National Institute for Health and Care Excellence

FINAL

Preterm labour and birth

[A] Evidence review for clinical effectiveness of prophylactic progesterone in preventing preterm labour

NICE guideline NG25

Evidence review

August 2019

Final

This evidence review was developed by the National Guideline Alliance hosted by the Royal College of Obstetricians and Gynaecologists

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Contents

Review question: What is the clinical effectiveness of prophylactic progesterone (vaginal or oral) in preventing preterm labour in pregnant women considered to be at risk of preterm labour and birth?

Introduction

Preterm birth is a major cause of neonatal morbidity and mortality. Children who are born preterm may also suffer long term health issues related to their early birth. Therefore, identification of measures to prevent or delay premature birth is of great importance.

Women at higher risk of preterm birth may be identified by screening using recognised risk factors. These may include a preterm birth in a previous pregnancy, a previous mid-trimester loss, a short cervix on ultrasound scan, or a variety of other risk factors. These women may benefit from interventions to try and reduce the risk of an early birth. The most common interventions offered are cervical cerclage (which was not reviewed as part of this update) or progesterone.

The aim of this evidence review is to consider the effectiveness of prophylactic progesterone treatment (with either vaginal or oral progesterone) at preventing preterm labour, for women considered to be at risk of preterm labour and birth.

Summary of the protocol

See Table 1 for a summary of the Population, Intervention, Comparison and Outcome (PICO) characteristics of this review.

Table 1: Summary of the protocol (PICO table)

Population	Pregnant women considered to be at risk of preterm labour and birth (<37^{+0} weeks' gestation) because they have any of the following: • a history of spontaneous preterm birth • a history of preterm pre-labour rupture of membranes (in a previous pregnancy) • a history of mid-trimester loss • mid-trimester bleeding • a history of cervical trauma • a short cervix that has been identified on scan and/or bulging membranes in the current pregnancy • a positive fetal fibronectin test
Intervention	• Vaginal progesterone • Oral progesterone
Comparison	• One intervention compared to another • Placebo • No treatment
Outcome	**Critical outcomes:** • Preterm birth <34^{+0} weeks' • Stillbirth

	• Infant mortality prior to discharge **Important outcomes:** • Gestational age at birth • Early onset neonatal sepsis (onset up to 72 hours) • Maternal satisfaction/HRQoL • Neurodevelopmental outcome at ≥ 18 months

HRQoL: health-related quality of life

Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual 2014. Please see the methods section of the 2015 guideline for further details. Methods specific to this review question are described in the review protocol in appendix A.

Declarations of interest were recorded according to NICE's 2014 conflicts of interest policy until 31st March 2018, and thereafter in accordance with NICE's 2018 conflicts of Interests Register (see Register of Interests).

Clinical evidence

Included studies

One Cochrane systematic review (Dodd 2013) including 9 randomised controlled trials (RCTs) was included (N=1892) (Akbari 2009, Cetingoz 2011, da Fonseca 2003, Fonseca 2007, Glover 2011, Hassan 2011, Majhi 2009, O´Brien 2007, Rai 2009). 5 further RCTs (N=2097) (Ashoush 2017, Azargoon 2016, Crowther 2017, Norman 2018, van Os 2015) were included in this systematic review. In addition, 1 individual patient data (IPD) meta-analysis (Romero 2018) including data from 5 of the included RCTs (N=974) was also included as this presented additional analysis using data unreported in the original articles (Fonseca 2007, O´Brien 2007, Cetingoz 2011, Hassan 2011, Norman 2016).

Participants consisted of women at risk of preterm labour and birth, mainly due to a history of preterm labour or due to a short cervix. No studies were found for women presenting with other risk factors for preterm labour and birth.

Some of the identified trials were suitable for meta-analyses and these have been performed as appropriate by the NGA technical team. No pooled estimates were extracted from the Cochrane review (Dodd 2013). Instead, estimates from the individual studies were extracted and used to combine with other studies as appropriate.

Pooled estimates from the IPD meta-analysis were included because individual estimates were not reported by the study authors. These results specifically included women with a short cervix (≤25 mm), therefore have been included separately as part of the subgroup analysis. The pooled estimates were not combined with other individual estimates because the results from the IPD meta-analysis would skew the variance. Where available, individual estimates from studies included in the IPD meta-analysis were extracted from the original studies and included in the overall analysis for the whole population.

See the literature search strategy in appendix B and study selection flow chart in appendix C.

Excluded studies

Studies not included in this review, with reasons for their exclusion, are provided in appendix K.

Summary of clinical studies included in the evidence review

Table 2 provides a brief summary of the included studies.

Table 2: Summary of included studies

Study	Participants	Intervention	Control	Outcomes
Ashoush 2017 RCT Egypt	N=187 women with history of spontaneous preterm birth	Oral progesterone (100 mg every 6 hours) Treatment started between 14 and 18 weeks' gestational age	Placebo	• Infant mortality • Gestational age at birth
Azargoon 2016 RCT Iran	N=100 women with a history of preterm birth (52%) or previous history of preterm birth and short cervix (≤28 mm) (27%)	Vaginal progesterone (400 mg/day) Treatment started between 16 and 22 weeks' gestational age	Placebo	• Preterm birth <34 weeks' • Infant mortality • Gestational age at birth
Crowther 2017 RCT Australia, New Zealand, Canada	N=799 women with history of spontaneous preterm birth	Vaginal progesterone (100mg/day) Treatment started at 20 weeks' gestational age, or from randomisation (if this occurred after 20 weeks)	Placebo	• Stillbirth • Infant mortality • Early neonatal sepsis • Health-related quality of life
Dodd 2013 Cochrane systematic review Iran, Brazil, US, India	K=9 • Akbari 2009 • Cetingoz 2011 • da Fonseca 2003 • Fonseca 2007 • Glover 2011 • Hassan 2011 • Majhi 2009 • O´Brien 2007	Vaginal progesterone (90 to 200 mg): • Akbari 2009 • Cetingoz 2011 • da Fonseca 2003 • Fonseca 2007 • Hassan 2011 • Majhi 2009 • O´Brien 2007	Placebo	• Preterm birth <34 weeks' • Stillbirth • Infant mortality • Gestational age at birth • Neonatal sepsis

Study	Participants	Intervention	Control	Outcomes
	• Rai 2009 N=1892 women with a history of spontaneous preterm birth or short cervix on ultrasound scan	Oral progesterone (100 to 200 mg): • Glover 2011 • Rai 2009 Treatment start week ranged between 16 and 24 weeks' gestational age		
Norman 2018 RCT UK	N=1225 women with risk factors for preterm birth (including previous preterm birth, cervical length ≤25mm, second trimester loss, preterm premature rupture of the membranes or history of cervical procedure to treat abnormal smears)	Vaginal progesterone (200 mg/day) Treatment started between 22 and 24 weeks' gestational age	Placebo	• Preterm birth <34 weeks' • Stillbirth • Infant mortality • Gestational age at birth • Health-related quality of life • Bayley-III cognitive composite score • Moderate or severe neuro-developmental impairment • Visual impairment • Hearing impairment
Romero 2018[a] IPD meta-analysis UK, USA, Turkey	K= 5 • Cetingoz 2011 • Fonseca 2007 • Hassan 2011 • Norman 2016 • O'Brien 2007 N=974 with a short cervix (≤25 mm)	Vaginal progesterone (90 to 200 mg/day) Treatment start week ranged between 18 and 24 weeks' gestational age	Placebo	• Preterm birth <34+0 weeks' • Stillbirth • Infant mortality • Gestational age at birth • Proven neonatal sepsis • Health-related quality of life • Bayley-III cognitive composite score • Moderate or severe neuro-developmental impairment • Visual or hearing impairment

Study	Participants	Intervention	Control	Outcomes
van Os 2015 RCT The Netherlands	N=80 women with a short cervix (≤30 mm)	Vaginal progesterone (200 mg) Treatment started at 22 weeks' gestational age	Placebo	• Preterm birth <34 weeks' • Infant mortality • Neonatal sepsis

[a]*Romero 2018 contacted the principal investigators of the eligible trials. Data included in the IPD meta-analysis may have not been reported in the main trials.*
mg: milligrams; mm: millimetres; RCT: randomised controlled trial; IPD: individual patient data

See appendix D for clinical evidence tables and appendix E for the Forest plots.

Quality assessment of clinical studies included in the evidence review

See appendix F for full GRADE tables.

Economic evidence

A systematic review of economic literature was conducted, but no studies were identified which were applicable to this review question.

Economic model

No economic modelling was undertaken for this review.

Evidence statements

Comparison 1. Vaginal progesterone versus placebo

Critical outcomes

Preterm birth <34^{+0} weeks'

Eight randomised controlled trials (N=2145) provided low quality evidence to show that those who received vaginal progesterone experienced a clinically important decrease in the number of preterm births (at <34 weeks' gestation), as compared to those who received placebo. There was inconsistency in the effect estimate across the different trials (I^2 = 60%), however, this resolved after conducting pre-specified subgroup analysis.

Subgroup analysis: Women with a history of spontaneous preterm birth

Five randomised controlled trials (N=507) provided moderate quality evidence to show that, for women with a history of spontaneous preterm birth, those who received vaginal progesterone experienced a clinically important decrease in preterm birth (at <34 weeks' gestation) as compared to those who received placebo.

Subgroup analysis: Women with a short cervix (<30 mm)

Three randomised controlled trials (N=357) provided low quality evidence to show that, for women with a short cervix (<30 mm), those who received vaginal progesterone experienced a clinically important decrease in the number of preterm births (at <34 weeks' gestation) as compared to those who received placebo.

Women with a short cervix (≤25 mm)

An individual participant data meta-analysis of five randomised controlled trials (N=974) provided low quality evidence to show that, for women with a short cervix (≤25mm), those who received vaginal progesterone experienced a clinically important decrease in the number of preterm births (at <34 weeks' gestation) as compared to those who received placebo.

Stillbirth

Five randomised controlled trials (N=3339) provided very low quality evidence to show that there was no clinically important difference in the number of stillbirths between those who received vaginal progesterone or placebo.

Subgroup analysis: Women with a history of spontaneous preterm birth

Two randomised controlled trials (N=1410) provided low quality evidence to show that, for women with a history of spontaneous preterm birth, there was no clinically important difference in the number of stillbirths between those who received vaginal progesterone or placebo.

Women with a short cervix (≤25 mm)

An individual participant data meta-analysis of five randomised controlled trials (N=974) provided very low quality evidence to show that, for women with a short cervix (≤25mm), there was no clinically important difference in the number of stillbirths between those who received vaginal progesterone or placebo.

Infant mortality

Nine randomised controlled trials (N=3810) provided moderate quality evidence to show a clinically important decrease in infant mortality for those who received vaginal progesterone, as compared to placebo.

Subgroup analysis: Women with a history of spontaneous preterm birth

Three randomised controlled trials (N=1551) provided low quality evidence to show that, for women with a history of spontaneous preterm birth, there may be a clinically important decrease in infant mortality in those who received vaginal progesterone as compared to those who received placebo, but there is uncertainty around the estimate (RR 0.53, 95% CI 0.25 to 1.12).

Subgroup analysis: Women with a short cervix (<30 mm)

Three randomised controlled trials (N=812) provided low quality evidence to show that, for women with a short cervix (<30 mm), there may be a clinically important decrease in infant mortality in those who received vaginal progesterone as compared to those who received placebo, but there is uncertainty around the estimate (RR 0.42, 95% CI 0.16 to 1.08).

Women with a short cervix (≤25 mm)

An individual participant data meta-analysis of five randomised controlled trials (N=974) provided low quality evidence to show that, for women with a short cervix (≤25 mm), there may be a clinically important decrease in infant mortality in those who received vaginal progesterone as compared to those who received placebo, but there is uncertainty around the estimate (RR 0.45, 95% CI 0.18 to 1.08).

Important outcomes

Gestational age at birth (mean weeks')

Three randomised controlled trials (N=1908) provided very low quality evidence to show that there was no clinically important difference in gestational age at birth between those who received vaginal progesterone or placebo. These results should be interpreted with caution as there was substantial heterogeneity in the effect estimates from the individual trials (I^2=82%).

Subgroup analysis: Women with a history of spontaneous preterm birth

Two randomised controlled trials (N=711) provided very low quality evidence to show that, for women with a history of spontaneous preterm birth, there was no clinically important difference in gestational age at birth between those who received vaginal progesterone or placebo. These results should be interpreted with caution as there was substantial heterogeneity in the effect estimates from the individual trials (I^2=91%).

Women with a short cervix (≤25 mm)

An individual participant data meta-analysis of five randomised controlled trials (N=974) provided moderate quality evidence to show that, for women with a short cervix (≤25 mm), there was a clinically important increase in gestational age at birth for those who received vaginal progesterone, compared to those who received placebo.

Neonatal sepsis

Six randomised controlled trials (N=1843) provided low quality evidence to show that infants of those who received vaginal progesterone experienced a clinically important decrease in the occurrence of neonatal sepsis, as compared to those who received placebo.

Subgroup analysis: Women with a history of spontaneous preterm birth

Three randomised controlled trials (N=1031) provided moderate quality evidence to show that, for women with a history of spontaneous preterm birth, infants of those who received vaginal progesterone experienced a clinically important decrease in the occurrence of neonatal sepsis, as compared to those who received placebo.

Subgroup analysis: Women with a short cervix (<30 mm)

Three randomised controlled trials (N=812) provided very low quality evidence to show that, for women with a short cervix (<30 mm), there was no clinically important difference in the occurrence of neonatal sepsis between those who received vaginal progesterone or placebo.

Women with a short cervix (≤25 mm)

An individual participant data meta-analysis of five randomised controlled trials (N=974) provided moderate quality evidence to show that, for women with a short cervix (≤25mm), there may be a clinically important decrease in neonatal sepsis for infants of those who received vaginal progesterone as compared to those who received placebo, but there is uncertainty around the estimate (RR 0.61, 95% CI 0.34 to 1.09).

Health-related quality of life (measured with Euro-QoL-5 Dimensions health utility scores)

Change from baseline to birth

One randomised controlled trial (N=390) provided high quality evidence to show that there was no clinically important difference in health-related quality of life scores from baseline to birth, as measured with the EuroQoL-5, between those who received vaginal progesterone or placebo.

Change from baseline to 12 months

One randomised controlled trial (N=553) provided high quality evidence to show that there was no clinically important difference in health-related quality of life scores from baseline to 12 months, as measured with the EuroQoL-5, between those who received vaginal progesterone or placebo.

Health-related quality of life (measured with SF-36); women with a history of spontaneous preterm birth

General health domain

One randomised controlled trial (N=787) provided high quality evidence to show that, for women with a history of spontaneous preterm birth, there was no clinically important difference in health-related quality of life scores, as measured by the SF-36 general health domain, between those who received vaginal progesterone or placebo.

Social functioning domain

One randomised controlled trial (N=787) provided high quality evidence to show that, for women with a history of spontaneous preterm birth, those who received vaginal progesterone experienced a clinically important decrease in mean health-related quality of life score, as measured by the SF-36 social functioning domain, as compared to those who received placebo.

Emotional role domain

One randomised controlled trial (N=787) provided high quality evidence to show that, for women with a history of spontaneous preterm birth, there was no clinically important difference in health-related quality of life scores, as measured by the SF-36 emotional role domain, between those who received vaginal progesterone or placebo.

Mental health domain

One randomised controlled trial (N=787) provided high quality evidence to show that, for women with a history of spontaneous preterm birth, there was no clinically important difference in health-related quality of life scores, as measured by the SF-36 mental health domain, between those who received vaginal progesterone or placebo.

Bayley-III cognitive composite score (2 years follow-up)

One randomised controlled trial (N=833) provided high quality evidence to show that there was no clinically important difference in Bayley-III cognitive composite score at 2 years follow-up between the infants of those women who received vaginal progesterone or placebo.

Women with a short cervix (≤25 mm)

An individual participant data meta-analysis including one randomised controlled trial (N=168) provided moderate quality evidence to show that, for infants of women with a short cervix (≤25 mm), there was no clinically important difference in Bayley-III cognitive composite score at 2 years follow-up between those who received vaginal progesterone or placebo.

Moderate or severe neurodevelopmental impairment (2 years follow-up)

One randomised controlled trial (N=782) provided moderate quality evidence to show that there was no clinically important difference in moderate or severe neurodevelopmental impairment at 2 years follow-up between the infants of those who received vaginal progesterone or placebo.

Women with a short cervix (≤25 mm)

An individual participant data meta-analysis including one randomised controlled trial (N=158) provided very low quality evidence to show that, for infants of women with a short cervix (≤25 mm), there was no clinically important difference in moderate or severe neurodevelopmental impairment events at 2 years follow-up between those who received vaginal progesterone or placebo.

Hearing impairment

One randomised controlled trial (N=931) provided low quality evidence to show that there was no clinically important difference in the number of infants with hearing impairment at 2 years follow-up between those who received vaginal progesterone or placebo.

Visual impairment

One randomised controlled trial (N=912) provided low quality evidence to show that there was no clinically important difference in the number of infants with visual impairment at 2 years follow-up between those who received vaginal progesterone or placebo.

Visual or hearing impairment (2 years follow-up); women with a short cervix (≤25 mm)

An individual participant data meta-analysis of one randomised controlled trial (N=187) provided very low quality evidence to show that, for infants of women with a short cervix (≤25 mm), there was no clinically important difference in visual or hearing impairment events at 2 years follow-up between those who received vaginal progesterone or placebo.

Comparison 2. Oral progesterone versus placebo

Critical outcomes

Preterm birth <34^{+0} weeks'

One randomised controlled trial (N=148) provided moderate quality evidence to show that, in those with a previous history of spontaneous preterm birth, women who received oral progesterone experienced a clinically important decrease in preterm birth (<34 weeks' gestation) as compared to those who received placebo.

Infant mortality

Two randomised controlled trials (N=335) provided moderate quality evidence to show that, in those with a previous history of spontaneous preterm birth, women who received oral progesterone experienced a clinically important decrease in infant mortality, as compared to those who received placebo.

Important outcomes

Gestational age at birth (mean weeks')

Two randomised controlled trials (N=220) provided moderate quality evidence to show that, for women with a history of spontaneous preterm birth, there was a clinically important increase in gestational age at birth for those who received oral progesterone, compared to those who received placebo.

The committee's discussion of the evidence

Interpreting the evidence

The outcomes that matter most

The aim of this review was to assess the effectiveness and safety of prophylactic oral or vaginal progesterone in women at risk of preterm birth due to different risk factors. The committee therefore designated 3 critical outcomes: preterm birth <34^{+0} weeks', stillbirth and infant mortality prior to discharge. These outcomes were selected as the most direct indicators of the efficacy and safety of prophylactic progesterone in women at risk of preterm birth.

The committee identified 4 further outcomes as important: gestational age at birth, early onset neonatal sepsis (up to 72 hours), maternal satisfaction/ health-related quality of life (HRQoL), and neurodevelopmental outcome at ≥ 18 months. These outcomes were important because a reduced gestational age can put babies at significant risk of morbidity and mortality, early onset neonatal sepsis may occur if birth takes place preterm, and women's perceived health was also prioritised to assess the effect of the intervention on maternal satisfaction/HRQoL. As preterm birth may be associated with neurodevelopmental impairment, the committee believed it was important to include neurodevelopmental outcome at ≥18 months.

The quality of the evidence

One Cochrane systematic review, 1 IPD meta-analysis and 5 RCTs were included in this review. The quality of the evidence ranged from very low to high as assessed by the NGA technical team using GRADE.

The main reason for downgrading was the risk of bias due to studies failing to report how randomisation was performed or concealed, or because women, investigators and assessors were aware of treatment allocation. Other reasons for downgrading the quality of the evidence included high heterogeneity, which is due to differences in the studies included in a meta-analysis. Where considerable heterogeneity was present (an I-squared value of 50% or more), predefined subgroup analyses were performed to identify the effect in different subpopulations of women.

Additionally, outcomes were also downgraded because of imprecision, as the trials had few women included, and therefore the confidence intervals around the estimate for each of the outcomes were wide.

The majority of studies included in this review incorporated a broad population of women – all of whom were perceived to be at high risk of preterm birth, but often for a variety of reasons. Many women had a previous history of preterm birth, but some had other risk factors, including a short cervix, uterine malformations or previous cervical surgery. For some of the studies, it was also noted that these populations were overlapping.

Benefits and harms

Babies born before 34 weeks of gestational age are at an increased risk of complications in the immediate postnatal period and later in life. There are certain characteristics of women's past and current pregnancies that may predispose women to preterm birth – such as a previous history of preterm birth or a short cervical length. Progesterone has been used in these women, to try and reduce the risk of an early birth. However, whether progesterone benefits all women, or only those with specific risk factors, is unclear.

The committee noted that the overall estimate showed a benefit of vaginal progesterone for women considered to be at risk of preterm birth. However, they were aware that the studies recruited women with a wide range of different risk factors, and that vaginal progesterone may be of most benefit for specific subpopulations of women.

The committee noted that the subgroup analysis for women with a previous history of preterm birth, and for women with a short cervix (≤25mm) showed an important benefit with the use of vaginal progesterone. Therefore, the committee agreed that progesterone should be offered to women with both of these risk factors.

The use of cerclage was not considered in this update, but the first recommendation in the previous version of the guideline had been a combined recommendation for progesterone and cerclage, even though the previous evidence reviews were carried out separately and did not compare progesterone to cerclage. As, following this review of the effectiveness of progesterone, the indications to offer progesterone did not change (a history of preterm birth and a short cervix) the committee therefore adopted the recommendation from the previous guideline which stated this. Also, as in the previous guideline, the committee agreed that as there was no evidence comparing progesterone and cerclage (and a research recommendation had been made in the previous guideline stating this) the choice of cerclage or progesterone should be determined after discussion between the woman and health care professionals.

Although there was evidence of benefit for progesterone in women with previous preterm birth and evidence of benefit in women with a short cervix, the committee were aware that these subpopulations of women overlapped. Therefore some women with a previous history of preterm birth will also have a cervical length ≤25mm, and some women with a cervical length ≤25mm will also have a history of preterm birth. Consequently, determining which of these two risk factors best identified women who would benefit from progesterone was not possible.

However, due to the clear improvement in outcome for women with a previous history of preterm birth (RR of preterm birth at <34 weeks 0.27 [95% CI 0.15 to 0.49]), the committee agreed progesterone should be considered for women with a history of preterm birth, even if the cervical length was not ≤25mm, or was unknown. Similarly, the IPD meta-analysis confirmed an important overall risk reduction for progesterone in women with a cervix of ≤25mm (RR 0.65 [95% CI 0.51-0.83]). Again, this analysis included women with and without a previous history of preterm birth. Therefore the committee agreed that progesterone should be considered for women with a short

cervix identified on scan, but without a previous history of preterm birth. Due to the uncertainty over the benefits of progesterone in these subgroups (women who have risk factors for a preterm birth but do not have a short cervix, and women who have a short cervix but no other risk factors for preterm birth) the committee made research recommendations.

The analysis for women with a cervical length of <30mm showed a benefit to vaginal progesterone at reducing preterm birth <34 weeks. However, it was noted that the majority of the women included in this analysis actually had a cervical length which was considerably shorter than 30mm, with Hassan 2011 including women with a cervical length of 10-20mm, and Fonseca 2007 including those with a cervical length <15mm. Furthermore, the committee agreed that the normal range for cervical length in pregnancy was not well understood, but that it was known that it gradually reduced over the course of pregnancy. A cervical length of 25mm has been identified as being on or below the 5th centile up until 24 weeks' of gestational age by one study (Salomon 2009). Therefore, the committee agreed that 25mm represented a reasonable threshold at which to consider progesterone treatment.

The studies included in this evidence review commenced treatment with vaginal progesterone at a variety of different time points, ranging from 14 to 25 weeks. The committee agreed that it was important to provide guidance on when progesterone should be started, but noted that the evidence base for this was poor. Based on their expertise, and the time frame for starting treatment in the studies, they recommended that progesterone should be commenced between 16 and 24 weeks. The committee anticipated that women would discuss the risks and benefits of progesterone treatment (or cerclage, where appropriate) with an obstetrician, rather than their GP. Therefore, this would enable the risks and benefits of progesterone to be discussed and treatment to be commenced prior to 24 weeks, if appropriate. Similarly, it was not clear when progesterone should be stopped. The committee discussed the fact that, in their experience, it should be continued to at least 34 weeks but that the exact stoppage time remains uncertain. Because of the uncertainty about when progesterone should be started and stopped, the committee made a research recommendation to highlight that the optimal timing of treatment was unclear and should be assessed.

No subgroup analysis was possible for women with the other risk factors identified in the review protocol – preterm pre-labour rupture of the membranes, mid-trimester bleeding, previous cervical trauma or surgery or a positive fetal fibronectin test. Therefore, the committee were unable to make recommendations regarding the use of progesterone in women with these risk factors.

The committee were aware that the stimulus to update the Preterm Labour and Birth guideline was the publication of the OPPTIMUM trial - a large, UK based trial designed to identify the potential benefit of vaginal progesterone for women at risk of preterm birth. The overall conclusion of this study was that vaginal progesterone was not of benefit in the prevention of preterm birth for women with recognised risk factors. Data from the OPPTIMUM trial has been included in this evidence review, as part of the overall analyses (including women with any risk factors), and as part of the IPD meta-analysis for women with a short cervix. The reasons why the overall conclusions of the OPPTIMUM study are different to this meta-analysis are not entirely clear. However, the heterogeneity of the underlying population may well contribute. The OPPTIMUM study recruited women with a variety of risk factors for preterm birth, including previous preterm birth, cervical length ≤25mm, preterm premature rupture of the membranes or previous procedure to treat abnormal cervical smears. Data for the outcomes specified on our review protocol for these subgroups of women were not available. The OPPTIMUM trial authors have

themselves highlighted the need for detailed subgroup analysis using individual participant data, to identify specific populations of women in whom progesterone may be of benefit.

Some limited evidence suggested that prophylactic oral progesterone reduced the risk of preterm birth <34 weeks, reduced the risk of infant mortality and increased gestational age in women with a history of spontaneous preterm birth. However, the committee raised some concerns regarding the conduct and applicability of the studies to the UK setting. For instance, one of the studies was conducted in Egypt and reported a neonatal mortality rate of 25% in the placebo arm. This perinatal mortality is much higher than that seen in UK practice, and may reflect more limited neonatal care facilities in other countries. Oral progesterone is currently not used routinely in UK practice, and no trials were identified which directly compared oral and vaginal preparations, therefore the committee agreed that vaginal progesterone should be the preparation of choice.

Cost effectiveness and resource use

Vaginal progesterone is a relatively inexpensive preparation, and is already recommended for use in some women at risk of preterm birth. Therefore, the recommendations are not anticipated to increase the cost of medication significantly. However, the cost of a preterm birth is very high – in terms of immediate care in the neonatal unit, long term health effects for the infant, and health related quality of life for women and their babies. As vaginal progesterone is anticipated to reduce the incidence of preterm birth this should be a valuable and cost-effective use of resources.

Other factors the committee took into account

The committee were aware that cervical scanning is not currently recommended by the National Screening Committee for all pregnant women, but they regularly review this decision. Therefore cervical length scanning is currently only offered to women in whom there is a clinical concern regarding the risk of preterm labour. Individual units will have local procedures in place to determine which, if any, women received a cervical length scan. However, the committee were aware that the document Saving Babies' Lives (Version 2), from NHS England, provides some guidance regarding who should undergo cervical length scanning.

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Hassan SS, Romero R, Vidyadhari D, Fusey S, Baxter JK, Khandelwal M, Vijayaraghavan J, Trivedi Y, Soma-Pillay P, Sambarey P, Dayal A. Vaginal progesterone reduces the rate of preterm birth in women with a sonographic short cervix: a multicenter, randomized, double-blind, placebo-controlled trial. Ultrasound in Obstetrics & Gynecology. 2011 Jul;38(1):18-31.

Majhi 2009

Majhi P, Bagga R, Kalra J, Sharma M. Intravaginal use of natural micronised progesterone to prevent pre-term birth: a randomised trial in India. Journal of Obstetrics and Gynaecology. 2009 Jan 1;29(6):493-8.

Norman 2018

Norman JE, Marlow N, Messow CM, Shennan A, Bennett PR, Thornton S, Robson SC, McConnachie A, Petrou S, Sebire NJ, Lavender T. Does progesterone prophylaxis to prevent preterm labour improve outcome? A randomised double-blind placebo-controlled trial (OPPTIMUM). Health Technology Assessment, No. 22.35

O'Brien 2007

O'Brien JM, Adair CD, Lewis DF, Hall DR, Defranco EA, Fusey S, Soma-Pillay P, Porter K, How H, Schackis R, Eller D. Progesterone vaginal gel for the reduction of recurrent preterm birth: primary results from a randomized, double-blind, placebo-controlled trial. Ultrasound in Obstetrics and Gynecology. 2007 Oct;30(5):687-96.

Romero 2018

Romero R, Conde-Agudelo A, Da Fonseca E, O'brien JM, Cetingoz E, Creasy GW, Hassan SS, Nicolaides KH. Vaginal progesterone for preventing preterm birth and adverse perinatal outcomes in singleton gestations with a short cervix: a meta-analysis of individual patient data. American Journal of Obstetrics and Gynecology. 2018 Feb 1;218(2):161-80.

Salomon 2009

Salomon LJ, Diaz-Garcia C, Bernard JP, Ville Y. Reference range for cervical length throughout pregnancy: non-parametric LMS-based model applied to a large sample. Ultrasound in Obstetrics and Gynecology. 2009 Apr 33(4):459-64.

Saving Babies' Lives 2019

Saving Babies' Lives Version Two: A care bundle for reducing perinatal mortality. NHS England 2019. https://www.england.nhs.uk/wp-content/uploads/2019/03/saving-babies-lives-care-bundle-version-two-final-version-4.pdf

van Os 2015

van Os MA, van der Ven AJ, Kleinrouweler CE, Schuit E, Kazemier BM, Verhoeven CJ, de Miranda E, van Wassenaer-Leemhuis AG, Sikkema JM, Woiski MD, Bossuyt PM. Preventing preterm birth with progesterone in women with a short cervical length from a low-risk population: a multicenter double-blind placebo-controlled randomized trial. American Journal of Perinatology. 2015;32(10):993-1000.

1 Appendix A – Review protocols

2 **Table 3: Review protocol for clinical effectiveness of prophylactic progesterone in preventing preterm labour**

Field (based on PRISMA-P)	Content
Key area in the scope	Prophylactic use of progesterone for women considered to be at risk of preterm labour and birth
Actual review question	What is the clinical effectiveness of prophylactic progesterone (vaginal or oral) in preventing preterm labour in pregnant women considered to be at risk of preterm labour and birth?
Type of review question	Intervention
Objective of the review	To establish if progesterone is effective in preventing preterm labour when given antenatally, and what is the most clinically effective type of progesterone (or has fewer/less severe adverse effects).
Eligibility criteria – **population**/disease/condition/issue/domain	Pregnant women considered to be at risk of preterm labour and birth (<37+0 weeks gestation) because they have any of the following: • a history of spontaneous preterm birth • a history of preterm pre-labour rupture of membranes (in a previous pregnancy) • a history of mid-trimester loss • mid-trimester bleeding • a history of cervical trauma (including surgery – for example, previous cone biopsy [cold knife or laser], large loop excision of the transformation zone [LLETZ – any number] and radical diathermy). • a short cervix that has been identified on scan and/or bulging membranes in the current pregnancy • a positive fetal fibronectin test
Eligibility criteria – **intervention**(s)/exposure(s)/prognostic factor(s)	• vaginal progesterone • oral progesterone
Eligibility criteria – **comparator(s)**/control or reference (gold) standard	• one intervention compared to another • placebo • no treatment

Field (based on PRISMA-P)	Content
Outcomes and prioritisation	**Critical:** • Preterm birth <34+0 weeks • Stillbirth • Infant mortality prior to discharge (includes neonatal mortality and additional mortality post 28 days, but prior to discharge) **Important:** • Gestational age at birth • Early onset neonatal sepsis (onset up to 72 hours) • Maternal satisfaction/HRQOL • Neurodevelopmental outcome at >/= 18 months
Eligibility criteria – **study design**	Only published full text papers • Systematic reviews of RCTs • RCTs
Other **exclusion criteria**	Women in actual preterm labour (as opposed to women at high risk for preterm labour) Multiple pregnancy Women with ruptured membranes (in the current pregnancy)
Proposed stratified, sensitivity/**sub-group analysis**, or meta-regression	Stratified analysis will be conducted for the following groups: • a history of spontaneous preterm birth • a history of preterm pre-labour rupture of membranes • a history of mid-trimester loss • mid-trimester bleeding • a history of cervical trauma (including surgery)

Field (based on PRISMA-P)	Content

	• a short cervix that has been identified on scan and/or bulging membranes in the current pregnancy
	  ○ ≤25 mm
	  ○ ≤15 mm
	• a positive fetal fibronectin test
	
	The following groups will be considered for subgroup analysis:
	
	• gestational age groups (treatment commenced at <20 weeks, treatment commenced at ≥20 weeks)

Selection process – duplicate screening/selection/analysis	Duplicate screening/selection/analysis will not be undertaken for this review as this question was not prioritised for it. Included and excluded studies will be cross checked with the committee and with published systematic reviews when available.
Data management (software)	If pairwise meta-analyses are undertaken, they will be performed using Cochrane Review Manager (RevMan5). GRADE will be used to assess the quality of evidence for each outcome. STAR will be used for bibliographies/citations and study sifting, data extraction and quality assessment/critical appraisal
Information sources – databases and dates	Sources to be searched: Medline, Medline In-Process, CCTR, CDSR, Embase. Limits (e.g. date, study design): All study designs will be included. Standard animal/non-English language filters will be applied. the search date will be limited to 2015 onwards . No supplementary search techniques will be used. See appendix B for full strategies. <u>Key papers:</u>

Field (based on PRISMA-P)	Content
	Norman JE et al. Vaginal progesterone prophylaxis for preterm birth (the OPPTIMUM study): a multicentre, randomised, double-blind trial. The Lancet. 2016 May 27;387(10033):2106-16. Health Technol Assess. 2018 Jun;22(35):1-304. doi: 10.3310/hta22350. Does progesterone prophylaxis to prevent preterm labour improve outcome? A randomised double-blind placebo-controlled trial (OPPTIMUM). Norman JE et al. PLoS Med. 2017 Sep 26;14(9):e1002390. doi: 10.1371/journal.pmed.1002390. eCollection 2017 Sep.Vaginal progesterone pessaries for pregnant women with a previous preterm birth to prevent neonatal respiratory distress syndrome (the PROGRESS Study): A multicentre, randomised, placebo-controlled trial. Crowther CA, Ashwood P, McPhee AJ, Flenady V, Tran T, Dodd JM, Robinson JS; PROGRESS Study Group. Am J Obstet Gynecol. 2018 Feb;218(2):161-180. doi: 10.1016/j.ajog.2017.11.576. Epub 2017 Nov 17. Vaginal progesterone for preventing preterm birth and adverse perinatal outcomes in singleton gestations with a short cervix: a meta-analysis of individual patient data. Romero R JAMA. 2017 Dec 19;318(23):2317-2324. doi: 10.1001/jama.2017.18956.Effect of Cervical Pessary on Spontaneous Preterm Birth in Women With Singleton Pregnancies and Short Cervical Length: A Randomized Clinical Trial.Saccone G Acta Obstet Gynecol Scand. 2017 Dec;96(12):1460-1466. doi: 10.1111/aogs.13236. Epub 2017 Oct 19. The value of oral micronized progesterone in the prevention of recurrent spontaneous preterm birth: a randomized controlled trial. Ashoush S Obstet Gynecol. 2017 Jul;130(1):64-70. doi: 10.1097/AOG.0000000000002065.Progestogens for Maintenance Tocolysis in Women With a Short Cervix: A Randomized Controlled Trial. Facchinetti F Cervical Pessary Compared With Vaginal Progesterone for Preventing Early Preterm Birth: A Randomized Controlled Trial. Cruz-Melguizo S, San-Frutos L, Martínez-Payo C, Ruiz-Antorán B,

Field (based on PRISMA-P)	Content
	Adiego-Burgos B, Campillos-Maza JM, García-González C, Martínez-Guisasola J, Pérez-Carbajo E, Teulón-González M, Avendaño-Solá C, Pérez-Medina T. Obstet Gynecol. 2018 Oct;132(4):907-915. Syst Rev. 2017 Nov 28;6(1):235. doi: 10.1186/s13643-017-0600-x. Evaluating progestogens for prevention of preterm birth international collaborative (EPPPIC) individual participant data (IPD) meta-analysis: protocol. Stewart LA1, Simmonds M2, Duley L3, Dietz KC2, Harden M2, Hodkinson A2, Llewellyn A2, Sharif S2, Walker R2, Wright K2; EPPPIC group.
Identify if an update	Yes. Relevant evidence included in the existing guideline that aligns with this protocol will also be included in the updated review.
Author contacts	Developer: National Guideline Alliance NGA-enquiries@RCOG.org.uk
Highlight if amendment to previous protocol	For details please see section 4.5 of Developing NICE guidelines: the manual
Search strategy – for one database	For details please see appendix B.
Data collection process – forms/duplicate	A standardised evidence table format will be used, and published as appendix D (clinical evidence tables) or H (economic evidence tables).
Data items – define all variables to be collected	For details please see evidence tables in appendix D (clinical evidence tables) or H (economic evidence tables).
Methods for assessing bias at outcome/study level	Appraisal of methodological quality: The methodological quality of each study will be assessed using an appropriate checklist: • ROBIS for systematic reviews • Cochrane risk of bias tool for randomised studies For details please see section 6.2 of Developing NICE guidelines: the manual

Field (based on PRISMA-P)	Content
	The risk of bias across all available evidence will evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group http://www.gradeworkinggroup.org/
Criteria for quantitative synthesis	For details please see section 6.4 of Developing NICE guidelines: the manual
Methods for quantitative analysis – combining studies and exploring (in)consistency	The methods used are described in more detail in the Methods section of the 2015 Preterm labour and birth full guideline. Synthesis of data: Meta-analysis will be conducted where appropriate using Review Manager. Minimally important differences Any significant difference will be used as the MID for mortality outcomes. For the remaining outcomes, default values will be used of: 0.8 and 1.25 for dichotomous outcomes; 0.5 times SD for continuous outcomes, unless more appropriate values are identified by the guideline committee or in the literature. Double sifting, data extraction and methodological quality assessment: Sifting, data extraction, appraisal of methodological quality and GRADE assessment will be performed by the systematic reviewer. Quality control will be performed by the senior systematic reviewer. Dual quality assessment and data extraction will not be performed.
Meta-bias assessment – publication bias, selective reporting bias	For details please see section 6.2 of Developing NICE guidelines: the manual.
Confidence in cumulative evidence	For details please see sections 6.4 and 9.1 of Developing NICE guidelines: the manual
Rationale/context – what is known	For details please see the introduction to the evidence review.
Describe contributions of authors and guarantor	A multidisciplinary committee developed the guideline. The committee was convened by the National Guideline Alliance and chaired by Sarah Fishburn in line with section 3 of Developing NICE guidelines: the manual. Staff from the National Guideline Alliance undertook systematic literature searches, appraised the evidence, conducted meta-analysis and cost-effectiveness analysis where appropriate, and drafted the guideline in collaboration with the committee. For details please see the methods chapter of the full guideline (published in 2015).

Field (based on PRISMA-P)	Content
Sources of funding/support	The National Guideline Alliance is funded by NICE and hosted by the Royal College of Obstetricians and Gynaecologists
Name of sponsor	The National Guideline Alliance is funded by NICE and hosted by the Royal College of Obstetricians and Gynaecologists
Roles of sponsor	NICE funds the National Guideline Alliance to develop guidelines for the NHS in England.
PROSPERO registration number	Not registered with PROSPERO

1

Appendix B – Literature search strategies

Review question search strategies

Table 4: Databases: Medline; Medline EPub Ahead of Print; and Medline In-Process & Other Non-Indexed Citations

#	Searches
1	META-ANALYSIS/
2	META-ANALYSIS AS TOPIC/
3	(meta analy* or metanaly* or metaanaly*).ti,ab.
4	((systematic* or evidence*) adj2 (review* or overview*)).ti,ab.
5	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
6	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
7	(search* adj4 literature).ab.
8	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
9	cochrane.jw.
10	or/1-9
11	randomized controlled trial.pt.
12	controlled clinical trial.pt.
13	pragmatic clinical trial.pt.
14	randomi#ed.ab.
15	placebo.ab.
16	randomly.ab.
17	CLINICAL TRIALS AS TOPIC/
18	trial.ti.
19	or/11-18
20	or/10,19
21	exp OBSTETRIC LABOR, PREMATURE/
22	exp INFANT, PREMATURE/
23	exp INFANT, LOW BIRTH WEIGHT/
24	GESTATIONAL AGE/
25	(pre term or preterm or pre matur$ or prematur$ or pre#mie? or premie or premies or low birth weight? or low birthweight? or LBW? or VLBW?).ti,ab.
26	or/21-25
27	PROGESTINS/
28	exp PROGESTERONE/
29	PROGESTERONE CONGENERS/
30	GONADAL STEROID HORMONES/
31	GESTONORONE CAPROATE/
32	(progest$ or gestagen$ or gestonorone? or hydroxyprogest$ or alphahydroxyprogest$ or 17alphahydroxyprogest$ or 17 OHP? or 17OHP?).mp.
33	(crinone or clycogest or gestone or utrogestan).mp.
34	or/27-33
35	CHEMOPREVENTION/
36	pc.fs. [Prevention & Control]
37	(prevent$ or reduc$ or prophyla$ or chemoprophyla$ or chemoprevent$ or prolong$ or inhibit$).ti,ab.
38	PRENATAL CARE/
39	(antenatal$ or ante natal$ or prenatal$ or pre natal$).ti,ab.
40	or/35-39
41	26 and 34 and 40
42	limit 41 to english language
43	LETTER/
44	EDITORIAL/
45	NEWS/
46	exp HISTORICAL ARTICLE/
47	ANECDOTES AS TOPIC/
48	COMMENT/
49	CASE REPORT/
50	(letter or comment*).ti.
51	or/43-50
52	RANDOMIZED CONTROLLED TRIAL/ or random*.ti,ab.
53	51 not 52

#	Searches
54	ANIMALS/ not HUMANS/
55	exp ANIMALS, LABORATORY/
56	exp ANIMAL EXPERIMENTATION/
57	exp MODELS, ANIMAL/
58	exp RODENTIA/
59	(rat or rats or mouse or mice).ti.
60	or/53-59
61	42 not 60
62	20 and 61
63	(2015$ or 2016$ or 2017$ or 2018$).ed,yr.
64	62 and 63

Table 5: Databases: Embase; and Embase Classic

#	Searches
1	SYSTEMATIC REVIEW/
2	META-ANALYSIS/
3	(meta analy* or metanaly* or metaanaly*).ti,ab.
4	((systematic or evidence) adj2 (review* or overview*)).ti,ab.
5	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
6	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
7	(search* adj4 literature).ab.
8	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
9	((pool* or combined) adj2 (data or trials or studies or results)).ab.
10	cochrane.jw.
11	or/1-10
12	random*.ti,ab.
13	factorial*.ti,ab.
14	(crossover* or cross over*).ti,ab.
15	((doubl* or singl*) adj blind*).ti,ab.
16	(assign* or allocat* or volunteer* or placebo*).ti,ab.
17	CROSSOVER PROCEDURE/
18	SINGLE BLIND PROCEDURE/
19	RANDOMIZED CONTROLLED TRIAL/
20	DOUBLE BLIND PROCEDURE/
21	or/12-20
22	11 or 21
23	PREMATURE LABOR/
24	PREMATURITY/
25	exp LOW BIRTH WEIGHT/
26	GESTATIONAL AGE/
27	(pre term or preterm or pre matur$ or prematur$ or pre#mie? or premie or premies or low birth weight? or low birthweight? or LBW? or VLBW?).ti,ab.
28	or/23-27
29	exp GESTAGEN/
30	PROGESTERONE/
31	exp PROGESTERONE DERIVATIVE/
32	SEX HORMONE/
33	GESTONORONE CAPROATE/
34	(progest$ or gestagen$ or gestonorone? or hydroxyprogest$ or alphahydroxyprogest$ or 17alphahydroxyprogest$ or 17 OHP? or 17OHP?).mp.
35	(crinone or clycogest or gestone or utrogestan).mp.
36	or/29-35
37	CHEMOPROPHYLAXIS/
38	pc.fs. [Prevention & Control]
39	(prevent$ or reduc$ or prophyla$ or chemoprophyla$ or chemoprevent$ or prolong$ or inhibit$).ti,ab.
40	PRENATAL CARE/
41	(antenatal$ or ante natal$ or prenatal$ or pre natal$).ti,ab.
42	or/37-41
43	28 and 36 and 42
44	limit 43 to english language
45	letter.pt. or LETTER/
46	note.pt.

#	Searches
47	editorial.pt.
48	CASE REPORT/ or CASE STUDY/
49	(letter or comment*).ti.
50	or/45-49
51	RANDOMIZED CONTROLLED TRIAL/ or random*.ti,ab.
52	50 not 51
53	ANIMAL/ not HUMAN/
54	NONHUMAN/
55	exp ANIMAL EXPERIMENT/
56	exp EXPERIMENTAL ANIMAL/
57	ANIMAL MODEL/
58	exp RODENT/
59	(rat or rats or mouse or mice).ti.
60	or/52-59
61	44 not 60
62	22 and 61
63	(2015$ or 2016$ or 2017$ or 2018$).dd,yr.
64	62 and 63

Table 6: Databases: Cochrane Central Register of Controlled Trials; and Cochrane Database of Systematic Reviews

#	Searches
#1	MeSH descriptor: [OBSTETRIC LABOR, PREMATURE] explode all trees
#2	MeSH descriptor: [INFANT, PREMATURE] explode all trees
#3	MeSH descriptor: [INFANT, LOW BIRTH WEIGHT] explode all trees
#4	MeSH descriptor: [GESTATIONAL AGE] this term only
#5	("pre term" or preterm or "pre matur*" or prematur* or premie or premies or "low birth weight*" or "low birthweight*" or LBW* or VLBW*):ti,ab
#6	#1 or #2 or #3 or #4 or #5
#7	MeSH descriptor: [PROGESTINS] this term only
#8	MeSH descriptor: [PROGESTERONE] explode all trees
#9	MeSH descriptor: [PROGESTERONE CONGENERS] this term only
#10	MeSH descriptor: [GONADAL STEROID HORMONES] this term only
#11	MeSH descriptor: [GESTONORONE CAPROATE] this term only
#12	(progest* or gestagen* or gestonorone* or hydroxyprogest* or alphahydroxyprogest* or 17alphahydroxyprogest* or "17 OHP*" or 17OHP*):ti,ab
#13	#7 or #8 or #9 or #10 or #11 or #12
#14	MeSH descriptor: [CHEMOPREVENTION] this term only
#15	[mh /PC]
#16	(prevent* or reduc* or prophyla* or chemoprophyla* or chemoprevent* or prolong* or inhibit*):ti,ab
#17	MeSH descriptor: [PRENATAL CARE] this term only
#18	(antenatal* or "ante natal*" or prenatal* or "pre natal*"):ti,ab
#19	#14 or #15 or #16 or #17 or #18
#20	#6 and #13 and #19 with Publication Year from 2015 to 2018, in Trials
#21	#6 and #13 and #19 with Cochrane Library publication date Between Jan 2015 and Dec 2018, in Cochrane Reviews

Health economics search strategies

Table 7: Databases: Medline; Medline EPub Ahead of Print; and Medline In-Process & Other Non-Indexed Citations

#	Searches
1	ECONOMICS/
2	VALUE OF LIFE/
3	exp "COSTS AND COST ANALYSIS"/
4	exp ECONOMICS, HOSPITAL/
5	exp ECONOMICS, MEDICAL/
6	exp RESOURCE ALLOCATION/
7	ECONOMICS, NURSING/

#	Searches
8	ECONOMICS, PHARMACEUTICAL/
9	exp "FEES AND CHARGES"/
10	exp BUDGETS/
11	budget*.ti,ab.
12	cost*.ti,ab.
13	(economic* or pharmaco?economic*).ti,ab.
14	(price* or pricing*).ti,ab.
15	(financ* or fee or fees or expenditure* or saving*).ti,ab.
16	(value adj2 (money or monetary)).ti,ab.
17	resourc* allocat*.ti,ab.
18	(fund or funds or funding* or funded).ti,ab.
19	(ration or rations or rationing* or rationed).ti,ab.
20	ec.fs.
21	or/1-20
22	exp OBSTETRIC LABOR, PREMATURE/
23	exp INFANT, PREMATURE/
24	exp INFANT, LOW BIRTH WEIGHT/
25	GESTATIONAL AGE/
26	(pre term or preterm or pre matur$ or prematur$ or pre#mie? or premie or premies or low birth weight? or low birthweight? or LBW? or VLBW?).ti,ab.
27	or/22-26
28	PROGESTINS/
29	exp PROGESTERONE/
30	PROGESTERONE CONGENERS/
31	GONADAL STEROID HORMONES/
32	GESTONORONE CAPROATE/
33	(progest$ or gestagen$ or gestonorone? or hydroxyprogest$ or alphahydroxyprogest$ or 17alphahydroxyprogest$ or 17 OHP? or 17OHP?).mp.
34	(crinone or clycogest or gestone or utrogestan).mp.
35	or/28-34
36	CHEMOPREVENTION/
37	pc.fs. [Prevention & Control]
38	(prevent$ or reduc$ or prophyla$ or chemoprophyla$ or chemoprevent$ or prolong$ or inhibit$).ti,ab.
39	PRENATAL CARE/
40	(antenatal$ or ante natal$ or prenatal$ or pre natal$).ti,ab.
41	or/36-40
42	27 and 35 and 41
43	limit 42 to english language
44	LETTER/
45	EDITORIAL/
46	NEWS/
47	exp HISTORICAL ARTICLE/
48	ANECDOTES AS TOPIC/
49	COMMENT/
50	CASE REPORT/
51	(letter or comment*).ti.
52	or/44-51
53	RANDOMIZED CONTROLLED TRIAL/ or random*.ti,ab.
54	52 not 53
55	ANIMALS/ not HUMANS/
56	exp ANIMALS, LABORATORY/
57	exp ANIMAL EXPERIMENTATION/
58	exp MODELS, ANIMAL/
59	exp RODENTIA/
60	(rat or rats or mouse or mice).ti.
61	or/54-60
62	43 not 61
63	21 and 62
64	(2015$ or 2016$ or 2017$ or 2018$).ed,yr.
65	63 and 64

Table 8: Databases: Embase; and Embase Classic

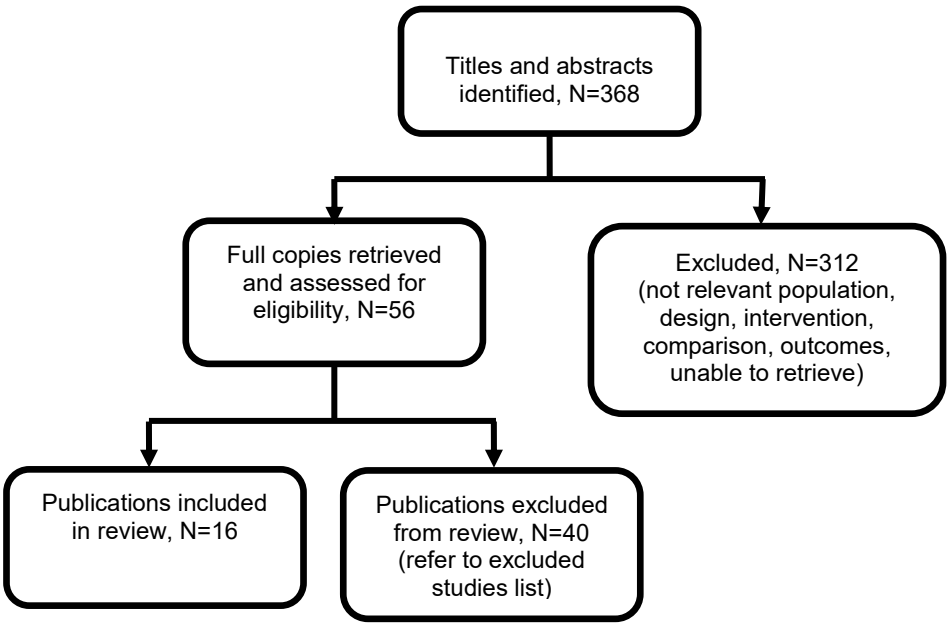
#	Searches
1	HEALTH ECONOMICS/
2	exp ECONOMIC EVALUATION/
3	exp HEALTH CARE COST/
4	exp FEE/
5	BUDGET/
6	FUNDING/
7	RESOURCE ALLOCATION/
8	budget*.ti,ab.
9	cost*.ti,ab.
10	(economic* or pharmaco?economic*).ti,ab.
11	(price* or pricing*).ti,ab.
12	(financ* or fee or fees or expenditure* or saving*).ti,ab.
13	(value adj2 (money or monetary)).ti,ab.
14	resourc* allocat*.ti,ab.
15	(fund or funds or funding* or funded).ti,ab.
16	(ration or rations or rationing* or rationed).ti,ab.
17	or/1-16
18	PREMATURE LABOR/
19	PREMATURITY/
20	exp LOW BIRTH WEIGHT/
21	GESTATIONAL AGE/
22	(pre term or preterm or pre matur$ or prematur$ or pre#mie? or premie or premies or low birth weight? or low birthweight? or LBW? or VLBW?).ti,ab.
23	or/18-22
24	exp GESTAGEN/
25	PROGESTERONE/
26	exp PROGESTERONE DERIVATIVE/
27	SEX HORMONE/
28	GESTONORONE CAPROATE/
29	(progest$ or gestagen$ or gestonorone? or hydroxyprogest$ or alphahydroxyprogest$ or 17alphahydroxyprogest$ or 17 OHP? or 17OHP?).mp.
30	(crinone or clycogest or gestone or utrogestan).mp.
31	or/24-30
32	CHEMOPROPHYLAXIS/
33	pc.fs. [Prevention & Control]
34	(prevent$ or reduc$ or prophyla$ or chemoprophyla$ or chemoprevent$ or prolong$ or inhibit$).ti,ab.
35	PRENATAL CARE/
36	(antenatal$ or ante natal$ or prenatal$ or pre natal$).ti,ab.
37	or/32-36
38	23 and 31 and 37
39	limit 38 to english language
40	letter.pt. or LETTER/
41	note.pt.
42	editorial.pt.
43	CASE REPORT/ or CASE STUDY/
44	(letter or comment*).ti.
45	or/40-44
46	RANDOMIZED CONTROLLED TRIAL/ or random*.ti,ab.
47	45 not 46
48	ANIMAL/ not HUMAN/
49	NONHUMAN/
50	exp ANIMAL EXPERIMENT/
51	exp EXPERIMENTAL ANIMAL/
52	ANIMAL MODEL/
53	exp RODENT/
54	(rat or rats or mouse or mice).ti.
55	or/47-54
56	39 not 55
57	17 and 56
58	(2015$ or 2016$ or 2017$ or 2018$).dd,yr.
59	57 and 58

Table 9: Database: Cochrane Central Register of Controlled Trials

#	Searches
#1	MeSH descriptor: [ECONOMICS] this term only
#2	MeSH descriptor: [VALUE OF LIFE] this term only
#3	MeSH descriptor: [COSTS AND COST ANALYSIS] explode all trees
#4	MeSH descriptor: [ECONOMICS, HOSPITAL] explode all trees
#5	MeSH descriptor: [ECONOMICS, MEDICAL] explode all trees
#6	MeSH descriptor: [RESOURCE ALLOCATION] explode all trees
#7	MeSH descriptor: [ECONOMICS, NURSING] this term only
#8	MeSH descriptor: [ECONOMICS, PHARMACEUTICAL] this term only
#9	MeSH descriptor: [FEES AND CHARGES] explode all trees
#10	MeSH descriptor: [BUDGETS] explode all trees
#11	budget*:ti,ab
#12	cost*:ti,ab
#13	(economic* or pharmaco?economic*):ti,ab
#14	(price* or pricing*):ti,ab
#15	(financ* or fee or fees or expenditure* or saving*):ti,ab
#16	(value near/2 (money or monetary)):ti,ab
#17	resourc* allocat*:ti,ab
#18	(fund or funds or funding* or funded):ti,ab
#19	(ration or rations or rationing* or rationed) .ti,ab.
#20	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19
#21	MeSH descriptor: [OBSTETRIC LABOR, PREMATURE] explode all trees
#22	MeSH descriptor: [INFANT, PREMATURE] explode all trees
#23	MeSH descriptor: [INFANT, LOW BIRTH WEIGHT] explode all trees
#24	MeSH descriptor: [GESTATIONAL AGE] this term only
#25	("pre term" or preterm or "pre matur*" or prematur* or premie or premies or "low birth weight*" or "low birthweight*" or LBW* or VLBW*):ti,ab
#26	#21 or #22 or #23 or #24 or #25
#27	MeSH descriptor: [PROGESTINS] this term only
#28	MeSH descriptor: [PROGESTERONE] explode all trees
#29	MeSH descriptor: [PROGESTERONE CONGENERS] this term only
#30	MeSH descriptor: [GONADAL STEROID HORMONES] this term only
#31	MeSH descriptor: [GESTONORONE CAPROATE] this term only
#32	(progest* or gestagen* or gestonorone* or hydroxyprogest* or alphahydroxyprogest* or 17alphahydroxyprogest* or "17 OHP*" or 17OHP*):ti,ab
#33	#27 or #28 or #29 or #30 or #31 or #32
#34	MeSH descriptor: [CHEMOPREVENTION] this term only
#35	[mh /PC]
#36	(prevent* or reduc* or prophyla* or chemoprophyla* or chemoprevent* or prolong* or inhibit*):ti,ab
#37	MeSH descriptor: [PRENATAL CARE] this term only
#38	(antenatal* or "ante natal*" or prenatal* or "pre natal*"):ti,ab
#39	#34 or #35 or #36 or #37 or #38
#40	#26 and #33 and #39
#41	#20 and #40 with Publication Year from 2015 to 2018, in Trials

Appendix C – Clinical evidence study selection

Figure 1: Flow diagram of clinical article selection for clinical effectiveness of prophylactic progesterone in preventing preterm labour



Appendix D – Clinical evidence tables

Table 10: Clinical evidence for clinical effectiveness of prophylactic progesterone in preventing preterm labour

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Ashoush, Sherif, El-Kady, Osama, Al-Hawwary, Gehan, Othman, Ahmed, The value of oral micronized progesterone in the prevention of recurrent spontaneous preterm birth: a randomized controlled trial, Acta obstetricia ET gynecologica scandinavica, 96, 1460-1466, 2017 **Ref Id** 930343 **Country/ies where the study was carried out** Egypt	**Sample size** N=212 were initially randomised (N= 106 in the progesterone group and N= 106 in the placebo group). N= 7 were lost to follow-up (N= 3 in the progesterone group and N=4 in the placebo group) due to loss of contact. N= 18 women had a miscarriage (N= 7 in the progesterone group and N=11 in the placebo group). N=187 women were included in the analysis (N=96 in the progesterone group and N=91 in the placebo group). **Characteristics** Maternal age, mean (SD): Oral progesterone (N=96) 29.3 (4.5); Placebo (N=91) 29.5 (3.5) Elective cervical cerclage, N (%): Oral progesterone (N=96) 55 (57.3); Placebo (N=91) 57 (62.6) Rescue cerclage, N (%): Oral progesterone (N=96) 15 (15.6); Placebo (N=91) 16 (17.5)	**Interventions** Interventions were started between 14 and 18 weeks of gestational age. Women randomised to the progesterone group received 100 mg of oral progesterone every 6 hours. Women randomised to the placebo group received 100 mg of placebo every 6 hours. The composition of the tablets was not reported, but had the same appearance as the progesterone ones. Women with <15mm of cervical length were offered cervical cerclage.	**Details** Cervical length and gestational age were determined through US between 14 and 18 weeks of gestational age. Participants were randomised with a computer program and randomisation was concealed using opaque sealed envelopes. Study was double blind. Sample size calculations were done and with a power of 80%, it was	**Results** Infant mortality (unclear if before discharge) Oral progesterone:7/96 Placebo:23/91 Gestational age at birth Oral progesterone: 35.4 (2.7) Placebo: 33.9 (2.9)	**Limitations** Methodological limitations assessed using the Cochrane collaboration's tool for assessing risk of bias **Random sequence generation:** low risk (computer-generated) Allocation concealment: low risk (opaque sealed envelope) **Blinding of participants and personnel:** low risk (blinded) **Blinding of outcome assessment:** unclear risk (no details reported) **Blinding (performance bias and detection bias):** unclear risk (see details above) **Incomplete outcome data:** low risk (there was a low rate of drop-outs <20% and reasons for these were provided) **Selective reporting:** low risk (outcomes reported match with those in the study protocol

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

Aim of the study
To assess whether oral progesterone prevents the recurrence of preterm birth.

Study dates
June 2015 to December 2016

Source of funding
Ghamra Military Hospital</td><td>Inclusion criteria
Women with singleton pregnancies; gestational age between 14 and 18 weeks; past history of spontaneous preterm labour

Exclusion criteria
Premature rupture of membranes; persistent uterine contractions; fetal anomalies incompatible with life; progesterone use in the current pregnancy (ongoing or past); liver disease</td><td></td><td>established that a sample size of 212 was needed to observe a difference of 20.3% of spontaneous preterm births between the progesterone and placebo group (this was based in a previous study by Rai 2009).</td><td></td><td>https://clinicaltrials.gov/ct2/show/NCT02571296)
Other sources of bias: low risk</td></tr>
<tr><td>Full citation
Azargoon, Azam, Ghorbani, Raheb, Aslebahar, Fereshteh, Vaginal progesterone on the prevention of preterm birth and neonatal complications in high risk women: A</td><td>Sample size
N=100 (N=50 randomised to vaginal progesterone and N=50 randomised to placebo)

Characteristics<table><tr><td></td><td>Vaginal progesterone (N=50)</td><td>Placebo (N=50)</td></tr><tr><td>Age, mean (SD)</td><td>25.4 (4.8)</td><td>24.6 (4.9)</td></tr><tr><td>Previous pre</td><td>28 (56)</td><td>25 (50)</td></tr></table></td><td>Interventions
Treatment commenced between 16 and 22 weeks of gestational age. Women had to use 1 capsule every night until 36 weeks gestation. Women randomised to the vaginal progesterone group received a vaginal suppository with 400 mg of progesterone.

Women randomised to the placebo group received a vaginal</td><td>Details
Gestational age was determined by an US scan done in the first 12 weeks of pregnancy.

Cervical length was assessed by a US during the 14 to 18 weeks of gestation.</td><td>Results
Preterm birth < 34 weeks
All women
Vaginal progesterone: 9/50
Placebo: 21/50

Women with previous preterm birth
Vaginal progesterone: 5/28
Placebo: 11/25

Women with previous preterm birth and short cervix (≤28 mm)</td><td>Limitations
Methodological limitations assessed using the Cochrane collaboration's tool for assessing risk of bias

Random sequence generation: low risk (computer-generated)
Allocation concealment: unclear risk (details not reported)
Blinding of participants and personnel: low risk (blinded)</td></tr>
</table>

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
randomized placebo-controlled double-blind study, International journal of reproductive biomedicine (Yazd, Iran), 14, 309-16, 2016 **Ref Id** 930344 **Country/ies where the study was carried out** Iran **Study type** RCT **Aim of the study** To assess whether vaginal progesterone decreases preterm birth rate and neonatal complications in women considered to be at high risk	term birth, N (%) | | | Previous pre term birth and short cervix (≤28 mm), N (%) | 12 (24) | 15 (30) **Inclusion criteria** Women with singleton pregnancies at high risk of preterm labour, defined as: women with a previous history of preterm birth (<37 weeks); women with a previous history of preterm birth and short cervix (≤28 mm); women with uterine anomalies or women with uterine fibroids. **Exclusion criteria** Women with chorioamnionitis; allergies to progesterone; fetal anomalies leading to death; excess of amniotic fluid in the amniotic sac; intrauterine growth restriction; hyperthyroidism; gestational diabetes; high blood pressure (≤140/90 mmHg); heart disease; epilepsy and the use of antiepileptic drugs.	suppository in an identical pack as the progesterone group. The composition of the suppository has not been specified, but had the same shape and thickness as the progesterone one. All women received 2 doses of 12 mg IM betamethasone within an interval of 24 hours in the 28 weeks of gestation. Women with symptoms of preterm labour were administered magnesium sulfate (primary dose was 4 g, then 2 g/h for 12 h) and re-entered into the trial, unless they have already given birth.	Those whose cervix was ≤28 mm, underwent a cerclage surgery. Preterm labour was defined as 5 to 6 regular contractions in 30 minutes by ≥2 cm dilation or the presence of progressive dilation or cervical effacement Women were randomised with a computerised list of random allocated numbers. Participants and personnel were blinded to treatment allocation.	Vaginal progesterone: 0/12 Placebo: 4/15 Infant mortality (unclear whether prior to discharge) Vaginal progesterone: 2/50 Placebo: 21/50 Gestational age at birth Vaginal progesterone: 36.5 (3.8) Placebo: 33.6 (4.5)	**Blinding of outcome assessment:** unclear risk (no details reported) **Blinding (performance bias and detection bias):** unclear risk (see details above) **Incomplete outcome data:** low risk (there was a low rate of drop-outs <20% and reasons for these were provided) **Selective reporting:** low risk (outcomes reported match with those in the study protocol http://apps.who.int/trialsearch/Trial3.aspx?trialid=IRCT20101227338 6N2) **Other sources of bias:** low risk

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
of preterm birth due to a previous history of preterm birth, a previous history of preterm birth and a short cervical length (≤28 mm), uterine anomalies or uterine myomas. Study dates November 2010 to April 2012 **Source of funding** Semnan University of Medical Sciences					
Full citation Crowther, C. A., Ashwood, P., McPhee, A. J., Flenady, V., Tran, T., Dodd, J. M., Robinson, J. S., Vaginal progesterone pessaries for pregnant women with a	**Sample size** N= 799 (N=406 randomised to progesterone and N=393 randomised to placebo) **Characteristics** 	**Interventions** Women randomised to the vaginal progesterone group received a vaginal progesterone pessary with 100 mg of progesterone. Women randomised to the placebo group received a vaginal suppository in an identical pack as the progesterone group.	**Details** How gestational age was determined has not been reported. The study protocol did not require to measure cervical length at trial entry or	**Results** Stillbirth Vaginal progesterone: 4/406 Placebo: 5/393 Infant mortality (unclear whether prior discharge) Vaginal progesterone: 1/406 Placebo: 2/393 Early neonatal sepsis	**Limitations** Methodological limitations assessed using the Cochrane collaboration's tool for assessing risk of bias **Random sequence generation:** low risk (central telephone randomisation)

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
previous preterm birth to prevent neonatal respiratory distress syndrome (the PROGRESS Study): A multicentre, randomised, placebo-controlled trial, PLoS Medicine, 14 (9) (no pagination), 2017 **Ref Id** 703165 **Country/ies where the study was carried out** Australia, New Zealand, Canada **Study type** RCT **Aim of the study** To assess whether the use of vaginal progesterone	<table><tr><td>Age, mean (SD)</td><td>30.3 (5.5)</td><td>30.3 (5.6)</td></tr><tr><td>Gestational age at randomisation, median (IQR)</td><td>20.6 (19.3 - 22.1)</td><td>20.4 (19.3-22)</td></tr><tr><td>Current singleton pregnancy ,N (%)</td><td>390 (98)</td><td>385 (99)</td></tr></table> **Inclusion criteria** Women with a live singleton or twin pregnancy, between 18 and <24 weeks gestational age and a previous history of preterm birth at >20 weeks gestational age in their previous pregnancy **Exclusion criteria** Women whose previous preterm birth had been <37 weeks gestation in association with placenta praevia (if it was a multiple pregnancy) or if there had been iatrogenic decisions leading to preterm birth. Women whose current pregnancy was associated with vaginal bleeding after 17+6 weeks requiring hospital admission; preterm pre-labour rupture of membranes prior to trial entry; progesterone treatment after 16 weeks gestational age;	Women had to use 1 capsule every night between from 20 weeks gestation or from randomisation, if this occurred after 20 weeks gestation, until birth or 34 weeks gestation, whichever occurred first. Maximum number of days of treatment was 98.	during the pregnancy. Women were randomised using a central telephone randomisation service. Variable blocks with stratification by plurality of the pregnancy and collaborating centre were done. Participants, staff and investigators were blinded to treatment allocation.	Vaginal progesterone: 0/402 Placebo: 2/388 Health related quality of life (SF-36). Mean (SD); better indicated by higher values. *General health* Vaginal progesterone:76.61 (17.8) Placebo: 75.08 (17.8) *Social functioning* Vaginal progesterone:69.55 (27) Placebo: 73.35 (25.7) *Emotional role* Vaginal progesterone: 82.21 (32.2) Placebo: 85.52 (33.6) *Mental health* Vaginal progesterone:76.92 (17.9) Placebo: 77.24 (16.2)	**Allocation concealment:** unclear risk (details not reported) **Blinding of participants and personnel:** low risk (blinded) **Blinding of outcome assessment:** low risk (blinded) **Blinding (performance bias and detection bias):** low risk (see details above) **Incomplete outcome data:** low risk (there was a low rate of drop-outs <20% and reasons for these were provided) **Selective reporting:** low risk (outcomes reported match with those in the study protocol https://journals.plos.org/plosmedicine/article?id=10.1371/journal.pmed.1002390; attached as a supplement) **Other sources of bias:** low risk

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
in women with previous preterm birth reduces the risk of preterm birth in the current pregnancy and associated neonatal and maternal morbidity **Study dates** February 2006 - September 2012 **Source of funding** Australian National Health and Medical Research Council	contraindication to continuation of the pregnancy; contraindication to progesterone therapy				
Full citation Dodd, Jodie M., Jones, Leanne, Flenady, Vicki, Cincotta, Robert, Crowther, Caroline A., Prenatal administration of	**Sample size** K= 9 RCTs (N=1892) **Characteristics** Akbari 2009 Demographic characteristics could not be extracted as the study is written in Arabic. The systematic review did not report any demographic characteristics.	**Interventions** Akbari 2009 Intervention: 100 mg vaginal progesterone Control: No treatment, women were monitored When intervention started/ended: between 24 and 34 weeks of gestation.	**Details** A literature search was done in the Cochrane Pregnancy and Childbirth's Trials Register, hand searches of	**Results** **Preterm birth <34 weeks** Akbari 2009 Progesterone: 2/69 Placebo: 16/72 Cetingoz 2011* Progesterone: 7/80 Placebo: 17/70	**Limitations** Limitations Quality of the Cochrane SR Systematic review assessed using AMSTAR checklist. **Total score**:16/16 Limitations for each of the included studies assessed with the Cochrane Risk of Bias Tool

<table>
<tr><th>Study details</th><th>Participants</th><th>Interventions</th><th>Methods</th><th>Outcomes and Results</th><th>Comments</th></tr>
<tr>
<td>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
Iran, Brazil, US and India

Study type
Cochrane systematic review

Aim of the study
To assess the efficacy and safety of oral and vaginal progesterone in women considered to be at higher</td>
<td>Cetingoz 2011*
<table>
<tr><td></td><td>Vaginal progesterone (N=80)</td><td>Placebo (N=70)</td></tr>
<tr><td>Age between 18 and 35, N (%)*</td><td>72 (90)</td><td>64 (91.4)</td></tr>
<tr><td>Age ≥35, N (%)*</td><td>8 (10)</td><td>6 (9)</td></tr>
<tr><td>Previous preterm birth, N (%)¥</td><td>37 (46.2)</td><td>34 (40.6)</td></tr>
</table>
¥Based on the whole population of women included in the original study. In this systematic review, only women with previous preterm birth have been included

da Fonseca 2003*
<table>
<tr><td></td><td>Vaginal progesterone(N=72)</td><td>Placebo (N=70)</td></tr>
<tr><td>Age¥</td><td>27.6</td><td>26.8</td></tr>
<tr><td>Previous preterm birth, N (%)</td><td>66 (90.3)</td><td>68 (97.2)</td></tr>
</table>
</td>
<td>Cetingoz 2011
Intervention: 100 mg vaginal progesterone
Control: placebo
When intervention started/ended: between 24 and 34 weeks of gestation

da Fonseca 2003
Intervention: 100 mg vaginal progesterone
Control: placebo
When intervention started/ended: from 24 weeks until 28 weeks' gestation, or birth if earlier.

Fonseca 2007
Intervention: 200 mg vaginal progesterone
Control: placebo
Treatment started/ended:≥ 20 weeks gestational age

Glover 2011
Intervention: 200 mg oral progesterone twice/day
Control: placebo
When intervention started/ended: was initiated between 16+0 and 19+6 weeks and continued until the end of the 33rd week of gestation.</td>
<td>30 journals and the proceedings of major conferences were also searched. No language restrictions were applied. Two review authors assessed all potentially eligible studies. Disagreements were resolved with consensus. Two review authors extracted data, and authors of the original reports were contacted if any information was unclear. Risk of bias was assessed by 2 authors.</td>
<td>da Fonseca 2003
Progesterone:2/72
Placebo: 13/70

Majhi 2009
Progesterone: 2/50
Placebo: 3/50

Rai 2009
Progesterone: 22/74
Placebo: 37/74

Cetingoz 2011
Progesterone: 2/37
Placebo:9/34

Fonseca 2007*
Progesterone: 26/125
Placebo: 45/125

Stillbirth
Fonseca 2007
Progesterone: 1/136
Placebo: 1/138

Hassan 2011
Progesterone: 5/235
Placebo: 6/223

O'Brien 2007
Progesterone: 5/309
Placebo: 4/302

Infant mortality (unclear whether prior to discharge)
Akbari 2009*
Progesterone: 3/69</td>
<td>Akbari 2009
Random sequence generation: unclear risk
Allocation concealment: unclear risk
Blinding of participants and personnel: unclear risk
Blinding of outcome assessment: unclear risk
Incomplete outcome data: unclear risk
Selective reporting: low risk
Other bias: unclear risk (reasons not reported)

Cetingoz 2011
Random sequence generation: low risk
Allocation concealment: low risk
Blinding of participants and personnel: low risk
Blinding of outcome assessment: unclear risk
Incomplete outcome data: low risk
Selective reporting (reporting bias): low risk
Other bias: low risk

Fonseca 2007
Random sequence generation: low risk of bias
Allocation concealment: low risk of bias</td>
</tr>
</table>

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
risk of preterm birth **Study dates** The initial 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,	Uterine malforma-tions, N (%) 4 (5.6) 1 (1.4) Incompetent cervix, N (%) 2 (4.1) 1 (1.4) Gestational age at intake¥ 26.5 25.2 ¥Unclear whether reported as a mean or median (no SD or IQR was reported) Fonseca 2007* Vaginal progesterone (N=125) / Placebo (N=125) Age, median (IQR) 29 (24-34) / 29 (24-34) Singleton, N (%) 114 (91.2) / 112 (89.6) Glover 2011* Oral progesterone (N=19) / Placebo (N=14)	Hassan 2011 Intervention: 90 mg vaginal progesterone Control: placebo Treatment started/ended:≥ 20 weeks gestational age Majhi 2009 Intervention: 100 mg vaginal progesterone once daily at night Control: no treatment, just monitoring according to protocol When intervention started/ended: 20-24 weeks' gestation until 36 weeks. O'Brien 2007 Intervention: 90 mg vaginal progesterone once daily at night Control: placebo When intervention started/ended: Started between 18+0 and 22+6. It was unclear when did it end Rai 2009 Intervention: 100 mg oral progesterone, twice/day Control: placebo When intervention started/ended: 18-24 weeks until 36 weeks or delivery.		Placebo: 10/72 Cetingoz 2011* Progesterone: 3/80 Placebo: 3/70 Fonseca 2007* Progesterone: 2/136 Placebo: 7/138 Hassan 2011* Progesterone: 3/235 Placebo: 5/223 Rai 2009* Progesterone: 3/74 Placebo:7/74 O'Brien 2007* Progesterone: 6/309 Placebo:7/302 **Gestational age at birth** O'Brien 2007* Progesterone: 33.6 (3.8), N= 309 Placebo: 36.6 (4.2), N=302 Glover 2011* Progesterone: 37.0 (2.7), N= 19 Placebo: 35.9 (2.6), N=14 **Neonatal sepsis (unclear whether onset was up to 72 hours)**	da Fonseca 2003 **Random sequence generation:** low risk Allocation concealment: low risk **Blinding of participants and personnel:** low risk **Blinding of outcome assessment:** low risk **Incomplete outcome data:** low risk **Selective reporting:** low risk **Other bias:** low risk Glover 2011 **Random sequence generation:** low risk **Allocation concealment:** low risk **Blinding of participants and personnel:** low risk **Blinding of outcome assessment:** unclear risk **Incomplete outcome data:** low risk

<table>
<tr><th>Study details</th><th>Participants</th><th>Interventions</th><th>Methods</th><th>Outcomes and Results</th><th>Comments</th></tr>
<tr>
<td>Queensland, Australia; The University of Adelaide, Discipline of Obstetrics and Gynaecology, Australia. 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</td>
<td>
<table>
<tr><td>Age, mean (SD)</td><td>29.3 (4.7)</td><td>27.2 (4.9)</td></tr>
<tr><td>Previous preterm birth, N (%)</td><td>19 (100)</td><td>14 (100)</td></tr>
<tr><td>Gestational age at randomisation, mean (SD)</td><td>16.9 (2.6)</td><td>18.2 (2.7)</td></tr>
</table>
<u>Hassan 2011</u>*
<table>
<tr><td></td><td>Vaginal progesterone (N=235)</td><td>Placebo (N=223)</td></tr>
<tr><td>Age, mean (SD)</td><td>26.5 (5.8)</td><td>26.2 (5.1)</td></tr>
<tr><td>Cervical length, mean mm (SD)</td><td>17 (2.5)</td><td>17 (2.8)</td></tr>
</table>
<u>Majhi 2009</u>*
<table>
<tr><td></td><td>Vaginal progesterone (N=50)</td><td>Control (N=50)</td></tr>
<tr><td>Age, mean (SD)</td><td>26.5 (3.5)</td><td>26.4 (3.2)</td></tr>
<tr><td>Previous preterm birth, N (%)</td><td>25 (50)</td><td>25 (50)</td></tr>
</table>
</td>
<td></td>
<td></td>
<td><u>Akbari 2009</u>
Progesterone: 0/69
Placebo: 4/72

<u>Hassan 2011</u>
Progesterone: 7/235
Placebo: 6/223

<u>Fonseca 2007</u>
Progesterone: 3/316
Placebo: 11/138

<u>Majhi 2009</u>
Progesterone: 0/50
Placebo: 3/50

* data extracted from the original study</td>
<td><u>Hassan 2011</u>
Random sequence generation: low risk of bias
Allocation concealment: low risk of bias
Blinding of participants and personnel: low risk of bias
Blinding of outcome assessment: low risk of bias
Incomplete outcome data: low risk of bias
Selective reporting: low risk of bias

<u>Majhi 2009</u>
Random sequence generation: low risk
Allocation concealment: low risk
Blinding of participants and personnel: unclear risk
Blinding of outcome assessment: unclear risk
Incomplete outcome data: low risk
Selective reporting: low risk
Other bias: unclear risk

<u>O'Brien 2007</u></td>
</tr>
</table>

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	Previous premature rupture of membranes and preterm birth, N (%) — 25 (50) — 25 (50) Previous abortion - 1st trimester, N (%) — 28 (56) — 26 (52) Previous abortion - 2nd trimester, N (%) — 6 (12) — 7 (14) O'Brien 2007* Vaginal progesterone (N=309) / Control (N=302) Age, mean (SD) — 27.1 (5.8) — 27.3 (5.6) Previous preterm birth, N (%) — 309 (100) — 302 (100) Gestational age at randomisa — 19.9 (2.1) — 20.1 (3.3)				**Random sequence generation:** low risk **Allocation concealment:** low risk **Blinding of participants and personnel:** low risk **Blinding of outcome assessment:** low risk **Incomplete outcome data:** low risk **Selective reporting:** low risk **Other bias:** low risk Rai 2009 **Random sequence generation:** low risk **Allocation concealment:** low risk **Blinding of participants and personnel:** low risk **Blinding of outcome assessment:** unclear risk **Incomplete outcome data:** low risk **Selective reporting:** low risk **Other bias:** low risk **Other information** The data presented in this evidence table has been adapted from the Cochrane systematic review. We present the data that is relevant to the aims of this review. Individual studies were retrieved for accuracy and to check if other

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	tion, mean (SD)				outcomes of interest were reported. The risk of bias assessment was reproduced from the Cochrane review. Data extracted by the NGA technical team from the original study has been marked with an *.

Rai 2009*

	Oral progesterone (N=74)	Placebo (N=74)
Age, mean (SD)	26 (3.24)	25.72 (3.4)
Previous preterm birth, N (%)	74 (100)	74 (100)
Gestational age, mean (SD)	20.69 (2.83)	20.73 (1.78)

Inclusion criteria
RCTs of published and unpublished studies, 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
Studies in which progesterone was administered in the first trimester for the prevention of miscarriage; studies that utilised quasi-randomised methodology or cross-over design; studies where progesterone was administered as an acute tocolytic medication

<table>
<tr><th>Study details</th><th>Participants</th><th>Interventions</th><th>Methods</th><th>Outcomes and Results</th><th>Comments</th></tr>
<tr>
<td>Full citation
Norman, J. E., Marlow, N., Messow, C. M., Shennan, A., Bennett, P. R., Thornton, S., Robson, S. C., McConnachie, A., Petrou, S., Sebire, N. J., Lavender, T., Whyte, S., Norrie, J., Does progesterone prophylaxis to prevent preterm labour improve outcome? A randomised double-blind placebo-controlled trial (OPPTIMUM), Health Technology Assessment, 22, 1-304, 2018

Ref Id
916970</td>
<td>Sample size
N=1225 (N= 615 randomised to vaginal progesterone and N=610 randomised to placebo)

Characteristics
<table>
<tr><th></th><th>Vaginal progesterone (N=615)</th><th>Placebo (N=610)</th></tr>
<tr><td>Maternal age, mean (SD)</td><td>31.5 (5.6)</td><td>31.4 (5.8)</td></tr>
<tr><td>History of preterm birth (any), N (%)</td><td>493 (80)</td><td>473 (78)</td></tr>
<tr><td>History of spontaneous preterm birth, N (%)</td><td>473 (78)</td><td>448 (75)</td></tr>
<tr><td>Cervix length ≤25 mm, N (%)</td><td>137 (38)</td><td>119 (34)</td></tr>
</table>
Inclusion criteria
Women with risk factors for preterm birth (including previous preterm birth, cervical length ≤25mm, second trimester loss, preterm premature rupture of the membranes or history of cervical</td>
<td>Interventions
Interventions were started between 22 and 24 weeks of gestational age and ended at 34 weeks or birth of the baby, whichever was sooner.
Women randomised to the progesterone group received 200 mg of vaginal progesterone/day.
Women randomised to the placebo group received identical placebo capsules.</td>
<td>Details
Gestational age was determined by US scan done before 16 weeks of pregnancy.

Cervical length was determined through US scan at 18+0-24+0 week’s gestation.

Participants were randomised though a web-based program.

Study was double-blind. Sample size calculations were done and with a power of 80%, it was established that a sample size of 375 women per group were</td>
<td>Results
<u>Preterm birth <34 weeks*</u>
Vaginal progesterone: 88/592
Placebo: 101/590

<u>Stillbirth</u>
Vaginal progesterone: 8/600
Placebo: 7/597

<u>Infant mortality</u>
Vaginal progesterone: 1/600
Placebo: 6/597

<u>Gestational age at birth</u>
Vaginal progesterone: 36.9 (4.1), N=600
Placebo:36.8 (4.2), N=597

<u>HRQoL as measured by the EuroQoL-5 Dimensions health utility scores, mean (SD); better indicated by lower values</u>
Change from baseline to birth
Vaginal progesterone: -0.021 (0.207), N=191
Placebo:-0.023 (0.220), N=199</td>
<td>Limitations
<u>Methodological limitations assessed using the Cochrane collaboration´s tool for assessing risk of bias</u>
Random sequence generation: low risk of bias
Allocation concealment: low risk of bias
Blinding of participants and personnel: low risk of bias
Blinding of outcome assessment: low risk of bias
Incomplete outcome data: low risk
Selective reporting: low risk of bias
Other bias: high risk of bias

Other information: The data presented in this evidence table has been adapted from the original study. One additional study published by the same author (Norman 2016) has been retrieved. Additional data extracted from this study has been extracted has been marked with an*</td>
</tr>
</table>

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Country/ies where the study was carried out UK **Study type** RCT and HTA report **Aim of the study** To assess the effect of vaginal progesterone prophylaxis in women at high risk of preterm birth **Study dates** February 2009 to April 2013 **Source of funding** Medical Research Council (MRC)	procedure to treat abnormal smears), singleton pregnancies, with gestational age established by US scan before 16 weeks gestational age. **Exclusion criteria** Women < 16 years old at screening		needed to observe a reduction from 70% to 27% in preterm births between the progesterone and placebo groups.	*Change from baseline to 12 month follow-up* Vaginal progesterone: -0.009 (0.213), N=279 Placebo:-0.015 (0.221), N=274 <u>Bayley-III cognitive composite score at 2 years, mean (SD), better indicated by higher values</u> Vaginal progesterone: 99.7 (14.7), N= 410 Placebo: 99.5 (15.0), N=425 <u>Moderate or severe neurodevelopmental impairment</u> Vaginal progesterone: 47/379 Placebo:35/403 <u>Visual impairment</u> Vaginal progesterone: 0/447 Placebo: 4/466 <u>Hearing impairment</u> Vaginal progesterone: 1/466 Placebo:2/465	
Full citation Romero, Roberto, Conde-Agudelo, Agustin, Da	**Sample size** N= 974 (N=498 randomised to the vaginal progesterone group and N=476 randomised to the placebo group)	**Interventions**	**Details** A search was conducted from inception until the 30th of September	**Results** <u>Preterm birth <34+0 weeks</u> Vaginal progesterone: 86/498 Placebo: 126/476	**Limitations** <u>Limitations have been assessed using AMSTAR</u> Total score: 13/16.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Fonseca, Eduardo, O'Brien, John M., Cetingoz, Elcin, Creasy, George W., Hassan, Sonia S., Nicolaides, Kypros H., Vaginal progesterone for preventing preterm birth and adverse perinatal outcomes in singleton gestations with a short cervix: a meta-analysis of individual patient data, American Journal of Obstetrics and Gynecology, 218, 161-180, 2018 **Ref Id** 930508 **Country/ies where the study was carried out** UK, USA and Turkey	**Characteristics** Maternal age, median (IQR): Vaginal progesterone (N=498) 28 (23.6-33); Placebo (N=476) 27.5 (23.5-32.8) Gestational age, median (IQR): Vaginal progesterone (N=498) 22.6 (21.4-23.6); Placebo (N=476) 22.6 (21.4-23.4) Cervix <10 mm, N (%): Vaginal progesterone (N=498) 48 (9.6); Placebo (N=476) 57 (12) Cervix 10 to 20 mm, N (%): Vaginal progesterone (N=498) 379 (76.1); Placebo (N=476) 362 (76) Cervix 12 to 25 mm, N (%): Vaginal progesterone (N=498) 71 (14.3); Placebo (N=476) 57 (12) Inclusion criteria RCTs comparing vaginal progesterone (any dose) with placebo or no treatment for the prevention of preterm birth and/or adverse perinatal outcomes in women with a singleton gestation and a short cervix (≤25 mm) Exclusion criteria Quasi-randomised trials, trials that assessed vaginal progesterone in	Fonseca 2007: Intervention: 200 mg/d vaginal progesterone; Comparison: Placebo; Start/ end week of treatment: 24 to 33+6/7 O'Brien 2007: Intervention: 90 g/d vaginal progesterone; Comparison: Placebo; Start/ end week of treatment: 18-22 to 37+0/7 Cetingoz 2011: Intervention: 100 mg/d vaginal progesterone; Comparison: Placebo; Start/ end week of treatment: 24 to 34 Hassan 2011	2017 in MEDLINE, EMBASE, LILACS, CINAHL, the Cochrane Central Register, research registers of ongoing trials, and Google Scholar. No language restrictions were set. Grey literature was also searched to locate unpublished studies. Two authors assessed all the eligible studies. Disagreements were resolved by consensus. Authors of the original studies were provided a standardise sheet for data extraction. This information	I2= 0% Stillbirth Vaginal progesterone: 9/498 Placebo: 8/476 I2= 0% Infant mortality (unclear if prior discharge) Vaginal progesterone:7/498 Placebo:15/476 I2= 0% Gestational age at birth Mean gestational age at birth in the intervention group was 0.74 higher (0.18 to 1.3 higher) Proven neonatal sepsis (unclear whether early onset) Vaginal progesterone: 18/494 Placebo: 28/470 Bayley-III cognitive composite score (age 2 years); better indicated by higher values Vaginal progesterone: 95.5 (16.1), N=88 Placebo: 97.7 (16.9), N= 80 MD= -2.17 (-7.16 to 2.83)	The following aspects were not met in this IPD MA: review authors did not provide a list of excluded studies, justifying the exclusions; sources of funding of the included studies were not reported; publication bias was not discussed **Limitations for each of the included studies assessed with the Cochrane Risk of Bias Tool** Fonseca 2007 **Random sequence generation:** low risk of bias **Allocation concealment**: low risk of bias **Blinding of participants and personnel:** low risk of bias **Blinding of outcome assessment:** low risk of bias **Incomplete outcome data:** low risk of bias **Selective reporting:** low risk of bias **Other bias:** low risk of bias O'Brien 2007 **Random sequence generation:** low risk of bias

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Study type IPD MA **Aim of the study** To assess whether vaginal progesterone prevents preterm birth and improves perinatal outcomes in women with a short cervix (≤ 25 mm) **Study dates** Searches were done from inception until 30th September 2018 **Source of funding** National Institutes of Health, Department of Health and Human Services (USA) (extracted	women with threatened or arrested preterm birth, and trials in which vaginal progesterone was administered during the first 3 months of pregnancy to prevent miscarriage	90 mg/d vaginal progesterone; Placebo; 20-23+6/7 to 36+6/7 Norman 2016 200 mg/day vaginal progesterone; Placebo; 22-24 to 34	was cross-checked with the data from the original studies and authors were contacted as necessary. Risk of bias was done by 2 investigators with the Cochrane Risk of Bias Tool. Disagreements were resolved by consensus.	Moderate/severe neurodevelopmental impairment (age 2 years) Vaginal progesterone:10/81 Placebo:7/77 Visual or hearing impairment (age 2 years) Vaginal progesterone: 0/100 Placebo:2/87	**Allocation concealment:** low risk of bias **Blinding of participants and personnel**: low risk of bias **Blinding of outcome assessment**: low risk of bias **Incomplete outcome data:** low risk of bias **Selective reporting:** low risk of bias **Other bias:** low risk of bias Cetingoz 2011 **Random sequence generation:** low risk of bias **Allocation concealment:** low risk of bias **Blinding of participants and personnel:** low risk of bias **Blinding of outcome assessment:** low risk of bias **Incomplete outcome data:** low risk of bias **Selective reporting:** low risk of bias **Other bias:** low risk of bias Hassan 2011 **Random sequence generation:** low risk of bias **Allocation concealment**: low risk of bias

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
from Romero 2016). Conflicts of interest (extracted from Romero 2016 unless otherwise specified): John M. O'Brien was involved in studies sponsored by a manufacturer of progesterone gel. He was a consultant and has received honoraria from Cook Biotech (extracted from O'Brien 2007). The co-author worked in advisory boards for Watson Pharmaceuticals (company with financial interest in marketing vaginal progesterone gel). This co-author and					**Blinding of participants and personnel:** low risk of bias **Blinding of outcome assessment:** low risk of bias **Incomplete outcome data:** low risk of bias Selective reporting: low risk of bias **Other bias:** low risk of bias Norman 2016 **Random sequence generation:** low risk of bias **Allocation concealment:** low risk of bias **Blinding of participants and personnel:** low risk of bias **Blinding of outcome assessment:** low risk of bias **Incomplete outcome data:** low risk of bias for obstetric and neonatal primary outcomes; high risk of bias for childhood primary outcome **Selective reporting:** low risk of bias **Other bias:** high risk of bias **Other information** The risk of bias assessment was reproduced from the original study.

<table>
<tr><th>Study details</th><th>Participants</th><th>Interventions</th><th>Methods</th><th>Outcomes and Results</th><th>Comments</th></tr>
<tr><td>others are listed in a patent on the use of progesterone products to prevent preterm birth. George W. Creasy is a former employee of Columbia Laboratories.</td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Full citation
van Os, Melanie A., van der Ven, A. Jeanine, Kleinrouweler, C. Emily, Schuit, Ewoud, Kazemier, Brenda M., Verhoeven, Corine J., de Miranda, Esteriek, van Wassenaer-Leemhuis, Aleid G., Sikkema, J. Marko, Woiski, Mallory D., Bossuyt, Patrick M., Pajkrt, Eva, de</td><td>Sample size
N=80 (N= 41 randomised to vaginal progesterone and N=39 randomised to placebo)

Characteristics<table><tr><th></th><th>Vaginal progesterone (N=41)</th><th>Placebo (N=39)</th></tr><tr><td>Age, mean (SD)</td><td>31 (5)</td><td>30 (5)</td></tr><tr><td>Gestational age at randomisation, median (IQR)</td><td>21.7 (20.7-22.6)</td><td>21.6 (20.9-22.7)</td></tr></table></td><td>Interventions
Women randomised to the vaginal progesterone group received a vaginal suppository with 200 mg of micronized progesterone (Utrogestan).
Women randomised to the placebo group received a vaginal suppository with the same appearance as the progesterone group (Medicaps).
Women had to use 1 capsule daily between 22 and 34 weeks gestation.</td><td>Details
How gestational age was determined or how was preterm birth defined has not been reported.
Cervical length was assessed by a US during the 18 to 22 weeks of gestation.
Short cervix was defined as cervical length ≤30 mm measured twice within 2 weeks.</td><td>Results
<u>Preterm birth < 34 weeks</u>
Vaginal progesterone: 5/41
Placebo: 6/39

<u>Infant mortality before discharge</u>
Vaginal progesterone: 1/41
Placebo: 2/39

<u>Proven sepsis</u>
<u>Vaginal progesterone:</u> 0/41
Placebo: 0/39</td><td>Limitations
<u>Methodological limitations assessed using the Cochrane collaboration's tool for assessing risk of bias</u>

Random sequence generation: low risk (computer-generated)
Allocation concealment: unclear risk (details not reported)
Blinding of participants and personnel: low risk (double blinded)
Blinding of outcome assessment: unclear risk (no details reported)
Blinding (performance bias and detection bias): unclear risk (see details above)</td></tr>
</table>

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Groot, Christianne J. M., Mol, Ben Willem J., Haak, Monique C., Preventing Preterm Birth with Progesterone in Women with a Short Cervical Length from a Low-Risk Population: A Multicenter Double-Blind Placebo-Controlled Randomized Trial, American Journal of Perinatology, 32, 993-1000, 2015 **Ref Id** 930538 **Country/ies where the study was carried out** The Netherlands **Study type**	Cervical length, median mm (IQR) | 26 (23-29) | 27 (25-28) **Inclusion criteria** Women with a singleton pregnancy and a cervical length ≤30 mm **Exclusion criteria** Women <18 years old; cervical cerclage; previous preterm birth <34 weeks gestation age; preterm labour or congenital malformations.		Randomisation was web-based, study was double blinded.		**Incomplete outcome data:** low risk (no drop-outs were reported, ITT analysis) **Selective reporting:** unclear risk (protocol does not appear to have been registered)

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
RCT **Aim of the study** To assess whether vaginal progesterone decreases preterm birth rate and neonatal complications in low-risk pregnant women with a short cervix (≤ 30 mm) Study dates Not reported **Source of funding** ZonMw					

Appendix E – Forest plots

Comparison 1. Vaginal progesterone versus placebo

Critical outcomes

Figure 1: Preterm birth <34+0 weeks

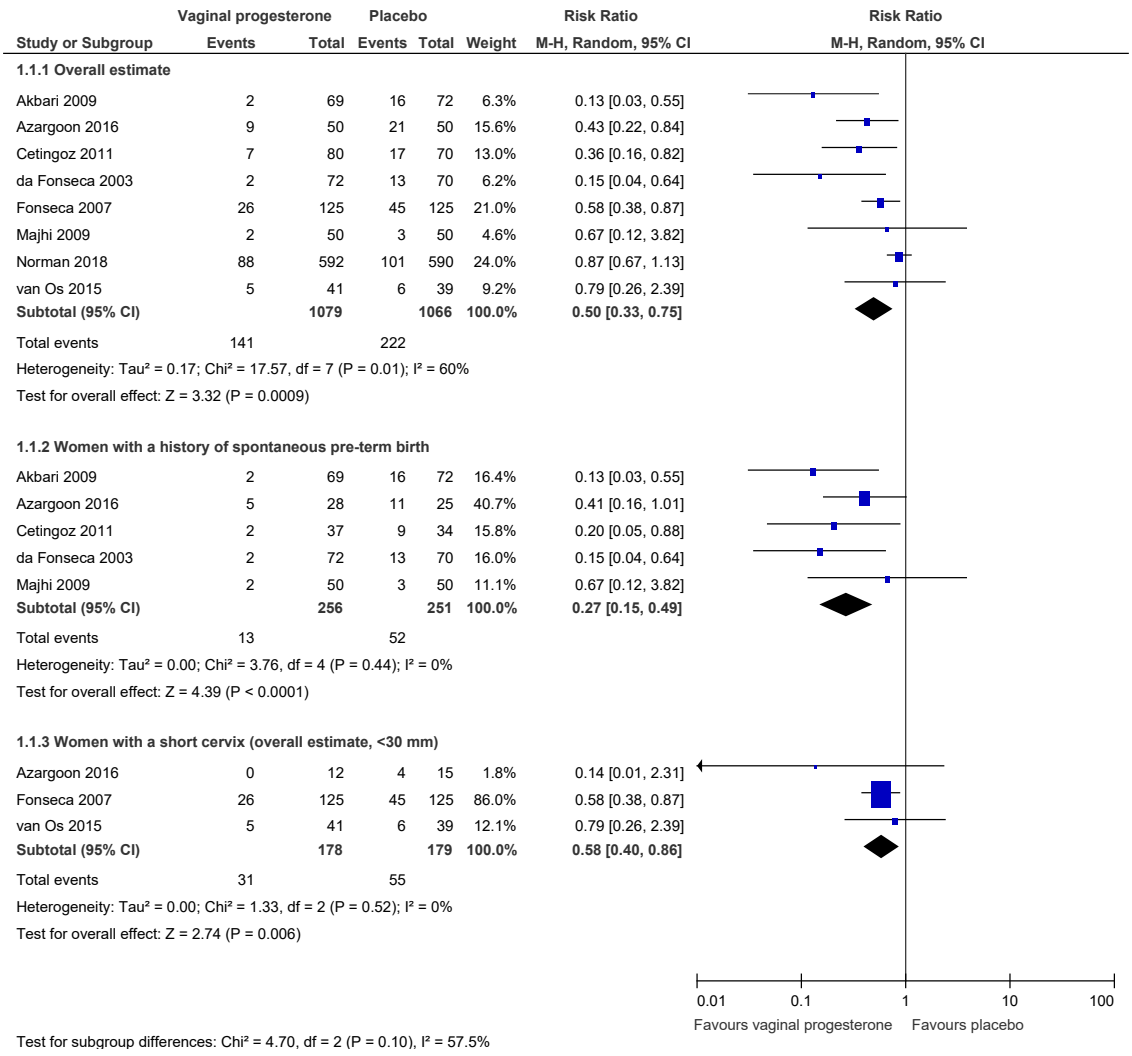


Figure 2: Stillbirth

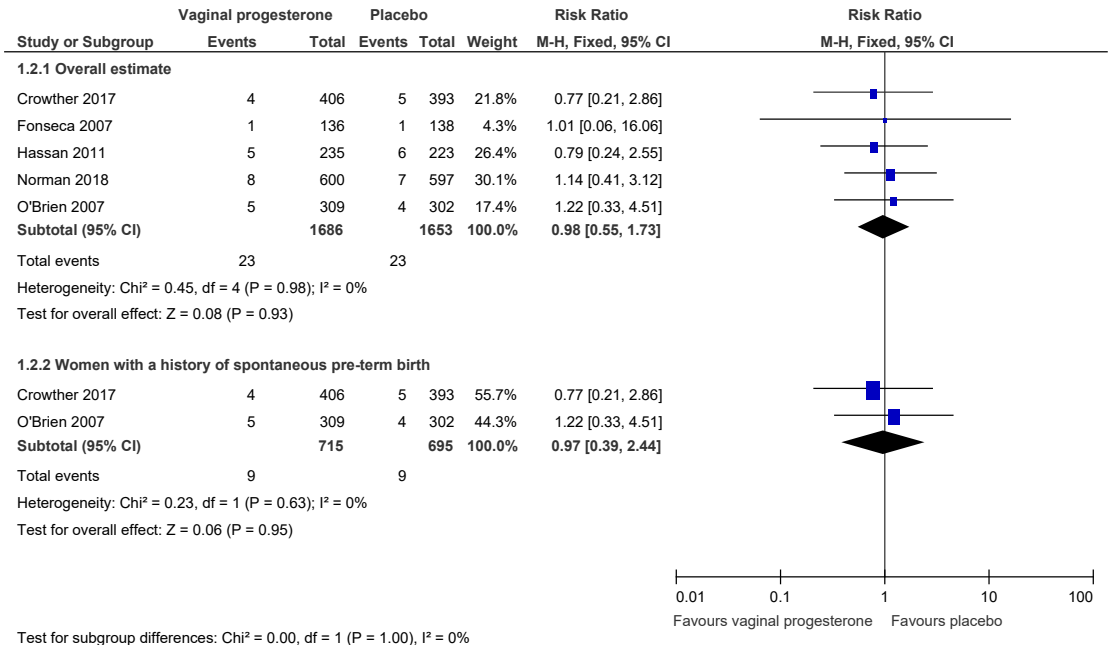
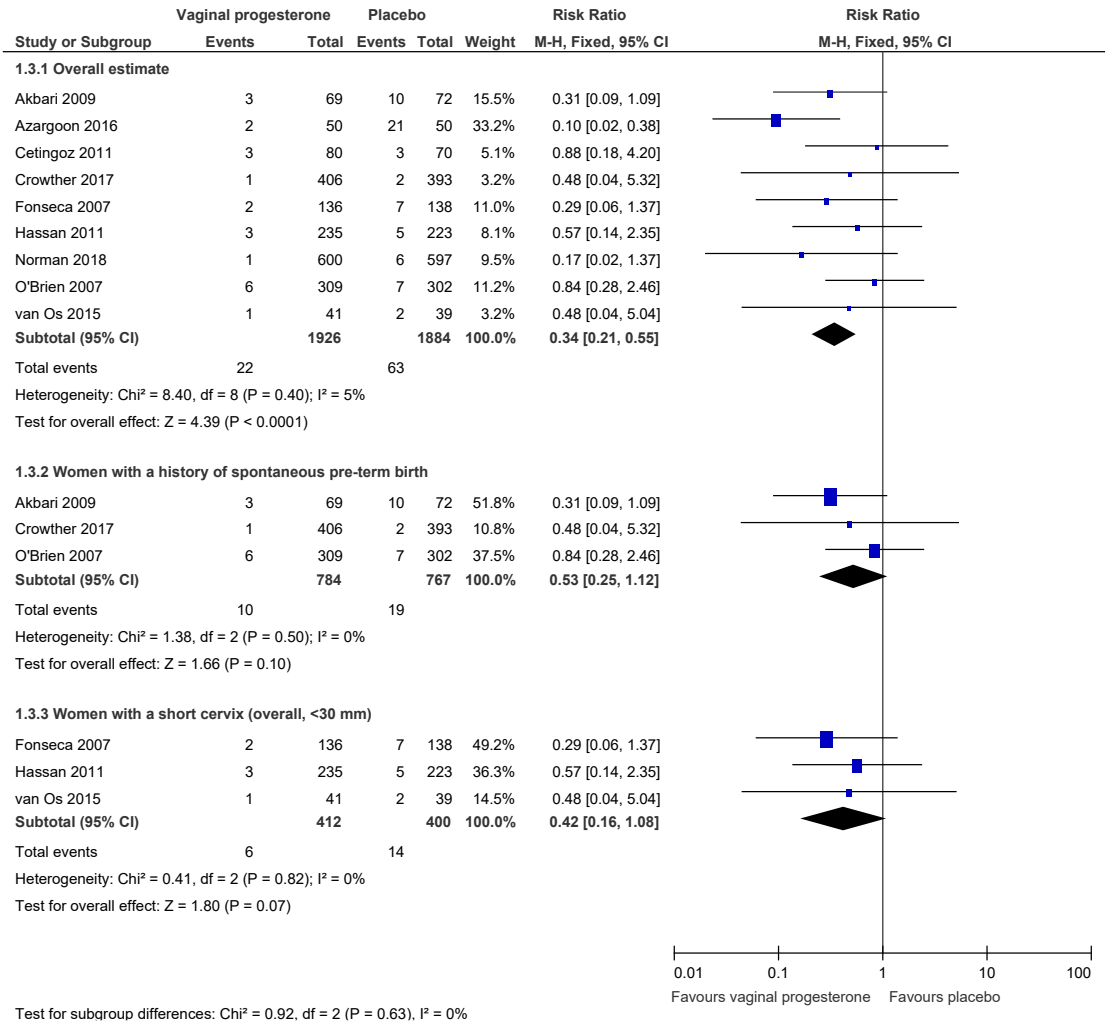


Figure 3: Infant mortality



Important outcomes

Figure 4: Gestational age at birth (mean weeks)

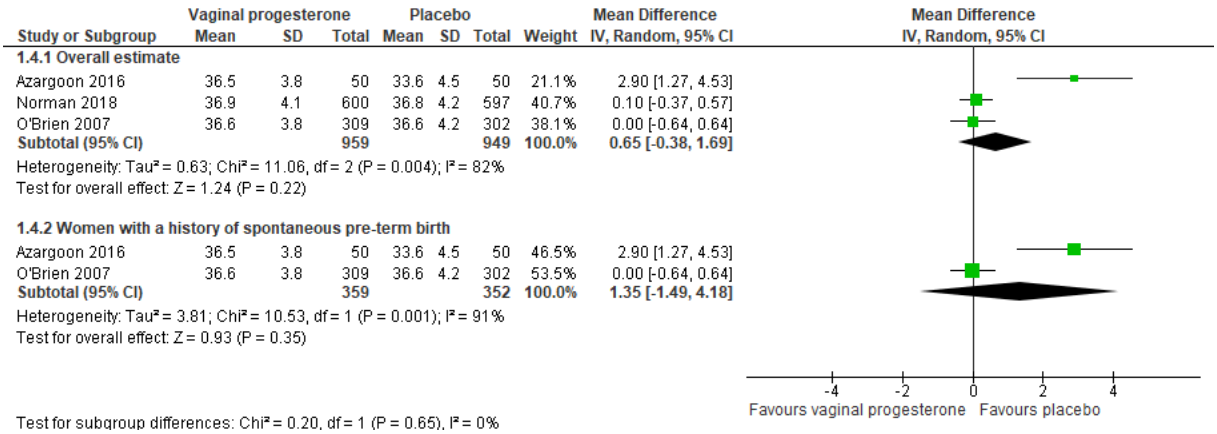


Figure 5: Neonatal sepsis

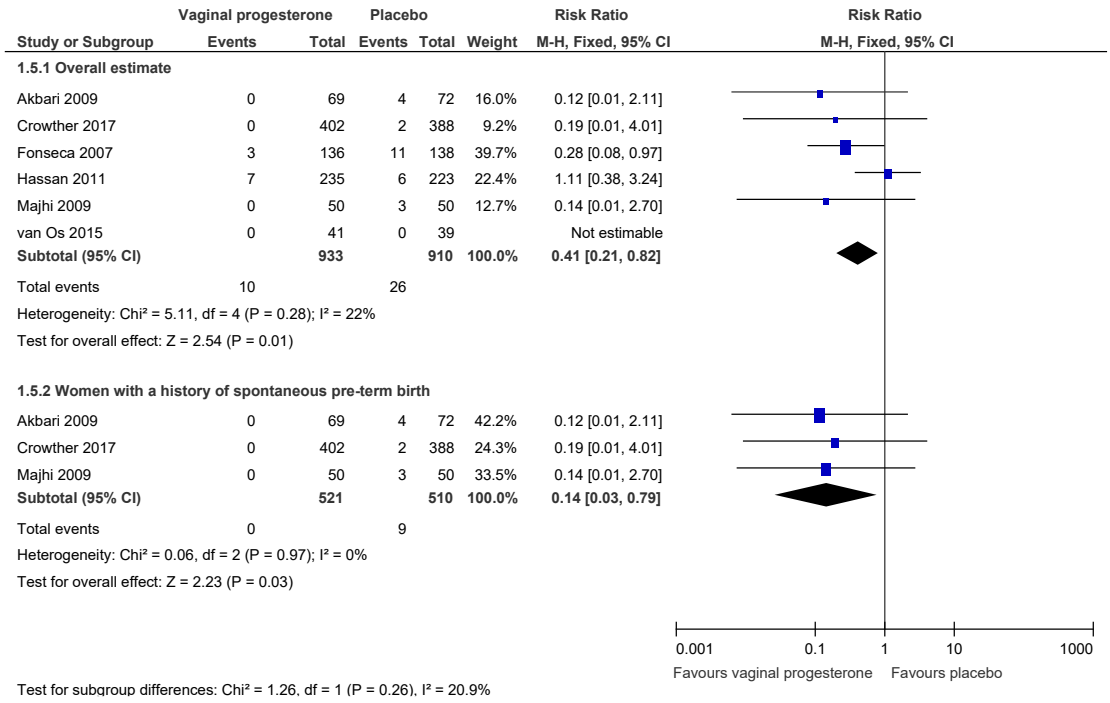
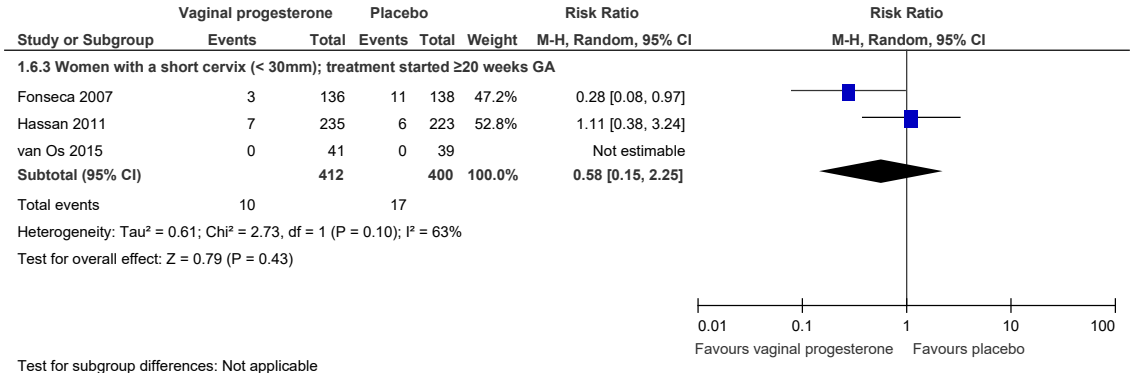


Figure 6: Neonatal sepsis; women with a short cervix (<30 mm); treatment started ≥ 20 weeks gestational age



[This figure is presented separately from figure 5 because a random effects model was utilised due to high heterogeneity for this subgroup]

Comparison 2. Oral progesterone versus placebo

Critical outcomes

Figure 7: Infant mortality

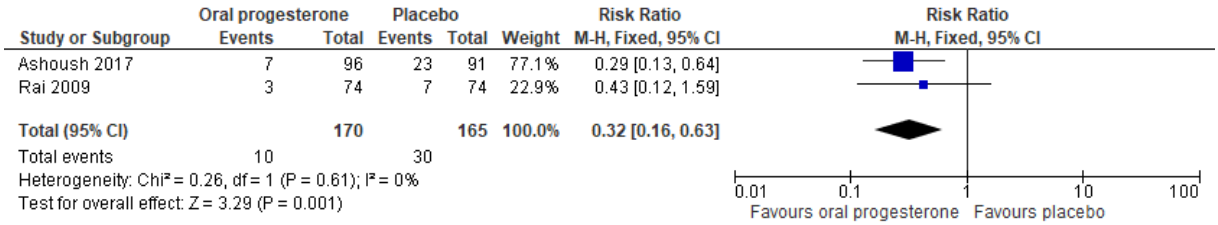
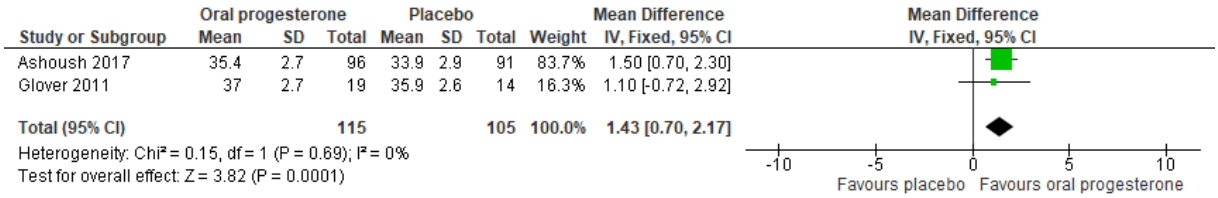


Figure 8: Gestational age at birth (mean weeks)



Appendix F – GRADE tables

Table 11: Comparison 1. Vaginal progesterone versus placebo

Quality assessment							Number of patients		Effect			
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Vaginal progesterone	Placebo	Relative (95% CI)	Absolute	Quality	Importance
Preterm birth <34+0 weeks - Overall estimate												
8 (Akbari 2009, Azargoon 2016, Cetingoz 2011, da Fonseca 2003, Fonseca 2007, Majhi 2009, Norman 2018, van Os 2015)	Randomised trials	Serious[1]	Serious[2]	No serious indirectness	No serious imprecision	None	141/1079 (13.1%)	222/1066 (20.8%)	RR 0.50 (0.33 to 0.75)	104 fewer per 1000 (from 52 fewer to 140 fewer)	LOW	CRITICAL
Preterm birth <34+0 weeks – Subgroup analysis: Women with a history of spontaneous preterm birth												
5 (Akbari 2009, Azargoon 2016, Cetingo 2011, da Fonseca 2003, Majhi 2009)	Randomised trials	Serious[3]	No serious inconsistency	No serious indirectness	No serious imprecision	None	13/256 (5.1%)	52/251 (20.7%)	RR 0.27 (0.15 to 0.49)	151 fewer per 1000 (from 106 fewer to 176 fewer)	MODERATE	CRITICAL
Preterm birth <34+0 weeks - Subgroup analysis: Women with a short cervix (overall estimate, <30 mm)												
3 (Azargoon 2016, Fonseca 2007, van Os 2015)	Randomised trials	Serious[4]	No serious inconsistency	No serious indirectness	Serious[5]	None	31/178 (17.4%)	55/179 (30.7%)	RR 0.58 (0.40 to 0.86)	129 fewer per 1000 (from 43 fewer to 184 fewer)	LOW	CRITICAL
Preterm birth <34+0 weeks - Subgroup analysis: Women with a short cervix (≤25 mm)												

Quality assessment							Number of patients		Effect		Quality	Importance
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Vaginal progesterone	Placebo	Relative (95% CI)	Absolute		
1 (Romero 2018)	Randomised trials	Serious[6]	No serious inconsistency	No serious indirectness	Serious[5]	None	86/498 (17.3%)	126/476 (26.5%)	RR 0.65 (0.51 to 0.83)	93 fewer per 1000 (from 45 fewer to 130 fewer)	LOW	CRITICAL
Stillbirth - Overall estimate												
5 (Crowther 2017, Fonseca 2007, Hassan 2011, Norman 2018, O'Brien 2007)	Randomised trials	Serious[7]	No serious inconsistency	No serious indirectness	Very serious[8]	None	23/1686 (1.4%)	23/1653 (1.4%)	RR 0.98 (0.55 to 1.73)	0 fewer per 1000 (from 6 fewer to 10 more)	VERY LOW	CRITICAL
Stillbirth - Subgroup analysis: Women with a history of spontaneous preterm birth												
2 (Crowther 2017, O'Brien 2007)	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious[8]	None	9/715 (1.3%)	9/695 (1.3%)	RR 0.97 (0.39 to 2.44)	0 fewer per 1000 (from 8 fewer to 19 more)	LOW	CRITICAL
Stillbirth - Subgroup analysis: Women with a short cervix (≤25 mm)												
1 (Romero 2018)	Randomised trials	Serious[6]	No serious inconsistency	No serious indirectness	Very serious[8]	None	9/498 (1.8%)	8/476 (1.7%)	RR 1.08 (0.42 to 2.76)	1 more per 1000 (from 10 fewer to 30 more)	VERY LOW	CRITICAL
Infant mortality - Overall estimate												
9 (Akbari 2009, Azargoon 2016, Catingoz 2011, Crowther 2017, Fonseca 2007, Hassan	Randomised trials	Serious[9]	No serious inconsistency	No serious indirectness	No serious imprecision	None	22/1926 (1.1%)	63/1884 (3.3%)	RR 0.34 (0.21 to 0.55)	22 fewer per 1000 (from 15 fewer to 26 fewer)	MODERATE	CRITICAL

Quality assessment							Number of patients		Effect		Quality	Importance
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Vaginal progesterone	Placebo	Relative (95% CI)	Absolute		
2011, Norman 2018, O'Brien 2007, van Os 2015)												
Infant mortality - Subgroup analysis: Women with a history of spontaneous preterm birth												
3 (Akbari 2009, Crowther 2017, O'Brien 2007)	Randomised trials	Serious[10]	No serious inconsistency	No serious indirectness	Serious[5]	None	10/784 (1.3%)	19/767 (2.5%)	RR 0.53 (0.25 to 1.12)	12 fewer per 1000 (from 19 fewer to 3 more)	LOW	CRITICAL
Infant mortality - Subgroup analysis: Women with a short cervix (overall, <30 mm)												
3 (Fonseca 2007, Hassan 2011, van Os 2015)	Randomised trials	Serious[11]	No serious inconsistency	No serious indirectness	Serious[5]	None	6/412 (1.5%)	14/400 (3.5%)	RR 0.42 (0.16 to 1.08)	20 fewer per 1000 (from 29 fewer to 3 more)	LOW	CRITICAL
Infant mortality - Subgroup analysis: Women with a short cervix (≤25 mm)												
1 (Romero 2018)	Randomised trials	Serious[6]	No serious inconsistency	No serious indirectness	Serious[5]	None	7/498 (1.4%)	15/476 (3.2%)	RR 0.45 (0.18 to 1.08)	17 fewer per 1000 (from 26 fewer to 3 more)	LOW	CRITICAL
Gestational age at birth, weeks - Overall estimate (Better indicated by higher values)												
3 (Azargoon 2016, Norman 2018, O'Brien 2007)	Randomised trials	Serious[12]	Very serious[13]	No serious indirectness	No serious imprecision	None	959	949	-	MD 0.65 higher (0.38 lower to 1.69 higher)	VERY LOW	IMPORTANT
Gestational age at birth, weeks - Subgroup analysis: Women with a history of spontaneous preterm birth (Better indicated by higher values)												
2 (Azargoon 2016, O'Brien 2007)	Randomised trials	Serious[12]	Very serious[13]	No serious indirectness	No serious imprecision	none	359	352	-	MD 1.35 higher (1.49 lower to 4.18 higher)	VERY LOW	CRITICAL
Gestational age at birth, weeks - Subgroup analysis: Women with a short cervix (≤25mm) (Better indicated by higher values)												

Quality assessment							Number of patients		Effect		Quality	Importance
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Vaginal progesterone	Placebo	Relative (95% CI)	Absolute		
1 (Romero 2018)	Randomised trials	Serious[6]	No serious inconsistency	No serious indirectness	No serious imprecision	None	498	476	-	MD 0.74 higher (0.18 to 1.30 higher)	MODERATE	IMPORTANT
Neonatal sepsis - Overall estimate												
6 (Akbari 2009, Crowther 2017, Fonseca 2007, Hassan 2011, Majhi 2009, van Os 2015)	Randomised trials	Serious[14]	No serious inconsistency	No serious indirectness	Serious[5]	None	10/933 (1.1%)	26/910 (2.9%)	RR 0.41 (0.21 to 0.82)	17 fewer per 1000 (from 5 fewer to 23 fewer)	LOW	IMPORTANT
Neonatal sepsis - Subgroup analysis: Women with a history of spontaneous preterm birth												
3 (Akbari 2009, Crowther 2017, Majhi 2009)	Randomised trials	Serious[15]	No serious inconsistency	No serious indirectness	No serious imprecision	None	0/521 (0%)	9/510 (1.8%)	RR 0.14 (0.03 to 0.79)	15 fewer per 1000 (from 4 fewer to 17 fewer)	MODERATE	IMPORTANT
Neonatal sepsis - Subgroup analysis: Women with a short cervix (overall estimate, <30mm)												
3 (Fonseca 207, Hassan 2011, van Os 2015)	Randomised trials	Serious[11]	Serious[2]	No serious indirectness	Serious[8]	None	10/412 (2.4%)	17/400 (4.3%)	RR 0.58 (0.15 to 2.25)	18 fewer per 1000 (from 36 fewer to 53 more)	VERY LOW	IMPORTANT
Neonatal sepsis - Subgroup analysis: Women with a short cervix (≤25 mm)												
1 (Romero 2018)	Randomised trials	Serious[6]	No serious inconsistency	No serious indirectness	Serious[5]	None	18/494 (3.6%)	28/470 (6%)	RR 0.61 (0.34 to 1.09)	23 fewer per 1000 (from 39 fewer to 5 more)	LOW	IMPORTANT
Health-related quality of life (measured with EuroQoL-5 Dimensions health utility scores) - Change between groups from baseline to birth (Better indicated by lower values)												
1 (Norman 2018)	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	191	199	-	MD 0.00 higher (0.04 lower to	HIGH	IMPORTANT

Quality assessment							Number of patients		Effect			
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Vaginal progesterone	Placebo	Relative (95% CI)	Absolute	Quality	Importance
										0.04 higher)		
Health-related quality of life (measured with EuroQoL-5 Dimensions health utility scores) - Change between groups from baseline to 12 months (Better indicated by lower values)												
1 (Norman 2018)	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	279	274	-	MD 0.01 higher (0.03 lower to 0.04 higher)	HIGH	IMPORTANT
Health-related quality of life (measured with SF-36) [history of spontaneous PTB] - General health (Better indicated by higher values)												
1 (Crowther 2017)	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	398	389	-	MD 1.53 higher (0.96 lower to 4.02 higher)	HIGH	IMPORTANT
Health-related quality of life (measured with SF-36) [history of spontaneous PTB] - Social functioning (Better indicated by higher values)												
1 (Crowther 2017)	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	398	389	-	MD 3.8 lower (7.48 to 0.12 lower)	HIGH	IMPORTANT
Health-related quality of life (measured with SF-36) [history of spontaneous PTB] - Emotional role (Better indicated by higher values)												
1 (Crowther 2017)	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	398	389	-	MD 3.31 lower (7.91 lower to 1.29 higher)	HIGH	IMPORTANT
Health-related quality of life (measured with SF-36) [history of spontaneous PTB] - Mental health (Better indicated by higher values)												
1 (Crowther 2017)	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	398	389	-	MD 0.32 lower (2.7 lower to 2.06 higher)	HIGH	IMPORTANT
Bayley-III cognitive composite score (2 years follow-up) [overall estimate] (Better indicated by higher values)												
1 (Norman 2018)	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	410	423	-	MD 0.20 higher (1.82 lower to	HIGH	IMPORTANT

Quality assessment							Number of patients		Effect		Quality	Importance
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Vaginal progesterone	Placebo	Relative (95% CI)	Absolute		
										2.22 higher)		
Bayley-III cognitive composite score (2 years follow-up) Subgroup analysis: women with short cervix ≤25 mm (Better indicated by higher values)												
1 (Romero 2018)	Randomised trials	Serious[6]	No serious inconsistency	No serious indirectness	No serious imprecision	None	88	80	-	MD 2.2 lower (7.2 lower to 2.8 higher)	MODERATE	IMPORTANT
Moderate or severe neurodevelopmental impairment (2 years follow-up) [overall estimate]												
1 (Norman 2018)	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[5]	None	47/379 (12.4%)	35/403 (8.7%)	RR 1.43 (0.94 to 2.16)	37 more per 1000 (from 5 fewer to 101 more)	MODERATE	IMPORTANT
Moderate or severe neurodevelopmental impairment (2 years follow-up) Subgroup analysis: Women with short cervix ≤25 mm												
1 (Romero 2018)	Randomised trials	Serious[6]	No serious inconsistency	No serious indirectness	Very serious[8]	None	10/81 (12.3%)	7/77 (9.1%)	RR 1.36 (0.54 to 3.39)	33 more per 1000 (from 42 fewer to 217 more)	VERY LOW	IMPORTANT
Hearing impairment (2 years follow-up) [overall estimate]												
1 (Norman 2018)	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious[8]	None	1/466 (0.21%)	2/465 (0.43%)	RR 0.50 (0.05 to 5.48)	2 fewer per 1000 (from 4 fewer to 19 more)	LOW	IMPORTANT
Visual impairment (2 years follow-up) [overall estimate]												
1 (Norman 2018)	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious[8]	None	0/447 (0%)	4/465 (0.86%)	RR 0.12 (0.01 to 2.15)	8 fewer per 1000 (from 9 fewer to 10 more)	LOW	IMPORTANT
Visual or hearing impairment (2 years follow-up) [women with short cervix ≤25 mm]												
1 (Romero 2018)	Randomised trials	Serious[6]	No serious inconsistency	No serious indirectness	Very serious[8]	None	0/100 (0%)	2/87 (2.3%)	RR 0.17 (0.01 to 3.58)	19 fewer per 1000 (from 23 fewer to 59 more)	VERY LOW	IMPORTANT

[1] The quality of the evidence was downgraded by one level due to unclear risk of random sequence generation in one study; unclear risk of allocation concealment in one study; unclear risk of blinding of participants and personnel in two studies; unclear risk of blinding of outcome assessors in four studies; unclear risk of incomplete outcome data in one study and unclear risk of other bias in two studies
[2] The quality of the evidence was downgraded by one level as the I^2 was >50%
[3] The quality of the evidence was downgraded by one level due to unclear risk of random sequence generation in one study; unclear risk of allocation concealment in two studies; unclear risk of blinding of participants and personnel in two studies; unclear risk of blinding of outcome assessors in three studies; unclear risk of incomplete outcome data in one study; unclear risk of other bias in two studies
[4] The quality of the evidence was downgraded by one level due to unclear risk of allocation concealment in two studies; unclear risk of blinding of participants and personnel in one study; unclear risk of blinding of outcome assessors in two studies and unclear risk of selective reporting in one study
[5] The quality of the evidence was downgraded by one level as the 95% CI crossed 1 default MID threshold (0.8)
[6] The quality of the evidence was downgraded by one level as the review authors did not provide a list of excluded studies justifying the reasons for exclusion, sources of funding of the studies were not provided and publication bias was not discussed in one study
[7] The quality of the evidence was downgraded by one level due to unclear risk of allocation concealment in one study and high risk of other bias in one study
[8] The quality of the evidence was downgraded by two levels as the 95% CI crossed 2 default MID thresholds (0.8 and 1.25)
[9] The quality of the evidence was downgraded by one level due to unclear risk of random sequence generation in one study; unclear risk of allocation concealment in four studies; unclear risk of blinding of outcome assessors in three studies; unclear risk of incomplete outcome data in one study; unclear risk of other bias in one study and unclear risk of selective reporting in one study
[10] The quality of the evidence was downgraded by one level due to unclear risk of random sequence generation in one study; unclear risk of allocation concealment in two studies; unclear risk of blinding of participants and personnel in one study; unclear risk of blinding of outcome assessors in one study; unclear risk of incomplete outcome data in one study; unclear risk of other bias in one study
[11] The quality of the evidence was downgraded by one level due to unclear risk of allocation concealment in one study; unclear risk of blinding of outcome assessors in one study and unclear risk of selective reporting in one study
[12] The quality of the evidence was downgraded by one level due to unclear risk of allocation concealment in one study and unclear risk of blinding of outcome assessors in one study
[13] The quality of the evidence was downgraded by two levels as the I^2 was >70%
[14] The quality of the evidence was downgraded by one level due to unclear risk of random sequence generation in one study; unclear risk of allocation concealment in three studies; unclear risk of blinding of participants and personnel in one study; unclear risk of blinding of outcome assessors in two studies; unclear risk of incomplete outcome data in one study; unclear risk of selective reporting in one study and unclear risk of other bias in two studies
[15] The quality of the evidence was downgraded by one level due to unclear risk of random sequence generation in one study; unclear risk of allocation concealment in two studies; unclear risk of blinding of participants and personnel in two studies; unclear risk of blinding of outcome assessors in one study; unclear risk of incomplete outcome data in one study; unclear risk of other bias in one study

Table 12: Comparison 2. Oral progesterone versus placebo

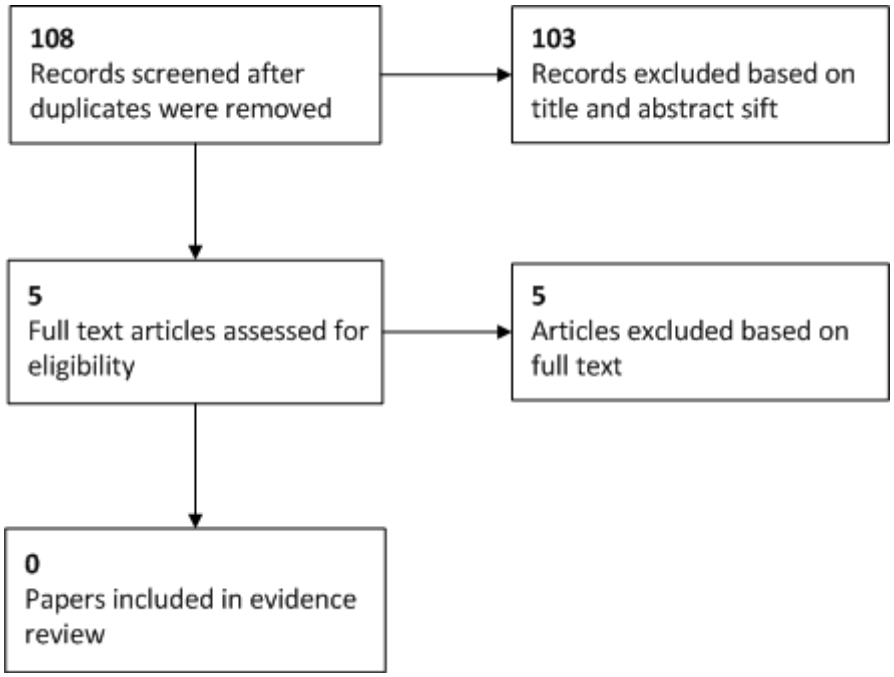
Quality assessment							Number of patients		Effect		Quality	Importance
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oral progesterone	Placebo	Relative (95% CI)	Absolute		
Preterm birth <34+0 weeks [history of spontaneous PTB]												
1 (Rai 2009)	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[1]	None	22/74 (29.7%)	37/74 (50%)	RR 0.59 (0.39 to 0.90)	205 fewer per 1000 (from 50 fewer to 305 fewer)	MODERATE	CRITICAL
Infant mortality [history of spontaneous PTB]												
2 (Ashoush 2017, Rai 2009)	Randomised trials	Serious[2]	No serious inconsistency	No serious indirectness	No serious imprecision	None	10/170 (5.9%)	30/165 (18.2%)	RR 0.32 (0.16 to 0.63)	124 fewer per 1000 (from 67 fewer to 153 fewer)	MODERATE	CRITICAL
Gestational age at birth, weeks [history of spontaneous PTB] (Better indicated by higher values)												
2 (Ashoush 2017, Glover 2011)	Randomised trials	Serious[3]	No serious inconsistency	No serious indirectness	No serious imprecision	None	115	105	-	MD 1.43 higher (0.70 to 2.17 higher)	MODERATE	IMPORTANT

The quality of the evidence was downgraded by one level as the 95% CI crossed 1 default MID threshold (0.8)
[2] The quality of the evidence was downgraded by one level due to unclear risk of blinding of outcome assessors in two studies
[3] The quality of the evidence was downgrade by one level due to unclear risk of blinding outcome assessors and unclear risk of selective reporting in one study

Appendix G – Economic evidence study selection

No economic evidence was identified for this review question.

Figure 9: Economic evidence study selection



Appendix H – Economic evidence tables

No economic evidence was identified for this review question.

Appendix I – Health economic evidence profiles

No economic evidence was identified for this review question.

Appendix J – Health economic analysis

No health economic analysis was carried out for this review question.

Appendix K – Excluded studies

Table 13: Clinical studies

Study	Reason for Exclusion
Ahn, K. H., Bae, N. Y., Hong, S. C., Lee, J. S., Lee, E. H., Jee, H. J., Cho, G. J., Oh, M. J., Kim, H. J., The safety of progestogen in the prevention of preterm birth: meta-analysis of neonatal mortality, Journal of Perinatal Medicine, 45, 11-20, 2017	This systematic review also considered studies including women with multiple pregnancies or where progesterone was administered intramuscularly. Relevant studies have been assessed and included as appropriate
Areeruk, W., Phupong, V., A randomized, double blinded, placebo controlled trial of oral dydrogesterone supplementation in the management of preterm labor, Scientific reports, 6, 20638, 2016	Progesterone was used as tocolytic - acute treatment
Arya, R., Randomized trial of natural micronized progesterone in prevention of preterm birth in women at high risk, BJOG: an international journal of obstetrics and gynaecology. Conference: 2018 world congress of the royal college of obstretriscians and gynaecologists, RCOG 2018. Singapore, 125, 67, 2018	Conference abstract
Barinov, Sergey V., Shamina, Inna V., Di Renzo, Gian Carlo, Lazareva, Oksana V., Tirskaya, Yuliya I., Medjannikova, Irina V., Ledovskikh, Inna O., Klementyeva, Lyudmila L., Dudkova, Galina V., The role of cervical pessary and progesterone therapy in the phenomenon of placenta previa migration, The journal of maternal-fetal & neonatal medicine : the official journal of the European Association of Perinatal Medicine, the Federation of Asia and Oceania Perinatal Societies, the International Society of Perinatal Obstetricians, 1-11, 2018	Mixed population. Most women (90%) were included for other risk factors than the ones stated in the protocol
Barinov, Sergey V., Shamina, Irina V., Lazareva, Oksana V., Tirskaya, Yuliya I., Ralko, Vyacheslav V., Shkabarnya, Lyudmila L., Dikke, Galina B., Kochev, Dmitry M., Klementyeva, Lyudmila L., Comparative assessment of arabin pessary, cervical cerclage and medical management for preterm birth prevention in high-risk pregnancies, The journal of maternal-fetal & neonatal medicine : the official journal of the European Association of Perinatal Medicine, the Federation of Asia and Oceania Perinatal Societies, the International Society of Perinatal Obstetricians, 30, 1841-1846, 2017	No relevant comparators (cerclage/ pessary with no progesterone)
Chaman-Ara, K., Bahrami, M. A., Bahrami, E., Bahrami, S., Bahrami, M. N., Moosazadeh, M., Barati, O., Efficacy of progesterone therapy in the prevention of preterm labor in women with mixed risk-factors: A systematic review and meta-analysis of randomized clinical trials, Erciyes Tip Dergisi, 38, 48-52, 2016	This systematic review included 3 studies; 2 of which are not relevant due to population and intervention characteristics (Dudas,Johnson). The remaining study (Cetingoz) has already been included in this review
Choi, Suk-Joo, Use of progesterone supplement therapy for prevention of preterm birth: review of	This systematic review has also considered studies including women with multiple

Study	Reason for Exclusion
literatures, Obstetrics & gynecology science, 60, 405-420, 2017	pregnancies or where progesterone was administered intramuscularly. Relevant studies have been assessed and included as appropriate
Choudhary, Manju, Suneja, Amita, Vaid, Neelam B., Guleria, Kiran, Faridi, M. M. A., Maintenance tocolysis with oral micronized progesterone for prevention of preterm birth after arrested preterm labor, International journal of gynaecology and obstetrics: the official organ of the International Federation of Gynaecology and Obstetrics, 126, 60-3, 2014	Progesterone is being used as tocolytic - acute treatment
Conde-Agudelo, Agustin, Romero, Roberto, Da Fonseca, Eduardo, O'Brien, John M., Cetingoz, Elcin, Creasy, George W., Hassan, Sonia S., Erez, Offer, Pacora, Percy, Nicolaides, Kypros H., Vaginal progesterone is as effective as cervical cerclage to prevent preterm birth in women with a singleton gestation, previous spontaneous preterm birth, and a short cervix: updated indirect comparison meta-analysis, American Journal of Obstetrics and Gynecology, 219, 10-25, 2018	Cervical cerclage comparison is not relevant
Coomarasamy, Arri, Williams, Helen, Truchanowicz, Ewa, Seed, Paul T., Small, Rachel, Quenby, Siobhan, Gupta, Pratima, Dawood, Feroza, Koot, Yvonne E. M., Bender Atik, Ruth, Bloemenkamp, Kitty W. M., Brady, Rebecca, Briley, Annette L., Cavallaro, Rebecca, Cheong, Ying C., Chu, Justin J., Eapen, Abey, Ewies, Ayman, Hoek, Annemieke, Kaaijk, Eugenie M., Koks, Carolien A. M., Li, Tin-Chiu, MacLean, Marjory, Mol, Ben W., Moore, Judith, Ross, Jackie A., Sharpe, Lisa, Stewart, Jane, Vaithilingam, Nirmala, Farquharson, Roy G., Kilby, Mark D., Khalaf, Yacoub, Goddijn, Mariette, Regan, Lesley, Rai, Rajendra, A Randomized Trial of Progesterone in Women with Recurrent Miscarriages, The New England journal of medicine, 373, 2141-8, 2015	Women with recurrent miscarriages, not pre term birth
Cruz-Melguizo, Sara, San-Frutos, Luis, Martinez-Payo, Cristina, Ruiz-Antoran, Belen, Adiego-Burgos, Begona, Campillos-Maza, Jose Manuel, Garcia-Gonzalez, Celso, Martinez-Guisasola, Javier, Perez-Carbajo, Esther, Teulon-Gonzalez, Maria, Avendano-Sola, Cristina, Perez-Medina, Tirso, Cervical Pessary Compared With Vaginal Progesterone for Preventing Early Preterm Birth: A Randomized Controlled Trial, Obstetrics and Gynecology, 132, 907-915, 2018	No relevant comparison (pessary without progesterone)
Dodd, J. M., Grivell, R. M., Obrien, C. M., Deussen, A. R., Prenatal administration of progestogens for preventing spontaneous preterm birth in women with a singleton	Protocol

Study	Reason for Exclusion
pregnancy, Cochrane Database of Systematic Reviews, 2017, CD012531, 2017	
Dugoff, L., Berghella, V., Sehdev, H., Mackeen, A. D., Goetzl, L., Ludmir, J., Prevention of preterm birth with pessary in singletons (PoPPS): randomized controlled trial, Ultrasound in obstetrics & gynecology, 51, 573-579, 2018	No relevant comparison (pessary without progesterone)
Eichelberger, Kacey Y., Manuck, Tracy A., Progesterone has no place in the prevention of preterm delivery: AGAINST: A call for a measured response to the OPPTIMUM trial, BJOG : an international journal of obstetrics and gynaecology, 123, 1511, 2016	Comment letter
Eke, Ahizechukwu C., Chalaan, Tina, Shukr, Ghadear, Eleje, George U., Okafor, Charles I., A systematic review and meta-analysis of progestogen use for maintenance tocolysis after preterm labor in women with intact membranes, International journal of gynaecology and obstetrics: the official organ of the International Federation of Gynaecology and Obstetrics, 132, 11-6, 2016	No relevant studies have been included
Facchinetti, Fabio, Vergani, Patrizia, Di Tommaso, Mariarosaria, Marozio, Luca, Acaia, Barbara, Vicini, Roberto, Pignatti, Lucrezia, Locatelli, Anna, Spitaleri, Marina, Benedetto, Chiara, Zaina, Barbara, D'Amico, Roberto, Progestogens for Maintenance Tocolysis in Women With a Short Cervix: A Randomized Controlled Trial, Obstetrics and Gynecology, 130, 64-70, 2017	Women in the control group received progesterone IM
Garmi, G., Hakim, M., Zafran, N., Nachum, Z., Romano, S., Salim, R., The impact of progesterone on the risk of preterm birth among women with second trimester bleeding. A multicenter, randomized, double-blind, placebo controlled trial, American journal of obstetrics and gynecology. Conference: 38th annual meeting of the society for maternal-fetal medicine: the pregnancy meeting. United states, 218, S108, 2018	Abstract
Grabovac, M., Lewis-Mikhael, A. M., McDonald, S. D., Interventions to Try to Prevent Preterm Birth in Women With a History of Conization: A Systematic Review and Meta-analyses, Journal of Obstetrics and Gynaecology Canada, 2018	No relevant interventions
Hermans, F. J. R., Karolinski, A., Othenin-Girard, V., Bertolino, M. V., Schuit, E., Salgado, P., Hosli, I., Irion, O., Laterra, C., Mol, B. W. J., Martinez de Tejada, B., Population differences and the effect of vaginal progesterone on preterm birth in women with threatened preterm labor*, Journal of Maternal-Fetal and Neonatal Medicine, 29, 3223-3228, 2016	No relevant outcomes have been reported
Hermans, Frederik J. R., Schuit, Ewoud, Opmeer, Brent C., Oudijk, Martijn A., Bekker,	Protocol

Study	Reason for Exclusion
Mireille, Woiski, Mallory, Bax, Caroline J., Sueters, Marieke, Scheepers, Hubertina C. J., Franssen, Maureen T. M., Pajkrt, Eva, Mol, Ben Willem J., Kok, Marjolein, Effectiveness of a cervical pessary for women who did not deliver 48 h after threatened preterm labor (Assessment of perinatal outcome after specific treatment in early labor: Apostel VI trial), BMC Pregnancy and Childbirth, 16, 154, 2016	
Hezelgrave, Natasha L., Watson, Helena A., Ridout, Alexandra, Diab, Falak, Seed, Paul T., Chin-Smith, Evonne, Tribe, Rachel M., Shennan, Andrew H., Rationale and design of SuPPoRT: a multi-centre randomised controlled trial to compare three treatments: cervical cerclage, cervical pessary and vaginal progesterone, for the prevention of preterm birth in women who develop a short cervix, BMC Pregnancy and Childbirth, 16, 358, 2016	Protocol
Hui, C. Y. Y., Siew, S. J. Y., Tan, T. C., Biochemical and clinical outcomes following the use of micronised progesterone and dydrogesterone for threatened miscarriage - A randomised controlled trial, BJOG: An International Journal of Obstetrics and Gynaecology, 122, 276, 2015	Conference abstract
Iwami, N., Hirayama, N., Kobayashi, Y., Kanaya, M., Yagi, A., Saito, T., Ozawa, J., Yamamoto, T., Watanabe, E., Moriwaka, O., Kamiya, H., New trial of dydrogesterone regimen as an effective oral alternative for suppression of premature luteinizing hormone surges during controlled ovarian stimulation of assisted reproductive therapy, Human Reproduction, 32, 2017	Conference abstract
Jarde, A., Lutsiv, O., Park, C. K., Beyene, J., Dodd, J. M., Barrett, J., Shah, P. S., Cook, J. L., Saito, S., Biringer, A. B., Sabatino, L., Giglia, L., Han, Z., Staub, K., Mundle, W., Chamberlain, J., McDonald, S. D., Effectiveness of progesterone, cerclage and pessary for preventing preterm birth in singleton pregnancies: a systematic review and network meta-analysis, BJOG: An International Journal of Obstetrics & Gynaecology, 124, 1176-1189, 2017	Intramuscular and oral progesterone were combined in the meta-analyses. The relevant studies have already been included in Dodd 2013
Lucovnik, Miha, Trojner Bregar, Andreja, Bombac, Lea, Gersak, Ksenija, Garfield, Robert E., Effects of vaginal progesterone for maintenance tocolysis on uterine electrical activity, The journal of obstetrics and gynaecology research, 44, 408-416, 2018	Progesterone used as tocolytic-acute treatment
Martinez de Tejada, B., Karolinski, A., Ocampo, M. C., Laterra, C., Hosli, I., Fernandez, D., Surbek, D., Huespe, M., Drack, G., Bunader, A., Rouillier, S., Lopez de Degani, G., Seidenstein, E., Prentl, E., Anton, J., Krahenmann, F., Nowacki, D., Poncelas, M., Nassif, J. C.,	No relevant population (women were in preterm labour)

Study	Reason for Exclusion
Papera, R., Tuma, C., Espoile, R., Tiberio, O., Breccia, G., Messina, A., Peker, B., Schinner, E., Mol, B. W., Kanterewicz, L., Wainer, V., Boulvain, M., Othenin-Girard, V., Bertolino, M. V., Irion, O., P. trial group, Martinez de Tejada B, Irion O. Boulvain M. Tellenbach M. Othenin-Girard V. Vogele E. Azbar R. Hosli I. Raggi A. Birkenmaier A. Kann S. Surbek D. Scheibner K. Huguelet M. Amann E. Baumann M. Jakob E. Biedermann K. Hodel M. Drack G. Fischer T. Pfau K. Estermann K. Hohlfeld P. Gerber S. Rouiller-Cornu S. Capoccia Brugger R. Nessi A. Rodriguez-Maillot C. Pradervand P. A. Bodenmann P. Fornage S. Prentl E. Amann E. Krahenmann F. Zimmermann R. Karolinski A. Bertolino M. V. Ocampo M. C. Wainer V. Kanterewicz L. Rodriguez C. Colazo L. Laterra C. Ramirez Almanza S. Swistak E. Gonzalez Y. Fernandez D. Zalazar G. Rubino M. Sanchez B. Rivara A. Mercado C. Sagarna S. Huespe M. Luca R. Claus L. Castellano V. Domingo L. Castro C. Gil D. Rodriguez M. E. Bunader A. Capua N. E. Romano M. Longo M. E. Balbo E. Martinez Lozano S. Petros C. Lopez de Degani G. Coniglio M. Harris R. Leanga M. Martinez R. Felici F. de Bueno M. Reffino F. Castagnola J. Brarda P. Parra M. E. Montenegro R. Fernandez G. Schmadke G. Seidenstein E. Pontoriero R. Gonzalez C. Alduncin J. Anton J. Damiano M. Sanchez G. Rebottaro M. Altamira L. Garbarino V. Rebottaro C. Nowacki D. Ferrary M. Buttner C. Gonzalez P. Godoy Y. Poncelas M. Bertola E. Langdon L. Jimenez O. Mezzabota L. Nassif J. C. Becker C. A. Baier J. M. Grichener M. Trotti P. Papera R. Chaloupka M. Zarate M. Bogino L. Bertone E. Olmedo F. Barrionuevo M. Mariojouls N. Tuma C. Gregoris C. Espoile R. Muzio C. Nocetto C. Carozzi D. Pelaez V. De Moura C. Tiberio O. Sagastume M. Martinez L. Morales D. Penna J. Breccia G. Aguilera E. Werbicki E. Bover S. Alvarez T. Messina A. Stillo M. F. Joao M. Crema D. Wiliams L. Espada C. Gomariz V. Calo M. E. Peker B. Longhi D. Pisanelli M. L. Giglio L. Rodriguez J. Perez Petruzzelli R. Gores I. Schinner E. Morcillo M. V. Terenzani F. Izbizky G. Gimenez M. L. Meller C. Grasso M. Martinotti M. Scheller I. Marinelli J. Carrizo L. Baro S. Marasco N., Prevention of preterm delivery with vaginal progesterone in women with preterm labour (4P): randomised double-blind placebo-controlled trial, BJOG : an international journal of obstetrics and gynaecology, 122, 80-91, 2015	
Martinez de Tejada, Begona, Karolinski, Ariel, Vaginal progesterone for maintenance tocolysis: a systematic review and metaanalysis of	Comment letter

Study	Reason for Exclusion
randomized trials, American Journal of Obstetrics and Gynecology, 213, 438-9, 2015	
Medley, N., Poljak, B., Mammarella, S., Alfirevic, Z., Clinical guidelines for prevention and management of preterm birth: a systematic review, BJOG: An International Journal of Obstetrics & Gynaecology, 20, 20, 2018	Review of current clinical practice guidelines, no data was presented
Nicolaides, K. H., Syngelaki, A., Poon, L. C., Picciarelli, G., Tul, N., Zamprakou, A., Skyfta, E., Parra-Cordero, M., Palma-Dias, R., Calvo, J. R., A randomized trial of a cervical pessary to prevent preterm singleton birth, New England journal of medicine, 374, 1044-1052, 2016	Progesterone was provided to women with a short cervix, but the study was not designed to test its effectiveness as women in both treatment arms received it
Norman JE, Marlow N, Messow CM, Shennan A, Bennett PR, Thornton S, Robson SC, McConnachie A, Petrou S, Sebire NJ, Lavender T. Vaginal progesterone prophylaxis for preterm birth (the OPPTIMUM study): a multicentre, randomised, double-blind trial. The lancet. 2016 May 21;387(10033):2106-16.	Relevant outcomes have been extracted under Norman 2018
Palacio, M., Cobo, T., Antolin, E., Ramirez, M., Cabrera, F., De Rosales, F. M., Bartha, J. L., Juan, M., Marti, A., Oros, D., Rodriguez, A., Scazzocchio, E., Olivares, J. M., Varea, S., Rios, J., Gratacos, E., Vaginal Progesterone as Maintenance Treatment after an Episode of Preterm Labour (PROMISE) Study: A Multicentre, Double-blind, Randomised, Placebo-Controlled Trial, Obstetrical and Gynecological Survey, 72, 151-153, 2017	Progesterone used as maintenance treatment
Palacio, M., Cobo, T., Antolin, E., Ramirez, M., Cabrera, F., Mozo de Rosales, F., Bartha, J. L., Juan, M., Marti, A., Oros, D., Rodriguez, A., Scazzocchio, E., Olivares, J. M., Varea, S., Rios, J., Gratacos, E., Trilla, A., Carralero, I., Mendez, F., Arnaiz, J. A., Ramos, N., Pejenaute, A., Garcia, D., Carne, X., Murphy, K. E., Crowther, C., Ohlsson, A., Torres, F., Vaginal progesterone as maintenance treatment after an episode of preterm labour (PROMISE) study: a multicentre, double-blind, randomised, placebo-controlled trial, BJOG: An International Journal of Obstetrics and Gynaecology, 123, 1990-1999, 2016	Progesterone used as maintenance treatment
Prior, M., Hibberd, R., Asemota, N., Thornton, J. G., Inadvertent P-hacking among trials and systematic reviews of the effect of progestogens in pregnancy? A systematic review and meta-analysis, BJOG: An International Journal of Obstetrics & GynaecologyBjog, 20, 20, 2017	The main aim of this study does not match with the main aim of this review
Romero, R., Nicolaides, K. H., Conde-Agudelo, A., O'Brien, J. M., Cetingoz, E., Da Fonseca, E., Creasy, G. W., Hassan, S. S., Vaginal progesterone decreases preterm birth<=34weeks of gestation in women with a singleton pregnancy and a short cervix: an	Updated by Romero 2018

Study	Reason for Exclusion
updated meta-analysis including data from the OPPTIMUM study, Ultrasound in Obstetrics & Gynecology, 48, 308-17, 2016	
Saccone, G., Maruotti, G. M., Giudicepietro, A., Martinelli, P., Effect of Cervical Pessary on Spontaneous Preterm Birth in Women with Singleton Pregnancies and Short Cervical Length: A Randomized Clinical Trial, Obstetrical and Gynecological Survey, 73, 267-268, 2018	Progesterone was provided to women with a short cervix, but the study was not designed to test its effectiveness as women in both treatment arms received it
Saccone, Gabriele, Schoen, Corina, Franasiak, Jason M., Scott, Richard T., Jr., Berghella, Vincenzo, Supplementation with progestogens in the first trimester of pregnancy to prevent miscarriage in women with unexplained recurrent miscarriage: a systematic review and meta-analysis of randomized, controlled trials, Fertility and Sterility, 107, 430-438.e3, 2017	Women with recurrent miscarriages, not pre term birth
Stewart, L. A., Simmonds, M., Duley, L., Dietz, K. C., Harden, M., Hodkinson, A., Llewellyn, A., Sharif, S., Walker, R., Wright, K., Evaluating progestogens for prevention of preterm birth international collaborative (EPPPIC) individual participant data (IPD) meta-analysis: Protocol, Systematic Reviews, 6 (1) (no pagination), 2017	Protocol
Suhag, Anju, Saccone, Gabriele, Berghella, Vincenzo, Vaginal progesterone for maintenance tocolysis: a systematic review and metaanalysis of randomized trials, American Journal of Obstetrics and Gynecology, 213, 479-87, 2015	Progesterone used as maintenance treatment
van Zijl, Maud D., Koullali, Bouchra, Naaktgeboren, Christiana A., Schuit, Ewoud, Bekedam, Dick J., Moll, Etelka, Oudijk, Martijn A., van Baal, Wilhelmina M., de Boer, Marjon A., Visser, Henricus, van Drongelen, Joris, van de Made, Flip W., Vollebregt, Karlijn C., Muller, Moira A., Bekker, Mireille N., Brons, Jozien T. J., Sueters, Marieke, Langenveld, Josje, Franssen, Maureen T., Schuitemaker, Nico W., van Beek, Erik, Scheepers, Hubertina C. J., de Boer, Karin, Tepe, Eveline M., Huisjes, Anjoke J. M., Hooker, Angelo B., Verheijen, Evelyn C. J., Papatsonis, Dimitri N., Mol, Ben Willem J., Kazemier, Brenda M., Pajkrt, Eva, Pessary or Progesterone to Prevent Preterm delivery in women with short cervical length: the Quadruple P randomised controlled trial, BMC Pregnancy and Childbirth, 17, 284, 2017	Pessary does not contain progesterone
Van't Hooft, J., Cuijpers, C., Schneeberger, C., Van Der Lee, J. H., Opmeer, B. C., Steenis, L., Liem, S., Van De Beek, C., Van Os, M., Van Der Ven, J., De Groot, C. J. M., Mol, B. W. J., Van Wassenaer-Leemhuis, A. G., Preventing preterm birth with progesterone in women with short cervical length, outcomes in children at 24	Abstract

Study	Reason for Exclusion
months of age, American Journal of Obstetrics and Gynecology, 216, S492, 2017	

Table 14: Excluded economic studies

Study	Reason for Exclusion
Eke A, Buras A, Drnec S, Woo J. Vaginal progesterone versus cervical cerclage for the prevention of preterm births in women with a sonographically short cervixea cost effectiveness and decision analysis. American Journal of Obstetrics and Gynecology, S37-38 2015	Available as abstract only
Fonseca EB, Nishikawa AM, Paladini L, Clark O AC. Cervical Assessment With Progesterone in the Prevention of Preterm Birth: A Strategy Based On Cost-Effectiveness. Value in Health 2014	Considers cost-effectiveness of screening for preterm delivery, which is not being considered in this question.
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Appendix L – Research recommendations

1. **Does progesterone reduce the risk of preterm birth in women who have risk factors for preterm birth, but do not have a short cervix (cervical length >25mm)?**

Why this is important

Preterm birth is a cause of significant morbidity for women and babies, and impacts negatively on women and their families, as well as being costly to the NHS. There is good evidence for the use of progesterone to reduce preterm birth, however studies include women with a combination of risk factors for preterm birth, such as a history of preterm birth and a shortened cervix. There is no evidence for the effectiveness of progesterone in women who do not have a short cervix, but who do have other risk factors for preterm birth. It is therefore difficult to decide if progesterone should be recommended for these women, and also whether measuring the cervical length to guide treatment is necessary.

Table 15: Research recommendation rationale

Research question	Does progesterone reduce the risk of preterm birth in women who have risk factors for preterm birth, but do not have a short cervix (cervical length ≥25mm)?
Importance to 'patients' or the population	This question is important to women to guide treatment recommendations. It would enable vaginal progesterone to be offered appropriately to women at high risk, and avoid unnecessary treatment of women who may not be at such high risk of preterm birth.
Relevance to NICE guidance	The NICE guideline currently recommends consideration should be given to the use of progesterone for women with a short cervix or previous history of preterm birth.
Relevance to the NHS	Identifying women most at risk of preterm birth, and offering appropriate prophylaxis (such as vaginal progesterone) has the potential for significant cost savings, by reducing the incidence of preterm birth.
National priorities	60,000 babies are born prematurely each year, many of whom will require specialist neonatal care, often for many weeks or months. The report on the impact of preterm birth, Born too Soon (WHO, 2012) identifies the short-term consequences both on babies' development and on their families, as well as the possible long-term consequences which can include life-long disabilities.
Current evidence base	Current evidence suggests a benefit of vaginal progesterone for women with a previous preterm birth, and for women with a short cervix (≤25mm). However, it is not clear to what extent these populations overlap. It is possible that vaginal progesterone is not of benefit for women in whom the cervix is found to be >25mm.
Equality	Cervical length scanning is not a routine part of antenatal care, therefore vaginal progesterone may be offered more commonly in units where this scan takes place, resulting in inequalities in care.

Table 16: Research recommendation modified PICO table

Criterion	Explanation
Population	Women who have had a previous premature birth and have cervical length >25mm
Intervention	Use of vaginal progesterone in pregnancy

Criterion	Explanation
Prognostic or risk factor	Previous premature birth, less than 34 weeks' gestation
Comparator (without the risk factor)	• No vaginal progesterone/placebo
Outcome	• Incidence of premature birth prior to 34 weeks' gestation • Neonatal outcomes
Study design	Randomised controlled trial or IPD meta-analysis
Timeframe	Minimum duration of follow up: until discharge

2. Does progesterone reduce the risk of preterm birth in women who have a cervical length ≤25mm but no history of preterm birth?

Why this is important

Preterm birth is a cause of significant morbidity for women and babies, and impacts negatively on women and their families, as well as being costly to the NHS. There is good evidence for the use of progesterone to reduce preterm birth, however studies include women with a combination of risk factors for preterm birth, such as a history of preterm birth and a shortened cervix. There is a lack of evidence for the effectiveness of progesterone in women with a cervical length ≤25mm, but without other risk factors for preterm birth. It is therefore difficult to decide if progesterone should be recommended for these women, and consequently whether measuring the cervix to guide treatment is necessary for women without other risk factors.

Table 17: Research recommendation rationale

Research question	Does progesterone reduce the risk of preterm birth in women who have a cervical length ≤25mm, but no history of preterm birth?
Importance to 'patients' or the population	This question is important to women to guide treatment recommendations. It would allow vaginal progesterone to be offered appropriately to women at high risk of preterm birth, and avoid unnecessary treatment of women who may not be at such high risk of preterm birth.
Relevance to NICE guidance	The NICE guideline currently recommends consideration should be given to the use of progesterone for women with a cervical length ≤25mm or previous history of preterm birth.
Relevance to the NHS	Identifying women most at risk of preterm birth, and offering appropriate prophylaxis (such as vaginal progesterone) has the potential for significant cost savings, by reducing the incidence of preterm birth.
National priorities	60,000 babies are born prematurely each year, many of whom will require specialist neonatal care, often for many weeks or months. The report on the impact of preterm birth, Born too Soon (WHO, 2012) identifies the short-term consequences both on babies' development and their families, as well as the possible long-term consequences which can include life-long disabilities.
Current evidence base	Current evidence suggests a benefit of vaginal progesterone for women with a previous preterm birth, and for women with a short cervix (≤25mm). However, it is not clear to what extent these populations overlap. It is possible that vaginal progesterone is not of benefit for women in whom the cervical length is ≤25mm, but who do not have a history of preterm birth.
Equality	Cervical length scanning is not a routine part of antenatal care, therefore vaginal progesterone may be offered more commonly in units where this scan takes place, resulting in inequalities in care.

Table 18: Research recommendation modified PICO table

Criterion	Explanation
Population	Women who have a cervical length ≤25mm but no previous history of preterm birth
Intervention	Use of vaginal progesterone in pregnancy
Prognostic or risk factor	Cervical length ≤25mm
Comparator (without the risk factor)	• No vaginal progesterone/placebo
Outcome	• Incidence of premature birth prior to 34 weeks' gestation • Neonatal outcomes
Study design	Randomised controlled trial or IPD meta-analysis
Timeframe	Minimum duration of follow up: until discharge

3. At what gestation should treatment with prophylactic vaginal progesterone for the prevention of preterm birth be started and stopped?

Why this is important

Preterm birth is a cause of significant morbidity for women and babies, and impacts negatively on women and their families, as well as being costly to the NHS. There is good evidence for the use of progesterone to reduce preterm birth, however studies do not define the optimal gestational age that this treatment should be started and stopped, and it is therefore difficult to recommend when it should started and the optimal duration of treatment.

Table 19: Research recommendation rationale

Research question	At what gestation should treatment with prophylactic vaginal progesterone for the prevention of preterm birth be started and stopped?
Importance to 'patients' or the population	For some women, progesterone has clearly been shown to reduce the risk of preterm birth. However, it is unclear when this treatment should be started, and for how long it should be continued.
Relevance to NICE guidance	The current guideline recommends the use of progesterone during pregnancy for some women considered to be at high risk of preterm birth. Committee members noted that this guidance should recommend when treatment should be started and stopped, but no evidence was identified to address this issue.
Relevance to the NHS	Treatment with progesterone has the potential to reduce the incidence of preterm birth if used correctly. The most cost effective use of progesterone would be to use it for the shortest duration, timed to be of maximal benefit.
National priorities	60,000 babies are born prematurely each year, many of whom will require specialist neonatal care, often for many weeks or months. The report on the impact of preterm birth, Born too Soon (WHO, 2012) identifies the short-term consequences both on babies' development and their families, as well as the possible long-term consequences which can include life-long disabilities.
Current evidence base	A number of studies have identified the value of progesterone for certain groups of women, but they vary in the gestation at which progesterone was

Research question	At what gestation should treatment with prophylactic vaginal progesterone for the prevention of preterm birth be started and stopped?
	started (and stopped). There is therefore a lack of evidence regarding which is the optimal gestation at which to use progesterone.
Equality	There is considerable variation in the timing of progesterone administration at present, and this may result in some women being provided with more effective care than others.

Table 20: Research recommendation modified PICO table

Criterion	Explanation
Population	Women with risk factors for premature birth
Intervention	Vaginal progesterone started during early pregnancy (e.g. ≤16 weeks) and stopped at 34 weeks
Prognostic or risk factor	Preterm birth, less than 34 weeks gestation
Comparator (without the risk factor)	o Vaginal progesterone started during early pregnancy (e.g. ≤16 weeks) and stopped at 36 weeks o Vaginal progesterone started later in pregnancy (e.g. ≥20 weeks) and stopped at 34 weeks o Vaginal progesterone started later in pregnancy (e.g. ≥20 weeks) and stopped at 36 weeks
Outcome	Preterm birth <34 weeks Neonatal outcomes
Study design	Randomised controlled trial.
Timeframe	Minimum duration of follow up: until discharge from hospital