophil count > 20 g/l within the last 48 hours **Uterine malformation, polyhydramnios, cervical incompetency, alloimmunisation, abdominal trauma, diabetes, pyelonephritis, or cholestasis 116 (40.6%) of women in the magnesium sulphate group and 96 (34.7%) of women in the placebo group had a caesarean section (p = 0.15) **Inclusion criteria** Singleton, twin, or triplet pregnancy Under 33 weeks		Women and babies were followed up until discharge. Cranial ultrasounds were planned within the first week after birth, between dasy 15 and 21, and after 6 weeks. An additional scan was done before discharge from NICU for the most preterm babies. [Note: further follow-up is reported in another included study: Marret et al. (2008)] **Statistical analysis** The sample size was targeted at 1106 babies, based on detecting a 50% reduction of the risk of severe white matter injury from 8% to 4%, with 80% power at the two-sided 0.05 level. Given that twins and triplets were expected, 906 women had to be recruited. No interim analyses were planned; however a steering committee oversaw the trial and were informed of major complications. They were consulted when another trial suggesting increased mortality was published; however, they authorised the trial to continue. Analysis was done intention-to-treat. Analysis accounted for correlation of outcomes among twins or triplets through a generalised estimating equation	major postpartum haemorrhage] b. Cardiac arrest Magnesium sulphate: 0/286 (0) Placebo: 0/278 (0) c. Prolonged mechanical ventilation Magnesium sulphate: 0/286 (0) Placebo: 0/278 (0) d. Severe postpartum haemorrhage Magnesium sulphate: 2/286 (0.7) Placebo: 1/278 (0.4) e. Nausea and vomiting Magnesium sulphate: 9/286 (3.1) Placebo: 2/278 (0.7) f. Tendon reflex abolition Magnesium sulphate: 2/286 (0.7) Placebo: 1/278 (0.4) g. Hypotension Magnesium sulphate: 3/286 (1.0) Placebo: 0/278 (0) h. Curarisation	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	gestational age (based on early ultrasound and menstrual history) Birth expected or planned within 24 hours Having not received betamimetics, aminoglycosides or steroids for at least 1 hour Signed written informed consent **Exclusion criteria** Baby with severe malformations or chromosomal abnormalities Hypotension Cardiac rhythm abnormalities Hydroelectrolyte abnormalities Renal insufficiency Ingestion of calcium channel blockers, digitalins or indomethacin during previous 24 hours Persistent signs of cardiovascular toxicity or tachycardia for over an hour after cessation of tocolytics		approach within logistic regression. Comparisons of primary outcomes and the secondary ultrasound findings were adjusted for gestational age, singleton/multiple, and birthweight. No further significant change was obtained with further adjustment for Apgar score (found to be predictive of primary outcomes), and the prolonged prelabour rupture of membranes and infection (that occurred more often in magnesium sulphate group). Odds ratios and 95% CI were reported, with $p < 0.05$ considered significant. **Outcomes reported** **- Perinatal/neonatal death:** Up to discharge **- Severe white matter injury (WMI):** Judged on cranial ultrasound scan by a blinded senior neonatologist or radiologist. Severe WMI was considered present when at least one of the three following parenchymal abnormalities was detected: cystic periventricular leucomalacia, periventricular parenchymal haemorrhagic involvement (a large unilateral parenchymal hyperdensity), or a large single unilateral porencephalic cyst caused by ischaemic-haemorrhagic infarction.	Magnesium sulphate: 1/286 (0.3) Placebo: 0/278 (0) i. Headache Magnesium sulphate: 4/286 (1.4) Placebo: 1/278 (0.4) j. Flushes Magnesium sulphate: 23/286 (8.0) Placebo: 0/278 (0)	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	Myasthenia Indication for emergency caesarean section Pregnancy associated vascular disease (i.e. pre-eclampsia, growth restriction, haemolysis, elevated liver-function test results, low-platelet syndrome, retroplacental haematoma)		**- Intracranial haemorrhage:** incidences of intraparenchymal and nonparenchymal haemorrhages are reported, as judged on cranial ultrasound scans **- Maternal adverse effects:** incidence of major effects (death, cardiac arrest and prolonged mechanical ventilation) as well as more moderate/minor adverse effects are reported.		
Full citation Marret,S., Marpeau,L., Benichou,J., Benefit of magnesium sulfate given before very preterm birth to protect infant brain, Pediatrics, 121, 225-226, 2008 **Ref Id** 236127 **Country/ies where the study was carried out** France **Study type** Follow-up to a randomised controlled trial (Marret et al., 2007)	**Sample size** N = 616 [Note: The original trial randomised 573 women, carrying 688 live babies at the point of randomisation. Of these, 72 later died. Of the 616 survivors, 472 (76.6%) were followed-up with a clinical examination, 134 were assessed via a telephone interview and 10 were lost to follow-up] **Characteristics** See evidence table for Marret et al. (2007) for details of the characteristics of the original study population. Specific characteristics of those followed-up are not	**Interventions** Magnesium sulphate (n = 352 initially randomised) Placebo (n = 336 initially randomised))	**Details** For further details of the original trial methodology (including treatment protocols), please see evidence table for the original trial, Marret et al. (2007). **<u>Follow-up procedures</u>** Paediatricians (blinded to treatment allocation) assessed children at 2 years of age. If direct examination was not possible, they assessed children via a telephone interview with the parents (134 children were assessed in this manner). The authors report that this approach has been shown to be reliable in 2 year olds. **<u>Statistical analysis</u>**	**Results** All outcomes below are assessed at 2 years of age. Odds ratios were adjusted for clustering within mother, gestational age (< 27, 27-29, and 29-32 weeks), singleton/multiple, and birth weight. **<u>Paediatric mortality (n/total (%))</u>** Magnesium sulphate: 34/352 (9.7) Placebo: 38/336 (11.3) Adjusted OR 0.74 (95% CI 0.42 to 1.32) [p = 0.31] **<u>Gross motor dysfunction among surviving babies</u>**	**Limitations** **Appropriate randomisation:** Yes (as reported in Marret et al., 2007) **Allocation concealment:** Yes (as reported in Marret et al., 2007) **Groups comparable at baseline:** The groups in the original trial were comparable (as reported in Marret et al., 2007); however, specific characteristics of those who were followed-up are not reported **Groups received same care (apart from intervention):** Yes (as reported in Marret et al., 2007) **Blinding of participants:**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Aim of the study Not stated in this paper, but the aim of the original trial was stated as to evaluate if magnesium sulphate given to women at risk of preterm birth would provide neuroprotection and prevent neonatal mortality and white matter injury **Study dates** Recruitment for the original trial was between 1997 and 2004. Follow-up was at 2 years. **Source of funding** Funded by a 3-year grant from the French Department of Health and a grant from Rouen University Hospital	reported. **Inclusion criteria** See evidence table for Marret et al. (2007) **Exclusion criteria** See evidence table for Marret et al. (2007)		Statistical analysis was done on an intention-to-treat basis. Comparisons between groups accounted for correlation between outcomes for twins and triplets born to the same mother via a generalised estimating equation approach within logistic regression, and were further adjusted for gestational age, singleton/multiple pregnancy and birth weight. **Outcomes reported** - **Paediatric mortality:** This includes both the deaths up to discharge reported in the original trial paper, and those occuring up to 2 years of age. **- Gross motor dysfunction:** Paediatricians evaluated motor functions by using a questionnaire with development items extracted from the Amiel-Tison and Denver scales **- Cerebral palsy:** Paediatricians assessed this outcome using the European Cerebral Palsy Network definition **- Cognitive dysfunction:** Paediatricians evaluated cognitive functions by using a questionnaire with development items extracted from the Amiel-Tison and Denver scales	**available for follow-up (n/total (%))** Magnesium sulphate: 55/313 (17.6) Placebo: 64/293 (21.8) Adjusted OR 0.65 (95% CI 0.41 to 1.02) [p = 0.06] **Cerebral palsy among surviving babies avaiable for follow-up (n/total (%))** Magnesium sulphate: 22/313 (7.0) Placebo: 30/293 (10.2) Adjusted OR 0.63 (95% CI 0.35 to 1.15) [p = 0.13] **Cognitive dysfunction among surviving babies available for follow-up (n/total (%))** Magnesium sulphate: 57/313 (18.2) Placebo: 62/293 (21.2) Adjusted OR 0.82 (95% CI 0.52 to 1.28) [p = 0.38] **Composite outcomes (denominators are those randomised - those lost to follow-up) (n/total (%))**	Yes (as reported in Marret et al., 2007) **Blinding of staff providing care:** No (as reported in Marret et al., 2007) **Blinding of outcome assessors:** Yes - paediatricians were blinded **Missing data/loss to follow-up:** Yes - of the 616 survivors, 10 babies (1.6% of survivors; 1.5% of those originally randomised) were lost to follow-up before 2 years (5 from each arm). **Precise definition of outcomes:** Yes **Valid and reliable method of outcome assessment:** Generally yes, although 134 (21.8%) had to be assessed by telephone. **Intention-to-treat analysis performed:** Yes Recruitment was stopped before the study reached its sample size due to lack of motivation of some investigators and therefore a dramatically decreased rate of enrolment (as reported in Marret et al., 2007). **Indirectness:** In the original trial, 64 (22.4%) women from the magnesium sulphate group

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			- Composite outcomes: Combinations of the above outcomes are also reported	a. Combined death or gross motor dysfunction Magnesium sulphate: 89/347 (25.6) Placebo: 102/331 (30.8) Adjusted OR 0.62 (95% CI 0.41 to 0.93) [p = 0.02] b. Combined death or cerebral palsy Magnesium sulphate: 56/347 (16.1) Placebo: 67/331 (20.2) Adjusted OR 0.65 (95% CI 0.42 to 1.03) [p = 0.07] c. Combined death and motor or cognitive dysfunction Magnesium sulphate: 121/347 (34.9) Placebo: 134/331 (40.5) Adjusted OR 0.68 (95% CI 0.47 to 0.99) [p = 0.04] d. Combined death and cerebral palsy or cognitive dysfunction Magnesium sulphate: 102/347 (29.4) Placebo: 116/331 (35.0)	and 58 (20.9%) women from the placebo group had a multiple pregnancy. The specific characteristics of those who were followed-up are not reported. **Other information** This is a follow-up of Marret et al. (2007). It is reported as a brief letter only.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				Adjusted OR 0.68 (95% CI 0.47 to 1.00) [p = 0.05]	
Full citation Mittendorf,R., Dambrosia,J., Pryde,P.G., Lee,K.S., Gianopoulos,J.G., Besinger,R.E., Tomich,P.G., Association between the use of antenatal magnesium sulfate in preterm labor and adverse health outcomes in infants, American Journal of Obstetrics and Gynecology, 186, 1111-1118, 2002 **Ref Id** 222991 **Country/ies where the study was carried out** USA **Study type** Randomised controlled trial **Aim of the study** To evaluate whether antenatal magnesium sulphate prevents adverse outcomes (neonatal intraventricular	**Sample size** N = 149 women randomised (However, 92 women were taking part in the tocolytic arms of the trial [which are not relevant for this review question and will not be reported here] therefore the actual sample size of interest is N = 47 (denoted the "preventive" half of the study) **Characteristics** **Multiple pregnancy (n/total (%))** Magnesium sulphate: 1/29 (3) Saline: 1/28 (4) [p > 0.99] **Maternal race: black (n/total (%))** Magnesium sulphate: 23/28 (82) Saline: 23/28 (82) [p > 0.99] **Gestational age < 28 weeks (n/total (%))**	**Interventions** Magnesium sulphate (n = 29 mothers; n = 30 babies) Saline control (n = 28 mothers; n = 29 babies)	**Details** **Recruitment and randomisation** Eligible women in preterm labour were first divided according to whether they were suitable for the "tocolytic" half of the trial (which will not be reported here) or the "preventive" half of the trial. They were then randomised (using a computer program) in stratified blocks of 6 on the basis of race (black vs. other) and gestational age (≤ 28 or > 28 weeks). Several months after the start of the trial, women were also stratified on the basis of twin vs. singleton. **Care protocol** - Magnesium sulphate The drug was given as a 4 gram intravenous bolus (with no further infusions) - Saline solution No details are given; however, the authors state that this half of the trial was "doubly masked" and therefore it is likely to have been a similar protocol to the above **Follow-up**	**Results** **Death (n/total (%))** Magnesium sulphate: 2/30 (6.7) Saline: 1/29 (3.4) [Note: it is unclear at what point these deaths occurred] **Cerebral palsy (n/total (%))** Magnesium sulphate: 3/30 (10) Saline: 0/29 (0) [Note: these cases of cerebral palsy were a case of mild hemiplegia and spastic quadriplegia in babies born to 2 women who had received 4g magnesium sulphate, and a case of moderate hemiplegia in a baby born to a woman who never received it] **Intraventricular haemorrhage (IVH) (n/total (%))** Magnesium sulphate: 5/30 (16.7) Saline: 5/29 (17.2) [Note: all five cases of IVH in the magnesium sulphate arm were grade I; in the saline arm,	**Limitations** **Appropriate randomisation:** Yes **Allocation concealment:** Unclear - no particular details are given; however, it seems likely given that the allocation is described as being "doubly masked" **Groups comparable at baseline:** Yes **Groups received same care (apart from intervention):** No reason to suspect not, although very few details given about care protocol **Blinding of participants:** Yes **Blinding of staff providing care:** Yes **Blinding of outcome assessors:** Those assessing cerebral palsy were reported as being blinded. For the remaining outcomes it is unclear - the authors only report the trial as being "doubly masked" and therefore it unclear whether the outcome assessors were blind to group allocation **Missing data/loss to**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
haemorrhage, periventricular haemorrhage, periventricular leucomalacia, death and cerebral palsy) **Study dates** October 1995 to January 1997 **Source of funding** Funding was provided by the United Cerebral Palsy Research and Educational Foundation	Magnesium sulphate: 6/28 (21) Saline: 5/28 (18) [p = 0.74] **Inclusion criteria** Women in preterm labour (with or without premature rupture of membranes) Gestational age > 24 but < 34 completed weeks Reassuring fetal assessment Absence of clinical features suggestive of infection or pre-eclampsia **Specific additional inclusion criteria for "preventive" half of trial:** Active labour with dilation > 4 cm **Exclusion criteria** Triplet or higher order gestations		In the neonatal period, babies had a minimum of 3 cranial ultrasound scans in the first, second and fourth weeks of life. Follow-up neurodevelopment examinations were conducted in follow-up clinic visits at 4, 8, 12 and 18 months. **Statistical analysis** The sample size calculation was based on anticipated reductions in neonatal intraventricular haemorrhage from 18.9% to 4.4% after the use of magnesium sulphate. With an alpha of 0.05 and power of 80%, a total of 140 babies were needed; for an alpha of 0.05 and power of 90%, 188 babies were needed; for an alpha of 0.01 and power of 80%, 208 babies were needed; and for an alpha of 0.01 and power of 90%, 266 babies were needed. Statistical analyses were performed using chi-squared test, Student's t-test, Mann-Whitney test, and Fisher's exact test. All tests were two-sided and significance was defined as an alpha of 0.05. **Outcomes reported** **- Death** **- Cerebral palsy:** Diagnosis was made after the last examination at the 18-month visit. It was made or	3 were grade I and 2 were grade III] **Periventricular leukomalacia (PVL) (n/total (%))** Magnesium sulphate: 1/30 (3.3) Saline: 0/29 (0) [Note: 1 baby in each arm had more than one of the above outcomes (1 baby with both PVL and cerebral palsy in the magnesium sulphate arm; 1 baby with IVH who then died in the saline arm). In total, 10/30 babies from the magnesium sulphate arm and 5/29 babies from the saline arm had at least one of the above.]	**follow-up:** No **Precise definition of outcomes:** Criteria for judging cerebral palsy are not described **Valid and reliable method of outcome assessment:** Yes **Intention-to-treat analysis performed:** Yes (although the details of who did not receive their allocation intervention are not reported) **Indirectness:** 1 woman in each arm had a multiple pregnancy (3.5% of the study population)

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			verified by a developmental paediatrician blinded to allocation. **- Intraventricular haemorrhage:** Ultrasound diagnoses (including grading) were made by consensus of two paediatric radiologists **- Periventricular leukomalacia (PVL):** Ultrasound presumptive diagnosis was confirmed by MRI		
Full citation Rouse,D.J., Hirtz,D.G., Thom,E., Varner,M.W., Spong,C.Y., Mercer,B.M., Iams,J.D., Wapner,R.J., Sorokin,Y., Alexander,J.M., Harper,M., Thorp,J.M.,Jr., Ramin,S.M., Malone,F.D., Carpenter,M., Miodovnik,M., Moawad,A., O'Sullivan,M.J., Peaceman,A.M., Hankins,G.D., Langer,O., Caritis,S.N., Roberts,J.M., Eunice Kennedy Shriver NICHD Maternal-Fetal Medicine Units Network., A randomized, controlled trial of magnesium sulfate for the prevention of cerebral palsy, New England Journal of Medicine, 359, 895-905, 2008 **Ref Id**	**Sample size** N = 2241 women randomised **Characteristics** **Weeks of gestation at randomisation (mean ± SD)** Magnesium sulphate: 28.3 ± 2.5 Placebo: 28.2 ± 2.4 **Twin gestation (n (%))** Magnesium sulphate: 92 (8.4) Placebo: 111 (9.7) **Magnesium sulphate prior to enrollment (n (%))** Magnesium sulphate: 201 (18.3)	**Interventions** **Magnesium sulphate** (n = 1096 women; n = 1188 babies) **Placebo** (n = 1145 women; n = 1256 babies)	**Details** **Recruitment and randomisation** This was a multicentre trial, conducted at 20 sites. Duration of gestation, as per the inclusion criteria, was determined using an algorithm that used the date of last menstrual period (where available) and the results of the earliest ultrasound exam. Women meeting the inclusion criteria were randomised using a computer-generated random sequence, with stratification acccording to: study centre, twin pregnancy, and weeks of gestation (< 28 or ≥ 28). **Care protocol** The use of tocolytics was prohibited. Once randomised, women received one of the following in a double-blind manner:	**Results** **Composite outcome of moderate or severe cerebral palsy or death (n/total (%))*** a. All pregnancies Magnesium sulphate: 118/1041 (11.3) Placebo: 128/1095 (11.7) RR 0.97 (95% CI 0.77 to 1.23); p = 0.80 **b. Pregnancies without major congenital anomalies** Magnesium sulphate: 100/997 (10.0) Placebo: 117/1063 (11.0) RR 0.91 (95% CI 0.71 to 1.17); p = 0.47 * In one twin pregnancy in the magnesium sulphate group and	**Limitations** **Appropriate randomisation:** Yes - computer generated random sequence **Allocation concealment:** Unclear - no particular details are given; however, it seems likely given that the allocation is described as being "double-blind" **Groups comparable at baseline:** Yes **Groups received same care (apart from intervention):** Yes **Blinding of participants:** Yes **Blinding of staff providing care:** Yes **Blinding of outcome assessors:** Unclear - the authors only report the trial as being "double-blind" and therefore it unclear whether the outcome assessors

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
223152 **Country/ies where the study was carried out** USA **Study type** Randomised controlled trial **Aim of the study** To evaluate whether giving magnesium sulphate to women at high risk for early preterm birth would reduce the risk of cerebral palsy in their babies **Study dates** December 1997 to May 2004 **Source of funding** Supported by grants from the NICHD and the National Institute of Neurological Disorders and Stroke	Placebo: 218 (19.0) **<u>Qualifying eligibility criteria for trial (n (%))</u>** **a. Premature rupture of membranes** Magnesium sulphate: 947 (86.4%) - Time since rupture (median [IQR])/hours: 25.2 [10.7 - 61.1] Placebo: 995 (86.9%) - Time since rupture (median [IQR])/hours: 24.4 [10.8 - 62.9] **b. Advanced preterm labour** Magnesium sulphate: 116 (10.6%) - Cervical dilation (mean ± SD)/cm: 4.8 ± 1.2 Placebo: 114 (10.0%) - Cervical dilation (mean ± SD)/cm: 4.6 ± 1.0 **c. Indicated preterm delivery** Magnesium sulphate: 33 (3.0%) Placebo: 36 (3.1%) **<u>Receipt of antenatal corticosteroids (n (%))</u>** Magnesium sulphate: 1062 (96.9) Placebo: 1116 (97.5)		- Magnesium sulphate It was given IV in the form of a 6 gram loading dose infused for 20-30 minutes, followed by a maintenance infusion of 2 grams per hour (median total dose received was 31.5 grams [IQR 29.0 to 44.6]). 996/1096 women received it for ≥ 3 hours, 82/1096 received it for < 3 hours, and 18/1096 gave birth without receiving magnesium sulphate. - Placebo Identical looking placebo, given as per the magnesium sulphate protocol described above. 1024/1145 women received it for ≥ 3 hours, 101/1145 received it for < 3 hours, and 120/1145 gave birth without receiving placebo. If birth had not occured after 12 hours and was no longer considered imminent (e.g. if woman was not having regular contractions), the infusion was stopped and then restarted when birth was imminent again. If at least 6 hours had passed since the loading dose, another loading dose was given. Retreatment was not given if - preeclampsia or eclampsia developed, in which case open-label magnesium sulphate was given as prophylaxis - it was thought that a delay in	in three twin pregnancies in the placebo group, one of the babies was stillborn or died in the first year, whereas the other survived but then later received a diagnosis of moderate/severe cerebral palsy. Therefore, the sum of the individual components of the composite is higher than the incidence of the composite (as the denominator for both is pregnancy) **<u>Moderate or severe cerebral palsy (n/total (%))</u>** <u>a. All pregnancies</u> Magnesium sulphate: 20/1041 (1.9) Placebo: 38/1095 (3.5) RR 0.55 (95% CI 0.32 to 0.95); p = 0.03 <u>b. Pregnancies without major congenital anomalies</u> Magnesium sulphate: 18/997 (1.8) Placebo: 34/1063 (3.2) RR 0.56 (95% CI 0.32 to 0.99); p = 0.04 **<u>Perinatal or neonatal death as a proportion of pregnancies (n/total (%))</u>**	were blind to group allocation **Missing data/loss to follow-up:** 9 (0.8%) of women from the $MgSO_4$ arm and 4 (0.3%) of women from the placebo arm were lost to follow-up before birth; a further 46 babies (3.9%) from the $MgSO_4$ arm and 49 (3.9%) of babies from the placebo arm were lost to follow-up after initial discharge and before follow-up. There also appear to be missing data for the Bayley Scales of Infant Development Scores. **Precise definition of outcomes:** Yes, apart from definitions of the Bayley Scales of Infant Development for which no explanation is provided (information from other sources seems to suggest that a score of 85 represents the threshold of a 'normal' score, with lower scores indicating worse disability) **Valid and reliable method of outcome assessment:** Yes **Intention-to-treat analysis performed:** Yes **Indirectness:** - 9.1% of the randomised

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	Maternal age/years (mean ± SD) Magnesium sulphate: 26.1 ± 6.3 Placebo: 25.9 ± 6.2 **Maternal prepregancy BMI (mean ± SD)** Magnesium sulphate: 26.0 ± 6.7 Placebo: 26.4 ± 6.9 [Note: there was missing data for 111 women in the magnesium sulphate group and 128 women in the placebo group] **Proportion of women who were nulliparous (n (%))** Magnesium sulphate: 391 (35.7) Placebo: 414 (36.2) **Previous preterm delivery (n (%))** Magnesium sulphate: 292 (26.6) Placebo: 310 (27.1) **No prenatal care (n (%))** Magnesium sulphate: 78 (7.1) Placebo: 88 (7.7)		birth to give retreatment would be detrimental to woman or baby - gestational age had reached 34 weeks 639 (28.5%) of women were not eligible for retreatment. Of those that were, 947/1602 (59.1%) were receiving the study drug at birth. The most common reasons for this not occuring were staff error and urgent caesarean section. 103 women in the magnesium sulphate arm had modification of the study regimen: 7 initiated treatment for pre-eclampsia, 1 initiated treatment for arrhythmia, 19 initiated magnesium sulphate tocolysis and 76 requested discontinuation. This occurred in 31 women in the placebo arm: 5 initiated treatment for pre-eclampsia, 13 initiated magnesium sulphate tocolysis and 13 requested discontinuation. **Follow-up** Certified research nurses collected information on demographic characteristics and medical/social history, as well as collecting data on neonatal and maternal outcomes at birth and at scheduled follow-up visits. Follow-up was done when the babies reached 6, 12 and 24 months of age (corrected for prematurity). At follow-up at 1 year, babies who	a. All pregnancies Magnesium sulphate: 99/1041 (9.5) Placebo: 93/1095 (8.5) RR 1.12 (95% CI 0.85 to 1.47); p = 0.41 b. Pregnancies without major congenital anomalies Magnesium sulphate: 83/997 (8.3) Placebo: 86/1063 (8.1) RR 1.03 (95% CI 0.77 to 1.37); p = 0.85 **Perinatal, neonatal or paediatric deaths as a proportion of babies (n/total)** a. Stillbirths Magnesium sulphate: 5/1179 Placebo: 8/1252 b. Deaths before discharge Magnesium sulphate: 80/1179 Placebo: 71/1252 c. Deaths between discharge and 1 year follow-up examination Magnesium sulphate: 18/1179	women were carrying twins - 7.4% of women had no prenatal care **Other information** **Gestational age at birth/weeks (mean ± SD)** Magnesium sulphate: 29.8 ± 3.1 Placebo: 29.7 ± 3.1 [p = 0.32] **Further information on Gross Motor Function Classification System** Scores range from 0 to 5, with higher scores indicating greater impairment. A child with a score of 2 or above cannot walk independently. Mild cerebral palsy was defined as a grade of level 1, moderate as a grade of level 2 or 3 and severe as a grade of level 4 or 5.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	Smoking during pregnancy (n (%)) Magnesium sulphate: 299 (27.3) Placebo: 319 (27.9) **Alcohol use during pregnancy (n (%))** Magnesium sulphate: 93 (8.5) Placebo: 96 (8.4) **Illicit substance use during pregnancy (n (%))** Magnesium sulphate: 108 (9.9) Placebo: 104 (9.1) The groups were also similar in the distribution of race/ethnic group, proportion of women who were married, and educational level. 417 (38.4%) of the magnesium sulphate group and 448 (39.3%) of the placebo group were born by caesarean section (p = 0.68). **Inclusion criteria** Carrying singletons or twins at 24-31 weeks of gestation Either:		had a normal neurological examination, could walk 10 steps independently, and had bilateral pincer grasp were declared free of cerebral palsy were considered normal and free of cerebral palsy. They did not require any further neurological examination. If the children were not available during the 24-28 months window for a 2-year follow-up, efforts were made to rearragned appointments. There were 28 children who were not evaluated at 2 years, after having not been declared free of cerebral palsy at 1 year. For these babies, two blinded paediatric neurologists made a judgement about whether the child had moderate or severe cerebral palsy on the basis of their 1 year examination. **Statistical analysis** The power calculation was based on the primary outcome occuring in 14% of the placebo group (death rate of 6% and moderate/severe cerebral palsy rate of 8%). A sample size of 2000 was calculated to detect a 30% reduction in the outcome, with a type-I error of 5% and power of at least 80%. A sample size of 2200 was aimed for, to account for loss to follow-up. Four interim analyses were	Placebo: 17/1252 [Note: 95 women were lost to follow-up, but the number of babies this corresponds to is not reported] d. Total deaths Magnesium sulphate: 103/1179 Placebo: 96/1252 **Any cerebral palsy at 2 years, among those who survived and were available for follow-up (n/total (%))** Magnesium sulphate: 40/942 (4.2) Placebo: 73/1002 (7.3) [p = 0.004] (Note: The denominator for this outcome is number of pregnancies. It is the number of pregnancies included in the analysis of the primary outcome minus the number of pregnancies that were accompanied by a stillbirth or neonatal death. The numbers of children were 41 and 74 respectively) **Scores on the Bayley Scales of Infant Development (n/total (%))**†	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	- High risk for spontaneous birth because of rupture of membranes occuring at 22-31 weeks of gestation **or** advanced preterm labour with dilation of of 4-8 cm and intact membranes - Indicated preterm delivery was anticipated within 2-24 hours (e.g. due to fetal growth restriction) **Exclusion criteria** Indicated preterm delivery anticipated within 2 hours Cervical dilation of more than 8 cm Rupture of membranes before 22 weeks Unwillingness of obstetircian to intervene for the benefit of the baby Major fetal anomalies or feath Maternal hypertension or pre-eclampsia Maternal contraindication to magnesium sulphate (e.g. severe pulmonary disorders) Receipt of intravenous magnesium sulphate within the previous 12 hours		performed and an independent data and safety monitoring committee monitored the trial and reviewed interim results. Data were analysed intention-to-treat. For the primary outcome (including its components) and maternal outcomes, the unit of analysis was the pregnancy; therefore, a pregnancy was 'credited' with an event if it occurred in either twin. Continuous outcomes were compared using Wilcoxon rank-sum test, and categorical variables with the chi-square test, Fisher's exact test or the Mantel-Haenszel test for trend. For the other outcomes, the unit of analysis was the baby, with generalised estimating equations used to account for clustering of babies within pregnancies. For the primary outcome, a two tailed p-value of < 0.043 was considered to indicate statistical significance; for the rest, the value was 0.05. Prespecified subgroup analyses were done according to gestational age, singleton/twin, and previous exposure to magnesium sulphate. An analysis was also done excluding babies with major congenital anomalies (as classified by a blinded geneticist on the basis of medical records).	<u>a. Psychomotor Development Index</u> - Score < 70 Magnesium sulphate: 134/876 (15.3) Placebo: 144/919 (15.7) RR 0.98 (95% CI 0.79 to 1.21); p = 0.83 - Score < 85 Magnesium sulphate: 299/876 (34.1) Placebo: 315/919 (34.3) RR 1.00 (95% CI 0.88 to 1.13); p = 0.95 <u>b. Mental Development Index</u> - Score < 70 Magnesium sulphate: 165/876 (18.8) Placebo: 171/919 (18.6) RR 1.01 (95% CI 0.83 to 1.23); p = 0.90 - Score < 85 Magnesium sulphate: 406/876 (46.3) Placebo: 427/919 (46.5) RR 1.00 (95% CI 0.90 to 1.10); p = 0.96 † It is unclear why the denominators for this outcome are lower	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			<u>Outcomes reported</u> **- Stillbirth or death by 1 year of age or moderate or severe cerebral palsy at 2 years:** This composite outcome was the primary outcome of the study. The authors report that only moderate or severe cerebral palsy were included in the primary outcome, because this severity at or beyond 2 years of age is linked to lifelong motor dysfunction, whereas mild cerebral palsy can resolve. - **Moderate/severe cerebral palsy:** The diagnosis of cerebral palsy was made by a certified paediatrician or paediatric neurologist if two or more of the following features were present: a) delay of at least 30% in gross motor development milestones; b) abnormality in muscle tone (e.g. scissoring), 4+ or absent deep-tendon reflexes, or movement abnormality (e.g. posturing or gait assymetry); c) persistence of primitive reflexes or absence of protective reflexes. When cerebral palsy was diagnosed, the Gross Motor Function Classification System (GMFCS) was used to assess severity. At a corrected age of 2 years or more, a child who had GMFCS level of 2 or above or who did not have the ability to	**<u>Findings on cranial ultrasound (n/total (%))</u>** <u>a. Any intraventricular haemorrhage (IVH)</u> Magnesium sulphate: 218/1112 (19.6) Placebo: 252/1184 (21.3) RR 0.91 (95% CI 0.78 to 1.08) <u>b. Grade III or IV intraventricular haemorrhage</u> Magnesium sulphate: 23/1112 (2.1) Placebo: 38/1184 (3.2) RR 0.64 (95% CI 0.38 to 1.06) <u>c. Periventricular leukomalacia</u> Magnesium sulphate: 21/1112 (1.9) Placebo: 27/1184 (2.3) RR 0.83 (95% CI 0.47 to 1.45) **<u>Maternal death (n/total (%))</u>** Magnesium sulphate: 0/1096 (0) Placebo: 0/1145 (0) **<u>Maternal adverse effects in women who received study medication (n/total (%))</u>**	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			grasp and release a 1-inch block with both hands was considered to have moderate/severe cerebral palsy. (see further information section for more details on this scale) **- Death** **- Any cerebral palsy:** reported as a proportion of the babies assessed in the primary outcome, minus the babies who died **- Scores on the Bayley Scales of Infant Development (II):** Psychomotor Development Index and Mental Development Index are reported, as assessed at the 2-year examination by a trained psychologist or psychometrist **- Findings on cranial ultrasound:** incidence of intraventricular haemorrhage (including grade III or IV) and periventricular leukomalacia are reported. Cranial ultrasounds were performed on all babies and interpreted centrally by 3 independent paediatric radiologists **- Maternal death** - **Maternal adverse events:** incidence of any adverse event, flushing, sweating, pain or burning at IV site, nausea or vomiting, and respiratory	<u>a. Any adverse effect</u> Magnesium sulphate: 833/1078 (77.3) Placebo: 140/1125 (12.4) [p < 0.001] <u>b. Flushing</u> Magnesium sulphate: 703/1078 (65.2) Placebo: 74/1125 (6.6) [p < 0.001] <u>c. Sweating</u> Magnesium sulphate: 307/1078 (28.5) Placebo: 28/1125 (2.5) [p < 0.001] <u>d. Pain or burning at IV site</u> Magnesium sulphate: 259/1078 (24.0) Placebo: 29/1125 (2.6) [p < 0.001] <u>e. Nausea or vomiting</u> Magnesium sulphate: 166/1078 (15.4) Placebo: 19/1125 (1.7) [p < 0.001] <u>f. Respiratory depression</u> Magnesium sulphate: 7/1078 (0.6) Placebo: 3/1125 (0.3)	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			depression are reported in the women who received the study medication	[p = 0.22] g. Infusion stopped because of adverse event Magnesium sulphate: 45/1078 (4.2) Placebo: 16/1125 (1.4) [p < 0.001] **SUBGROUP ANALYSES OF PRIMARY OUTCOMES AND COMPONENTS** **Composite outcome of moderate or severe cerebral palsy or death (n/total (%))** a. By weeks of gestation at randomisation - < 28 weeks Magnesium sulphate: 89/442 (20.1) Placebo: 105/496 (21.2) RR 0.95 (95% CI 0.74 to 1.22) - ≥ 28 weeks Magnesium sulphate: 29/599 (4.8) Placebo: 23/599 (3.8) RR 1.26 (95% CI 0.74 to 2.15) b. By magnesium sulphate treatment before randomisation - Yes Magnesium sulphate: 27/192	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				(14.1) Placebo: 26/210 (12.4) RR 1.14 (95% CI 0.69 to 1.88) - No Magnesium sulphate: 91/849 (10.7) Placebo: 102/885 (11.5) RR 0.93 (95% CI 0.71 to 1.21) <u>c. Singleton or twin pregnancy</u> - Singleton Magnesium sulphate: 97/950 (10.2) Placebo: 103/985 (10.5) RR 0.98 (95% CI 0.75 to 1.27) - Twin Magnesium sulphate: 21/91 (23.1) Placebo: 25/110 (22.7) RR 1.02 (95% CI 0.61 to 1.69) **<u>Moderate or severe cerebral palsy (n/total (%))</u>** <u>a. By weeks of gestation at randomisation</u> - < 28 weeks Magnesium sulphate: 12/442 (2.7) Placebo: 30/496 (6.0)	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				RR 0.45 (95% CI 0.23 to 0.87) - ≥ 28 weeks Magnesium sulphate: 8/599 (1.3) Placebo: 8/599 (1.3) RR 1.00 (95% CI 0.38 to 2.65) <u>b. By magnesium sulphate treatment before randomisation</u> - Yes Magnesium sulphate: 6/192 (3.1) Placebo: 11/210 (5.2) RR 0.60 (95% CI 0.23 to 1.58) - No Magnesium sulphate: 14/849 (1.6) Placebo: 27/885 (3.1) RR 0.54 (95% CI 0.29 to 1.02) <u>c. Singleton or twin pregnancy</u> - Singleton Magnesium sulphate: 14/950 (1.5) Placebo: 28/985 (2.8) RR 0.52 (95% CI 0.27 to 0.98) - Twin Magnesium sulphate: 6/91 (6.6) Placebo: 10/110 (9.1) RR 0.73 (95% CI 0.27 to 1.92)	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				<u>Fetal or infant death (n/total (%))</u> <u>a. By weeks of gestation at randomisation</u> - < 28 weeks Magnesium sulphate: 78/442 (17.6) Placebo: 78/496 (15.7) RR 1.12 (95% CI 0.84 to 1.49) - ≥ 28 weeks Magnesium sulphate: 21/599 (3.5) Placebo: 15/599 (2.5) RR 1.40 (95% CI 0.73 to 2.69) <u>b. By magnesium sulphate treatment before randomisation</u> - Yes Magnesium sulphate: 21/192 (10.9) Placebo: 15/210 (7.1) RR 1.53 (95% CI 0.81 to 2.88) - No Magnesium sulphate: 78/849 (9.2) Placebo: 78/885 (8.8) RR 1.04 (95% CI 0.77 to 1.41) <u>c. Singleton or twin pregnancy</u>	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				- Singleton Magnesium sulphate: 83/950 (8.7) Placebo: 75/985 (7.6) RR 1.15 (95% CI 0.85 to 1.55) - Twin Magnesium sulphate: 16/91 (17.6) Placebo: 18/110 (16.4) RR 1.07 (95% CI 0.58 to 1.98)	

H.9.281 **Health economics**

Bibliographic details	Interventions and comparisons	Data Sources	Time horizon & Method	Results	Reviewer comment
Full citation Cahill,A.G., Odibo,A.O., Stout,M.J., Grobman,W.A., Macones,G.A., Caughey,A.B., Magnesium sulfate therapy for the prevention of cerebral palsy in preterm infants: a decision-analytic and economic analysis, American Journal of Obstetrics and Gynecology, 205, 542-547, 2011 **Ref Id** 282017	**Study dates** 2002-2008 **Intervention** Magnesium Sulphate **Comparison(s)** No treatment (standard of care)	**Source of effectiveness data** Published evidence based on 4 randomised controlled trials. **Source of cost data** Cost data was based on published literature and Medicaid reimbursement rates. Charges were multiplied by a cost-charge ratio of 0.6 as an approximation to third-party reimbursements for Medicaid reimbursement rates.	**Time horizon and discount rate** Time Horizon: Lifetime Discount Rate (costs): 3% Discount Rate (QALYS): 3% **Method of eliciting health valuations (if applicable)** Published literature **Modelling approach** Decision Analytic Cost-Utility analysis	**Cost per patient per alternative** All women population: MgSO4: USD 1,739.00 No MgSO4: USD 1,917.20 PPROM only: MgSO4: USD 1,462.60 No MgSO4: USD 1,607.50 <28 weeks: MgSO4: USD 920.60 No MgSO4: USD 1,019.00 **Effectiveness per patient per alternative** All women population: MgSO4: 56.6836 QALYs No MgSO4: 56.6784 QALYs	**Limitations** **Other information**

Bibliographic details	Interventions and comparisons	Data Sources	Time horizon & Method	Results	Reviewer comment
Economic study type Cost-utility analysis **Country(ies) where the study was done** USA **Perspective & Cost Year** Perspective: Societal Cost Year: Not Stated **Source of funding** Not stated		Costs included were treatment, reactions, CP, and neonatal survival and neonatal death **Other data sources e.g. transition probabilities** Published evidence		PPROM only: MgSO4: 56.7022 QALYs No MgSO4: 56.6972 QALYs <28 weeks: MgSO4: 56.7411 QALYs No MgSO4: 56.7355 QALYs **Incremental cost-effectiveness** All women population: MgSO4: dominates PPROM only: MgSO4: dominates <28 weeks: MgSO4: dominates **Other reporting of results** **Uncertainty** Probabilistic sensitivity analysis	

H.10 Tocolysis

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Houtzager BA,Hogendoorn SM,Papatsonis DN,Samsom JF,van Geijn HP,Bleker OP,van Wassenaer AG, Long-term follow up of children exposed in utero to nifedipine or ritodrine for the management of preterm labour, BJOG : an international journal of obstetrics and gynaecology, - , 2006 **Ref Id** 259877 **Country/ies where the study was carried out** The Netherlands **Study type** Randomised control trial **Aim of the study** To compare the long-term psychosocial and motor effects on children exposed in utero to nifedipine or ritodrine for the management of preterm labour. **Study dates** 1992 to 1995	**Sample size** Total n = 102 **Characteristics** Maternal age mean (SD) Nifedipine group 29.3 (4.9) Ritodrine group 30.7 (4.9) Gestational age mean (SD)(days) Nifedipine group 239.3 (31) Ritodrine group 226.6 (27.2) Nulliparity mean (SD) Nifedipine group 24 (50) Ritodrine group 29 (54) Ruptured membranes mean (SD) Nifedipine group 12 (25) Ritodrine group 16 (54) **Inclusion criteria** Not specified **Exclusion criteria** Not specified	**Interventions** Nifedipine or ritodrine for the management of preterm labour	**Details** Data collected from a multicentre study in two universities and one primary hospital during the study period in the Netherlands. This study is follow up of a previously conducted clinical trials (Papatsonis 1997 and 2000). In the original trial, 185 women were randomised to either nifedipine (n = 95) or ritodrine (n = 90). Indomethacine was used equally in both groups as a second line tocolytic agent. Of the 185 liveborn children, 171 survived (92%), and of these 102 (61%) were followed up at age 9-12 years. Age-specific questionnaires were administered to the parent and teacher. Additional data were obtained from medical records. Questionnaires were used to assess the child's behavioural-emotional problems, quality of life (QoL), motor functioning, parenting distress and the child's education. Of the 171 eligible families, 102 (61%) agreed to participate and completed the questionnaires. Response was equal in the ritodrine group (n = 54 of 83 surviving children, 65%) compared with the nifedipine group (n= 48 of 88 surviving children, 55%). Definition of outcomes Respiratory distress syndrome (RDS) was defined as tachypnoea, chest wall retractions and oxygen	**Results** Caesarean section Nifedipine 12/48 (25%) Ritodrine 11/54 (20%) Respiratory distress syndrome (RDS) Nifedipine 5/48 (10%) Ritodrine 16/54 (30%) Sepsis/meningitis (RDS) Nifedipine 8/48 (17%) Ritodrine 15/54 (28%) Periventricular lecucomalacia (PVL) Nifedipine 1/48 (2%) Ritodrine 1/54 (2%) No intracranial haemorrhage Nifedipine 40/48 (83%) Ritodrine 42/54 (78%) Minor intracranial haemorrhage Nifedipine 8/48 (17%) Ritodrine 10/54 (18%) Major intracranial haemorrhage Nifedipine 0/48 (0%) Ritodrine 2/54 (4%) Mean gestational age at birth Nifedipine 34 (4) Ritodrine 32 (3)	**Limitations** No clear inclusion/exclusion criteria hence high risk of selection bias

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Source of funding Not specified			requirement in the presence of a chest X-ray. Necrotising entrocolitis was diagnosed by pneumatosis on abdominal radiography or finding during the surgery. The child long term outcomes were assessed using the Dutch version of the Child Behaviour Checklist (CBCL) was completed by parents. The child's teacher completed the teacher Report Form (TRF). High score on the CBCL and TRF represent more problematic behaviour. Total score were for internalising problems such as anxiety, depression, or social behaviour, non compliance, or hyper activity. The child quality of life (QoL) was assessed using the Dutch TNO AZL Children's Quality of Life Questionnaire (TACQOL). The questionnaire provides score based on the seven domains: physical functioning, motor functioning, autonomy, cognitive emotions. High score represent a more favourable QoL. Analysis Intention to treat analysis was performed. Student t test and chi square test were used for continuous and categorical data respectively. Multivariable regression analysis were performed, correcting for mother characteristics, perinatal outcome and background variables (mother's age at admission, maternal education, ethnicity, parity, ruptured	Mean umbilical cord pH Nifedipine 7.3 (0.1) Ritodrine 7.2 (0.1) **Long-term psychosocial functioning (follow up at age of 9 -12 yr)** Mean behavioural-emotional functioning (using child behaviour checklist [CBCL]) higher score represent more psychosocial problem Nifedipine 50 (11.9) Ritodrine 52 (11.6) p = 0.39 Mean behavioural-emotional functioning (using teacher report form [TRF]) higher score represent more psychosocial problem Nifedipine 49 (10) Ritodrine 50 (9.9) p = 0.55 **Quality of life (QoL)** Mean children's quality of life (using quality of life questionnaire [TRF]) higher score represent a more favourable QoL Physical Nifedipine 25 (5.3) Ritodrine 26 (4.5)	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			membranes and mother's smoking behaviour). Birth weight and gestational age were added to the model in the second step. Psychosocial functioning was compared with the available normative data of the general population of children of same age.	p = 0.26 Motor Nifedipine 30 (3.1) Ritodrine 30 (2.5) p = 0.30 Autonomy Nifedipine 31 (1.2) Ritodrine 31 (1.6) p = 0.88 Cognitive Nifedipine 28 (4) Ritodrine 28 (3.8) p = 0.95 Positive emotion Nifedipine 13 (2.7) Ritodrine 14 (2.4) p = 0.80 Negative emotion Nifedipine 12 (2.7) Ritodrine 13 (2.3) p = 0.05 **Mean motor quality** Movement ABC (higher score represent more motot problem) Nifedipine 5 (6.9) Ritodrine 9.3 (17.2) p = 0.16 **Other psychosocial variables** Psychcosocial care for chid	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				Nifedipine n = 25/46 (55.6%) Ritodrine n = 22/45 (41.5%) p = 0.17 <u>Repeat class</u> Nifedipine n = 13/46 (27.7%) Ritodrine n = 14/45 (26.4%) p = 0.89 <u>Special education</u> Nifedipine n = 3/46 (6.5%) Ritodrine n = 4/45 (7.5%) p = 0.84	
Full citation Jaju,P.B., Dhabadi,V.B., Nifedipine versus ritodrine for suppression of preterm labor and analysis of side effects, Journal of Obstetrics and Gynaecology of India, 61, 534-537, 2011 **Ref Id** 259925 **Country/ies where the study was carried out** India **Study type** Randomised control trial **Aim of the study** To compare the tocolytic	**Sample size** Total n = 120 Nifedipine n = 60 Ritodrine n = 60 **Characteristics** <u>Mean gestational age</u> (weeks) Nifedipine 33 Ritodrine 33 <u>0 parity</u> Nifedipine n = 45/60 (75%) Ritodrine n = 48/60 (80%) <u>parity</u> ≥ 1 Nifedipine n = 15/60 (25%) Ritodrine n = 12/60 (20%) <u>Booked</u> Nifedipine n = 40/60 (66.6%) Ritodrine n = 35/60 (58.3%) <u>Not booked</u> Nifedipine n = 20/60 (33.3%) Ritodrine n = 25/60 (41.7%)	**Interventions** Ritodrine versus Nifedipine (N)	**Details** Women presenting to Medical College Hospital and research centre who met the inclusion criteria, were randomised to receive nifedipine or ritodrine tocolytic drugs. Preterm labour was defined as regular uterine contractions of four in 20 min with cervical dilatation of > 1 cm and effacement of 80% or more. Women were randomly assigned to two groups; ritodrine or nifedipine. Each tocolytic was administered as first line treatment. Nifedipine was administered as an initial oral loading dose of 30 mg. If uterine contractions continued after 90 minutes another 20 mg nifedipine was given orally. If the labour was suppressed then a maintenance dose of 20 mg nifedipine was given orally every 8 hourly till 37 weeks.	**Results** **<u>Prolongation of pregnancy up to 37 weeks</u>** Nifedipine 28/60 (46.6%) Ritodrine 16/60 (26.6%) p = 0.033 **<u>Prolongation of pregnancy up to 7 days</u>** Nifedipine 42/60 (70%) Ritodrine 36/60 (60%) p = 0.338 **<u>Prolongation of pregnancy up to 48 hours</u>** Nifedipine 54/60 (90%) Ritodrine 41/60 (83.3%) p = 0.006 **<u>Side effects</u>** Nifedipine 18/60 (30%) Ritodrine 48/60 (80%) p < 0.001 **<u>Success</u>** Nifedipine 54/60 (90%)	**Limitations** Unclear who analysed the data Unclear blinding Unclear allocation concealment Unclear intention to treat analysis Data loss not reported

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
efficacy of Nifedipine and Ritodrine, their adverse effects and neonatal outcome **Study dates** October 2006 to September 2008 **Source of funding** Not specified	**Inclusion criteria** • Intact membranes • Singleton gestations • Vertex presentation • Cervical dilatation from 1 to 3 cm • 28 to 36 weeks gestation **Exclusion criteria** • Fetal malformation • Chorioamnionitis • Intrauterine growth restriction (<5 percentile) • Antepartum haemorrhage • Hypertension • Bronchial asthma • Diabetes mellitus • cardiovascular disease • Severe anaemia • Hydramnios		Intravenous ritodrine (100 mg added to 500 ml ringers lactate). The infusion started at the rate of 50 µg every 15 minutes until the uterine contraction ceased, up to maximum rate of 350 µg . Infusion was stopped if unacceptable side effects like palpitations, chest pain and tachycardia>120 developed. All women in the study were given betamethasone and prophylactic antibiotixcs. Metronidazole was given to those with sign of bacterial vaginosis. Treatment failure was defined if uterine relaxation was not achieved after administration of the maximum dose or development of side-effects that caused discontinuation of the therapy Analysis Epi Info software and Chi square test were used	Ritodrine 41/60 (68.3%) p = 0.003 **Failure** Nifedipine 6/60 (10%) Ritodrine 19/60 (31.6%) p = 0.002 **Mean gestational age at birth** Nifedipine 35 weeks and 3 days Ritodrine 34 weeks p = not reported **Perinatal death** Nifedipine 6/60 (10%) Ritodrine 9/60 (15%) p = not reported **Respiratory distress syndrome** Nifedipine 8/60 (13.3%) Ritodrine 10/60 (16.6%) p = not reported **NICU admission** Nifedipine 33/60 (55%) Ritodrine 39/60 (65%) p = not reported	
Full citation Klauser,C.K., Briery,C.M., Keiser,S.D., Martin,R.W., Kosek,M.A., Morrison,J.C., Effect of antenatal tocolysis on neonatal outcomes, Journal of Maternal-Fetal and Neonatal Medicine, 25, 2778-2781, 2012	**Sample size** Total women randomised n = 301 Total women analysed n = 276 Indomethacin n = 87 (plus 16 twins n = 103 babies) Magnesium sulfate n = 85 (plus 10 twins n = 95 babies) Nifedipine n = 104 (plus 15 twins n = 119 babies) **Characteristics**	**Interventions** Indomethacin (I) Magnesium sulfate (M) Nifedipine (N)	**Details** Women presenting to University of Mississippi Medical centre between 20 - 32 weeks gestation, in acute preterm labour with cervical dilatation 1-6 cm, were randomised to receive one of three first-line tocolytic drugs. Consecutive women meeting study criteria were randomised into the study population. Women were randomly	**Results** Neonatal death Indomethacin n = 7/103 (7%) Magnesium sulphate n = 5/95 (5%) Nifedipine n = 4/109 (3%) p = 0.50 Respiratory distress syndrome (RDS)	**Limitations** No intention to treat analysis

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Ref Id 236134 **Country/ies where the study was carried out** USA **Study type** Randomised control trial **Aim of the study** To examine adverse neonatal effects in pregnancies treated with indomethacin (I), magnesium sulfate (M) or nifedipine (N) **Study dates** 2004 to 2008 **Source of funding** Not specified	Not specified **Inclusion criteria** • Intact membranes • Singleton or twins gestations • Vertex presentation with decrease in station • Cervical dilatation from 1 to 6 cm • Sufficient cervical effacement **Exclusion criteria** • Fetal malformation • Chorioamnionitis • Intrauterine growth restriction (<5 percentile) • Non reassuring fetal heart rate tracing • Those who refused randomisation		assigned to three groups; indomethacin, magnesium sulphate or nifedipine. Each tocolytic was administered as first line treatment. Indomethacin was given a 100 mg rectal suppository, which could be repeated one time, two hours after the initial dose if contractions continued. This was followed by 50 mg oral indomethacin 6 hourly until contraction had been extinguished for 12 hours. Indomethacin was used only for 48 hours as a total treatment cycle. Pepcid 20 mg were given to each case orally to minimise gastrointestinal irritation. Women randomised to magnesium sulphate were given 6 mg intravenously over a 20 min period and then maintained at 4 to 6 gr per hour until contraction had been stopped for 1 - 2 hours and then it was discontinued. Women who were randomised to nifedipine were given loading dose of 30 mg orally, followed by 20 - 30 mg every 4 - 6 hours until contractions stopped. During the treatment antenatal steroids were begun and no antibiotics were used and women were observed for signs and symptoms of chorioamnionitis and placenta abruption. Fetal Heart rate and uterine contraction were monitored until the uterine activity was abolished for 12 hours. After observation for 2 -3 days in hospital, women were discharged if preterm labour did not reappear.	Indomethacin n = 42/103 (41%) Magnesium sulphate n = 39/95 (41%) Nifedipine n = 34/109 (28%) p = 0.08 <u>Sepsis</u> Indomethacin n = 13/103 (13%) Magnesium sulphate n = 10/95 (10%) Nifedipine n = 10/109 (8%) p = 0.59 <u>Intraventricular haemorraghe (IVH)</u> Indomethacin n = 14/103 (14%) Magnesium sulphate n = 11/95 (11%) Nifedipine n = 10/109 (8%) p = 0.66 <u>Periventricular leukomalacia (PVL)</u> Indomethacin n = 2/103 (2%) Magnesium sulphate n = 0/95 (0%) Nifedipine n = 0/109 (0%) p = 0.12 <u>Necrotizing enterocolitis (NEC)</u> Indomethacin n = 5/103 (5%) Magnesium sulphate n = 5/95 (5%)	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			Definition of outcomes Respiratory distress syndrome (RDS) was defined based on oxygen requirement > 24 hours plus typical findings a chest X-ray. Necrotising entrocolitis was diagnosed by pneumatises on abdominal radiography or and clinical findings. Intraventricular haemorrhage (IVH) was diagnosed by head sonography and periventricular leukomalacia (PVL) by head ultrasound as well as computed tomography and MRI when necessary Analysis A sample size calculation performed and 300 babies was required to have 80% power of detecting increase in composite neonatal outcomes (RDS, sepsis, IVH, PVL, NEC) between three groups. Chi square test was used for categorical data. ANOVA was used for continuous data with normal distribution and Krustall – Wallis one way ANOVA on ranks was used if continuous data were not normally distributed	Nifedipine n = 4/109 (3%) p = 0.50 Gestational age at birth Indomethacin 31.8 ± 4.2 Magnesium sulphate 31.2 ± 3.9 Nifedipine 31.8 ± 4.5 Cord pH Indomethacin 7.28 ± 0.07 Magnesium sulphate 7.24 ± 0.46 Nifedipine 7.30 ± 0.06 NICU days Indomethacin 31.2 ± 32.4 Magnesium sulphate 38.6 ± 46.4 Nifedipine 34.8 ± 39.4	
Full citation Salim,R., Garmi,G., Nachum,Z., Zafran,N., Baram,S., Shalev,E., Nifedipine compared with atosiban for treating preterm labor: a randomized controlled trial, Obstetrics and Gynecology, 120, 1323-1331,	**Sample size** Total n = 145 Nifedipine n = 75 Atosiban n = 70 **Characteristics** Mean maternal age (weeks) Nifedipine 27 (19 - 48) Atosiban 28 (15.2 - 44.8) p = 0.88	**Interventions** Atosiban versus Nifedipine (N)	**Details** Pregnant women admitted with preterm labour and intact membranes who met the inclusion criteria, were randomly assigned to either atosiban or nifedipine treatment. Treatment Women assigned to atosiban group	**Results** **Did not deliver and did not require an alternate agent at 48 hours** Nifedipine: n = 39 (52%) Atosiban n = 48 (68.6%) P*= 0.03 **Did not deliver at 7 days**	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
2012 **Ref Id** 260598 **Country/ies where the study was carried out** Israel **Study type** Randomised control trial **Aim of the study** To compare the tocolytic efficacy and tolerability of nifedipine with that of atosiban among pregnant women with preterm labor. **Study dates** January 2008 to December 2011 **Source of funding** Not specified	Mean gestational age at randomisation (weeks) Nifedipine 31.8 (25.0 - 33.8) Atosiban 31.1 (24.1 - 33.8) p = 0.24 Mean gestational age at randomisation (weeks) Nifedipine 31.8 (25.0 - 33.8) Atosiban 31.1 (24.1 - 33.8) p = 0.24 ≤ 28 weeks at randomisation (singleton) (weeks) Nifedipine n = 5 (6.7%) Atosiban n = 6 (8.6%) p = not reported > 28 weeks at randomisation (singleton) (weeks) Nifedipine n = 5 (6.7%) Atosiban n = 4 (5.7%) p = not reported Progesterone treatment Nifedipine n = 17 (22.7%) Atosiban n = 16 (22.9%) One more previous preterm birth Nifedipine n = 12 (16.0%) Atosiban n = 15 (21.4%) No maternal disease Nifedipine n = 53 (70.7%) Atosiban n = 44 (62.9%) **Inclusion criteria** • Intact membranes • Singleton and twins gestations • presence of 4 or more contractions each lasting 30		was given a single loading intravenous dose, 6.75 mg in 0.9% sodium chloride solution, followed by an intravenous infusion of 300 micrograms/min in 0.9% sodium chloride solution for the first 3 hours and then 100 microgram/min for another 45 hours. Women in the nifedipine group was given a loading dose of 20 mg orally followed by another two doses of 20 mg, 20 -30 minutes apart as needed. Maintenance was started after 6 hours with 20 to 40 mg four times a day for a total of 48 hours. Tocolytic drugs were discontinued if dilatation of cervix progress to ≥5 cm or membranes ruptured. Labour was considered to have progressed (after 1 hour of observation during treatment) if there was no change or increase in the frequency of contractions or increase in cervical dilatation of 1 cm or more. If labour progressed after 1 hour and more but before 48 hours, or if adverse effects developed a crossover of the study drugs was performed and alternative rescue treatment was initiated (two 100-mg per rectum tablets, 1 hour apart, followed by oral tablets of 25 mg four times a day for the rest of 48 hours). prophylactics antibiotics for group B strep and corticosteroids were administered according to standard clinical indications. Analysis An intention to treat analysis performed. Sample size calculation	**from enrolment** Nifedipine n = 67 (89.3%) Atosiban n = 55 (78.6%) P*= 0.02 **Mean gestational age at birth** (weeks) Nifedipine 36.4 ± 2.8 Atosiban 35.2 ± 3.0 P*= 0.01 **Delay birth > 48 hours** Nifedipine n = 69/75 (92%) Atosiban n = 60/75 (85.7%) P*= 0.27 **Subgroup analysis for singleton babies** **Neonatal mortality** Nifedipine n = 0/52 (0%) Atosiban n = 0/49(0%) **Sepsis** Nifedipine n = 69/52 (1.9%) Atosiban n = 60/49(2.0%) P* >0.99 **Respiratory distress syndrome** Nifedipine n =29/52 (3.8%) Atosiban n = 60/49(10.2%) P* = 0.26 **Inrtaventricular haemorrhage (IVH)** Nifedipine n =2/52 (3.8%) Atosiban n = 2/49(4.1%) P* >0.99 *adjusted for twins, previous preterm babies, progesterone treatment, closed cervix and additional tocolytics	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	seconds or more within 30 minutes • Cervical effacement of 50% with dilatation from 0 to 4 cm (nulliparous) and 1- 4 cm in multiparous • 24 to 33 weeks + 6 days gestation **Exclusion criteria** • Fetal malformation • Vaginal bleeding resulting from placenta previa or placenta abruption • Rupture of membranes • Fever above 38°C • Severe preeclampsia • Intrauterine growth restriction • Systolic blood pressure < 90 mm Hg • None reassuring fetal status • Maternal cardiovascular or liver diseases • Multiple gestation rather than twins • Fetal death		performed. Seventy (n=70) women per group was sufficient to show a difference of 25% in the tocolytic efficacy and tolerability of Atosiban as compared with nifedipine. Wilcoxon rank-sum test was usd for continuous data and $\chi 2$ or fisher exact tests where appropriate were used for categorical data.		
Full citation Klauser,C.K., Briery,C.M., Martin,R.W., Langston,L., Magann,E.F., Morrison,J.C.,	**Sample size** Total women randomised n = 301 Total women analysed n = 276 Indomethacin n = 87 (plus 16 twins n = 103 babies)	**Interventions** Indomethacin (I) Magnesium sulfate (M) Nifedipine (N)	**Details** Women presenting to University of Mississippi Medical centre between 20 - 32 weeks gestation, in acute preterm labour with cervical	**Results** **<u>Gestational age at birth</u>** Indomethacin 31.8 ± 4.2 Magnesium sulphate 31.2 ± 3.9	**Limitations** No intention to treat analysis

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
A comparison of three tocolytics for preterm labor: a randomized clinical trial, Journal of Maternal-Fetal and Neonatal Medicine, 27, 801-806, 2014 **Ref Id** 323536 **Country/ies where the study was carried out** USA **Study type** Randomised control trial **Aim of the study** To examine adverse neonatal effects in pregnancies treated with indomethacin (I), magnesium sulfate (M) or nifedipine (N) **Study dates** 2004 to 2008 **Source of funding** Not specified	Magnesium sulfate n = 85 (plus 10 twins n = 95 babies) Nifedipine n = 104 (plus 15 twins n = 119 babies) **Characteristics** Not specified **Inclusion criteria** • Intact membranes • Singleton or twins gestations • Vertex presentation with decrease in station • Cervical dilatation from 1 to 6 cm • Sufficient cervical effacement **Exclusion criteria** • Fetal malformation • Chorioamnionitis • Intrauterine growth restriction (<5 percentile) • Non reassuring fetal heart rate tracing • Those who refused randomisation		dilatation 1-6 cm, were randomised to receive one of three first-line tocolytic drugs. Consecutive women meeting study criteria were randomised into the study population. Women were randomly assigned to three groups; indomethacin, magnesium sulphate or nifedipine. Each tocolytic was administered as first line treatment. Indomethacin was given a 100 mg rectal suppository, which could be repeated one time, two hours after the initial dose if contractions continued. This was followed by 50 mg oral indomethacin 6 hourly until contraction had been extinguished for 12 hours. Indomethacin was used only for 48 hours as a total treatment cycle. Pepcid 20 mg were given to each case orally to minimise gastrointestinal irritation. Women randomised to magnesium sulphate were given 6 mg intravenously over a 20 min period and then maintained at 4 to 6 gr per hour until contraction had been stopped for 1 - 2 hours and then it was discontinued. Women who were randomised to nifedipine were given loading dose of 30 mg orally, followed by 20 - 30 mg every 4 - 6 hours until contractions stopped. During the treatment antenatal steroids were begun and no antibiotics were used and women were observed for signs and symptoms of chorioamnionitis and placenta abruption. Fetal Heart rate	Nifedipine 31.8 ± 4.5 p = 0.55 **Days gained** Indomethacin 22.7 ± 21.1 Magnesium sulphate 22.5 ± 43.8 Nifedipine 21.7 ± 21.7 p = 0.35 **Birth > 48 hours** Indomethacin n = 66/87 (77%) Magnesium sulphate n = 60/85 (70%) Nifedipine n = 80/104 (77%) p = 0.57 **Birth > 7 days** Indomethacin n = 53/87 (61%) Magnesium sulphate n = 46/85 (54.1%) Nifedipine n = 61/104 (58.6%) p = 0.65	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			and uterine contraction were monitored until the uterine activity was abolished for 12 hours. After observation for 2 -3 days in hospital, women were discharged if preterm labour did not reappear. <u>Definition of outcomes</u> Respiratory distress syndrome (RDS) was defined based on oxygen requirement > 24 hours plus typical findings a chest X-ray. Necrotising entrocolitis was diagnosed by pneumatises on abdominal radiography or and clinical findings. Intraventricular haemorrhage (IVH) was diagnosed by head sonography and periventricular leukomalacia (PVL) by head ultrasound as well as computed tomography and MRI when necessary <u>Analysis</u> A sample size calculation performed and 275 babies was required to have 80% power of detecting a significant difference in delivery at > 48 hours and/or > 7days post treatment. Chi square test was used for categorical data. ANOVA was used for continuous data with normal distribution and Krustall – Wallis one way ANOVA on ranks was used if continuous data were not normally distributed		
Full citation Kashanian,M., Zamen,Z., Sheikhansari,N., Comparison	**Sample size** NG group: n = 60 Nifedipine group: n = 60	**Interventions** Nitro-glycerine (NG) dermal vs	**Details** Study carried out in a teaching hospital in Tehran (Iran).	**Results** **<u>Birth was postponed for 2h</u>**	**Limitations** Unclear power calculation

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
between nitroglycerin dermal patch and nifedipine for treatment of preterm labor: a randomized clinical trial, Journal of Perinatology, 34, 683-687, 2014 **Ref Id** 323616 **Country/ies where the study was carried out** Iran **Study type** Randomised control trial **Aim of the study** To compare the effect of nifedipine and nitro-glycerine (NG) dermal patch for taking control of preterm labour **Study dates** June 2010 to March 2011 **Source of funding** Not specified	**Characteristics** **Pervious abortion** Nifedipine: n = 14/60 (32.2%) NG group: n = 8/60 (13.3%) P = 0.157 **previous preterm birth** Nifedipine: n = 4/60 (6.7%) NG group: n = 3/60 (5%) P=0.82 **Maternal age** (mean ± SD/yr) Nifedipine: 26.33 ± 6.37 NG group: 24.31 ± 4.26 P = 0.155 **Women's BMI** (mean ± SD) Nifedipine: 27.01 ± 3.12 NG group: 26.13 ± 5.34 P = 0.03 **Gestational age at study's entry** (mean ± SD/weeks) Nifedipine: 31.4 ± 2.3 NG group: 31.5 ± 1.9 P = 0.83 **Inclusion criteria** • Gestational age 26 - 34 weeks • Singleton pregnancy • At least 4 contractions during 60 minutes plus cervical dilatation > 1 cm	nifedipine	Women who were admitted to the hospital for preterm labour were included in the study. In order to obtain a power of 90% (with significance level of 5%) n = 120 women were recruited (unclear how and for what outcome the calculation performed). Written consent obtained from all participants. Eligible women were randomly assigned to two groups. Randomisation performed using sealed sequentially distributed envelopes to which letter A, B, C and D had been allocated (the letter AC to NG group and the letter B and D to the nifidipine group). The women chose one of the envelopes, which was opened by the investigator's colleague. Treatment All eligible women were infused with 500cc normal saline during 30 min and had intramuscular betamethasone (12 mg every 24 hours up to 2 doses) then women were randomised to the groups. No blinding performed because of the obvious different shape of the drugs. In the NG group (n = 63) at first a 10 mg patch was applied and a second 10 mg patch was used if the contractions continued. In case of arrest of the contractions within 1 hour, the second patch was not used. In the nifedipine group (n = 64) women were given a 10 mg nifedipine every 20 minutes up to maximum of 4 doses. In cases whose contractions had subsided,	NG group: n = 59/60 (98.3%) Nifedipine: n = 48/60 (80%) P=0.001 **Birth was postponed for 48h** NG group: n = 52/60 (86.7%) Nifedipine: n = 41/60 (68.3%) P=0.016) **Birth was postponed for 7 days** NG group: n = 47/60 (78.3%) Nifedipine: n = 37/60 (61.7%) P = 0.046 **Gestational age at the time of birth** (mean ± SD/weeks) NG group: 35.6 ± 1.9 Nifedipine: 34.3 ± 2.05 P = 0.155 **Duration of stay at neonatal intensive care unit (NICU)(mean ± SD/days)** NG group: 21.41 ± 22.18 Nifedipine: 8.43 ± 15.15 P = 0.03	No blinding of investigator and his colleagues No intention to treat analysis performed

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	and cervical effacement of ≥ 50% **Exclusion criteria** • Ruptured membranes • Maternal and fetal indication for termination of pregnancy • Intrauterine fetal death • Cervical dilatation > 5 cm • Known hypersensitivity to NG • vaginal bleeding • Tocolytic therapy during pervious 24 hours • Smoking • Any systematic disorder or any drug use except ordinary supplementations (Iron, folic acid) • Fetal anomalies • Known uterine anomalies • polyhydramnious • Oligohydramnious • Intrauterine growth restriction • Any sign and symptoms of Chorioamnionitis		20 mg , every 6 hour up to 24 hours given and then 20 mg every 8 hours for the second 24 hours and finally 10 mg every 8 hours for the next 24 hours were prescribed. If the contractions contined or blood pressure < 90/50 mm Hg, the administration of the nifedipine discontinued. Data analysis Data were analysed using SPSS 18 software. The student t test, χ2-test and Mann-Whitney test were used for analysis.	**NICU admission** NG group: n = 30/60 (50%) Nifedipine: 21/60 (35%) P = 0.09 **Caesarean section** NG group: n = 30/60 (50%) Nifedipine: 17/60 (29%) P = 0.03 **Treatment discontinued (because of hypertension)** NG group: n = 2/60 (3.33%) Nifedipine: 0/60 (0%) P = not reported **Headache** NG group: n = 4/60 (6.66%) Nifedipine: n = 3/60 (5%) P = not reported **Hypotension (BP < 100/70 mm Hg)** NG group: n = 14/60 (23.3%) Nifedipine: n = 9/60 (15%) P = not reported **Maternal tachycardia** NG group: n = 0/60 (0%) Nifedipine: n = 0/60 (0%) P = not reported **Dermal irritation** NG group: n = 0/60 (0%) Nifedipine: n = 3/60 (5%) P = not reported	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Nikbakht,R., Taheri,Moghadam M., Ghane'ee,H., Nifedipine compared to magnesium sulfate for treating preterm labor: A randomized clinical trial, Iranian Journal of Reproductive Medicine, 12, 145-150, 2014 **Ref Id** 323768 **Country/ies where the study was carried out** Iran **Study type** Randomised control trial **Aim of the study** To compare the efficacy and safety of magnesium sulfate and nifedipine in the management of preterm labour. **Study dates** Year 2002 **Source of funding** Research Deputy of Ahvaz Jundishapour University of Medical Science	**Sample size** Total n = 100 Nifedipine n = 50 Magnesium sulphate n = 50 **Characteristics** **Maternal age < 18 years** Nifedipine n = 4/50 (8%) Magnesium sulphate n = 2/50 (4) p = 0.51 **Maternal age 18 - 40 years** Nifedipine n = 43/50 (86%) Magnesium sulphate n = 46/50 (92%) p = 0.50 **Maternal age > 40 years** Nifedipine n = 3/50 (6%) Magnesium sulphate n = 2/50 (4%) p = 0.54 **Primiparous** Nifedipine n = 27/50 (54%) Magnesium sulphate n = 24/50 (48%) p = 0.50 **Multiparous** Nifedipine n = 27/50 (54%) Magnesium sulphate n = 24/50 (48%) p = 0.50 **Gestational age < 34 weeks** Nifedipine n = 31/50 (62%) Magnesium sulphate n = 29/50 (58%) p = 0.50 **Gestational age > 34 weeks** Nifedipine n = 19/50 (38%) Magnesium sulphate n = 21/50 (42%)	**Interventions** Nifedipine versus magnesium sulphate	**Details** The study carried out in two university hospital in Ahvaz (Iran). Consent obtained from the participant before enrolling in the study. Women who met the inclusion criteria were randomly assigned to two groups. in the first step , all women were hydrated by 500 ml of Ringer solutions and bed rest. Dextra methasone were given to women with < 34 weeks gestation. The women were randomly selected to receive oral nifedipine or intravenous magnesium sulphate. Women in nifedipine were initially given 10 mg capsule which was repeated every 20 min up to maximal dose of 30 mg during the first hour of treatment and then nifedipine maintenance dose of 10 mg given every six hours. Women in the magnesium sulphate group received 10 gr (IV) and 5g (IM) of magnesium sulphate every 4 hours. Treatment was considered as a success if women were delivered after 48 hours and after 7 days. For those who contractions did not subside other tocolytic such as isoxsuprine or indomethacin was given (treatment failure)	**Results** **Delaying delivery >7 days** Nifedipine n = 28/50 (56%) Magnesium sulphate n = 32/60 (64%) **Delaying delivery > 48 days** Nifedipine n = 4/50 (8%) Magnesium sulphate n = 2/50 (4%) **Discontinuation due to severe symptoms** Nifedipine n = 3/50 (6%) Magnesium sulphate n = 1 (2%) **Total success rate** Nifedipine n = 10/50 (20%) Magnesium sulphate n = 8/50 (16%)	**Limitations** Randomisation not described unclear blinding Unclear allocation concealment Loss of data not discussed Unclear who performed the analysis

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	p = 0.50 **Prior preterm birth** Nifedipine n = 2/50 (4%) Magnesium sulphate n = 1/50 (2%) p = 0.54 **twin gestation** Nifedipine n = 2/50 (4%) Magnesium sulphate n = 1/50 (2%) p = 0.54 **Inclusion criteria** • Intact membranes • Singleton or twins gestations • 24 to 37 weeks gestation • showing sign of preterm labour: -Cervical dilatation from 0 to 4 cm -50% cervical effacement -Presence of ≥4 uterine contractions over 30 min lasting at least 30 seconds each **Exclusion criteria** • Clinical intrauterine infection • Chorioamnionitis • Cervical dilatation of > 5 cm • Non reassuring fetal heart rate tracing • Lethal fetal abnormality				

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	• Maternal cardiac or liver disease • Sever preeclampsia • Antepartum haemorrhage				
Full citation Nankali,A., Jamshidi,P.K., Rezaei,M., The Effects of Glyceryl Trinitrate Patch on the Treatment of Preterm Labor: A Single-blind Randomized Clinical Trial, Journal of Reproduction and Infertility, 15, 71-77, 2014 **Ref Id** 323891 **Country/ies where the study was carried out** Iran **Study type** Randomised control trial **Aim of the study** To investigate the effect of glyceryl trinitrate (GTN) patch on the treatment and complications of PTL **Study dates** October 2011 to August 2012 **Source of funding**	**Sample size** Total n = 84 **Characteristics** Mean age (years) GTN 29 ± 0.84 Placebo 26 ±0.77 p = 0.23 Mean gestational age at admission (weeks) GTN 31.5 ± 0.4 Placebo 31.3 ±0.4 p = 0.66 Cervical dilatation at admission (cm) GTN 1.8 ± 0.14 Placebo 1.7 ± 0.13 p = 0.52 **Inclusion criteria** • Singleton gestations • Regular uterine contraction ≥ 4 within 20 min or Bishop score ≥ 3 • 27 to 35 weeks gestation **Exclusion criteria** • Fetal malformation • Chorioamnionitis • Antepartum haemorrhage	**Interventions** Glglyceryl trinitrate (GTN) versus placebo	**Details** The study conducted in the maternity unit of hospital in kermanshah (Iran) on 84 singleton pregnant women with gestational age of 27-35 weeks who were admitted to hospital for preterm labour. Preterm labour was clinically diagnosed and the women were randomly divided into two groups who were treated with GTN or placebo for 48 hours. Treatment At first, all women were infused with normal saline followed by intravenous ampicillin and intramuscular betamethasone. After randomisation and gaining consent, each women received either a 10 mg of GTN patch or placebo which was applied on their skin (top of the navel) Analysis Data were analyzed with chi square test, paired and unpaired t tests by SPSS software and p<0.05 was considered significant	**Results** **Birth within the first 24 hours** GTN n n = 5 (12.50%) Placebo n = 8 (20%) p = 0.58 **Birth within the 24 to 48 hours** GTN n n = 6 (15%) Placebo n = 7 (17.5%) p = 0.58 **Birth within after 48 hours** GTN n n = 29 (72.5%) Placebo n = 25 (62.5%) p = 0.58 **Birth during hospitalisation** GTN n n = 13 (32.5%) Placebo n = 18 (45%) p = 0.25 **Successful tocolysis**, **Delivered during the hospitalisation (hr)** GTN 31± 4.4 Placebo 18.3 ± 2.2 p=0.01 **Headache** GTN n n = 14 (35%) Placebo n = 4 (10%) p=0.007	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Not specified	• Treatment with other tocolytic agent 24 hours before birth • Previous caesarean section • Cervical dilatation ≥ 5 cm • Preterm premature rupture of membranes • Multiple pregnancy • Cardiovascular disease • Placenta previa • Susceptibility to glycerin compounds			**Maternal palpitation** GTN n n = 6 (15%) Placebo n = 4 (10%) p=0.49	
Full citation Haas,D.M., Caldwell,D.M., Kirkpatrick,P., McIntosh,J.J., Welton,N.J., Tocolytic therapy for preterm delivery: systematic review and network meta-analysis, BMJ, 345, e6226-, 2012 **Ref Id** 259796 **Country/ies where the study was carried out** USA **Study type** Systematic review and network meta-analysis **Aim of the study**	**Sample size** n = 159 full text articles were retrieved n = 95 met the study inclusion n = 8 were articles were non English, (four in Chinese, one in French, and one each in German, Portuguese, and Spanish). Mean number of participants in the trials: Mean = 111.9 (SD 108.8, range 20-708) Published from 1966 to 2011 **Characteristics** Details of the characteristics of the trials and comparison of are not reported n = 25 trials contained a placebo arm n = 60 (63%) included beta mimetics	**Interventions** Tocolytic therapy: - beta mimetics (ritodrine, terbutaline, nylidrin, salbutamol, fenoterol, hexoprenaline, isoxsuprine) - calcium channel blockers (nifedipine, nicardipine) - magnesium sulfate - nitrates (nitroglycerine, nitric oxide) - oxytocin receptor blockers (atosiban,	**Details** Systematically search performed on the Cochrane Central Register of Controlled Trials (February 2012), Medline (1950-present), Medline In-Process/Daily Update (17 February 2012), Embase (1988-2012), and CINAHL (1982-2012) for published randomized controlled trials of tocolytic therapy. Search was limited to articles reporting trials in humans, and excluded duplicate trial entries. Search results were cross referenced with the Cochrane reviews of tocolytic medications, hand searching was conducted for additional titles. Data extraction was carried out by two reviewers. Discrepancy between the reviewers was resolved by consensus. Non English languages abstract were reviewed for inclusion. Quality assessment:	**Results** Delivery delayed by 48 hours n = 64 trials (n = 55 meta-analysis, n = 54 pairwise meta-analysis) n =16 treatments n = 8 drug classes Respiratory distress syndrome n = 60 trials n = 19 treatments n = 7 drug classes Maternal side effects (all cause) n = 68 trials n = 18 treatment n = 7 drug classes **Neonatal mortality, result**	**Limitations** **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
To determine the most effective tocolytic agent at delaying birth **Study dates** 17 February 2012 **Source of funding** Not specified	n = 29 (26%) included magnesium sulfate n = 30 (31%) included calcium channel blockers n = 30 (31%) included prostaglandin inhibitors n = 13 (19%) included oxytocin receptor blockers (atosiban or barusiban) n = 4 (4%) included nitratesn n = 5 (5%) included other drugs No trials compared atosiban with magnesium sulfate **Inclusion criteria** • The trial that reported a comparison between different medications or between a medication and a placebo or usual care for delaying preterm delivery. **Exclusion criteria** • Not randomized controlled trials • Did not study women at risk of preterm delivery (defined by trial) • Did not study at least one tocolytic drug • Used combination drug therapies for tocolysis, • Did not report maternal or	barusiban) - prostaglandin inhibitors (indomethacin, celecoxib, sulindac, ketorolac, rofecoxib) - others (alcohol, human chorionic gonadotropin, combination tocolytic drugs) Vesus placebo: - placebo (placebo or usual or standard care without a tocolytic drug)	Using the Cochrane's assessment tool, risk of bias was assessed based on seven specific factors: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other sources of bias. Overall quality of each study was considered to be high if at least four domains had a low risk score, with at least one of the domains needing to be sequence generation or allocation concealment. Statistical analysis The primary effectiveness outcome for the network meta-analysis was: - delivery successfully delayed for 48 hours The secondary outcomes were: - neonatal mortality - neonatal respiratory distress syndrome - all cause of maternal side effects For binary outcomes: - the studies with zero or 100% events on all arms were excluded. - Analyses were done within a Bayesian framework using WinBUGS 1.4.3. - A random effects network meta-analysis was carried out to concurrently compare the 18 treatments and eight (8) tocolytic classes for each outcome. Where head to head data were available pairwise "direct" meta-analyses was also carried out using a random effects model.	**from pairwise meta analysis** Beta mimetics v placebo NMA RR 0.62 (95% CI 0.14 to 2.48) Direct pairwise analysis RR 0.39 (95% CI 0.10 to 1.42) Prostaglandin inhibitors v placebo NMA 0.62 RR (95% CI 0.04 to 4.63) Direct pairwise analysis RR 1.08 (95% CI 0.14 to 10.03) Calcium channel blocker v placebo NMA RR 0.39 (95% CI 0.09 to 1.49) Others v placebo NMA RR 2.79 (95% CI 0.28 to 31.75) Magnesium sulphate v placebo NMA RR 0.97 (95% CI 0.29 to 3.29) Direct pairwise analysis RR 1.08 (95% CI 0.15 to 6.82) Oxytocin receptor blocker v placebo NMA RR 4.74 (95% CI 1.12 to 34.19)	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	neonatal outcomes in relation to preterm delivery • Published abstracts that did not contain enough information for complete data to be extracted • Personal communications cited in Cochrane reviews		- Heterogeneity was assessed using the posterior median between trial variance, t^2. However, for ease of interpretation they report the χ2 test for heterogeneity and I^2 statistic for the pairwise meta-analyses (calculated using Stata). - P=0.10 were used fo the assessment of heterogeneity. - In the case of two or fewer trials a fixed effect meta-analysis was carried out. - The pairwise meta-analyses were done using the drug classes and not individual treatments as the subject of interest. -Posterior median odds ratios and 95% credible intervals were calculated. - A meta-regression analyzed the impact of planned duration of treatment (acute or short term tocolysis versus prolonged therapy) on the results. - For the network meta-analysis a class effect model was implemented where each treatment effect in the same class is assumed to come from a family of treatment effects with a class specific mean effect and between treatment variability within class (assumed equal across all classes). - Goodness of fit was measured by the posterior mean of the residual deviance. In a well fitting model the residual deviance should be close to the number of data points. - Because of the way in which the residual deviance is calculated, zero	Prostaglandin inhibitors v beta mimetics NMA RR 0.98 (95% CI 0.05 to 10.01) Direct pairwise analysis RR 1.05 (95% CI 0.18 to 6.22) Calcium channel blocker s v beta mimetics NMA RR 0. 63 (95% CI 0.13 to 3.16) Direct pairwise analysis RR 0.56 (95% CI 0.13 to 2.00) Others s v beta mimetics NMA RR 4.50 (95% CI 0.47 to 51.29) Direct pairwise analysis RR 3.63 (95% CI 1.15 to 14.11) Magnesium sulphate v beta mimetics NMA RR 1.00(95% CI 0.32 to 8.30) Direct pairwise analysis RR 1.16 (95% CI 0.18 to 6.44) Oxytocin receptor blockers v beta mimetics NMA RR 1.58 (95% CI 0.21 to 5.11) Direct pairwise analysis RR 0.62 (95% CI 0.17 to 1.92) Calcium channel blockers	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			cells on the baseline (control) arm can cause computational difficulties. For the purposes of model selection those trials were removed but included in the final model on which the results are based. Consistency between the direct and indirect evidence: Inconsistency in each of the three networks was assessed by comparing a model assuming consistency with that of an inconsistency model using the deviance information criterion. A difference of 3 or more points is considered meaningful. Convergence was assessed using two chains and was achieved by 25 000 simulations for delivery delayed by 48 hours, 30 000 for neonatal mortality and respiratory distress syndrome, and 35 000 for maternal side effects (based on the Brooks-Gelman-Rubin diagnostic tool in WinBUGS). A further 50,000 updates were run after convergence for delivery delayed by 48 hours, 60,000 for neonatal mortality and respiratory distress syndrome, and 70,000 for maternal side effects.	v prostaglandin inhibitors NMA RR 0.64 (95% CI 0.06 to 11.82) Direct pairwise analysis RR 0.05 (95% CI 0.00 to 1.02) Others v prostaglandin inhibitors NMA RR 4.78 (95% CI 0.24 to 159.10) Magnesium sulphate v prostaglandin inhibitors NMA RR 1.61 (95% CI 0.21 to 24.95) Direct pairwise analysis RR 3.16 (95% CI 0.35 to 43.64) Oxytocin receptor blockers v prostaglandin inhibitors NMA RR 1.03 (95% CI 0.10 to 19.60) Others v calcium channel blockers NMA RR 7.16 (95% CI 0.68 to 93.55) Magnesium sulphate v calcium channel blockers NMA RR 2.50 (95% CI 0.58 to 11.77) Direct pairwise analysis RR 0.40 (95% CI 0.01 to 5.26) Oxytocin receptor blockers v calcium channel blockers	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				NMA RR 1.61 (95% CI 0.38 to 7.05) Direct pairwise analysis RR 1.16 (95% CI 0.29 to 4.79) <u>Magnesium sulphate v others</u> NMA RR 0.35 (95% CI 0.03 to 3.88) <u>Oxytocin receptor blockers v others</u> NMA RR 0.23 (95% CI 0.02 to 2.31) <u>Magnesium sulphate v oxytocin receptor blockers</u> NMA RR 1.56 (95% CI 0.33 to 7.92) **<u>48 hours delay in birth, result from pairwise meta analysis</u>** <u>Beta mimetics v placebo</u> NMA RR 2.52 (95% CI 1.34 to 4.89) Direct pairwise analysis RR 3.37 (95% CI 0.96 to 16.05) <u>Prostaglandin inhibitors v placebo</u> NMA 2.49 RR (95% CI 2.17 to 13.63) Direct pairwise analysis RR 14.57 (95% CI 4.30 to 60.85) <u>Calcium channel blocker v</u>	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				placebo NMA RR 2.78 (95% CI 1.26 to 8.61) Others v placebo NMA RR 2.02 (95% CI 0.50 to 4.40) Magnesium sulphate v placebo NMA RR 2.82 (95% CI 1.59 to 3.29) Direct pairwise analysis RR 2.69 (95% CI 0.37 to 19.73) Oxytocin receptor blocker v placebo NMA RR 2.06 (95% CI 1.12 to 3.99) Direct pairwise analysis RR 1.51 (95% CI 1.06 to 2.15) Nitrates v placebo NMA RR 1.35 (95% CI 0.39 to 4.40) Direct pairwise analysis RR 1.13 (95% CI 0.54 to 2.38) Prostaglandin inhibitors v beta mimetics NMA RR 2.15 (95% CI 0.88 to 5.11) Direct pairwise analysis RR 3.04 (95% CI 0.77 to 12.73) Calcium channel blocker s v beta mimetics NMA RR 1.10(95% CI 0.54	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				to 2.35) Direct pairwise analysis RR 1.12 (95% CI 0.70 to 1.76) <u>Others s v beta mimetics</u> NMA RR 0.80 (95% CI 0.21 to 3.04) Direct pairwise analysis RR 3.63 (95% CI 1.15 to 14.11) <u>Magnesium sulphate v beta mimetics</u> NMA RR 1.12(95% CI 0.64 to 2.01) Direct pairwise analysis RR 1.09 (95% CI 0.51 to 2.16) <u>Nitrates v beta mimetics</u> NMA RR 0.53 (95% CI 0.15 to 1.96) <u>Calcium channel blockers v prostaglandin inhibitors</u> NMA RR 0.51 (95% CI 0.20 to 1.45) Direct pairwise analysis RR 79.82 (95% CI 5.50 to 35.12) <u>Others v prostaglandin inhibitors</u> NMA RR 0.37 (95% CI 0.09 to 1.75) <u>Magnesium sulphate v prostaglandin inhibitors</u> NMA RR 0.52 (95% CI 0.24 to 1.18)	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				Oxytocin receptor blockers v prostaglandin inhibitors NMA RR 0.38 (95% CI 0.15 to 1.00) Nitrates v prostaglandin inhibitors NMA RR 0.25 (95% CI 0.06 to 1.14) Others v calcium channel blockers NMA RR 0.73 (95% CI 0.17 to 3.02) Magnesium sulphate v calcium channel blockers NMA RR 1.02 (95% CI 0.50 to 2.02) Direct pairwise analysis RR 0.88 (95% CI 0.46 to 1.80) Oxytocin receptor blockers v calcium channel blockers NMA RR 0.74 (95% CI 0.34 to 1.62) Nitrates v calcium channel blockers NMA RR 0.48 (95% CI 0.13 to 3.02) Direct pairwise analysis RR 0.77 (95% CI 0.13 to 4.08) Magnesium sulphate v others NMA RR 1.41 (95% CI 0.38 to 5.03) Direct pairwise analysis RR 1.46 (95% CI 0.42 to	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				5.38) <u>Oxytocin receptor blockers v others</u> NMA RR 1.03 (95% CI 0.26 to 4.41) <u>Nitrates v others</u> NMA RR 0.66 (95% CI 0.11 to 4.07) <u>Oxytocin receptor blockers v nitrates</u> NMA RR 1.55 (95% CI 0.42 to 5.61) <u>Magnesium sulphate v nitrates</u> NMA RR 2.12 (95% CI 0.58 to 7.56) <u>Magnesium sulphate v Oxytocin receptor blockers</u> NMA RR 1.37 (95% CI 0.72 to 2.62) **<u>Neonatal respiratory distress syndrome, result from pairwise meta analysis</u>** <u>Beta mimetics v placebo</u> NMA RR 0.85 (95% CI 0.50 to 1.45) Direct pairwise analysis RR 0.62 (95% CI 0.28 to 1.02) <u>Prostaglandin inhibitors v placebo</u>	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				NMA 0.87 RR (95% CI 0.40 to 1.75) Direct pairwise analysis RR 0.99 (95% CI 0.16 to 5.68) <u>Calcium channel blocker v placebo</u> NMA RR 0.71 (95% CI 0.37 to 1.43) <u>Others v placebo</u> NMA RR 1.54 (95% CI 0.55 to 4.71) <u>Oxytocin receptor blocker v placebo</u> NMA RR 0.89 (95% CI 0.55 to 1.37) Direct pairwise analysis RR 1.36 (95% CI 0.92 to 2.04) <u>Magnesium sulphate v placebo</u> NMA RR 0.99 (95% CI 0.58 to 1.71) Direct pairwise analysis RR 1.04 (95% CI 0.52 to 2.07) <u>Prostaglandin inhibitors v beta mimetics</u> NMA RR 1.03 (95% CI 0.44 to 2.22) Direct pairwise analysis RR 0.79 (95% CI 0.32 to 1.87) <u>Calcium channel blocker s</u>	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				v beta mimetics NMA RR 0.85 (95% CI 0.62 to 5.72) Direct pairwise analysis RR 2.84 (95% CI 1.06 to 8.49) Others s v beta mimetics NMA RR 1.80 (95% CI 0.21 to 3.04) Direct pairwise analysis RR 3.63 (95% CI 1.15 to 14.11) Oxytocin receptor blocker v beta mimetics NMA RR 1.04 (95% CI 0.60 to 1.84) Direct pairwise analysis RR 0.90 (95% CI 0.34 to 3.14) Magnesium sulphate v beta mimetics NMA RR 1.16(95% CI 0.62 to 2.26) Direct pairwise analysis RR 1.78 (95% CI 0.55 to 6.18) Calcium channel blockers v prostaglandin inhibitors NMA RR 0.82 (95% CI 0.36 to 2.11) Others v prostaglandin inhibitors NMA RR 1.77 (95% CI 0.58 to 5.48) Oxytocin receptor blockers v prostaglandin inhibitors	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				NMA RR 1.02 (95% CI 0.47 to 2.28) <u>Magnesium sulphate v prostaglandin inhibitors</u> NMA RR 1.13 (95% CI 0.62 to 2.25) Direct pairwise analysis RR 1.01 (95% CI 0.40 to 2.72) <u>Others v calcium channel blockers</u> NMA RR 2.14 (95% CI 0.69 to 6.83) <u>Oxytocin receptor blockers v calcium channel blockers</u> NMA RR 1.24 (95% CI 0.62 to 2.39) Direct pairwise analysis RR 0.84 (95% CI 0.41 to 1.70) <u>Magnesium sulphate v calcium channel blockers</u> NMA RR 1.39 (95% CI 0.67 to 2.78) Direct pairwise analysis RR 1.18 (95% CI 0.66 to 2.15) <u>Oxytocin receptor blockers v others</u> NMA RR 0.58 (95% CI 0.19 to 1.64) <u>Magnesium sulphate v others</u> NMA RR 0.65 (95% CI 0.24 to 1.71) Direct pairwise analysis	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				RR 0.99 (95% CI 0.35 to 2.79) Magnesium sulphate v Oxytocin receptor blockers NMA RR 1.11 (95% CI 0.62 to 2.13) **Maternal side effects, result from pairwise meta analysis** Beta mimetics v placebo NMA RR 22.68 (95% CI 7.51 to 73.67) Direct pairwise analysis RR 12.26 (95% CI 3.66 to 61.03) Prostaglandin inhibitors v placebo NMA 1.63 RR (95% CI 0.40 to 6.85) Direct pairwise analysis RR 2.31 (95% CI 0.62 to 9.60) Calcium channel blocker v placebo NMA RR 3.80 (95% CI 1.02 to 16.92) Direct pairwise analysis RR 2.91 x 10^{8} (95% CI 389.2 to 1.40 x 10^{26}) Others v placebo NMA RR 3.19 (95% CI 0.41 to 20.84) Direct pairwise analysis RR	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				2.27 (95% CI 1.18 to 4.43) Magnesium sulphate v placebo NMA RR 8.15 (95% CI 2.47 to 27.70) Direct pairwise analysis RR 8.20 (95% CI 1.30 x 10^{6} to 1.73 x 10^{17}) Oxytocin receptor blocker v placebo NMA RR 1.99 (95% CI 0.61 to 6.94) Direct pairwise analysis RR 2.08 (95% CI 1.24 to 3.55) Prostaglandin inhibitors v beta mimetics NMA RR 0.07 (95% CI 0.02 to 0.27) Direct pairwise analysis RR 0.05 (95% CI 0.01 to 0.19) Calcium channel blocker s v beta mimetics NMA RR 0.17 (95% CI 0.06 to 0.59) Direct pairwise analysis RR 0.14 (95% CI 0.05 to 0.36) Nitrates s v beta mimetics NMA RR 0.14 (95% CI 0.02 to 1.03) Magnesium sulphate v beta mimetics NMA RR 0.36 (95% CI 0.13	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				to 1.01) Direct pairwise analysis RR 0.45 (95% CI 0.11 to 1.71) <u>Oxytocin receptor blockers v beta mimetics</u> NMA RR 0.09 (95% CI 0.03 to 0.26) Direct pairwise analysis RR 0.05 (95% CI 0.03 to 0.14) <u>Calcium channel blockers v prostaglandin inhibitors</u> NMA RR 2.32 (95% CI 0.56 to 12.57) Direct pairwise analysis RR 2.25 (95% CI 0.90 to 5.95) <u>Nitrates v prostaglandin inhibitors</u> NMA RR 1.90 (95% CI 0.20 to 18.16) <u>Magnesium sulphate v prostaglandin inhibitors</u> NMA RR 4.97 (95% CI 1.32 to 20.44) Direct pairwise analysis RR 3.02 (95% CI 0.44 to 27.95) <u>Oxytocin receptor blockers v prostaglandin inhibitors</u> NMA RR 1.22 (95% CI 0.27 to 5.93) <u>Nitrates v calcium channel blockers</u>	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				NMA RR 0.82 (95% CI 0.09 to 6.50) Direct pairwise analysis RR 2.08 (95% CI 0.59 to 8.19) Magnesium sulphate v calcium channel blockers NMA RR 0.52 (95% CI 0.13 to 1.87) Direct pairwise analysis RR 0.91 (95% CI 0.45 to 1.84) Magnesium sulphate v others NMA RR 2.61 (95% CI 0.37 to 21.15) Direct pairwise analysis RR 8.12 (95% CI 0.92 to 243.20) Oxytocin receptor blockers v others NMA RR 0.63 (95% CI 0.08 to 5.85) Oxytocin receptor blockers v magnesium sulphate NMA RR 0.25 (95% CI 0.07 to 0.84)	

H.10.3.1 Health economics

Bibliographic details	Interventions and comparisons	Data Sources	Time horizon & Method	Results	Reviewer comment
Full citation	Study dates	Source of effectiveness	Time horizon and	Cost per patient per	Limitations

Bibliographic details	Interventions and comparisons	Data Sources	Time horizon & Method	Results	Reviewer comment
Cahill,A.G., Odibo,A.O., Caughey,A.B., Stamilio,D.M., Hassan,S.S., Macones,G.A., Romero,R., Universal cervical length screening and treatment with vaginal progesterone to prevent preterm birth: a decision and economic analysis, American Journal of Obstetrics and Gynecology, 202, 548-548, 2010 **Ref Id** 281888 **Economic study type** Cost effectiveness analysis **Country(ies) where the study was done** USA **Perspective & Cost Year** Perspective: not stated Cost year: not stated **Source of funding** The Perinatology	Published in June 2010. Study dates not stated. **Intervention** Vaginal progesterone (VP) **Comparison(s)** No treatment	**data** Published evidence **Source of cost data** Published evidence. Underlying assumptions and scope was not stated. **Other data sources e.g. transition probabilities**	**discount rate** Time Horizon: NA Discount Rate: NA **Method of eliciting health valuations (if applicable)** NA **Modelling approach** Decision Analytic Cost-Utility analysis	**alternative** Based on a population of 4 million deliveries: Vaginal progesterone: USD 333.0 mln No treatment: USD 462.4 mln **Effectiveness per patient per alternative** Preterm births prevented Vaginal progesterone: 95,920 No treatment: 0 **Incremental cost-effectiveness** Vaginal progesterone dominates **Other reporting of results** **Uncertainty** Probabilistic sensitivity analysis. A single value was reported. Limited applicability to outcome of interest.	Absence of detail regarding cost build up, specific sources of data, perspective and study dates. There was also no list of references. As such claims in this study cannot be verified. Data in the report is based on single values. There are no confidence intervals. **Other information**

Bibliographic details	Interventions and comparisons	Data Sources	Time horizon & Method	Results	Reviewer comment
Research Branch, Division of Intramural Research, Eunice Kennedy Shriver National Institute of Child Health and Human Development, NIH/DHHS					
Full citation Fleming,A., Bonebrake,R., Istwan,N., Rhea,D., Coleman,S., Stanziano,G., Pregnancy and economic outcomes in patients treated for recurrent preterm labor, Journal of Perinatology, 24, 223-227, 2004 **Ref Id** 222641 **Economic study type** Cost effectiveness analysis **Country(ies) where the study was done** USA **Perspective & Cost Year** Perspective: Third Party Payer Cost Year: Not Stated	**Study dates** June 1992 to June 2000 **Intervention** Continuous subcutaneous terbutaline infusion (SQT) and oral nifedipine (NIF) **Comparison(s)** Continuous subcutaneous terbutaline infusion (SQT) and oral nifedipine (NIF)	**Source of effectiveness data** Computerised database: Matria Healthcare, Marietta, Ga. **Source of cost data** Costs data obtained from Agency for healthcare Research and Quality, nationwide Inpatient sample for 1999. Intervention: charges for antepartum hospitalization, outpatient services, nursery days. Costs include accommodation and ancillary charges. Indirect costs are excluded. **Other data sources e.g. transition probabilities**	**Time horizon and discount rate** Time Horizon: NA Discount Rate: NA **Method of eliciting health valuations (if applicable)** Computerised database Matria Healthcare, Marietta, Ga. **Modelling approach** Decision Analytic Cost-Effectiveness analysis	**Cost per patient per alternative** NIF: USD 37,040 SQT: USD 26,546 **Effectiveness per patient per alternative** Mean gestation age at delivery NIF: 35.7 weeks SQT: 36.6 weeks **Incremental cost-effectiveness** SQT dominates **Other reporting of results** **Uncertainty** Standard deviation given for many data points. No sensitivity analysis performed	**Limitations** The generalization of this study is limited as it is retrospective. **Other information**

Bibliographic details	Interventions and comparisons	Data Sources	Time horizon & Method	Results	Reviewer comment
Source of funding Not stated					
Full citation Valdes,E., Salinas,H., Toledo,V., Lattes,K., Cuellar,E., Perucca,E., Diaz,R., Montecinos,F., Reyes,A., Nifedipine versus fenoterol in the management of preterm labor: a randomized, multicenter clinical study, Gynecologic and Obstetric Investigation, 74, 109-115, 2012 **Ref Id** 260856 **Economic study type** Cost effectiveness analysis **Country(ies) where the study was done** Chile **Perspective & Cost Year** Perspective: Hospital Cost Year: Not Stated	**Study dates** May 2007 and November 2008 **Intervention** Nifedipine (oral) and Fenoterol (intravenous) **Comparison(s)** Nifedipine (oral) and Fenoterol (intravenous)	**Source of effectiveness data** Randomised controlled trial (RCT) **Source of cost data** Data generated by investigators based on the information supplied by the Division de Operaciones of the Hospital Clinico of the Universidad de Chile **Other data sources e.g. transition probabilities**	**Time horizon and discount rate** Time Horizon: NA Discount Rate: NA **Method of eliciting health valuations (if applicable)** NA **Modelling approach** Decision Analytic Cost-Effectiveness analysis	**Cost per patient per alternative** Cost savings: Nifedipine: USD 588 Fenoterol: USD 951 **Effectiveness per patient per alternative** Efficacy of tocolytic as first-line agent Nifedipine: 54/58 = 0.9310 Fenoterol: 61/64 = 0.9531 **Incremental cost-effectiveness** Fenoterol dominates **Other reporting of results** **Uncertainty** No sensitivity analysis was performed	**Limitations** 1) The trial is not blinded; 2) Only cost saved are reported. This will make it difficult to generalise the cost outside the specific setting of Chile. **Other information**

Bibliographic details	Interventions and comparisons	Data Sources	Time horizon & Method	Results	Reviewer comment
Source of funding Fondo Nacional de Investigacion en Salud, IIIrd Project					
Full citation Lam,F., Istwan,N.B., Jacques,D., Coleman,S.K., Stanziano,G.J., Managing perinatal outcomes: the clinical benefit and cost-effectiveness of pharmacologic treatment of recurrent preterm labor, Managed Care, 12, 39-46, 2003 **Ref Id** 222867 **Economic study type** Cost effectiveness analysis **Country(ies) where the study was done** USA **Perspective & Cost Year** Perspective: Third Party Payer	**Study dates** April 1995 to January 1999 **Intervention** Continuous subcutaneous terbutaline infusion (SQT)and oral terbutaline (OT) **Comparison(s)** Continuous subcutaneous terbutaline infusion (SQT)and oral terbutaline (OT)	**Source of effectiveness data** Computerised database: Matria Healthcare, Marietta, Ga. **Source of cost data** Authors estimated cost data. Assumptions for estimate not provided. Intervention: charges for antepartum hospitalization, outpatient services, nursery days. Costs include accommodation and ancillary charges. Indirect costs, physician charges, increased first year and life time medical costs are excluded. **Other data sources e.g. transition probabilities**	**Time horizon and discount rate** Time Horizon: NA Discount Rate: NA **Method of eliciting health valuations (if applicable)** Computerised database Matria Healthcare, Marietta, Ga. **Modelling approach** Decision Analytic Cost-Effectiveness analysis	**Cost per patient per alternative** OT: USD 21,935 SQT: USD 16,649 **Effectiveness per patient per alternative** Mean gestational age at birth OT: 35.7 weeks SQT: 36.5 weeks **Incremental cost-effectiveness** SQT dominates **Other reporting of results** **Uncertainty** No sensitivity analysis performed	**Limitations** Limited generalization of this study as it is retrospective. Costs are estimated but the underlying assumptions are not clearly stated. Author makes mention of difference in their costs estimates and published data on costs. **Other information**

Bibliographic details	Interventions and comparisons	Data Sources	Time horizon & Method	Results	Reviewer comment
Cost Year: Not Stated **Source of funding** Not stated					
Full citation Siassakos,D., O'Brien,K., Draycott,T., Healthcare evaluation of the use of atosiban and fibronectin for the management of pre-term labour, Journal of Obstetrics and Gynaecology, 29, 507-511, 2009 **Ref Id** 203798 **Economic study type** Cost-minimisation analysis **Country(ies) where the study was done** UK **Perspective & Cost Year** Perspective: Hospital Cost Year: Not Stated	**Study dates** Not stated **Intervention** fFN test followed by atosiban **Comparison(s)** fFN test followed by nifedipine and nifedipine alone	**Source of effectiveness data** Systematic review of published literature. **Source of cost data** Local data from Southmead Hospital, Bristol, UK and is based on outpatient costs for test, inpatient costs for those diagnosed with preterm labour, administration of steroids and tocolytics **Other data sources e.g. transition probabilities**	**Time horizon and discount rate** Time Horizon: NA Discount Rate: NA **Method of eliciting health valuations (if applicable)** Published literature **Modelling approach** A Decision Tree model was used to simulate the outcomes associated with each of the interventions. In 2 of 3 of the interventions, there was first a fFN test performed.	**Cost per patient per alternative** fFN-atosiban GBR 52,083 nifedipine GBR 2727,756 fFN-nifedipine GBR 42,923 **Effectiveness per patient per alternative** Atosiban and nifedipine considered to have the same effectiveness. **Incremental cost-effectiveness** NA **Other reporting of results** **Uncertainty** No sensitivity analysis was performed.	**Limitations** Costs are based on 1 hospital. Not clear if this cost data is generalizable across the UK. Also, costs do not include costs similar between the different tocolytics so costs have been estimated. **Other information**

Bibliographic details	Interventions and comparisons	Data Sources	Time horizon & Method	Results	Reviewer comment
Source of funding Not stated					
Full citation Wex,J., Connolly,M., Rath,W., Atosiban versus betamimetics in the treatment of preterm labour in Germany: an economic evaluation, BMC pregnancy and childbirth, 9, 23-, 2009 **Ref Id** 265596 **Economic study type** Cost-minimisation analysis **Country(ies) where the study was done** Germany **Perspective & Cost Year** Perspective: Third Party Payer and Hospital Cost Year: 2008 **Source of funding** Not stated	**Study dates** 1996 to 2008 **Intervention** Atosiban, bolus fenoterol, and continuous fenoterol **Comparison(s)** Atosiban, bolus fenoterol, and continuous fenoterol	**Source of effectiveness data** Systematic literature review of 6 randomised controlled trials (RCTs) **Source of cost data** Cost of drugs was calculated based on trial protocols and German hospital drug purchase costs. G-DRG Grouper was used to obtain cost per case. **Other data sources e.g. transition probabilities**	**Time horizon and discount rate** Time Horizon: NA Discount Rate: NA **Method of eliciting health valuations (if applicable)** Systematic literature review of 6 randomised controlled trials (RCTs) **Modelling approach** Decision Analytic Cost-Minimisation analysis	**Cost per patient per alternative** Cost savings Payer's perspective: EUR 423 atosiban versus fenoterol Perspective: Hospital : EUR 259 atosiban versus continuous fenoterol (18 hours) Perspective: Hospital : EUR 105 atosiban versus continuous fenoterol (48 hours) Perspective: Hospital : EUR 244 atosiban versus bolus fenoterol (18 hours) Perspective: Hospital : EUR 55 atosiban versus bolus fenoterol (48 hours) **Effectiveness per patient per alternative** Efficacy of treatments found to be identical based on literature review. **Incremental cost-effectiveness** As no single efficacy value given for each treatment,	**Limitations** There was no detailed analysis of resource utilization and micro-costing **Other information**

Bibliographic details	Interventions and comparisons	Data Sources	Time horizon & Method	Results	Reviewer comment
				there can be no incremental cost effectiveness. Based on cost-minimisation analysis, atosiban is least costly. **Other reporting of results** **Uncertainty** Probabilistic sensitivity analysis	
Full citation Wex,J., bou-Setta,A.M., Clerici,G., Di Renzo,G.C., Atosiban versus betamimetics in the treatment of preterm labour in Italy: clinical and economic importance of side-effects, European Journal of Obstetrics, Gynecology, and Reproductive Biology, 157, 128-135, 2011 **Ref Id** 223345 **Economic study type** Cost-minimisation analysis	**Study dates** 1994 to 2007 **Intervention** Atosiban and ritodrine **Comparison(s)** Atosiban and ritodrine	**Source of effectiveness data** Systematic literature review of 9 randomised controlled trials (RCTs) **Source of cost data** Costs were built up from adverse events and patient activity. DRG tariffs were obtained with DRG Grouper v.19 using national schedule. From the National health Service payer's perspective, all costs associated with treatment of preterm labour were encompassed by the flat	**Time horizon and discount rate** Time Horizon: NA Discount Rate: NA **Method of eliciting health valuations (if applicable)** Systematic literature review of 9 randomised controlled trials (RCTs) **Modelling approach** Decision Analytic Cost-Minimisation analysis	**Cost per patient per alternative** Cost savings (based on all RCTs) Payer's perspective: EUR 646 atosiban versus fenoterol Perspective: Hospital : EUR 261 atosiban versus ritodrine (18 hours) Perspective: Hospital : EUR 152 atosiban versus ritodrine (48 hours) **Effectiveness per patient per alternative** Efficacy of treatments found to be identical based on literature review.	**Limitations** Probabilistic sensitivity analysis **Other information** There was no detailed analysis of resource utilization and micro-costing

Bibliographic details	Interventions and comparisons	Data Sources	Time horizon & Method	Results	Reviewer comment
Country(ies) where the study was done Italy **Perspective & Cost Year** Perspective: National Health Service and hospital Cost year:2010 **Source of funding** Not stated		DRG rates per patient diagnosed. For the payer, only extended length of stay and occurrence of chest pain or dyspnoea had costs consequences resulting from DRG recoding. **Other data sources e.g. transition probabilities**		**Incremental cost-effectiveness** As no single efficacy value given for each treatment, there can be no incremental cost effectiveness. Based on cost-minimisation analysis, atosiban is least costly. **Other reporting of results** **Uncertainty**	
Full citation Pizzi,L.T., Seligman,N.S., Baxter,J.K., Jutkowitz,E., Berghella,V., Cost and cost effectiveness of vaginal progesterone gel in reducing preterm birth: an economic analysis of the PREGNANT trial, Pharmacoeconomics, 32, 467-478, 2014 **Ref Id** 323625 **Economic study type**	**Study dates** Not stated **Intervention** Vaginal Progesterone (VP) **Comparison(s)** Placebo	**Source of effectiveness data** Randomised multicenter controlled trial (RCT): PREGNANT. The trial was based in 44 sites in ten countries. **Source of cost data** Services costed include cervical length screening, VP gel, antenatal hospitalization, cerclage, maternal and neonatal costs. Assessment of	**Time horizon and discount rate** Time Horizon: NA Discount Rate: NA **Method of eliciting health valuations (if applicable)** NA **Modelling approach** A Decision Tree model was used to simulate the	**Cost per patient per alternative** Per mother VP USD 23,079 Placebo USD 36,436 **Effectiveness per patient per alternative** Incremental benefit for VP as 0.0426 preterm births averted **Incremental cost-effectiveness**	**Limitations** RCTs are are based on multiple countries so applying US costs models difficult. Costs include the cost of testing for a short cervix and cervical cerclage in some instances. Some of the cost data was based published evidence that studied twins. **Other information**

Bibliographic details	Interventions and comparisons	Data Sources	Time horizon & Method	Results	Reviewer comment
Cost effectiveness analysis **Country(ies) where the study was done** USA **Perspective & Cost Year** Perspective: US healthcare payer Cost Year: 2011 **Source of funding** Watson Pharmaceuticals (now Actavis)		costs based on published reimbursement sources and scientific literature. Published sources include Current Procedural Terminology, wholesale prices for progesterone, Medicare reimbursement rates, published literature Luke 1996, St John 2000, Institute of Medicine 2007. **Other data sources e.g. transition probabilities**	outcomes associated with each of the different treatments to predict costs and age of gestation.	VP dominates **Other reporting of results** **Uncertainty** Probabilistic sensitivity analysis	

H.11 Fetal monitoring

H.11.1 Monitoring options: cardiotocography and intermittent auscultation

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Luthy,D.A., Shy,K.K., van,Belle G., Larson,E.B., Hughes,J.P., Benedetti,T.J.,	**Sample size** Total: 376 randomised. The result analysed for infants < 1750 g (n	**Interventions** Intrapartum electronic fetal monitoring	**Details** Intrapartum electronic fetal monitoring (EFM) and fetal blood gas sampling were compared with periodic auscultation (PA) (also known as intermittent auscultation, IA) of FHR in a multicentre randomized	**Results** EFM (electronic fetal monitoring) n = 122 Periodic auscultation (PA) (also known	**Limitations** Detection bias: unclear how outcomes are ascertained,

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Brown,Z.A., Effer,S., King,J.F., Stenchever,M.A., A randomized trial of electronic fetal monitoring in preterm labor, Obstetrics and Gynecology, 69, 687-695, 1987 **Ref Id** 164089 **Country/ies where the study was carried out** USA **Study type** Randomised control trial **Aim of the study** To examine if electronic fetal heart rate (FHR) monitoring was associated with clinically important improvement in perinatal mortality and neurodevelopment at later age. **Study dates** November 1981 to February 1985 (Seattle) March 1982 to March 1983 (Tacoma) April 1983 to February 1985 (Vancouver)	= 246) Electronic FHR monitoring N = 122 Auscultation N = 124 **Characteristics** Included all women enrolled (not restricted to infants < 1750g): Maternal age, mean (SD) EFM: 25.7 (5.7) Periodic auscultation (PA) (also known as intermittent auscultation, IA): 25.6 (5.2) Married EFM: 71% PA: 69% No antenatal care EFM: 0% PA: 2% Birth weight (g), mean (SD) EFM: 1633 (696) PA: 1589 (623) **Inclusion criteria** • Singleton pregnancy • Cephalic presentation • 26 - 32 weeks	(EFM) versus periodic auscultation (PA) (also known as intermittent auscultation, IA)	trial of preterm singleton pregnancies with fetal weights of 700-1750g. The study was carried out in three centres (Seattle, Tacoma and Vancouver). All three hospitals were referral centres providing tertiary care for their catchment area. From 499 women who fulfilled the inclusion criteria, 123 not enrolled for the following reasons: women were missed by personnel (n = 53), women refused (n = 51), fetal abnormalities were detected upon admission (n = 11), physician refused (n = 6) and unknown (n = 2). Randomisation was done in each centre with two sets of numbered, sealed envelopes. Different coloured envelopes were used for babies of 30 weeks gestation or more and those of less than 30 weeks gestation. External monitoring was performed by continuous Doppler ultrasound and tocodynamometer when membranes were intact. Aminotomy was not performed until cervical dilation was 7cm unless clinically indicated or poor CTG recording or FHR abnormality was seen. At the onset of the non-reassuring or ominous FHR patterns, left lateral decubitus positioning, oxygen, and intravenous infusion were started. For non-reassuring or ominous patterns, fetal scalp sampling was performed when it was feasible (cervix dilated > 4cm). A simultaneous venous sample was obtained from antecubital vein in the mother. A fetal scalp pH > 7.25 considered reassuring, 7.20 to 7.25 as pre-acidotic < 7.20 was considered	as intermittent auscultation, IA) n = 124 **Total perinatal/infant death** EFM: 17/122 (13.9%) PA: 18/224 (14.5%) All deaths occurred in infants with birth weight < 1500g. The reason for death in 28/35 was due to cardiopulmonary failure associated with hyaline membrane disease. Of the seven remaining deaths, three were due to congenital abnormalities (two in EFM group and one in the PA group), two were due to pneumonia which developed after discharge home at one week and one month (both were in the PA group), one occured two days after birth (in EFM group) in a baby born at 26 weeks gestation following premature rupture of membranes and one still birth occurred (in PA group) in baby born at 30 weeks gestation following premature rupture of membranes four days before labour. **Perinatal/infant death unaffected by fetal monitoring** EFM: 14/122 (11.8%) PA: 14/224 (11.5%) **Number of women exposed to tocolytic agents** EFM: n = 65 PA: n = 77 **Premature rupture of membranes**	diagnosed or verified

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Source of funding Supported in part by grants from National Centre for Health Services Research and Health Care Technology and the National Centre for Health service Research and Health Care Technology	• Estimated fetal weight of 700 - 1750g **Exclusion criteria** • Noncephalic presentation • Inability to give informed consent • Delivery too rapid • Too young for institutional review board • Non-English speaking • Planned caesarean section before labour • Placenta previa • Known congenital abnormalities		acidotic if this value was 0.15 pH units less than that of the mother. A DeLee fetoscope or amplified doppler was performed for at least 30 sec every 15 min in the first stage of labour and every 5 min in second stage of labour. The protocol indicated that the study would be terminated if either electronic FHR monitoring or PA was seen to been associated with a significant improvement in survival rate. Women were cared for on one to one basis by a trained study nurse. Tocolytics were used based on the existing institutional policies and only given to those with intact membranes. **Statistical analysis** Intention to treat analysis was performed. Logistic regression was used for analysis of the major endpoint (mortality and caesarean section).	EFM: n = 68 PA: n = 58 p = 0.16 **Caesarean rate** EFM: n = 19/122 (16%) PA: n = 18/124 (15%) p = 0.25 **Umbilical cord arterial pH < 7.20** EFM: 6/122 PA: 9/124 **Umbilical cord arterial pH ≥ 7.20** EFM: 74/122 PA: 72/124 **Umbilical cord arterial not preformed** EFM: 20/122 PA: 19/124 **Umbilical cord venous pH < 7.20** EFM: 2/122 PA: 2/124 **Umbilical cord venous pH ≥ 7.20** EFM: 78/122 PA: 74/124 **Umbilical cord venous not preformed** EFM: 20/122 PA: 24/124 **Intracranial haemorrhage** Intracranial haemorrhage (501-700g) EFM: (grade I/II) n = 2/122 EFM: (grade III/V) n = 3/124 PA: (grade I/II) n = 1/122 PA: (grade III/V) n = 0/124 Intracranial haemorrhage (701-900g) EFM: (grade I/II) n = 3/122 EFM: (grade III/V) n = 4/124 PA: (grade I/II) n = 3/122 PA: (grade III/V) n = 4/124 Intracranial haemorrhage (900-1100g)	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				EFM: (grade I/II) n = 2/122 EFM: (grade III/V) n = 9/124 PA: (grade I/II) n = 7/122 PA: (grade III/V) n = 6/124 Subtotal Intracranial haemorrhage (501-1100g) EFM: (grade I/II) n = 7/122 EFM: (grade III/V) n = 16/124 PA: (grade I/II) n = 11/122 PA: (grade III/V) n = 10/124 Intracranial haemorrhage (1101-1300g) EFM: (grade I/II) n = 6/122 EFM: (grade III/V) n = 2/124 PA: (grade I/II) n = 7/122 PA: (grade III/V) n = 3/124 Intracranial haemorrhage (1301-1500g) EFM: (grade I/II) n = 3/122 EFM: (grade III/V) n = 2/124 PA: (grade I/II) n = 5/122 PA: (grade III/V) n = 3/124 Intracranial haemorrhage (1501-1750g) EFM: (grade I/II) n = 3/122 EFM: (grade III/V) n = 0/124 PA: (grade I/II) n = 4/122 PA: (grade III/V) n = 0/124 Subtotal Intracranial haemorrhage (1101-1750g) EFM: (grade I/II) n = 12/122 EFM: (grade III/V) n = 4/124 PA: (grade I/II) n = 16/122 PA: (grade III/V) n = 6/124 Total Intracranial haemorrhage (501-1750g) EFM: (grade I/II) n = 19/122 EFM: (grade III/V) n = 20/124 PA: (grade I/II) n = 27/122 PA: (grade III/V) n = 16/124 **Severe respiratory syndrome** Severe respiratory syndrome (501-	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				700g) EFM: n = 4/122 PA: n = 2/124 Severe respiratory syndrome (701-900g) EFM: n =9/122 PA: n = 10/124 Severe respiratory syndrome (900-1100g) EFM: n = 8/122 PA: n = 6/124 Subtotal Severe respiratory syndrome (501-1100g) EFM: n = 21/122 PA: n = 18/124 Severe respiratory syndrome (1101-1300g) EFM: n = 3/122 PA: n = 7/124 Severe respiratory syndrome (1301-1500g) EFM: n = 7/122 PA: n = 8/124 Severe respiratory syndrome (1501-1750g) EFM: n = 2/122 PA: n = 2/124 Subtotal Severe respiratory syndrome (1101-1750g) EFM: n = 12/122 PA: n = 17/124 Total Severe respiratory syndrome (501-1750g) EFM: n = 33/122 PA: n = 35/124 **Seizure** Seizure (501 - 700 g) EFM: n = 2/122 PA: n = 0/124	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				Seizure (701 - 900 g) EFM: n = 1/122 PA: n = 3/124 Seizure (900 - 1100 g) EFM: n = 3/122 PA: n = 3/124 Subtotal seizure (501 - 1100 g) EFM: n = 6/122 PA: n = 6/124 Seizure (1101 - 1300 g) EFM: n = 1/122 PA: n = 0/124 Seizure (1301 - 1500 g) EFM: n = 0/122 PA: n = 1/124 Seizure (1501 - 1750 g) EFM: n = 0/122 PA: n = 0/124 Subtotal seizure (1101 - 1750 g) EFM: n = 1/122 PA: n = 1/124 Total seizure (501 - 1750 g) EFM: n = 7/122 PA: n = 7/124 Spontanous vaginal birth EFM: 88/122 (72%) PA: 97/124 (78%) p = 0.27 **Primary indication for caesarean section** Failure to progress EFM: 3.3% PA: 2.4% Neonatal distress EFM: 8.2% PA: 5.6% Hemorraghe EFM: 0% PA: 2.4%	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				Non-cephalic presentation EFM: 4.1% PA: 4.8% failure to progress EFM: 3.3 PA: 2.4	
Full citation Shy,K.K., Olshan,A.F., Hickok,D.E., Luthy,D.A., Electronic fetal monitoring during premature labor and the occurrence of perinatal mortality in very low birthweight infants, Birth, 15, 14-18, 1988 **Ref Id** 305386 **Country/ies where the study was carried out** USA **Study type** Retrospective cohort **Aim of the study** To examine the relationship between intrapartum electronic fetal monitoring (EFM) and perinatal mortality in premature pregnancies **Study dates** 1977 to 1979	**Sample size** Total n = 304 EFM n = 213 Auscultation n = 91 **Characteristics** Not reported **Inclusion criteria** • Pregnancy resulted in infant with low birth weight (700-1500g) **Exclusion criteria** • No intrapartum fetal monitoring • Neonatal malformation incompatible with life • Multiple gestations	**Interventions** Intrapartum electronic fetal monitoring (EFM) versus periodic auscultation (PA) (also known as intermittent auscultation, IA).	**Details** In a multihospital study in King County, Washington, the effect of EFM compared with periodic auscultation (PA) (also known as intermittent auscultation, IA) in singleton infants with birth weights of 700-1500g. Obstetrics records were reviewed for all 304 such pregnancies delivered during 1977-1979 at the 14 area hospitals that provide obstetric care. The fetal heart monitoring technique used in each labour was determined by reviewing the labour and delivery record of women. Most pregnancies managed with EFM had auscultation at least for a short period before the electronic monitoring commenced. The technique of EFM was performed and classified by either external or internal. EFM patterns were interpreted based on the Kubli et al. classification. No standard protocol for periodic fetal auscultation was used in the 14 participating hospitals. Perinatal mortality (stillbirth and neonatal death) was determined from the mother's and infant's notes. All neonatal deaths in the study occurred in hospital between birth and 28 days. No attempt was made to verify that a neonatal death had not happened in the home. Statistical analysis	**Results** **Perinatal mortality** EFM: 31% Periodic auscultation (also known as intermittent auscultation, IA): 54% Adjusted* RR 0.91 (95%CI 0.65 to1.3) Crude RR 0.58 (95% CI 0.42 to 0.78) *Adjusted for birth weight, community hospital birth, premature rupture of membranes and non-cephalic presentation **Risk of perinatal mortality adjusted by birth weight, rupture of membranes, non-cephalic presentation and place of birth** Birth weight 700-1090g EFM: 68% Periodic auscultation: 72% Adjusted* RR 0.94 (95%CI 0.63 to 1.4) Birth weight 1100-1500g EFM: 22% Periodic auscultation: 27% Adjusted* RR 0.82 (95%CI 0.39 to 1.7) No premature rupture of membranes EFM: 50% Periodic auscultation: 57% Adjusted* RR 0.88 (95%CI 0.59 to 1.3) Premature rupture of membranes EFM: 43% Periodic auscultation: 44% Adjusted* RR 0.88 (95%CI 0.50 to 1.9)	**Limitations** No standard protocol for periodic fetal auscultation used in the 14 participating hospitals. Womens' characteristics not reported.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Source of funding Not specified			Mantel-Haenszel procedure was used to adjust the relative risk for the confounding effect of socioeconomic and pregnancy complication factors. Logistic regression used to evaluate the joint effects of confounding factors on the relationship between electronic fetal monitoring and perinatal mortality. The variable included in the full logistic regression model were birth weight, place of birth, rupture of membranes, full course of betamethasone, infant sex, and gestational age.	Non-cephalic presentation EFM: 44% Periodic auscultation: 67% Adjusted* RR 0.66 (95%CI 0.37 to 1.2) Cephalic presentation EFM: 51% Periodic auscultation: 46% Adjusted* RR 1.10 (95%CI 0.70 to 1.7) Birth in community hospital EFM: 60% Periodic auscultation: 63% Adjusted* RR 0.95 (95%CI 0.60 to 1.5) Birth in teritary centre EFM: 37% Periodic auscultation: 43% Adjusted* RR 0.86 (95%CI 0.48 to 1.5) All pregnancies EFM: 49% Periodic auscultation: 54% Adjusted* RR 0.91 (95%CI 0.65 to 1.3)	

Fetal scalp electrodeThere was no evidence that met the protocol.

H.112 CTG interpretation

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Althaus,J.E., Petersen,S.M., Fox,H.E., Holcroft,C.J., Graham,E.M., Can electronic fetal monitoring identify preterm neonates with cerebral white matter injury?, Obstetrics and	**Sample size** Total n = 246 Vaginal birth n = 136 (cases n = 64, control n = 72) Caesarean Birth n = 110 (cases n = 61, control n = 49) **Characteristics** **Characteristics of women**	**Interventions** Intraparum fetal heart rate monitor	**Details** All births between 23 and 34 weeks gestation at a single university hospital during the study period were identified. N = 150 babies with cerebral white matter injury characterized by ventricular dilatation due to white matter atrophy or periventricular leukomalacia were included. Control group consisted of n =	**Results** Agreement among 3 reviewers: Kappa correlation: 0.52 fair/moderate **Analysis of electronic FHR trace**	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Gynecology, 105, 458-465, 2005 **Ref Id** 59631 **Country/ies where the study was carried out** USA **Study type** Case control **Aim of the study** To examine if electronic monitoring can identify preterm fetuses diagnosed with brain injury during the neonatal period. **Study dates** May 1994 to September 2001 **Source of funding** Not specified	**with vaginal birth** <u>Gestational age</u> Cases (n = 64): 27 ± 2.6 Control (n = 72): 27.2 ± 3.0 p = ns <u>Birth weight</u> Cases (n = 64): 970 ± 259 Control (n = 72): 1064 ± 451 p = ns <u>Multiple gestation</u> Cases (n = 64): n = 8 Control (n = 72): n = 7 p = ns <u>Preeclamsia</u> Cases (n = 64): n = 11 Control (n = 72): n = 2 p = 0.007 <u>Histologic chorioamnionitis</u> Cases (n = 64): n = 40 Control (n = 72): n = 49 p = ns <u>Clinical chorioamnionitis</u> Cases (n = 64): n = 15		150 babies with no cerebral white matter injury who were matched to the next baby born of the same gestational age +/- 7 days. Pregnancy dating was by best clinical estimate using last menstrual period confirmed by ultrasonography. <u>Electronic fetal heart rate (FHR) monitoring</u> Electronic FHR traces were obtained for 125 (83%) of the cases and 121 (81%) of the controls. The last hour of electronic fetal monitoring before birth for those delivered by cesarean was reviewed. For cases and controls delivering vaginally, the last hour of interpretable fetal heart rate trace before birth was reviewed. <u>Assessment</u> The traces were interpreted by 3 independent maternal–fetal medicine specialists blinded to neonatal outcome. The traces were evaluated based on the National Institute of Child Health and Human Development guidelines. Each reviewer recorded: - Baseline fetal heart rate - Time with fetal heart rate more than 160 beats per minute (bpm) (tachycardia) or less than 110 bpm (bradycardia), - Number of accelerations - Reactivity - Total number of decelerations, - Number of late, variable, or early decelerations. <u>FHR classification</u> Short-term variability was classified according to the National Institutes of	<u>Baseline (bpm) mean (SD)*</u> Cases 144 (11.3) Control 145.5 (15) <u>Number of baseline > 160 bpm*</u> Cases n = 25/125 Control n = 26/121 <u>Time baseline > 160 bpm (min)*</u> Cases 37.0 (23) Control 33.0 (22.7) <u>Number of baseline < 110 bpm*</u> Cases n = 6/125 Control n = 5/121 <u>Time baseline < 110 bpm (min)*</u> Cases 17.1 (21.3) Control 33.5 (2.1) <u>Baseline variability < 5 bpm*</u> Cases n = 24/125 Control n = 30/121 <u>Accelerations*</u> Cases 36.9 (23) Control 33.5 (22.7) <u>Reactive accelerations</u> * Cases 25/125 Control 25/121 <u>Decelerations*</u> Cases 4.1 (4.2) Control 4.5 (4.45)	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	Control (n = 72): n = 19 p = ns <u>Premature rupture of membranes</u> Cases (n = 64): n = 27 Control (n = 72): n = 41 p =0.09 **Characteristics of women with caesarean birth** <u>Gestational age</u> Cases (n = 61): 26.5 ± 6.2 Control (n = 49): 26.7 ± 6.3 p = ns <u>Birth weight</u> Cases (n = 61): 989 ± 327 Control (n = 49): 1070 ± 316 p = ns <u>Multiple gestation</u> Cases (n = 61): n = 19 Control (n = 49): n = 3 p = 0.001 <u>Preeclamsia</u> Cases (n = 61): n = 10 Control (n = 49): n = 18 p = 0.02 <u>Histologic chorioamnionitis</u> Cases (n = 61): n = 20 Control (n = 49): n = 17 p = ns		Health guidelines, with: - Grade 1 indicating undetectable variability - Grade 2 minimal variability with amplitude range less than or equal to 5 bpm - Grade 3 moderate variability with amplitude range from 6 to 25 bpm - Grade 4 marked variability with amplitude range more than 25 bpm Severe variable decelerations: A decrease < 70 bpm or lasting > 60 seconds The number of bradycardic episodes lasting > 2 minutes was recorded, as well as the nadir and length of the most severe bradycardic episode. <u>Tocolysis</u> About half of the women in the cases and control group received tocolytics therapy. <u>Definition of outcomes</u> The diagnosis of cerebral white matter injury was made by neonatal head ultrasonogram. All neonates born between 23 and 32 weeks had at least 3 head ultrasonograms: the first at 24–72 hours after birth, the second at 10–14 days of life, and the third at 6 weeks to specifically look for periventricular leukomalacia. Infants born between 32 and 34 weeks underwent head ultrasonography only if it was felt warranted by the attending neonatologist. Preeclampsia: defined as proteinuria, oedema, and the presence of new-onset hypertension. Intraventricular haemorrhage defined:	<u>Late decelerations*</u> Cases 0.55 (1.57) Control 0.56 (1.06) <u>Variable decelerations*</u> Cases 3.36 (3.84) Control 3.71 (3.73) <u>Early decelerations*</u> Cases 0.19 (0.61) Control 0.31 (0.91) <u>Bradycardia episodes*</u> Cases n = 6/125 Control n = 9/121 <u>Bradicardia nadir (bpm)*</u> Cases 87.3 (4.1) Control 83.3 (23.4) <u>Bradicardia length (min)*</u> Cases 5.88 (4.1) Control 5.02 (2.20) * calculated by NCC-WCH technical team **<u>Women with vaginal birth</u>** <u>Neonatal death</u> Cases (n = 64): n = 3 Control (n = 72): n = 15 p = 0.006 <u>Umbilical cord artery pH</u> Cases (n = 64): 7.29 ± 0.09 Control (n = 72): 7.29 ± 0.10 p = 1.0	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	Clinical chorioamnionitis Cases (n = 61): n = 9 Control (n = 49): n = 5 p = ns Premature rupture of membranes Cases (n = 61): n = 17 Control (n = 49): n = 17 p = ns **Inclusion criteria** • 23 and 34 weeks gestation • With cerebral white matter injury **Exclusion criteria** • Babies with chromosomal abnormalities and congenital anomalies		Grade 1: indicating hemorrhage limited to the germinal matrix Grade 2: intraventricular hemorrhage Grade 3: hemorrhage with ventricular dilatation Grade 4: ventricular dilatation with parenchymal extension of hemorrhage. Chorioamnionitis: presence of maternal fever, with the presence of at least one other finding of fetal tachycardia, uterine tenderness, or purulent vaginal discharge. Histologic chorioamnionitis was diagnosed when any polymorphonuclear leukocytes were seen in either the chorion or amnion, or in significant amounts in the subchorionic space. Analysis Continuous data were analysed using the t test, and categorical data with $\chi 2$ or Fisher exact test using Stata 7.0 (Stata Corporation, College Station, TX) and SPSS 12.0 (SPSS Inc, Chicago, IL) software. Linear regression with determination of a Pearson correlation coefficient was performed to examine the relationship between the numbers of late decelerations per hour and umbilical arterial pH and base excess. Kappa correlation for interobserver reliability was calculated to measure the agreement among the 3 reviewers. For this study, a kappa value less than 0.2 indicated poor agreement; 0.2–0.6, fair/moderate agreement; and more than 0.6, substantial agreement. To show a 100% increase to late decelerations per hour in the case group, with an alpha of	Umbilical cord artery baes excess (mmol/L) Cases (n = 64): -2.71 ± 4.20 Control (n = 72): -2.74 ± 3.27 p = ns Umbilical cord artery ph < 7.0 baes excess < -12.0 mmol/L Cases (n = 64): n = 1 Control (n = 72): n = 1 p = ns Intraventricular hemorrhage Cases (n = 64): n = 40 Control (n = 72): n = 18 p = 0.001 Neonatal seizures Cases (n = 64): n = 2 Control (n = 72): n = 3 p = ns **Women with caesarean section** Neonatal death Cases (n = 64): n = 3 Control (n = 72): n = 3 p = ns Umbilical cord artery pH	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			0.05, a sample size of 23 babies in each group would have a 90% power to detect this difference.	Cases (n = 64): 7.22 ± 0.19 Control (n = 72): 7.23 ± 0.11 p = ns <u>Umbilical cord artery baes excess (mmol/L)</u> Cases (n = 64): -4.20 ± 4.01 Control (n = 72): -4.15 ± 4.80 p = ns <u>Umbilical cord artery ph < 7.0 baes excess < -12.0 mmol/L</u> Cases (n = 64): n = 2 Control (n = 72): n = 2 p = ns <u>Intraventricular hemorrhage</u> Cases (n = 64): n = 28 Control (n = 72): n = 8 p = 0.001 <u>Neonatal seizures</u> Cases (n = 64): n = 1 Control (n = 72): n = 1 p = ns	
Full citation Bowes,W.A.,Jr., Gabre,S.G., Bowes,C., Fetal heart rate monitoring in premature infants weighing 1,500 grams or less, American Journal of Obstetrics and Gynecology, 137, 791-796, 1980 **Ref Id** 299950	**Sample size** n = 61 **Characteristics** <u>Gestational age</u> 25 – 35 (mean 27 ± 2.6) <u>Birth weight</u> 660 – 1500g 1,039 ± 249.7 <u>Caesarean section</u> n = 23/61 (38%) Control (n = 72):	**Interventions** Electronic fetal heart rate monitor	**Details** Medical and fetal monitoring records of all births weighted 1500 grams or less was reviewed. N = 61 babies who had at least 30 minutes of fetal heart rate trace before birth, were included in the study. <u>FHR monitoring</u> Electronic fetal heart rate traces from last 30 minutes before birth evaluated <u>Assessment</u> The tracess were interpreted by one of the study's author without knowledge of	**Results** **<u>Severe variable late decelerations (ominous periodic changes)</u>** <u>Umbilical cord pH < 7.20</u> sensitivity 60.0% (CI 26.3 to 87.7) Specificity 100% (CI 86.6 to 100) Positive likelihood ratio 0.0 Negative likelihood ratio 0.40(CI 0.19 to 0.85)	**Limitations** High risk of selection bias. No clear inclusion and exclusion criteria. Unclear how data was analysed. unclear fetal heart rate definition.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Country/ies where the study was carried out USA **Study type** Case series **Aim of the study** To examine the association between abnormal fetal heart pattern and poor neonatal outcomes **Study dates** January 1975 to December 1978 **Source of funding** Not specified	**Inclusion criteria** • Birth weight < 150g • Available at least 30 minutes of interpretable FHR trace before birth **Exclusion criteria** Not specified		neonatal outcomes. The traces and baseline fetal heart variability evaluated as described by Paul et al., 1975 and Kubli et al., 1969. <u>FHR classification</u> Fetal heart rate accelerations, early decelerations and mild and moderate variable decelerations were regarded as 'benign periodic changes' whereas severe variable and late decelerations were classified as 'ominous periodic changes' <u>Tocolysis</u> The use of tocolytics not reported. <u>Definition of outcomes</u> Central nervous system (CNS) haemorrhage was diagnosed in babies who exhibited: • seizures • fullness of anterior fontanelle, • decrease in the haematocrit • blood in the cerebral spinal fluid • Respiratory distress syndrome (RDS) was diagnosed if the all following were present: • arterial Po2 was < 50mm Hg in room air, • increased ambient oxygen • continuous positive airway pressure or ventilation required > 24 hours to support respiration	<u>Central nervous system haemorrhage</u> Sensitivity 16.7% (CI 2.76 to 63.9) Specificity 12.7% (CI 5.30 to 24.5) Positive likelihood ratio 0.19 (CI 0.03 to 1.15) Negative likelihood ratio 6.55 (CI 3.00 to 14.27) <u>Respiratory distress syndrome</u> Sensitivity 12.0% (CI 2.69 to 31.2) Specificity 86.1% (CI 70.4 to 100) Positive likelihood ratio 0.86 (0.23 to 3.29) Negative likelihood ratio 1.02 (CI 0.84 to 1.24) <u>Neonatal death</u> Sensitivity 0.0 Specificity 84.3% (CI 71.4 to 93) Positive likelihood ratio 0.0 Negative likelihood ratio 1.19 (CI 1.05 to 1.34) **<u>Baseline variability < 5bpm</u>** <u>Umbilical cord pH < 7.20</u> Sensitivity 50.0% (CI 18.9 to 81.1) Specificity 92.3% (CI 74.9 to 98.3) Positive likelihood ratio 6.50 (CI 1.50 to 28.23) Negative likelihood ratio 0.54 (CI 0.29 to 1.02)	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			• chest x-ray evidence, no evidence of other disease caused RDS Analysis not specified	Central nervous system haemorrhage Sensitivity 10.0% (CI 1.66 to 44.5) Specificity 82.3% (CI 69.1 to 91.5) Positive likelihood ratio 6.57 (CI 0.08 to 3.99) Negative likelihood ratio 1.09 (CI 0.86 to 1.39) Respiratory distress syndrome Sensitivity 12.0% (CI 2.69 to 31.25) Specificity 85.3% (CI 86.9 to 94.9) Positive likelihood ratio 0.82 (CI 0.21 to 3.10) Negative likelihood ratio 1.03 (CI 0.84 to 1.26) Neonatal death Sensitivity 0.0 Specificity 81.8% (CI 69.1 to 90.9) Positive likelihood ratio 0.0 Negative likelihood ratio 1.22 (CI 1.08 to 1.38)	
Full citation Braithwaite,N.D.J., Milligan,J.E., Shennan,A.T., Fetal heart rate monitoring and neonatal mortality in the very preterm infant, American Journal of Obstetrics and Gynecology, 154, 250-254, 1986	**Sample size** n = 383 **Characteristics** • 26 to 30 weeks' gestational age **Inclusion criteria** • 26 to 30 weeks	**Interventions** Intraparum fetal heart rate monitor	**Details** All babies born <23 weeks gestation in the perinatal unit of a single university hospital during the study period were identified. In that population n = 39 babies died. Fetal heart rate patterns of n = 26 infants who died were matched for gestational age with those of infants who did not die or demonstrate	**Results** Abnormal trace in dead infants group n = 23/26 Normal trace in dead infants group n = 3*/26	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Ref Id 270540 **Country/ies where the study was carried out** Canada **Study type** Retrospective cohort **Aim of the study** To determine the usefulness of intrapartum fetal heart rate monitoring and its effect on neonatal outcome. **Study dates** January 1979 to December 1982 **Source of funding** Not specified	gestation **Exclusion criteria** • Congenital anomalies • <26 or >30 weeks gestation		developmental abnormalities after a 1-year follow-up were analyzed. <u>FHR monitoring</u> Electronic fetal heart rate traces were obtained by a combination of direct and indirect electronic signals. The FHR patterns were analysed during the last 30 minutes of first stage of labour for vaginal birth or the last 30 minutes of tracing before the caesarean section for those who had caesarean section. <u>Assessment</u> The tracings were interpreted by 2 independent observer blinded to each other and to neonatal outcome. The traces evaluated based on the Fischer et al (1976) and Hammacher (1974) to define whether a trace was normal or abnormal. The abnormal traces were further subdivided to base line >160 bpm, absent accelerations, decreased variability, or decelerative activity. <u>FHR classification</u> Benign variable deceleration was classified according to the Krebs et al (1979) classification. Variability was defined according to criteria of Fischer et al (1976) and Hammacher (1974) <u>Tocolysis</u> Use of tocolysis not specified. <u>Definition of outcomes</u> No outcomes definition reported. <u>Analysis</u>	<u>Abnormal trace in control infants group</u> n = 16/31 <u>Normal trace in control infants group</u> n = 15/31 <u>Abnormal vs normal trace</u> Sensitivity 86.5% (69.8 to 77.7)** Specificity 48.39 % (30.17 to 66.9)** Positive likelihood ratio 1.71 (1.19 to 2.48)** Negative likelihood ratio 0.24 (0.08 to 0.73)** *Reason for death two babies delivered by caesarean at 27 weeks because of placenta abruption. One died because of pulmonary hypoplasia, the second baby died of bilateral pneumothorax. The thrid baby died after caesarean birth for placenta previa complicated by premature rupture ofmembranes and choriamnionitis. **Calculated by NCC-WCH technical team.	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			Continuous data were analysed using the t test, and categorical data with $\chi 2$ analysis. In order to compare quantitative analysis with the widely used qualitative analysis, a second observer evaluated each tracing. Agreement between the observers was noted in 90% of cases		
Full citation Martin,Jr, Siassi,B., Hon,E.H., Fetal heart rate patterns and neonatal death in low birthweight infants, Obstetrics and Gynecology, 44, 503-510, 1974 **Ref Id** 196711 **Country/ies where the study was carried out** USA **Study type** Retrospective cohort **Aim of the study** To examine associations between fetal heart rate (FHR) patterns and perinatal outcome. **Study dates** 1978 and 1979 **Source of funding** Not specified	**Sample size** n = 73 **Characteristics** Not specified **Inclusion criteria** • infants weighing 500-1250g **Exclusion criteria** Not specified	**Interventions** Intraparum fetal heart rate monitor	**Details** The fetal heart rate (FHR) recording of 73 babies with the birth weight of < 2000 g, born during study period were studied retrospectively. FHR monitoring The traces were reviewed and classified according to Kubli et al. (1969) were employed and categorised based on the severity; early deceleration (head compression), mild and moderate variable deceleration (cord compression), mild and moderate deceleration (uteroplacental insufficiency), severe variable deceleration, and severe late deceleration. Assessment The maternal and neonatal charts were reviewed independantly FHR classification The recordings were also classified according to the baseline FHR: < 120, 120 - 160, 161 – 180 and > 180bpm. The magnitudes of the fluctuations were: 0-5, 6 – 25 and > 25 bpm. - Grade 1 indicating undetectable variability	**Results** **Neonatal outcomes for babies born < 35 weeks gestation** Respiratory distress syndrome (RDS) n = 17/73 Neonatal death due to RDS n = 11/73 Neonatal death due to other reason* n = 5/73 Tachycardia > 180 bpm n = 4/73 (3/4 died of RDS) FHR pattern in neonatal died due to RDS Severe late variable dedeleration n = 10/11 Mild/moderate variable decelerations n = 1/11 p < 0.05 * congenital abnormalities n	**Limitations** Unclear how and by whom the data was assessed

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			Tocolysis Tocolytics therapy not reported Definition of outcomes Neonatal respiratory distress syndrome (RDS) was determined base on recorded physical findings and clinical course, together with supporting data from x-ray and clinical laboratory. Analysis Not specified	=2, necrotizing enterocolitis, purulent meningitis, hydrops fetalis	
Full citation Kariniemi,V., Jarvenpaa,A.L., Teramo,K., Fetal heart rate patterns and perinatal outcome of very-low-birthweight infants, British Journal of Obstetrics and Gynaecology, 91, 18-22, 1984 **Ref Id** 196720 **Country/ies where the study was carried out** Finland **Study type** Case control **Aim of the study** To examine associations between fetal heart rate	**Sample size** n = 125 **Characteristics** Gestational age Monitored (n = 79): 29 ± 2 Not monitored (n = 46): 28 ± 3 Birth weight Monitored (n = 79): 1013 ± 177 Not monitored (n = 46): 821 ± 210 Intrapartum complications premature rupture of membranes (PROM): n = 32 Premature contractions without PROM: n = 28 Preeclampsia: n = 16 Twins: n = 21 Cervical insufficiency with cerclage: n = 10 Placental abruption: n = 8	**Interventions** Intrapartum fetal heart rate monitor	**Details** Data collected from a university hospital in Helsinki. the obstetrics' records of women and fetal heart rate (FHR) trace of babies weighted 500g to 1250g were reviewed and included in the study. the study population compromised a group of 79 babies for whom FHR trace were available compared with a group of n = 46 babies without FHR tracing. FHR Monitoring CTG Monitoring were mainly carried out by ultrasound (HP cardiotocograph) and in only few instance by direct or abdominal cardiotocography Assessment A total of 782 hours of recording was interpreted visually by on of the study's author from ante and intrapartum CTG without knowledge of the outcomes Tocolysis Tocolytics agent were often used	**Results** **Mode of birth** Spontaneous vaginal birth Monitored (n = 79): n = 29 Not monitored (n = 46): n = 38 Operative vaginal birth Monitored (n = 79): n = 3 Not monitored (n = 46): n = 3 Caesarean section Monitored (n = 79): n = 47 (59%) Not monitored (n = 46): n = 5 (11%) **Mortality**	**Other information** - n = 21 twins included - No clear inclusion/exclusion criteria - All CTG traces were included as most babies were delivered by caesarean before labour began - no clear definition of FHR patterns

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
(FHR) patterns and perinatal outcome **Study dates** 1978 - 1979 **Source of funding** Not specified however they acknowledged that one of the study's author was supported by the Foundation for Pediatric Research	Placenta praevia: n = 5 Major anomalies: n =8 Unexplained intrauterine death: n =6 Intrauterine death with umbilical complication: n = 1 **Inclusion criteria** • Birth-weight 50g to 1250g **Exclusion criteria** Not specified		therefore it was difficult to differentiate labour contraction and premature uterine activities FHR classification Reactive FHR: ≥ 2 accelerations > 1 bpm in 30minutes of recording Non-reactive FHR: < 2 accelerations > 15bpm in 30minutes of recording Deceleration: a deceleration were recorded when late or variable deceleration was observed. Pure late deceleration was rare Silent pattern: Total RHR variability was < 5bpm for > 5 minutes Combined distress patterns: When a deceleration and a silent pattern were observed together in the same 30 minutes recording Definition of outcomes Respiratory distress syndrome (RDS) was defined in the presence of tachypnoea, retraction and granting, hypoxaemia in room air and air bronchogram and reticulogranular pattern in X-ray when symptoms appears 6 hours after birth and lasted 24 hours Analysis Significance of relative risks was assessed by the X^2 test with Yates' correction	Total death Monitored (n = 79): n = 33 (42%) Not monitored (n = 46): n = 39 (85%) Still-born Monitored (n = 79): n = 5 Not monitored (n = 46): n = 22 Neonatal death Monitored (n = 79): n = 26 Not monitored (n = 46): n = 17 Postnatal death Monitored (n = 79): n = 2 Not monitored (n = 46): n = 0 **Main causes of death** Intracranial haemorrhage and respiratory distress Monitored (n = 31): n = 9 Not monitored (n = 39): n = 3 Intracranial haemorrhage Monitored (n = 31): n = 2 Not monitored (n = 39): n = 0 Respiratory distress	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				Monitored (n = 31): n = 4 Not monitored (n = 39): n = 1 <u>Immaturity</u> Monitored (n = 31): n = 5 Not monitored (n = 39): n = 9 <u>Infection</u> Monitored (n = 31): n = 2 Not monitored (n = 39): n = 3 <u>Anomalies</u> Monitored (n = 31): n = 4 Not monitored (n = 39): n = 5 <u>Rhesus isoimmunization</u> Monitored (n = 31): n = 1 Not monitored (n = 39): n = 0 <u>Fetofetal transfusion</u> Monitored (n = 31): n = 1 Not monitored (n = 39): n = 1 <u>Placental complication</u> Monitored (n = 31): n = 1 Not monitored (n = 39): n = 6	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				Not defined Monitored (n = 31): n = 2 Not monitored (n = 39): n = 11 **Neonatal death in presence of abnormal RHR patterns** Decelerations* Sensitivity 53.8% (33.4 to 73.4) Specificity 16.67% (7.50 to 30.2) Positive likelihood ratio 0.65 (0.44 to 0.94) Negative likelihood ratio 0.77 (1.30 to 5.60) Silent pattern* Sensitivity 42.3% (23.4 to 63.0) Specificity 29.2% (16.9 to 44.0) Positive likelihood ratio 0.60 (0.37 to 0.97) Negative likelihood ratio 0.77 (1.14 to 3.43) Combined distress pattern* Sensitivity 19.20% (6.63 to 39.4) Specificity 35.4% (22.2 to 50.4) Positive likelihood ratio 0.30 (0.13 to 0.67) Negative likelihood ratio 2.28 (1.49 to 3.49)	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				Non-reactive pattern* Sensitivity 50.0% (29.9 to 70.0) Specificity 14.6% (6.10 to 27.7) Positive likelihood ratio 0.59 (0.39 to 0.87) Negative likelihood ratio 0.77 (1.56 to 7.52) Abnormal pattern* Sensitivity 80.7% (60.6 to 93.3) Specificity 8.33% (2.37 to 20.2) Positive likelihood ratio 0.88 (0.72 to 1.08) Negative likelihood ratio 2.31 (0.68 to 7.86) **Respiratory distress syndrome in presence of abnormal RHR patterns** Decelerations* Sensitivity 59.3% (40.6 to 76.2) Specificity 18.9% (8.0 to 35.1) Positive likelihood ratio 0.73 (0.53 to 1.01) Negative likelihood ratio 2.15 (0.98 to 4.72) Silent pattern* Sensitivity 50.0% (31.9 to 68.1) Specificity 27.0% (13.8 to 44.1) Positive likelihood ratio 0.69 (0.46 to 1.02)	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				Negative likelihood ratio 1.85 (0.98 to 3.48) <u>Combined distress pattern*</u> Sensitivity 37.5% (21.1 to 56.3) Specificity 40.5% (24.7 to 57.9) Positive likelihood ratio 0.63 (0.37 to 1.06) Negative likelihood ratio 2.54 (0.96 to 2.48) <u>Non-reactive pattern*</u> Sensitivity 68.7% (49.9 to 83.8) Specificity 24.3% (11.8 to 41.2) Positive likelihood ratio 0.91 (0.68 to 1.22) Negative likelihood ratio 1.28 (0.60 to 2.76) <u>Abnormal pattern*</u> Sensitivity 81.2% (63.5 to 92.7) Specificity 8.11% (1.80 to 21.9) Positive likelihood ratio 0.88 (0.73 to 1.07) Negative likelihood ratio 2.31 (0.63 to 8.51) * Calculated by NCC-WCH technical team	
Full citation Nisenblat,V., Alon,E.,	**Sample size** n = 111	**Interventions** Intraparum	**Details** Babies born during the study period at	**Results**	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Barak,S., Gonen,R., Bader,D., Ohel,G., Fetal heart rate patterns and neurodevelopmental outcome in very low birth weight infants, Acta Obstetricia et Gynecologica Scandinavica, 85, 792-796, 2006 **Ref Id** 169851 **Country/ies where the study was carried out** Israel **Study type** Prospective cohort **Aim of the study** To evaluate the validity of fetal heart rate monitoring during the last hour prior to birth, as a predictor of long term neurodevelopmental outcome of very low birth weight infants. **Study dates** 1993 to 2000 **Source of funding** Not specified	**Characteristics** <u>Gestational age, weeks (mean ± SD)</u> Normal Function (n = 97): 30.2 ± 2.3 Mild/moderate impairment (n = 6): 29.3 ± 3.1 Severe impairment (n = 8): 29.1 ± 2.5 p = 0.36 <u>Birth weight</u> Normal Function (n = 97): 1,224.8 ± 223.9 Mild/moderate impairment (n = 6): 1,173.3 ± 323.9 Severe impairment (n = 8): 1,121.3 ± 181.4 p = 0.42 <u>Parity</u> Normal Function (n = 97): 1.2 ± 1.7 Mild/moderate impairment (n = 6): 1.8 ± 2.1 Severe impairment (n = 8): 1.1 ± 1.3 p = 0.65 <u>Caesarean section</u> Normal Function n = 70/97 (72.2%) Mild/moderate impairment n = 4/6 (66.7%) Severe impairment n = 5/8 (71.4%) p = 0.99	fetal heart rate monitor	the Bnai-Zion Hospital in Haifa who met the inclusion criteria were included in the study. Fetal heart rate traces were recorded electronically by Hewlett Packard or Corometrics monitors during the last hour prior to delivery. A perinatologist, blinded to the neonatal outcome, evaluated the tracings and divided them into three groups – reassuring, non-reassuring, and pathological. Neurodevelopmental status was evaluated at age 2 years. <u>FHR monitoring</u> Fetal heart rate tracings were obtained during the last hour prior to delivery <u>Assessment</u> The traces were reviewed by a single perinatologist who was blinded to the neonatal outcome but was aware whether the tracing were recorded in the active labour or not. The traces were classified as normal, pathological or non-reassuring. <u>FHR classification</u> Normal FHR trace was defined as: - Baseline fetal heart rate 110 -160bpm - Variability 6 – 25bpm - presence of the two accelerations in any 20 minute window (peak of 15bpm, from baseline and above, and duration of at least 15 seconds) Before 32 weeks gestation or in active labour, mild variable decelerations and absence of acceleration were considered a normal tracing Pathological tracing were defined as:	<u>Normal neurodevelopmental function at 2 years of age</u> n = 97/111 (87.4%) <u>Variable degrees of neurodevelopmental impairment</u> n = 14/111 (12.6%) <u>Abnormal neurodevelopmental outcome</u> Reassuring (normal) FHR (n = 35) 14.3% Pathological (n =20) (15.0%) p = 0.77 <u>Pathological fetal heart rate patterns as a predictor of neurodevelopmental outcome</u> Sensitivity 27% Specificity 74% Positive likelihood ratio 1.03* Negative likelihood ratio of 0.98* *Calculated by NCC-WCH technical team	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	Inclusion criteria • Singelton pregnancy • Birth weight ≤ 1500g • Continous fetal heart rate monitor one hour before birth • Follow up dat were available to the age of 2 years **Exclusion criteria** Not specified		- Baseline fetal heart rate >160bpm or < 110bpm - Absence of FHR variability (amplitude range undetectable) - Either recurrent late accelerations (deceleration is associated with the uterine contraction, with nadir of the deceleration occurring after peak of the contraction) or recurrent severe variable decelerations (decrease in FHR below 70 beats/minute lasting longer than 60 seconds or other decelerations with slow return to baseline, associated with the uterine contractions, the onset, depth, and duration vary with successive uterine contractions) Non-reassuring tracing was intermediate between normal and pathological, defined as: - Various combination of abnormal fetal heart rate baseline - Reduced FHR variability (detectable, but < 5bpm) - Absence of accelerations (at ≥ 32 weeks gestation and not in active labour,) and occasional variable or late decelerations <u>Tocolysis</u> Tocolytics therapy not reported <u>Definition of outcomes</u> For each baby a 'Health Status Questionnaire' was obtained at 2 years of age, at either a clinic follow-up visits or by telephone interview by parents. All children with any neurodevelopmental abnormality underwent formal assessment at the child developmental		

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			centre. Normal function included children with no functional disabilities or developmental delay. Cases with the very mild delay at age of 2 years (fine motor or mild expressive dysfunction or mild gait instability) were also classified as normal. Severe impairment included children with cerebral palsy, blindness or deafness. Mild moderate impairment included all cases that did not meet the criteria for either normal or severe impairment (squint, speech delay with hearing loss, growth retardation after bowel resection). Analysis Continuous data were analysed using the t test, and categorical data with $\chi 2$ or Fisher exact test. SPSS 11.5 (SPSS Inc, Chicago, IL) software was used for the statistical analysis.		
Full citation Aina-Mumuney,A.J., Althaus,J.E., Henderson,J.L., Blakemore,M.C., Johnson,E.A., Graham,E.M., Intrapartum electronic fetal monitoring and the identification of systemic fetal inflammation, Journal of Reproductive Medicine, 52, 762-768, 2007 **Ref Id** 117721	**Sample size** Preterm: n = 75 cases n = 75 controls **Characteristics** Birth weight Cases (n = 75): 1627 ± 553 Control (n = 75): 1609 ± 600 p = 0.71 Multiple gestation Cases (n = 75): n = 3 Control (n = 75): n = 22	**Interventions** Intrapartum fetal heart rate monitor	**Details** All births preterm and near term birth at a single university hospital during the study period were identified. Each case was required to have both histologically confirmed chorioamnionitis and funisitis. All birth at ≤ 34 weeks gestation had the pathological examination of placenta. The pathology data base was used to determine all the case with histologically confirmed chorioamnionitis during the study period. Each birth with histologically confirmed fetal inflammation (case) was matched with the subsequent birth within the 7 days of the same gestational age by the same mode of birth without the placental or	**Results** Kappa correlation for interobserver reliability (agreement between two trace reviewers): 0.49 fair/moderate agreement **Neonatal outcomes in preterm population** cases: n = 75 with systemic fetal inflammation control: n = 75 with no systemic fetal inflammation Neonatal death Cases (n = 75)	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Country/ies where the study was carried out USA **Study type** Case control study **Aim of the study** To determine if intrapartum electronic fetal heart rate monitoring (EFM) can identify the fetal in utero systemic inflammatory response or neonatal sepsis, risk factors for the development of brain injury **Study dates** June 1999 to July 2003 **Source of funding** Not specified	p = 0.01 <u>Preeclamsia</u> Cases (n = 75): n = 2 Control (n = 75): n = 23 p < 0.001 <u>Clinical chorioamnionitis</u> Cases (n = 75): n = 22 Control (n = 75): n = 4 p = 0.0001 <u>Premature rupture of membranes</u> Cases (n = 75): n = 22 Control (n = 75): n = 17 p =0.35 **Inclusion criteria** • All birth with histologically confirmed chorioamnionities and funisitis • preterm 23 - 36 weeks and term ≥37 (results were analysed separately) **Exclusion criteria** • Congenital malformations • Chromosomal		umbilical cord inflammation (control). Pregnancy dating was by best clinical estimate using last menstrual period confirmed by ultrasonography. <u>FHR monitoring</u> Electronic fetal heart rate tracings were stored electronically. The last 2 hours of electronic fetal monitoring before birth was reviewed. <u>Assessment</u> The tracings were interpreted by 3 maternal - fetal medicine specialists blinded to placental pathology result. <u>FHR classification</u> The traces evaluated based on the National Institute of Child Health and Human Development guidelines. <u>Tocolysis</u> The use of tocolysis not specified <u>Definition of outcomes</u> Chorioamnionitis: presence of maternal fever with the presence of at least one other finding of fetal tachycardia, uterine tenderness, or purulent vaginal discharge. Women diagnosed with chorioamnionitis were immediately started intravenous ampicillin and gentamycin if not allergic. <u>Analysis</u> Continuous data were analysed using the t test, and categorical data were compared using a McNemar's test, with p < 0.05 considered significant. The ability of FHR monitoring to predict sepsis were	n = 1 Control (n = 75): n = 2 p = 0.56 <u>Intraventricular haemorrhage</u> Cases (n = 75): n = 13 Control (n = 75): n = 14 p = 0.83 <u>Periventricular leukomalacia</u> Cases (n = 75): n = 3 Control (n = 75): n = 1 p = 0.31 <u>Sepsis</u> Cases (n = 75): n = 2 Control (n = 75): n = 7 p = 0.17 <u>Preterm birth</u> Cases (n = 75): n = 18 Control (n = 75): n = 18 n = 1.0 <u>Umbilical cord artery pH</u> Cases (n = 75): 7.30 ± 0.08 Control (n = 75): 7.25 ± 0.11 n = 0.01	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	abnormalities		assessed by constructing several unconditional linear regression models, which included gestational age and mode of birth. For each model receiver operative characteristic (ROC) curves were produced. Kappa correlation for interobserver reliability was calculated to measure the agreement among the 3 reviewers. For this study, a kappa value > 0.75 indicated excellent reproducibility; 0.4–0.75, fair/moderate agreement; and less than 0.4, poor agreement.	Umbilical cord artery pH Cases (n = 75): -2.6 ± 3.1 Control (n = 75): -3.7 ± 3.6 p = 0.13 **Estimated OR of systemic fetal inflammation, comapring electronic FHR parametere in term and pre-term** Preterm birth n = 150 Cases: n = 75 with systemic fetal inflammation Control: n = 75 with no systemic fetal inflammation Term birth n = 126 Cases: n = 63 with systemic fetal inflammation Control: n = 63 with no systemic fetal inflammation Baseline FHR (bpm) Term cases 153 ± 16 Pre-term cases 139 ± 13 p < 0.001 Tachycardia OR (CI) Pre-term birth 1.38 (0.30 to 6.42) OR (CI) Term cases 8.93 (2.43 to 32.84) p < 0.05 Decreased short term	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				variability OR (CI) Pre-term birth 0.71 (0.34 to 1.50) OR (CI) Term cases 2.12 (0.55 to 8.21) p = ns Reactivity OR (CI) Pre-term birth 0.96 (0.49 to 1.87) OR (CI) Term cases 0.41 (0.19 to 0.88) p < 0.05	
Full citation Douvas,S.G., Meeks,G.R., Graves,G., Intrapartum fetal heart rate monitoring as a predictor of fetal distress and immediate neonatal condition in low-birth weight (<1,800 grams) infants, American Journal of Obstetrics and Gynecology, 148, 300-302, 1984 **Ref Id** 299967 **Country/ies where the study was carried out** USA **Study type** Case series **Aim of the study**	**Sample size** n = 89 **Characteristics** Not specified **Inclusion criteria** Not specified **Exclusion criteria** Not specified	**Interventions** Intrapartum fetal heart rate monitor	**Details** From 1318 women delivered during the study period at a single university hospital n = 1,025 babies were monitored electronically during the intrapartum period. N = 89 low birth babies included in the study. All babies weighted < 1800 grams were admitted to neonatal intensive care unit irrespective of their condition. FHR monitoring Electronic fetal heart rate traces were obtained during the intrapartum period Assessment Three independent obstetricians blinded to neonatal outcome interpreted the traces FHR classification Fetal heart rate considered as abnormal in the following incidents: - late decelerations defined as persistent decelerations following 50% of	**Results** **Asphyxia, hyaline membrane disease and FHR among low birth-weight (≤ 1800g)** Abnormal fetal heart rate tracings n = 27 (30%) Normal fetal heart rate tracings n = 62 (72%) Birth asphyxia Abnormal fetal heart rate tracings n = 24/27 (89%) Normal fetal heart rate tracings n = 9/62 (14%) p < 0.001 Sensitivity 72.7% (54.4% to 86.7%) Specificity 94.6% (85.1% to 98.9%) Likelihood ratio positive 13.5 (4.43 to 41.6)* Likelihood ratio negative 0.29 (0.16 to 0.50)*	**Limitations** Inclusion/exclusion and women characteristics not reported hence high risk of selection bias

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
To examine predictive value of fetal heart rate monitoring for identifying those low-birth weight babies who are at high risk for asphyxia and hyaline membrane disease. **Study dates** January to April 1981 **Source of funding** Not specified			the contractions over a 30 minutes period - severe variable decelerations defined as decelerations < 70 bpm for > 60 seconds - absent or minimal beat to beat variability, defined as < 5 bpm over a 30 minute period - Prolonged bradycardia defined as FHR < 100 bpm persistently over a period of > 3 minutes <u>Tocolysis</u> About half of the women in the cases and control group received tocolytics therapy <u>Definition of outcomes</u> The measure of asphyxia was based on the one of the following: - Apgar score < 3 at 1 minute or < 6 at 5 minutes - immediate resuscitation requiring positive pressure oxygen for > 1 minute - pH < 7.25 on arrival in the neonatal intensive care unit The criterion for hyaline membrane disease was: - > 0.50 forced inspiratory oxygen needed for more that 24 hours - clinical and radiological features compatible with hyaline membrane disease. The diagnosis of transient tachypnea of the new born was made of a respiratory rate of > 60 breaths per minute which resolved without oxygen therapy <u>Analysis</u> The data was compared using	<u>Hyaline membrane disease</u> Abnormal fetal heart rate tracings n = 20/27 (74%) Normal fetal heart rate tracings n = 10 (16%) p < 0.001 Sensitivity 66.7% (47.2% to 82.7%)* Specificity 88.1% (77.0% to 95.0%)* Likelihood ratio positive 5.62 (2.68 to 11.78)* Likelihood ratio negative 0.38 (0.23 to 0.63)* * Calculated by NCC-WCH technical team	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			χ2 statistic for 2 x 2 tables		
Full citation Rayburn,W.F., Johnson,M.Z., Hoffman,K.L., Donn,S.M., Nelson,R.M.,Jr., Intrapartum fetal heart rate patterns and neonatal intraventricular hemorrhage, American Journal of Perinatology, 4, 98-101, 1987 **Ref Id** 195957 **Country/ies where the study was carried out** USA **Study type** Case control **Aim of the study** To examine the interpretations of intrapartum FHR patterns of low birth babies in predicting neonatal IVH. **Study dates** 1979 to 1984 **Source of funding** Not specified	**Sample size** n = 72 **Characteristics** <u>Gestational age at birth</u> IVH (n = 38): 28.5 ± 1.8 No IVH (n = 38): 29.2 ± 2.0 p = ns <u>Birth weight</u> IVH (n = 38): 1320 ± 78 No IVH (n = 38): 1392 ± 92 p = ns <u>Antepartum complication</u> IVH (n = 38): n = 7 No IVH (n = 38): n = 6 p = ns <u>Cephalic presentation</u> IVH (n = 38): n = 28 No IVH (n = 38): n = 31 p = ns <u>Vaginal birth</u> IVH (n = 38): n = 21 No IVH (n = 38):	**Interventions** Intrapartum fetal heart rate monitor	**Details** All births between 26 and 34 weeks gestation at two university hospitals during the study period were identified. All included babies were delivered after premature labour and weighed less than or equal to 2000g. Preterm birth defined as uterine contractions occurring at lease every 10 minutes and lasting at least 30 seconds. Labour was managed expectantly in cases with ruptured membranes. Cases with intraventricular haemorrhage (IVH) were identified and a matched group with no IVH was selected during the same period. Each infant in the control group was matched to each study infant if the there wasno evidence of IVH, had similar gestational age and birth weight, and had FHR monitor at the first stage of labour for the same duration. <u>FHR monitoring</u> Electronic fetal heart rate tracings were evaluated if the tracing was obtained for the minimum of the 20 minutes at the first stage of labour <u>Assessment</u> Two obstetricians independently blinded to neonatal outcome interpreted the tracings. If discrepancy found another independent interpretation was sought. The traces evaluated according to Strauss et al (1985) into three groups of reassuring, suspicious and ominous <u>FHR classification</u>	**Results** **<u>FHR patterns and preterm babies with IVH and with no IVH</u>** IVH n = 38 No IVH n = 38 Normal Pattern IVH n = 17/38 (45%) No IVH n = 18/38 (47%) n = ns Sensitivity 55.2 (38.3 to 71.3) Specificity 47.3 (31 to 61.1) Positive likelihood ratio 1.05 (0.69 to 1.59) Negative likelihood ratio 0.94 (0.58 to 1.54) Suspicious IVH n = 7/38 (18%) No IVH n = 8/38 (21%) p = ns Sensitivity 29.1 (12.6 to 51) Specificity 69.2 (48.2 to 85.6) Positive likelihood ratio 0.95 (0.41 to 2.22) Negative likelihood ratio 1.02 (0.71 to 1.47) Ominous IVH n = 14/38 (37%) No IVH n = 12/38 (32%) p = ns Sensitivity 45.1 (27.3 to 63.9)	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	n = 18 p = ns <u>Nulliparous</u> IVH (n = 38): n = 17 No IVH (n = 38): n = 20 p = ns **Inclusion criteria** • Singleton • Birth weight 600 - 2000g • 26- 34 gestational weeks • Documented labour for at least 20 minutes shortly before birth **Exclusion criteria** Not specified		- Reassuring trace defined as normal pattern with or without occasional mild or moderate variable decelerations - Suspicious: intermittent late deceleration, decreased variability, or tachycardia present - Ominous pattern: consistent with repetitive severe variable or late decelerations or repetitive prolonged decelerations (>2 minute) Suspicious or ominous pattern that were continuous and repetitive for > 30 minute were considered indicative of fetal distress <u>Tocolysis</u> Not specified <u>Definition of outcomes</u> The diagnosis IVH was made by neonatal ultrasound examinations within 24 hours and on the 7th day of life. Radiology staff without knowledge of any FHR abnormalities interpreted the ultrasound. Intraventricular haemorrhage defined: Grade 1: subpendymal only Grade 2: intraventricular with normal ventricular size Grade 3: haemorrhage with ventricular dilatation Grade 4: ventricular dilatation with parenchymal extension of haemorrhage <u>Analysis</u> Continuous were compared using	Specificity 60 (40.6 to 77.3) Positive likelihood ratio 1.13 (0.63 to 2.03) Negative likelihood ratio 0.91 (0.59 to 1.41)	
Full citation	**Sample size**	**Interventions**	**Details**	**Results**	**Limitations**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Matsuda,Y., Maeda,T., Kouno,S., The critical period of non-reassuring fetal heart rate patterns in preterm gestation, European Journal of Obstetrics, Gynecology, and Reproductive Biology, 106, 36-39, 2003 **Ref Id** 197099 **Country/ies where the study was carried out** Japan **Study type** Prospective cohort **Aim of the study** To investigate the correlations between non-reassuring FHR patterns and umbilical arterial pH **Study dates** 1992 to 1999 **Source of funding** Not specified	n = 772 **Characteristics** Not specified **Inclusion criteria** • Singleton birth • 26 - 36 weeks gestation **Exclusion criteria** Not specified	Intraparum fetal heart rate monitor	A review was conducted during the study period from medical records of all births between 23 and 36 weeks gestation at a single hospital. Pregnancy dating was by best clinical estimate using last menstrual period confirmed by ultrasonography. Caesarean birth was performed based on standard indication and the reason for birth was onset of active labour, non-reassuring fetal status, maternal indication, etc. FHR monitoring Eetal heart rate was monitored at least 2 hours before birth. Assessment Not reported FHR classification Fetal heart rate patterns were defined as non-reassuring if one of the following conditions were detected: persistent late decelerations, recurrent variable decelerations, prolong deceleration or loss of variability. These were defined according to ACOG Technical Bulletin 1995. Tocolysis Tocolytic therapy not reported. Definition of outcomes Umbilical cord was double clamped at birth and arterial cord blood taken for blood gas analysis. The low pH was defined as < 7.1. The relationship between the time from the appearance of non-reassuring FHR patterns and birth and pH at birth was also investigated	**Mean umbilical cord pH and reassuring FHR patterns** Reassuring FHR patterns (n = 591) Mean 7.29± 0.06 **Number of babies with umbilical cord PH < 7.1 (acidosis) and different FHR patterns** Reassuring FHR patterns n = 17/591 Late deceleration with loss of variabilit n = 7/29 Prolond decelerations n = 11/48 Severe variable decelerations n = 0/29 Late decelerations n = 0/29 **Mean Cord pH in non reassuring FHR** Late deceleration with loss of variability (n = 29) Mean 7.15 ± 0.11 Prolond decelerations (n = 48) Mean 7.17 ± 0.16 Severe variable decelerations (29) 7.29 ± 0.06 Late decelerations (75)	- Women characteristics and exclusion criteria not reported - Unclear how and by whom the data was assessed

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			following four periods: 15.30.60,and 90 minutes. Analysis Data were analysed using χ2 or Fisher exact test and Mann-Whitney test.	7.29 ± 0.06 Fetal acidosis Neonatal death group n = 5/13 Survival groups n = 30/759 P = 0.0001 **Prediction of fetal acidosis (pH < 7.1) in late and prolonged deceleration** **Late deceleration with loss of variability** **< 30 min** Sensitivity: 28.6% Specificity: 86.4% Likelihood ratio positive: 2.10 Likelihood ratio negative: 0.82 **< 60 min** Sensitivity: 85.7% Specificity: 68.2% Likelihood ratio positive: 2.69 Likelihood ratio negative: 0.20 **< 90 min** Sensitivity: 100% Specificity: 45.5% Likelihood ratio positive: 1.83 Likelihood ratio negative: 0.0 **Prolonged decelerations** **< 15 min** Sensitivity: 36.4% Specificity: 75.7% Likelihood ratio positive: 1.49 Likelihood ratio negative: 0.84	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				< 30 min Sensitivity: 81.8% Specificity: 56.8% Likelihood ratio positive: 1.9 Likelihood ratio negative: 0.32 **< 60 min** Sensitivity: 90.9% Specificity: 37.8% Likelihood ratio positive: 1.46 Likelihood ratio negative: 0.24 **< 90 min** Sensitivity: 100% Specificity: 16.2% Likelihood ratio positive: 1.19 Likelihood ratio negative: 0.0	
Full citation Holmes,P., Oppenheimer,L.W., Gravelle,A., Walker,M., Blayney,M., The effect of variable heart rate decelerations on intraventricular hemorrhage and other perinatal outcomes in preterm infants, Journal of Maternal-Fetal Medicine, 10, 264-268, 2001 **Ref Id** 169302 **Country/ies where the study was carried out** Canada	**Sample size** n = 82 **Characteristics** Gestational age Cases (n = 41): 30.6 ± 5.2 Control (n = 41): 27.4 ± 6.5 p =ns Birth weight Cases (n = 41): 1557 ± 465 Control (n = 41): 1548b± 448 p = ns Received tocolytic Cases (n = 41): n = 17	**Interventions** Intraparum fetal heart rate monitor	**Details** Data collected over a 20-month period from babies born at the Ottawa Hospital General Campus. Data related to labour and birth and FHR traces, were obtained from the hospital's computerised labour database. Feta heart rate traces were assessed for the presence of variable decelerations within 4 hours prior to birth. Three variable decelerations in one hour of tracing used as a threshold at which neonatal complication might anticipate. Cases had at least three variable decelerations in the hour prior to delivery and were matched 1:1 with controls for gestation, sex and birth weight. FHR monitoring Feta heart rate traces within 4 hours prior to birth were assessed	**Results** Median Variable decelerations 4 hours prior to birth Cases: 22 (range 5 - 71) **Acute morbidity outcome** Arterial cord pH <7.1 Cases n = 0/38 Control n = 2/41 p = ns Resuscitation (cardiac massage and drug therapy) Cases n = 1/41 Control n = 2/41 p = ns **Chronic morbid outcome**	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Study type Retrospective case-control **Aim of the study** To examine the hypothesis that repetitive variable heart rate decelerations in labor are associated with an increased incidence of neonatal complications in premature infants. **Study dates** 20 month period (date not specified) **Source of funding** Not specified	Control (n = 41): n = 17 p = ns <u>Caesarean section</u> Cases (n = 41): n = 6 Control (n = 41): n = 11 p = 0.007 <u>Nulliparous</u> Cases (n = 41): n = 22 Control (n = 41): n = 22 p = ns <u>Duration of rupture of membranes (h)</u> Cases (n = 41): 27.6 ± 42.3 Control (n = 41): 69.1 ± 65.2 p =ns **Inclusion criteria** • Singleton babies • Weighing between 750 and 2500g • 25-35 weeks' gestation **Exclusion criteria** • Babies delivered by caesarean section prior		<u>Assessment</u> A single study's author that was blinded to neonatal outcome interpreted the tracings. The traces evaluated based on the National Institute of Child Health and Human Development guidelines <u>FHR classification</u> Variable deceleration defined as an abrupt decrease in FHR of at least 15 bpm lasting for between 15 seconds and 2 minutes according to the National Institutes of Chid Health and Human Development (NICHD) research-planning workshop 1997 <u>Tocolysis</u> About half of the women in the cases and control group received tocolytics therapy <u>Definition of outcomes</u> Chorionic morbid outcomes were defined as intraventricular haemorrhage at least grade III, periventricular leukomalacia, necrotizing entrocolitis or death within 28 days <u>Analysis</u> Data were analysed using McNemar test for categorical data and paired t test for continuous outcomes	<u>Neonatal death (within 28 days)</u> Cases n = 2/41 Control n = 0/41 p = 0.15 <u>Intraventricular haemorrhage</u> Cases n = 4/41 Control n = 0/41 p = 0.04 <u>Necrotizing enterocolitis</u> Cases n = 1/41 Control n = 1/41 p = 1.0 <u>Periventricular leukomalacia</u> Cases n = 1/41 Control n = 0/41 p = 0.31	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	to labor • Congenital anomalies • An uninterpretable FHR trace for technical reason (loss of contact/signal,traces < 30 min in duration)				
Full citation Burrus,D.R., O'Shea,T.M.,Jr., Veille,J.C., Mueller-Heubach,E., The predictive value of intrapartum fetal heart rate abnormalities in the extremely premature infant, American Journal of Obstetrics and Gynecology, 171, 1128-1132, 1994 **Ref Id** 195054 **Country/ies where the study was carried out** USA **Study type** Case control **Aim of the study** To evaluate the validity of intrapartum fetal heart rate tracings in predicting short- and long-term outcomes of infants delivered between 24	**Sample size** n = 41 **Characteristics** Not specified **Inclusion criteria** • 24 - 26 weeks gestation **Exclusion criteria** Not specified	**Interventions** Intraparum fetal heart rate monitor	**Details** All births between 23 and 26 weeks gestation at a single hospital during the study period were reviewed those with good tracing and available follow up were identified. <u>FHR monitoring</u> Electronic fetal heart rate tracings were obtained form last hour before birth were assessed <u>Assessment</u> The tracings were interpreted by two independent maternal–fetal medicine specialists blinded to neonatal outcome and to each other's interpretations. . <u>FHR classification</u> The traces evaluated in 10 minutes windows for the following categories: Normal and abnormal FHR defined based on Kubli et al 1969 as: - Normal baseline (FHR 120 – 160) - Bradycardia (FHR 100 – 120 bpm)	**Results** **<u>Normal versus abnormal FHR pattern</u>** <u>Neonatal death</u> FHR abnormality (n = 19) n = 53% No fetal abnormality (n = 22) n = 14% p < 0.007 <u>Intraventricular haemorrhage</u> FHR abnormality (n = 19) n = 33% No fetal abnormality (n = 22) n = 12% <u>> 42 days on assisted ventilation</u> FHR abnormality (n = 7) n = 14% No fetal abnormality (n = 16) n = 13% <u>> 90 days of hospitalisation</u> FHR abnormality (n = 7) n = 11% No fetal abnormality (n = 16) n = 26%	**Limitations** Women's characteristic not reported Unclear inclusion/exclusion criteria hence high risk of selection bias

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
and 26 weeks. **Study dates** 1989 to 1991 **Source of funding** Not specified			- Severe bradycardia (FHR < 100 bpm) Variability - Normal variability (amplitude range > 5 bpm) - Moderately reduced variability (2 – 5 bpm) - Severely reduced variability (< 2 bpm) A salutatory or hyper-variable pattern was diagnosed if amplitude range exceeded 25 beats/min Decelerations - Mild variable deceleration (last <30 sec irrespective of level, if the nadir was >80 bpm irrespective of duration, or if their nadir was 70 -80 bpm if lasting <60). - Moderate variable deceleration (lasted 30 to 60 sec with the nadir was < 60 bpm, or lasted > 60 sec but with a nadir between 70 -80). - Severe variable deceleration (lasted > 60 sec with a nadir. They were defined as occasional (2 or fewer in a 10 min window) or frequent (3 or more)	<u>Cerebral palsy at 1 yr</u> FHR abnormality (n = 7) n = 14% No fetal abnormality (n = 16) n = 6% <u>Cord pH <7.0</u> FHR abnormality (n = 19) n = 0% No fetal abnormality (n = 22) n = 0%	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			Tocolysis Use of tocolytics not reported. Definition of outcomes Not specified Analysis Continuous data were analysed using χ2 or exact p value for contingency tables. and base excess. Kappa correlation for inter-observer reliability was calculated to measure the agreement among the 2 reviewers.		

H.11.3 Fetal blood sampling

There was no evidence that met the protocol.

H.12 Mode of birth

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Alfirevic,Zarko, Milan,Stephen J., Livio,Stefania, Caesarean section versus vaginal delivery for preterm birth in singletons, Cochrane Database of Systematic Reviews, -, 2013 **Ref Id**	**Sample size** Four trials, total n=116 women **Characteristics** Included studies: Penn et al., 1996 Sample size: n=15 Characteristics: Mean maternal age, years (range)* CS: 27.6 (24 to 34)	**Interventions** Immediate caesarean delivery versus vaginal birth	**Details** Searching for studies The Trials Search Co-ordinator was contacted on 5 August 2013, and asked to search the Cochrane Pregnancy and Childbirth Group's Trials Register. In addition, CENTRAL, MEDLINE, CINAHL and Dissertation Abstracts were searched. The reference list of identified studies was also searched, and any studies assessed for eligibility. No language restrictions were	**Results** **Neonatal outcomes** Perinatal deaths 3 trials, 89 women RR 0.29 (95% CI 0.07 to 1.14) Hypoxic	**Limitations** The authors assessed risk of bias for each of the individual studies: - Method of randomisation: 1 was at low risk of bias, 3 had unclear risk of bias - Allocation concealment: 2

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
291612 **Country/ies where the study was carried out** Various **Study type** Systematic review **Aim of the study** To assess the effectiveness of immediate caesarean section versus vaginal birth for women in preterm labour. **Study dates** Assessed as up to date: 28 August 2013 **Source of funding** Not specified	VB: 28.4 (19 to 37) Gestation at delivery, weeks (range) CS: 29.4 (26 to 31) VB: 28.6 (26 to 32) Mean birthweight, grams (range) CS: 1387.0 (1000 to 1925) VB: 1243.3 (770 to 2160) Inclusion criteria: - Singleton fetus with breech presentation - 26 to 32 completed weeks of gestation - Spontaneous preterm labor - Without a clear indication for VB or CS Exclusion criteria: - Known intrauterine death or congenital fetal malformation - If an elective CS was already planned - Clear indication for CS or VB at the time when entry was considered during labor Viegas et al., 1985 Sample size n = 73 Randomised n = 23* (live preterm breeches on admission satisfying the selection criteria) Descriptive study group n = 50 (the remaining preterm breeches) Characteristics: Birthweight, g, mean±SD CS (n = 32): 1944 ± 412 VB (n = 41): 1840 ± 474 *individual patient data supplied by the author. The data for randomised women re-analysed on an intention to treat analysis basis.		applied. Data collection and analysis Two review authors independently assessed studies for inclusion. They then extracted data into a pre-designed form and resolved discrepancies through discussion. Data were entered into RevMan and checked for accuracy. If there was any unclear information, the authors were contacted to provide details. Quality assessment Risk of bias was assessed independently by two authors using the The Cochrane Collaboration's tool for assessing risk of bias. The following criteria were considered: - Sequence generation - Allocation concealment - Blinding: due to the intervention, it would not be possible to blind participants or those provided care; however, the authors report that they did consider whether outcome assessors were blinded -Incomplete outcome data: low risk was defined as no missing data; missing outcomes data balanced across the group and high risk as number of missing data imbalanced across groups. - Selective reporting bias: established by cross checking the outcomes reported in the methods and results sections of the publication - Other sources of bias Missing data Levels of attrition were noted for the studies. All analyses were carried out on an intention-to-treat basis. Denominators were the number	ischaemic encephalopathy 1 trial, 12 women RR 4.00 (95% CI 0.20 to 82.01) Intracranial pathology 4 trials, 110 women RR 0.92 (95% CI 0.27 to 3.14) Respiratory distress syndrome 3 trials, 103 women RR 0.55 95% CI 0.27 to 1.10) Need for mechanical ventilation 1 trial, 12 women RR 1.87 (95% CI 0.71 to 4.88) Abnormal follow-up in childhood 1 trial, 38 women RR 0.65 95% CI 0.19 to 2.22)	were at low risk of bias, 2 had an unclear risk of bias - Blinding: all four were at high risk of bias - Incomplete outcome data: 4 were at unclear risk of bias - Selective reporting: 4 were at unclear risk of bias - Other bias: 4 were at unclear risk of bias

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	Inclusion criteria: - Breech presentation - 28 to 35 weeks gestation in established labor Exclusion criteria: - Conditions which were contraindications for CS or VB (hemorrhage, placenta praevia, cord prolapse, fetal distress or disproportion) - Maternal diseases eg diabetes mellitus, cardiac disease - Severe congenital malformation if diagnosed - Severe pre-eclampsia or intrauterine growth retardation Follow-up All cases assessed earlier or later than a month after the 12 month follow-up appointment data were excluded <u>Wallace et al., 1984</u> Study sample n=38 VB n=20 (includes 5 women randomised to CS who delivered vaginally prior to surgery) CS n=18 Characteristics: Mean gestational age ± SD (range) weeks VB: 30.4 ±1.8 (26 to 33) CS: 29.6±1.6 (27 to 32) p < 0.05 Birth weight, g VB: 1572±419 (880 to 2630) CS: 1714±641 (800 to 3110) p<0.05 Inclusion criteria:		randomised, minus any women whose outcomes were known to be missing. <u>Analysis</u> Statistical analysis was done in RevMan. A fixed effects model was used. It was assumed that studies were estimating the same underlying treatment effect. If substantial heterogeneity was detected, random effect meta-analysis was used.	**<u>Maternal outcomes</u>** <u>Postpartum haemorrhage</u> 4 trials, 105 women RR 3.69 95% (CI 0.16 to 83.27) <u>Other maternal infection</u> 3 trials, 103 women RR 2.63 95% (CI 1.02 to 6.78) <u>Wound infection</u> 3 trials, 103 women RR 1.16 (95% CI 0.18 to 7.70)	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	- Vertex persentation - 26 to 33 weeks estimate of gestational age - Labor (>4cm) - Indications for delivery including failed or contraindicated tocolysis, maternal indications and fetal indications Participants were entered on the basis of best estimate of gestational age Exclusion criteria: - Multiple gestation - Known congenital anomaly - Malpresentation including breech - Clinically documented amnionitis - Advanced labor (>7cm) - Cord prolapse - Vaginal hemorrhage - Previous CS Zlatnik et al., 1993 Sample size n = 38 Characteristics: Mean±SD Maternal age VB: 24.4±5.3 CS: 21.9±4.5 Weeks gestation VB: 31.3±2.0 CS: 32.3±2.4 Birthweight, gm VB: 1791±501 CS: 1873±561 Nulliparous, % VB: 45 CS: 44 Inclusion criteria: - Singleton breech presentations - 28 to 36 weeks gestation				

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	- In labor in which tocolytics were not employed or had failed Exclusion criteria: - Immediate labor - Contraindications to additional labor or CS - If a patient manifested fetal distress on admission in labor, CS was performed and she was not eligible for randomisation **Inclusion criteria** Randomised and quasi-randomised trials comparing a policy of planned immediate caesarean delivery versus vaginal delivery for preterm birth. **Exclusion criteria** Not specified				

H.12.1.1 Health economics

Bibliographic details	Interventions and comparisons	Data Sources	Time horizon & Method	Results	Reviewer comment
Full citation Cazan-London,G., Mozurkewich,E.L., Xu,X., Ransom,S.B., Willingness or unwillingness to perform cesarean section for impending preterm delivery at 24 weeks' gestation: a cost-effectiveness analysis, American Journal of Obstetrics and Gynecology, 193, 1187-	**Study dates** Not stated. **Intervention** Unplanned cesarean section **Comparison(s)** Vaginal birth	**Source of effectiveness data** Published evidence **Source of cost data** Costs estimates based on published data and the Morbidity and Mortality Weekly report. Initial Hospitalization was defined as inpatient care	**Time horizon and discount rate** Time Horizon: Lifetime Discount rate: Not stated **Method of eliciting health valuations (if applicable)** Published evidence	**Cost per patient per alternative** Cost per birth Caesarean: USD 399,761 Vaginal birth: USD 218,162 **Effectiveness per patient per alternative** Survivors per 100 births	**Limitations** Does not explicitly exclude women with multiple gestations. **Other information**

Bibliographic details	Interventions and comparisons	Data Sources	Time horizon & Method	Results	Reviewer comment
1192, 2005 **Ref Id** 220991 **Economic study type** Cost effectiveness analysis **Country(ies) where the study was done** USA **Perspective & Cost Year** Perspective: Societal Cost Year: 2004 **Source of funding** Not stated		before the first discharge. These costs include hospital costs and physician fees calculated using corresponding institutional cost-charge ratio. Long term morbidity costs were based on lifetime costs associated with MR, CP, hearing loss, and vision impairment. **Other data sources e.g. transition probabilities**	**Modelling approach** A Decision Tree model was used to simulate the outcomes associated with each of the delivery options.	Caesarean: 56 Vaginal birth: 32 **Incremental cost-effectiveness** Author calculates Cost per additional survivor : USD 766,241 NCC-WCH calculates Cost per additional survivor : USD 756,662.50 **Other reporting of results** **Uncertainty** One-way sensitivity analysis was performed based on probability of survival vs cost. Parameters of this analysis do not appear to be based on any probabilities.	

H.13 Timing of cord clamping for preterm babies

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation March,M., De,VecianaM, Parson,A., The efficacy of umbilical cord milking on the reduction of red blood cell transfusion rates in infants born between 24 and 28 6/7 weeks gestation - A randomized controlled trial, American Journal of Obstetrics and Gynecology, 204, S204-, 2011 **Ref Id** 225209 **Country/ies where the study was carried out** USA **Study type** Randomised control trial **Aim of the study** To examine if actively milking the umbilical cord before clamping the cord reduces the need for red cell transfusion in the neonatal period **Study dates** Not reported **Source of funding** Not specified	**Sample size** Intervention (cord milking) n = 21 Control n = 17 **Characteristics** The two groups had similar demographics (no further data provided) **Inclusion criteria** - Singleton pregnancy - Delivery anticipated between 24 and 28+6 weeks gestation - Sufficient time from admission to anticipated delivery to obtain consent from the women **Exclusion criteria** - Multiple gestation - Antenatally diagnosed major congenital anomaly - Rh sensitised pregnancy - Hydrops fetalis - Known previous positive maternal titers - Suspicion of placental abruption at birth - Maternal age < 18	**Interventions** <u>Intervention</u> Cord milking: 20 cm of umbilical cord was milked toward the baby immediately following delivery before the cord clamping <u>Control</u> The cord was not milked. Clamped immediately after birth	**Details** Pregnant women admitted to a tertiary centre to be delivered between 24 and 28 weeks gestation were randomised into one of two groups. Common reasons for needing to be delivered at this early gestational age included but were not limited to: preterm labour not responding to tocolytic medications, incompetent cervix with cervical dilation and no contractions, clinical chorioamnionitis requiring delivery for maternal/fetal benefit, severe pre-eclampsia, severe growth restriction with a non-reassuring fetal heart rate tracing. From 60 women eligible for participations, n = 55 consented and n = 14 delivered beyond the 28+6 weeks. The first arm received active milking of the umbilical cord towards the neonate's umbilicus prior to cord clamping at birth while the second arm did not include this intervention and had the cord immediately clamped (control). Neonatologists were blinded to the study group allocations.	**Results** **Red blood cell transfusion** <u>need for packed red blood cell transfusion in the first 28 days of neonatal life:</u> Intervention n = 17/21 (80%) Control n = 16/17 (94%) There were no differences in: - neonatal death - recitation procedure used - Apgar score - cord pH - initial blood pressure - hyperbilirubinemia - haematocrit - other neonatal complications No further details are provided	**Limitations** Published conference abstract with very limited data reported
Full citation	**Sample size** N = 738	**Interventions** Earlier and later cord	**Details** <u>Electronic searches</u>	**Results** **<u>More placental</u>**	**Limitations** Using the NICE

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Rabe,H., az-Rossello,J.L., Duley,L., Dowswell,T., Effect of timing of umbilical cord clamping and other strategies to influence placental transfusion at preterm birth on maternal and infant outcomes. [Update of Cochrane Database Syst Rev. 2004;(4):CD003248; PMID: 15495045], Cochrane Database of Systematic Reviews, 8, CD003248-, 2012 **Ref Id** 209071 **Country/ies where the study was carried out** Various **Study type** Systematic review of RCTs **Aim of the study** To assess the short- and long-term effects of early rather than delayed clamping of the umbilical cord for preterm births (< 37 completed weeks gestation). **Study dates** Assessed as up-to-date on November 2011 **Source of funding** Not specified	(from 15 trials) **Characteristics** **Aladagandy 2006** Participants: n = 46 mother-infant pairs at 24 weeks to 32 weeks gestation. Exclusions: known major malformation, haemolytic disease, intrauterine transfusion. Time of cord clamping: Early: immediately after birth. Late: 30-90 sec after birth, with infant held as low as the cord allowed. If caesarean section, mother received 5 IU syntocinon intravenously at delivery of presenting part. **Baezinger 2007** Participants: 39 mother-infant pairs at 24 weeks to 32 weeks gestation. Exclusions: known major malformation, haemolytic disease, intrauterine transfusion. Time of cord clamping: Early: immediately after birth (< 20 sec). Late: between 60-90s, with infant held as low as possible for vaginal births,	clamping	The Cochrane Pregnancy and Childbirth Group's Trials Register was searched (updated 26 June 2012) by contacting the Trials Search Coordinator. CENTRAL, MEDLINE, EMBASE were searched, and hand searching of journals and conference proceedings was done. No language restrictions were applied. Selection of studies Two review authors independently assessed all potential studies for inclusion. Any disagreement was resolved through consultation with the third review author. Data extraction and management A form was designed to extract data, and two authors extracted them. They were analysed in RevMan. Where information was unclear, the reviewers attempted to contact the original authors. Assessment of risk of bias Two review authors independently assessed risk of bias using criteria from the Cochrane Handbook for Systematic Reviews of Interventions: - Sequence generation - Allocation concealment - Blinding - Incomplete outcome data - Selective reporting bias - Other sources of bias - Overall risk of bias.	**transfusion (delayed clamping) versus less placental transfusion (early clamping)** Infant death (up to discharge/variable) n = 13 studies Later cord clamping: n = 10/319 Earlier cord clamping: n = 17/349 RR 0.63 (95% CI 0.31 to 1.28) Severe intraventricular haemorrhage n = 6 studies Later cord clamping: n = 5/154 Earlier cord clamping: n = 7/151 RR 0.68 (95% CI 0.23 to 1.96) Apgar score at 5 minute < 8 n = 3 studies Later cord clamping: n = 13/72 Earlier cord clamping: n = 18/89 RR 0.86 (95% CI 0.45 to 1.62) Temperature on admission (degrees Celsius) n = 3 studies Later cord clamping: n = 71 Earlier cord clamping: n = 72	methodology checklist for systematic reviews, there are no major limitations to this systematic review. The authors assessed risk of bias for each of the individual studies: - Method of randomisation: 3 were at low risk of bias, 12 had unclear risk of bias - Allocation concealment: 2 were at low risk of bias, 12 had an unclear risk of bias, 1 was at high risk of bias - Blinding: 1 was at low risk of bias, 8 had an unclear risk of bias, 6 were at high risk of bias - Incomplete outcome data: 8 were at low risk of bias, 4 had an unclear risk of bias and 3 were at high risk of bias - Selective reporting: 2 were at low risk of bias, 10 had an unclear risk of bias, 3 were at high risk of bias

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	and 15 cm below the placenta at caesarean section. All mothers received syntocinon intravenously. **Hofmeyr 1988** Participants: n = 38 mother-infant pairs, judged to be < 35 weeks gestation and in advanced labour. Exclusions: multiple pregnancies. Time of cord clamping: Control: immediately after birth. Intervention 1: delayed for 60 sec. Intervention 2: delayed for 60 sec and ergometrine given at delivery. **Hofmeyr 1993** Participants: n = 86 mother-infant pairs. Exclusion: cord around the neck. Time of cord clamping: Control: shortly after delivery, according to usual practice. Intervention: 60-120 sec after birth, with the infant held at the level of the uterus for vaginal births and the infant held just above the level of the uterus for caesarean		Measures of effect Dichotomous outcomes were presented as a risk ratio with 95% confidence intervals. For continuous data, mean difference and standardised mean difference were used, depending on whether trials had measured outcomes on the same or different scales. Dealing with missing data The authors investigated the effect of including trials with high levels of attrition using sensitivity analysis. Outcomes were assessed on an intention-to-treat basis, with the denominator being set as the number randomised minus any participants whose outcomes were known to be missing. Analysis Heterogeneity was regarded substantial if $T^2 > 0$ and/or $1^2 >$ 30% or $p < 0.1$. Fixed-effect meta-analysis was used where trials were comparing the same intervention and the populations and methods were judged to be similar enough. Random effects meta-analyses were used where heterogeneity was present or suspected.	Mean difference 0.14 (95% CI -0.03 to 0.31) Ventilated for respiratory distress syndrome n = 5 studies Later cord clamping: n = 40/119 Earlier cord clamping: n = 49/146 RR 0.97 (95% CI 0.71 to 1.31) Transfused for anaemia n = 7 studies Later cord clamping: n = 44/186 Earlier cord clamping: n = 75/206 RR 0.61 (95% CI 0.46 to 0.81) Number of transfusions n = 5 studies Later cord clamping: n = 104 Earlier cord clamping: n = 106 Mean -1.26 (95% CI -1.87 to -0.64) Hyperbilirubinemia (treated) n = 3 studies Later cord clamping: n = 51/82 Earlier cord clamping: n = 51/98 RR 1.21 (95% CI 0.94 to 1.55)	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	section (on the mothers' thighs). **Hosono 2008** Participants: n = 40 mother-infant pairs as 24-28 weeks gestation, and admitted at least 6h before enrolment. Exclusions: multiple pregnancies, major congenital anomalies or chromosomal anomalies, hydrops fetalis. Time of cord clamping: Control group: immediately. Intervention group: infant placed below or at the level of the placenta and about 20 cm of the umbilical cord milked vigorously towards umbilicus 2-3 times (estimated speed 20 cm/sec). **Kinmond 1993** Participants: 36 mother-infant pairs at > 27 to < 33 weeks gestation, vaginal delivery. Exclusions: haemolytic disease, major congenital malformations. Time of cord clamping: Intervention: positioning 20 cm below the introitus and			**More placental transfusion (delayed clamping) versus less placental transfusion (early clamping) by strategy for more placental transfusion** Infant death (up to discharge/variable)- **Delayed clamping** n = 12 studies Later cord clamping: n = 8/299 Earlier cord clamping: n = 14/329 RR 0.62 (95% CI 0.28 to 1.36) Infant death (up to discharge/variable) - **Cord milking** n = 1 study Later cord clamping: n = 2/20 Earlier cord clamping: n = 3/20 RR 0.67 (95% CI 0.12 to 3.57) **More placental transfusion (delayed clamping) versus less placental transfusion (early clamping) by risk of bias for concealment of allocation** Infant death (up to discharge/variable)- **Risk of bias unclear or high**	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	cord clamped at 30 sec (mean time to cord clamping 10 sec, clamping within 20 sec for 18/19 and at 25 sec for 1). Control group: management at the attendant's discretion. An observer recorded distance baby held relative to introitus, time, and time of cord clamping. **Kugelman 2007** Participants: n = 65 mother-infant pairs, at > 24 weeks and < 35 weeks gestation. Multiple pregnancies included. Time of cord clamping: Control: immediately < 10 sec. Intervention group: Time of cord clamping was not reported. Positioning of infant 20-30 cm below level of introitus (vaginal delivery) or below level of the incision at caesarean section. **McDonnell 1997** Participants: n = 46 infants at 26 to 33 weeks, vaginal or caesarean section, single or multiple pregnancies. Exclusions: severe fetal distress, intrauterine			n = 11 studies Later cord clamping: n = 8/267 Earlier cord clamping: n = 11/296 RR 0.74 (95% CI 0.32 to 1.73) Infant death (up to discharge/variable)- **Low risk of bias** n = 2 studies Later cord clamping: n = 2/52 Earlier cord clamping: n = 6/53 RR 0.40 (95% CI 0.1 to 1.59)	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	growth restriction (IUGR) with abnormal umbilical Doppler waveforms, fetal hydrops, fetal malformations, Rhesus incompatibility. Time of cord clamping: Control group: immediately. Intervention group: at 30s, infant positioned between legs of the mother, syntocinon at birth of the infant. **Mercer 2003** Participants: 32 mother-infant pairs < 32 weeks, vaginal or caesarean section delivery. Exclusion: obstetrician's refusal to participate, major congenital anomalies, multiple gestations, intend to withhold care, severe maternal illnesses, placenta abruption or praevia. Time of cord clamping: Control: between 5-10 sec after delivery. Intervention group: at 30-45 sec, infant held 10 to 15 inches below the level of the placenta in vaginal deliveries or below the incision at caesarean				

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	section. **Mercer 2006** Participants: n = 72 mother-infant pairs < 33 weeks, vaginal or caesarean section delivery. Exclusions: obstetrician's refusal to participate, major congenital anomalies, multiple gestations, intend to with hold care, severe maternal illnesses, placenta abruption or praevia. Time of cord clamping: Control group: between 5-10 sec after birth. Intervention group: at 30-45 sec. Infant held 10 to 15 inches below the level of the placenta in vaginal births or below the incision at caesarean section. **Nelle 1998** Participants: 19 infants < 1500 g born by caesarean section. Time of cord clamping: Control group: immediately after birth. Intervention: after 30 sec and positioning of the infant 30 cm below placenta.				

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	Oh 2002 Participants: 33 infants 24-28 weeks. Time of cord clamping: Control group: < 5 s. Intervention group: 30-45 s. **Rabe 2000** Participants: 40 infants < 33 weeks. Exclusions: multiple pregnancies, Rhesus incompatibility, fetal hydrops, congenital malformation, Apgar < 3 at 0 minutes. Time of cord clamping: Control group: at 20 sec. Intervention group: at 45 s and positioning of the infant below the level of placenta, if possible, oxytocin at delivery of the first shoulder. **Strauss 2008** Participants: 158 infants < 36 weeks gestation. Of whom 105 30-36 weeks. Exclusion: congenital abnormality. Time of cord clamping: Control group: cord clamping immediately within 2-5 sec (not exceeding 15 sec).				

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	Intervention group: at 60 s, vaginal delivery: infant positioned 10 to 12 inch below introitus of the mother. Caesarean section: infant positioned beside the supine mother's thigh and cord clamped. **Ultee 2008** Participants: 41 mother-infant pairs 34-36 weeks gestation, vaginal delivery only. Exclusion: congenital abnormality, maternal diabetes, expected serious perinatal pathology, and twins. Reasons for exclusion included post randomisation criteria: Apgar scores < 5 at 1 min, <7 at 5 min. Time of cord clamping: Control group: within 30 s (mean 13.4 sec SD 5.6 sec). Infant placed on mother's abdomen. Intervention group: after 180 sec. Infant placed on mother's abdomen. **Inclusion criteria** Randomised controlled trials (including cluster-randomised trials).				

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	Exclusion criteria Quasi-randomised trials				
Full citation Ranjit,T., Nesargi,S., Rao,P.N., Sahoo,J.P., Ashok,C., Chandrakala,B.S., Bhat,S., Effect of early versus delayed cord clamping on hematological status of preterm infants at 6 wk of age, Indian Journal of Pediatrics, 82, 29-34, 2015 **Ref Id** 346386 **Country/ies where the study was carried out** India **Study type** Randomised control trial **Aim of the study** To examine the effect of early cord clamping compared with delay cord clamping on hematocrit and serum ferritin at 6 weeks of life in preterm infants **Study dates** May to November 2010 **Source of funding** Not specified	**Sample size** Total n=100 **Characteristics** Birth weight ECC group: 1907±597 DCC group: 1864±568 Gestational age ECC group: 34±2.0 DCC group: 34±1.6 Caesarean section ECC group: 25 (50%) DCC group: 20 (45%) Maternal age ECC group: 25±4.0 DCC group: 26±4.0 Parity ECC group: 1.6±1.0 DCC group: 1.8±1.0 **Inclusion criteria** • Between 30+0 and 36+6 weeks gestation **Exclusion criteria** • Mother with Rhesus negative blood group • monochorionic twins	**Interventions** Early cord clamping (ECC) Delayed cord clamping (DCC)	**Details** The trial was conducted in a tertiary care hospital in South India. 100 women were randomised to two groups (ECC= 50 DCC=50). Six babies were excluded from DCC group because they did nor received the information due to the need for resuscitation. The obstetricians who were involved at birth were aware of the groups allocation. In the ECC group cord was clamped immediately after birth and in the DCC group cord was camped >2 min after birth. In case of vaginal birth baby were placed on mother's abdomen and in case of caesarean section on mother's thigh. In babies with need of resuscitation immediate cord clamping performed irrespective of the group allocation. Analysis Data were analysed using SPSS version 16. T-test were used for comparing continuous variables between the two groups. Categorical variables were compared using Chi-square test	**Results** Neonatal death ECC group: 5/50 (10%) DCC group: 0/44 (0%) RR 0.10 (0.006 to 1.81) Hypoxic ischemic encephalopathy ECC group: 2/50 (4%) DCC group: 1/44 (2%) RR 0.56 (0.05 to 6.03) Intraventricular haemorrhage ECC group: 1/50 (1%) DCC group: 0/44 (0%) RR 0.37 (0.02 to 9.04) Respiratory distress syndrome ECC group: 8/50 (16%) DCC group: 5/44 (11%) RR 0.58 (0.19 to 1.79) Significant jaundice ECC group: 37/50 (74%) DCC group: 37/44 (84%) RR 1.07 (0.76 to 1.51) Hct at day 1 ECC group: mean 50.8±5.2 DCC group: 58.5±5.1 Mean difference: 7.2 (5 to 9.5)	**Limitations** No intention to treat analysis Unclear if women received uterotonic

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Elimian,A., Goodman,J., Escobedo,M., Nightingale,L., Knudtson,E., Williams,M., Immediate compared with delayed cord clamping in the preterm neonate: a randomized controlled trial, Obstetrics and Gynecology, 124, 1075-1079, 2014 **Ref Id** 346394 **Country/ies where the study was carried out** USA **Study type** Randomised control trial **Aim of the study** To examine the short term effects of delayed umbilical cord clamping in preterm babies born between 24 and 34 weeks gestation **Study dates** January 2008 to May 2011 **Source of funding** Not specified	**Sample size** Total n = 200 Delayed cord clamping: n = 99 Immediate cord clamping: n = 101 **Characteristics** Baseline characteristics were similar in the two groups: Mean gestational week at birth Delayed cord clamping: 30.8 ± 3.1 Immediate cord clamping: 30.7 ± 2.8 p = 0.64 No further details provided **Inclusion criteria** - Singleton pregnancies - Signed consent to participate in the trial **Exclusion criteria** Major fetal anomaly or known fetal chromosomal abnormalities - Multiple gestation - Mothers with pre-existing and gestational diabetes - Refusal to participate in the trial	**Interventions** Delayed cord clamping: 30 - 35 seconds after birth Immediate cord clamping: within 5 seconds after birth	**Details** Study conducted at Oklahoma University Medical Centre among preterm neonates born between 24 weeks and 34 weeks 0 days gestation.	**Results** No significant difference observed between the two groups in: - neonatal mortality - blood transfusion rate - rate of various adverse neonatal outcomes (respiratory distress syndrome [RDS], intraventricular haemorrhage [IVH], periventricular leukomalacia [PVL], necrotizing enterocolitis [NEC]) <u>Mean initial haemoglobin</u> Delayed cord clamping: 17.4 ± 2.5 g/dl Immediate cord clamping: 16.3 ± 2.3 g/dl p = 0.001 <u>Mean haematocrit</u> Delayed cord clamping: 51.3 ± 7.3 Immediate cord clamping: 47.4 ± 7.3 p = 0.001 <u>Anaemia of prematurity</u> Delayed cord clamping: n = 36/99 (36.4%) Immediate cord clamping: n = 48/101 (47.5%) p = 0.11	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments