National Institute for Health and Care Excellence

Draft for consultation

# Preterm labour and birth

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

*NICE guideline NG25 (update)*

*Evidence review*

*April 2019*

*Draft for Consultation*

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

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ISBN:

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# Review question 1. 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.

## PICO table

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:<br>• a history of spontaneous preterm birth<br>• a history of preterm pre-labour rupture of membranes (in a previous pregnancy)<br>• a history of mid-trimester loss<br>• mid-trimester bleeding<br>• a history of cervical trauma<br>• a short cervix that has been identified on scan and/or bulging membranes in the current pregnancy<br>• a positive fetal fibronectin test |
| **Intervention** | • Vaginal progesterone<br>• Oral progesterone |
| **Comparison** | • One intervention compared to another<br>• Placebo<br>• No treatment |
| **Outcome** | **Critical outcomes:**<br>• Preterm birth <34$^{+0}$ weeks'<br>• Stillbirth |

| | |
|---|---|
| | • Infant mortality prior to discharge<br><br>**Important outcomes:**<br>• Gestational age at birth<br>• Early onset neonatal sepsis (onset up to 72 hours)<br>• Maternal satisfaction/HRQoL<br>• 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<br><br>RCT<br><br>Egypt | N=187 women with history of spontaneous preterm birth | Oral progesterone (100 mg every 6 hours)<br><br>Treatment started between 14 and 18 weeks' gestational age | Placebo | • Infant mortality<br>• Gestational age at birth |
| Azargoon 2016<br><br>RCT<br><br>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)<br><br>Treatment started between 16 and 22 weeks' gestational age | Placebo | • Preterm birth <34 weeks'<br>• Infant mortality<br>• Gestational age at birth |
| Crowther 2017<br><br>RCT<br><br>Australia, New Zealand, Canada | N=799 women with history of spontaneous preterm birth | Vaginal progesterone (100mg/day)<br><br>Treatment started at 20 weeks' gestational age, or from randomisation (if this occurred after 20 weeks) | Placebo | • Stillbirth<br>• Infant mortality<br>• Early neonatal sepsis<br>• Health-related quality of life |
| Dodd 2013<br><br>Cochrane systematic review<br><br>Iran, Brazil, US, India | K=9<br>• Akbari 2009<br>• Cetingoz 2011<br>• da Fonseca 2003<br>• Fonseca 2007<br>• Glover 2011<br>• Hassan 2011<br>• Majhi 2009<br>• O´Brien 2007 | Vaginal progesterone (90 to 200 mg):<br>• Akbari 2009<br>• Cetingoz 2011<br>• da Fonseca 2003<br>• Fonseca 2007<br>• Hassan 2011<br>• Majhi 2009<br>• O´Brien 2007 | Placebo | • Preterm birth <34 weeks'<br>• Stillbirth<br>• Infant mortality<br>• Gestational age at birth<br>• Neonatal sepsis |

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

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

<u>Subgroup analysis: Women with a history of spontaneous preterm birth</u>

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.

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

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.

<u>Women with a short cervix (≤25 mm)</u>

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/ 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 5$^{th}$ 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 part of routine antenatal care in the UK, and that individual units will have local procedures in place to determine which, if any, women received a cervical length scan. The committee discussed that it would be useful to have national recommendations stating which women should undergo measurement of their cervical length.

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Cetingoz E, Cam C, Sakallı M, Karateke A, Celik C, Sancak A. Progesterone effects on preterm birth in high-risk pregnancies: a randomized placebo-controlled trial. Archives of gynecology and obstetrics. 2011 Mar 1;283(3):423-9.

**Crowther 2017**

Crowther, Caroline A., et al. "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." PLoS medicine 14.9 (2017): e1002390.

**Cochrane risk of bias tool**

Higgins JP, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, Savović J, Schulz KF, Weeks L, Sterne JA. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. Bmj. 2011 Oct 18;343:d5928.

**Da Fonseca 2003**

da Fonseca EB, Bittar RE, Carvalho MH, Zugaib M. Prophylactic administration of progesterone by vaginal suppository to reduce the incidence of spontaneous preterm birth in women at increased risk: a randomized placebo-controlled double-blind study. American journal of obstetrics and gynecology. 2003 Feb 1;188(2):419-24.

**Dodd 2013**

Dodd JM, Jones L, Flenady V, Cincotta R, Crowther CA. Prenatal administration of progesterone for preventing preterm birth in women considered to be at risk of preterm birth. Cochrane Database Syst Rev. 2013 Jul 31;7(7).

**Fonseca 2007**

Fonseca EB, Celik E, Parra M, Singh M, Nicolaides KH. Progesterone and the risk of preterm birth among women with a short cervix. New England Journal of Medicine. 2007 Aug 2;357(5):462-9.

**Glover 2011**

Glover MM, McKenna DS, Downing CM, Smith DB, Croom CS, Sonek JD. A randomized trial of micronized progesterone for the prevention of recurrent preterm birth. American journal of perinatology. 2011 May;28(05):377-81.

**Hassan 2011**

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.

**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.

# Appendix A – Review protocols

**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:<br>• a history of spontaneous preterm birth<br>• a history of preterm pre-labour rupture of membranes (in a previous pregnancy)<br>• a history of mid-trimester loss<br>• mid-trimester bleeding<br>• 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).<br>• a short cervix that has been identified on scan and/or bulging membranes in the current pregnancy<br>• a positive fetal fibronectin test |
| Eligibility criteria – **intervention**(s)/exposure(s)/prognostic factor(s) | • vaginal progesterone<br>• oral progesterone |
| Eligibility criteria – **comparator(s)**/control or reference (gold) standard | • one intervention compared to another<br>• placebo<br>• no treatment |

| Field (based on PRISMA-P) | Content |
|---|---|
| | |
| **Outcomes and prioritisation** | **Critical:**<br>• Preterm birth <34+0 weeks<br>• Stillbirth<br>• Infant mortality prior to discharge (includes neonatal mortality and additional mortality post 28 days, but prior to discharge)<br><br>**Important:**<br>• Gestational age at birth<br>• Early onset neonatal sepsis (onset up to 72 hours)<br>• Maternal satisfaction/HRQOL<br>• Neurodevelopmental outcome at >/= 18 months |
| Eligibility criteria – **study design** | Only published full text papers<br>• Systematic reviews of RCTs<br>• RCTs |
| Other **exclusion criteria** | Women in actual preterm labour (as opposed to women at high risk for preterm labour)<br>Multiple pregnancy<br>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:<br>• a history of spontaneous preterm birth<br>• a history of preterm pre-labour rupture of membranes<br>• a history of mid-trimester loss<br>• mid-trimester bleeding<br>• 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<br>  ○ ≤25 mm<br>  ○ ≤15 mm<br>• a positive fetal fibronectin test<br><br>The following groups will be considered for subgroup analysis:<br><br>• 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).<br><br>GRADE will be used to assess the quality of evidence for each outcome.<br><br>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.<br>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 .<br>No supplementary search techniques will be used.<br>See appendix B for full strategies.<br><br><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.<br><br>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.<br><br>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.<br><br>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<br><br>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<br><br>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<br><br>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<br><br>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.<br><br>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.<br>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.<br>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<br>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:<br>The methodological quality of each study will be assessed using an appropriate checklist:<br><br>• ROBIS for systematic reviews<br>• Cochrane risk of bias tool for randomised studies<br><br>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.<br>Synthesis of data:<br>Meta-analysis will be conducted where appropriate using Review Manager.<br><br>Minimally important differences<br>Any significant difference will be used as the MID for mortality outcomes.<br>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.<br><br>Double sifting, data extraction and methodological quality assessment:<br>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.<br>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. |

| # | Searches |
|---|---|
| 53 | 51 not 52 |
| 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 |

| # | Searches |
|---|---|
| 45 | letter.pt. or LETTER/ |
| 46 | note.pt. |
| 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/ |

| # | Searches |
|---|---|
| 5 | exp ECONOMICS, MEDICAL/ |
| 6 | exp RESOURCE ALLOCATION/ |
| 7 | ECONOMICS, NURSING/ |
| 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**

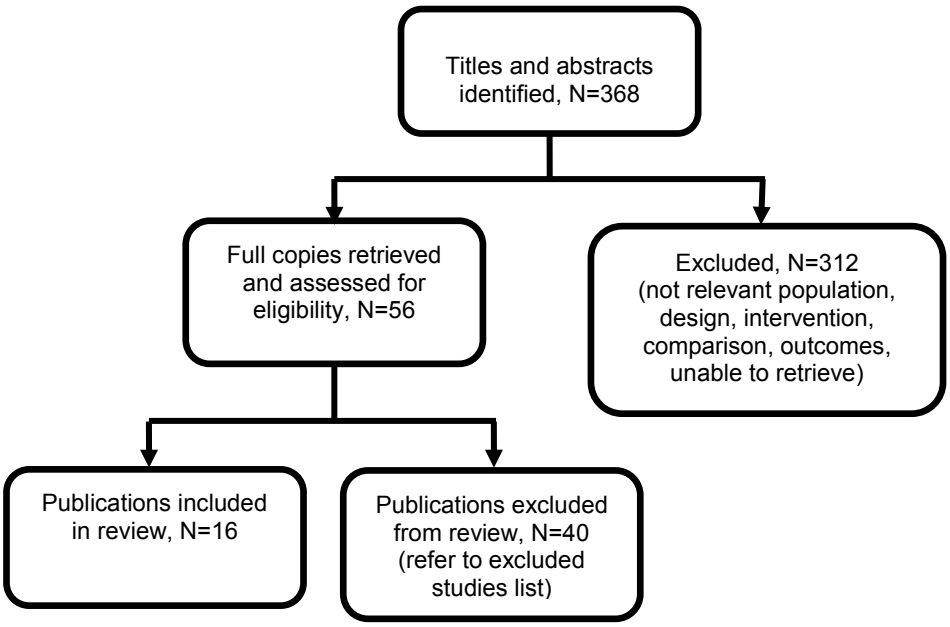
| # | Searches |
|---|---|
| 1 | HEALTH ECONOMICS/ |
| 2 | exp ECONOMIC EVALUATION/ |
| 3 | exp HEALTH CARE COST/ |
| 4 | exp FEE/ |
| 5 | BUDGET/ |
| 6 | FUNDING/ |
| 7 | RESOURCE ALLOCATION/ |
| 8 | budget*.ti,ab. |
| 9 | cost*.ti,ab. |
| 10 | (economic* or pharmaco?economic*).ti,ab. |
| 11 | (price* 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**

<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<br>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<br><br>Ref Id<br>930343<br><br>Country/ies where the study was carried out<br>Egypt</td>
<td>Sample size<br>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).<br>N=187 women were included in the analysis (N=96 in the progesterone group and N=91 in the placebo group).<br><br>Characteristics
<table>
<tr><td></td><td>Oral progesterone (N=96)</td><td>Placebo (N=91)</td></tr>
<tr><td>Maternal age, mean (SD)</td><td>29.3 (4.5)</td><td>29.5 (3.5)</td></tr>
<tr><td>Elective cervical cerclage, N (%)</td><td>55 (57.3)</td><td>57 (62.6)</td></tr>
<tr><td>Rescue cerclage, N (%)</td><td>15 (15.6)</td><td>16 (17.5)</td></tr>
</table>
</td>
<td>Interventions<br>Interventions were started between 14 and 18 weeks of gestational age.<br>Women randomised to the progesterone group received 100 mg of oral progesterone every 6 hours.<br>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.<br>Women with <15mm of cervical length were offered cervical cerclage.</td>
<td>Details<br>Cervical length and gestational age were determined through US between 14 and 18 weeks of gestational age.<br><br>Participants were randomised with a computer program and randomisation was concealed using opaque sealed envelopes.<br><br>Study was double blind.<br><br>Sample size calculations were done and with a power of 80%, it was</td>
<td>Results<br><u>Infant mortality (unclear if before discharge)</u><br>Oral progesterone:7/96<br>Placebo:23/91<br><br><u>Gestational age at birth</u><br>Oral progesterone: 35.4 (2.7)<br>Placebo: 33.9 (2.9)</td>
<td>Limitations<br><br><u>Methodological limitations assessed using the Cochrane collaboration's tool for assessing risk of bias</u><br><br>Random sequence generation: low risk (computer-generated)<br>Allocation concealment: low risk (opaque sealed envelope)<br>Blinding of participants and personnel: low risk (blinded)<br>Blinding of outcome assessment: unclear risk (no details reported)<br>Blinding (performance bias and detection bias): unclear risk (see details above)<br>Incomplete outcome data: low risk (there was a low rate of drop-outs <20% and reasons for these were provided)<br>Selective reporting: low risk (outcomes reported match with those in the study protocol</td>
</tr>
</table>

<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<br>RCT<br><br>Aim of the study<br>To assess whether oral progester one prevents the recurrence of preterm birth.<br><br>Study dates<br>June 2015 to December 2016<br><br>Source of funding<br>Ghamra Military Hospital</td><td>Inclusion criteria<br>Women with singleton pregnancies; gestational age between 14 and 18 weeks; past history of spontaneous preterm labour<br><br>Exclusion criteria<br>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)<br>Other sources of bias: low risk</td></tr>
<tr><td>Full citation<br>Azargoon, Azam, Ghorbani, Raheb, Aslebahar, Fereshteh, Vaginal progesterone on the prevention of preterm birth and neonatal complications in high risk</td><td>Sample size<br>N=100 (N=50 randomised to vaginal progesterone and N=50 randomised to placebo)<br><br>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<br>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.<br><br>Women randomised to the placebo group</td><td>Details<br>Gestational age was determined by an US scan done in the first 12 weeks of pregnancy.<br><br>Cervical length was assessed by a US during the 14 to 18</td><td>Results<br>Preterm birth < 34 weeks<br>All women<br>Vaginal progesterone: 9/50<br>Placebo: 21/50<br><br>Women with previous preterm birth<br>Vaginal progesterone: 5/28<br>Placebo: 11/25</td><td>Limitations<br>Methodological limitations assessed using the Cochrane collaboration's tool for assessing risk of bias<br><br>Random sequence generation: low risk (computer-generated)<br>Allocation concealment: unclear risk (details not reported)</td></tr>
</table>

| Study details | Participants | Interventions | Methods | Outcomes and Results | Comments |
|---|---|---|---|---|---|
| women: A randomized placebo-controlled double-blind study, International journal of reproductive biomedicine (Yazd, Iran), 14, 309-16, 2016<br><br>**Ref Id**<br>930344<br><br>**Country/ies where the study was carried out**<br>Iran<br><br>**Study type**<br>RCT<br><br>**Aim of the study**<br>To assess whether vaginal progesterone decreases preterm birth rate and neonatal complications in women considered to | term birth, N (%)<br><br>Previous pre term birth and short cervix (≤28 mm), N (%) 12 (24) 15 (30)<br><br>**Inclusion criteria**<br>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.<br><br>**Exclusion criteria**<br>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. | received a vaginal 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.<br><br>All women received 2 doses of 12 mg IM betamethasone within an interval of 24 hours in the 28 weeks of gestation.<br>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. | weeks of gestation.<br><br>Those whose cervix was ≤28 mm, underwent a cerclage surgery.<br><br>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<br>Women were randomised with a computerised list of random allocated numbers.<br>Participants and personnel were blinded to treatment allocation. | *Women with previous preterm birth and short cervix (≤28 mm)*<br>Vaginal progesterone: 0/12<br>Placebo: 4/15<br><br>Infant mortality (unclear whether prior to discharge)<br>Vaginal progesterone: 2/50<br>Placebo: 21/50<br><br>Gestational age at birth<br>Vaginal progesterone: 36.5 (3.8)<br>Placebo: 33.6 (4.5) | **Blinding of participants and personnel:** low risk (blinded)<br>**Blinding of outcome assessment:** unclear risk (no details reported)<br>**Blinding (performance bias and detection bias):** unclear risk (see details above)<br>**Incomplete outcome data:** low risk (there was a low rate of drop-outs <20% and reasons for these were provided)<br>**Selective reporting:** low risk (outcomes reported match with those in the study protocol http://apps.who.int/trialsearch/Trial3.aspx?trialid=IRCT20101227338 6N2)<br>**Other sources of bias:** low risk |

| Study details | Participants | Interventions | Methods | Outcomes and Results | Comments |
|---|---|---|---|---|---|
| be at high risk 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.<br>Study dates November 2010 to April 2012<br><br>**Source of funding**<br>Semnan University of Medical Sciences | | | | | |
| **Full citation**<br>Crowther, C. A., Ashwood, P., McPhee, A. J., Flenady, V., Tran, T., Dodd, J. M., Robinson, J. S., Vaginal progesterone pessaries for | **Sample size**<br>N= 799 (N=406 randomised to progesterone and N=393 randomised to placebo)<br><br>**Characteristics** | **Interventions**<br>Women randomised to the vaginal progesterone group received a vaginal progesterone pessary with 100 mg of progesterone.<br>Women randomised to the placebo group received a vaginal suppository in an | **Details**<br>How gestational age was determined has not been reported.<br>The study protocol did not require to measure | **Results**<br>Stillbirth<br>Vaginal progesterone: 4/406<br>Placebo: 5/393<br><br>Infant mortality (unclear whether prior discharge)<br>Vaginal progesterone: 1/406<br>Placebo: 2/393 | **Limitations**<br>Methodological limitations assessed using the Cochrane collaboration's tool for assessing risk of bias<br><br>**Random sequence generation:** low risk (central telephone randomisation ) |

| Study details | Participants | Interventions | Methods | Outcomes and Results | Comments |
|---|---|---|---|---|---|
| pregnant women with a 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<br><br>**Ref Id**<br>703165<br><br>**Country/ies where the study was carried out**<br>Australia, New Zealand, Canada<br><br>**Study type**<br>RCT<br><br>**Aim of the study**<br>To assess whether the | <table><tr><th></th><th>Vaginal progesterone (N=398)</th><th>Placebo (N=389)</th></tr><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><br>**Inclusion criteria**<br>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<br><br>**Exclusion criteria**<br>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. | identical pack as the progesterone group. 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. | cervical length at trial entry or 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. | Early neonatal sepsis<br>Vaginal progesterone: 0/402<br>Placebo: 2/388<br><br>Health related quality of life (SF-36). Mean (SD); better indicated by higher values.<br><br>*General health*<br>Vaginal progesterone:76.61 (17.8)<br>Placebo: 75.08 (17.8)<br><br>*Social functioning*<br>Vaginal progesterone:69.55 (27)<br>Placebo: 73.35 (25.7)<br><br>*Emotional role*<br>Vaginal progesterone: 82.21 (32.2)<br>Placebo: 85.52 (33.6)<br><br>*Mental health*<br>Vaginal progesterone:76.92 (17.9)<br>Placebo: 77.24 (16.2) | **Allocation concealment:** unclear risk (details not reported)<br>**Blinding of participants and personnel:** low risk (blinded)<br>**Blinding of outcome assessment:** low risk (blinded)<br>**Blinding (performance bias and detection bias):** low risk (see details above)<br>**Incomplete outcome data:** low risk (there was a low rate of drop-outs <20% and reasons for these were provided)<br>**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)<br>**Other sources of bias:** low risk |

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

<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>Prenatal administration of progesterone for preventing preterm birth in women considered to be at risk of preterm birth, Cochrane Database of Systematic Reviews, -, 2013<br><br>Ref Id<br>287641<br><br>Country/ies where the study was carried out<br>Iran, Brazil, US and India<br><br>Study type<br>Cochrane systematic review<br><br>Aim of the study<br>To assess the efficacy and safety of oral and vaginal progesterone in women</td>
<td>review did not report any demographic characteristics.<br><br>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<br><br>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>24 and 34 weeks of gestation.<br><br>Cetingoz 2011<br>Intervention: 100 mg vaginal progesterone<br>Control: placebo<br>When intervention started/ended: between 24 and 34 weeks of gestation<br><br>da Fonseca 2003<br>Intervention: 100 mg vaginal progesterone<br>Control: placebo<br>When intervention started/ended: from 24 weeks until 28 weeks' gestation, or birth if earlier.<br><br>Fonseca 2007<br>Intervention: 200 mg vaginal progesterone<br>Control: placebo<br>Treatment started/ended:≥ 20 weeks gestational age<br><br>Glover 2011<br>Intervention: 200 mg oral progesterone twice/day<br>Control: placebo<br>When intervention started/ended: was initiated between 16+0 and 19+6 weeks and continued until the end</td>
<td>Register, hand searches of 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>Progesterone: 7/80<br>Placebo: 17/70<br><br>da Fonseca 2003<br>Progesterone:2/72<br>Placebo: 13/70<br><br>Majhi 2009<br>Progesterone: 2/50<br>Placebo: 3/50<br><br>Rai 2009<br>Progesterone: 22/74<br>Placebo: 37/74<br><br>Cetingoz 2011<br>Progesterone: 2/37<br>Placebo:9/34<br><br>Fonseca 2007*<br>Progesterone: 26/125<br>Placebo: 45/125<br><br>Stillbirth<br>Fonseca 2007<br>Progesterone: 1/136<br>Placebo: 1/138<br><br>Hassan 2011<br>Progesterone: 5/235<br>Placebo: 6/223<br><br>O'Brien 2007<br>Progesterone: 5/309<br>Placebo: 4/302</td>
<td>Limitations for each of the included studies assessed with the Cochrane Risk of Bias Tool<br><br>Akbari 2009<br>Random sequence generation: unclear risk<br>Allocation concealment: unclear risk<br>Blinding of participants and personnel: unclear risk<br>Blinding of outcome assessment: unclear risk<br>Incomplete outcome data: unclear risk<br>Selective reporting: low risk<br>Other bias: unclear risk (reasons not reported)<br><br>Cetingoz 2011<br>Random sequence generation: low risk<br>Allocation concealment: low risk<br>Blinding of participants and personnel: low risk<br>Blinding of outcome assessment: unclear risk<br>Incomplete outcome data: low risk<br>Selective reporting (reporting bias): low risk<br>Other bias: low risk<br><br>Fonseca 2007<br>Random sequence generation: low risk of bias</td>
</tr>
</table>

| Study details | Participants | Interventions | Methods | Outcomes and Results | Comments |
|---|---|---|---|---|---|
| considered to be at higher risk of preterm birth<br><br>**Study dates**<br>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<br><br>**Source of funding**<br>Funding for the reviewers: Mater Research Sport Centre, Mater Health Services Brisbane, South Brisbane, Queensland, Australia; Department of Maternal Fetal Medicine, Mater Mothers' Hospital, | Uterine malforma-tions, N (%) 4 (5.6) 1 (1.4)<br>Incompetent cervix, N (%) 2 (4.1) 1 (1.4)<br>Gestational age at intake¥ 26.5 25.2<br>¥Unclear whether reported as a mean or median (no SD or IQR was reported)<br><br>Fonseca 2007*<br>Vaginal progesterone (N=125) / Placebo (N=125)<br>Age, median (IQR) 29 (24-34) 29 (24-34)<br>Singleton, N (%) 114 (91.2) 112 (89.6)<br><br>Glover 2011*<br>Oral progesterone (N=19) / Placebo (N=14) | of the 33rd week of gestation.<br><br>Hassan 2011<br>Intervention: 90 mg vaginal progesterone<br>Control: placebo<br>Treatment started/ended:≥ 20 weeks gestational age<br><br>Majhi 2009<br>Intervention: 100 mg vaginal progesterone once daily at night<br>Control: no treatment, just monitoring according to protocol<br>When intervention started/ended: 20-24 weeks' gestation until 36 weeks.<br><br>O'Brien 2007<br>Intervention: 90 mg vaginal progesterone once daily at night<br>Control: placebo<br>When intervention started/ended: Started between 18+0 and 22+6. It was unclear when did it end<br><br>Rai 2009<br>Intervention: 100 mg oral progesterone, twice/day<br>Control: placebo | | **Infant mortality (unclear whether prior to discharge)**<br>Akbari 2009*<br>Progesterone: 3/69<br>Placebo: 10/72<br><br>Cetingoz 2011*<br>Progesterone: 3/80<br>Placebo: 3/70<br><br>Fonseca 2007*<br>Progesterone: 2/136<br>Placebo: 7/138<br><br>Hassan 2011*<br>Progesterone: 3/235<br>Placebo: 5/223<br><br>Rai 2009*<br>Progesterone: 3/74<br>Placebo:7/74<br><br>O'Brien 2007*<br>Progesterone: 6/309<br>Placebo:7/302<br><br>**Gestational age at birth**<br>O'Brien 2007*<br>Progesterone: 33.6 (3.8), N= 309<br>Placebo: 36.6 (4.2), N=302<br><br>Glover 2011*<br>Progesterone: 37.0 (2.7), N= 19<br>Placebo: 35.9 (2.6), N=14 | **Allocation concealment:** low risk of bias<br>**Blinding of participants and personnel:** low risk of bias<br>**Blinding of outcome assessment:** low risk of bias<br>**Incomplete outcome data:** low risk of bias<br>**Selective reporting:** low risk of bias<br>**Other bias:** low risk of bias<br><br>da Fonseca 2003<br>**Random sequence generation:** low risk<br>Allocation concealment: low risk<br>**Blinding of participants and personnel:** low risk<br>**Blinding of outcome assessment:** low risk<br>**Incomplete outcome data:** low risk<br>**Selective reporting:** low risk<br>**Other bias:** low risk<br><br>Glover 2011<br>**Random sequence generation:** low risk<br>**Allocation concealment:** low risk<br>**Blinding of participants and personnel:** low risk<br>**Blinding of outcome assessment:** unclear 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>South Brisbane, 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>When intervention started/ended: 18-24 weeks until 36 weeks or delivery.</td>
<td></td>
<td>Neonatal sepsis (unclear whether onset was up to 72 hours)<br><u>Akbari 2009</u><br>Progesterone: 0/69<br>Placebo: 4/72<br><br><u>Hassan 2011</u><br>Progesterone: 7/235<br>Placebo: 6/223<br><br><u>Fonseca 2007</u><br>Progesterone: 3/316<br>Placebo: 11/138<br><br><u>Majhi 2009</u><br>Progesterone: 0/50<br>Placebo: 3/50<br><br>* data extracted from the original study</td>
<td>Incomplete outcome data: low risk<br>Selective reporting: unclear risk<br>Other bias: low risk<br><br><u>Hassan 2011</u><br>Random sequence generation: low risk of bias<br>Allocation concealment: low risk of bias<br>Blinding of participants and personnel: low risk of bias<br>Blinding of outcome assessment: low risk of bias<br>Incomplete outcome data: low risk of bias<br>Selective reporting: low risk of bias<br><br><u>Majhi 2009</u><br>Random sequence generation: low risk<br>Allocation concealment: low risk<br>Blinding of participants and personnel: unclear risk<br>Blinding of outcome assessment: unclear risk<br>Incomplete outcome data: low risk<br>Selective reporting: low risk<br>Other bias: unclear risk</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)<br>Previous abortion - 1st trimester, N (%) — 28 (56) — 26 (52)<br>Previous abortion - 2nd trimester, N (%) — 6 (12) — 7 (14)<br><br>O'Brien 2007*<br>Vaginal progesterone (N=309) / Control (N=302)<br>Age, mean (SD) — 27.1 (5.8) — 27.3 (5.6)<br>Previous preterm birth, N (%) — 309 (100) — 302 (100)<br>Gestational age at randomisa — 19.9 (2.1) — 20.1 (3.3) | | | | O'Brien 2007<br>**Random sequence generation:** low risk<br>**Allocation concealment:** low risk<br>**Blinding of participants and personnel:** low risk<br>**Blinding of outcome assessment:** low risk<br>**Incomplete outcome data:** low risk<br>**Selective reporting:** low risk<br>**Other bias:** low risk<br><br>Rai 2009<br>**Random sequence generation:** low risk<br>**Allocation concealment:** low risk<br>**Blinding of participants and personnel:** low risk<br>**Blinding of outcome assessment:** unclear risk<br>**Incomplete outcome data:** low risk<br>**Selective reporting:** low risk<br>**Other bias:** low risk<br><br>**Other information**<br>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 |

| Study details | Participants | Interventions | Methods | Outcomes and Results | Comments |
|---|---|---|---|---|---|
| | tion, mean (SD) | | | | and to check if other 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></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr>
<td>Full citation<br>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<br><br>Ref Id<br>916970</td>
<td>Sample size<br>N=1225 (N= 615 randomised to vaginal progesterone and N=610 randomised to placebo)<br><br>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<br>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<br>Interventions were started between 22 and 24 weeks of gestational age and ended at 34 weeks or birth of the baby, whichever was sooner.<br>Women randomised to the progesterone group received 200 mg of vaginal progesterone/day.<br>Women randomised to the placebo group received identical placebo capsules.</td>
<td>Details<br>Gestational age was determined by US scan done before 16 weeks of pregnancy.<br><br>Cervical length was determined through US scan at 18+0-24+0 week's gestation.<br><br>Participants were randomised though a web-based program.<br><br>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<br><u>Preterm birth <34 weeks*</u><br>Vaginal progesterone: 88/592<br>Placebo: 101/590<br><br><u>Stillbirth</u><br>Vaginal progesterone: 8/600<br>Placebo: 7/597<br><br><u>Infant mortality</u><br>Vaginal progesterone: 1/600<br>Placebo: 6/597<br><br><u>Gestational age at birth</u><br>Vaginal progesterone: 36.9 (4.1), N=600<br>Placebo:36.8 (4.2), N=597<br><br><u>HRQoL as measured by the EuroQoL-5 Dimensions health utility scores, mean (SD); better indicated by lower values</u><br>Change from baseline to birth<br>Vaginal progesterone: -0.021 (0.207), N=191<br>Placebo:-0.023 (0.220), N=199</td>
<td>Limitations<br><u>Methodological limitations assessed using the Cochrane collaboration´s tool for assessing risk of bias</u><br>Random sequence generation: low risk of bias<br>Allocation concealment: low risk of bias<br>Blinding of participants and personnel: low risk of bias<br>Blinding of outcome assessment: low risk of bias<br>Incomplete outcome data: low risk<br>Selective reporting: low risk of bias<br>Other bias: high risk of bias<br><br>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**<br>UK<br><br>**Study type**<br>RCT and HTA report<br><br>**Aim of the study**<br>To assess the effect of vaginal progesterone prophylaxis in women at high risk of preterm birth<br><br>**Study dates**<br>February 2009 to April 2013<br><br>**Source of funding**<br>Medical Research Council (MRC) | procedure to treat abnormal smears), singleton pregnancies, with gestational age established by US scan before 16 weeks gestational age.<br><br>**Exclusion criteria**<br>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*<br>Vaginal progesterone: -0.009 (0.213), N=279<br>Placebo:-0.015 (0.221), N=274<br><br><u>Bayley-III cognitive composite score at 2 years, mean (SD), better indicated by higher values</u><br>Vaginal progesterone: 99.7 (14.7), N= 410<br>Placebo: 99.5 (15.0), N=425<br><br><u>Moderate or severe neurodevelopmental impairment</u><br>Vaginal progesterone: 47/379<br>Placebo:35/403<br><br><u>Visual impairment</u><br>Vaginal progesterone: 0/447<br>Placebo: 4/466<br><br><u>Hearing impairment</u><br>Vaginal progesterone: 1/466<br>Placebo:2/465 | |
| **Full citation**<br>Romero, Roberto, Conde-Agudelo, | **Sample size**<br>N= 974 (N=498 randomised to the vaginal progesterone group and N=476 randomised to the placebo group) | **Interventions** | **Details**<br>A search was conducted from inception until the 30th | **Results**<br><u>Preterm birth <34+0 weeks</u><br>Vaginal progesterone: 86/498 | **Limitations**<br><u>Limitations have been assessed using AMSTAR</u><br>Total score: 13/16. |

| Study details | Participants | Interventions | Methods | Outcomes and Results | Comments |
|---|---|---|---|---|---|
| Agustin, Da 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<br><br>**Ref Id**<br>930508<br><br>**Country/ies where the study was carried out** | **Characteristics**<br><br>Maternal age, median (IQR): Vaginal progesterone (N=498) 28 (23.6-33); Placebo (N=476) 27.5 (23.5-32.8)<br>Gestational age, median (IQR): 22.6 (21.4-23.6); 22.6 (21.4-23.4)<br>Cervix <10 mm, N (%): 48 (9.6); 57 (12)<br>Cervix 10 to 20 mm, N (%): 379 (76.1); 362 (76)<br>Cervix 12 to 25 mm, N (%): 71 (14.3); 57 (12)<br><br>Inclusion criteria<br>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)<br><br>Exclusion criteria | Fonseca 2007: 200 mg/d vaginal progesterone; Placebo; 24 to 33+6/7<br>O'Brien 2007: 90 g/d vaginal progesterone; Placebo; 18-22 to 37+0/7<br>Cetingoz 2011: 100 mg/d vaginal progesterone; Placebo; 24 to 34<br>Hassan 2011 | of September 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 | Placebo: 126/476<br>I2= 0%<br><br>Stillbirth<br>Vaginal progesterone: 9/498<br>Placebo: 8/476<br>I2= 0%<br><br>Infant mortality (unclear if prior discharge)<br>Vaginal progesterone:7/498<br>Placebo:15/476<br>I2= 0%<br><br>Gestational age at birth<br>Mean gestational age at birth in the intervention group was 0.74 higher (0.18 to 1.3 higher)<br><br>Proven neonatal sepsis (unclear whether early onset)<br>Vaginal progesterone: 18/494<br>Placebo: 28/470<br><br>Bayley-III cognitive composite score (age 2 years); better indicated by higher values<br>Vaginal progesterone: 95.5 (16.1), N=88<br>Placebo: 97.7 (16.9), N= 80<br>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<br><br>**Limitations for each of the included studies assessed with the Cochrane Risk of Bias Tool**<br><br>Fonseca 2007<br>**Random sequence generation:** low risk of bias<br>**Allocation concealment**: low risk of bias<br>**Blinding of participants and personnel:** low risk of bias<br>**Blinding of outcome assessment:** low risk of bias<br>**Incomplete outcome data:** low risk of bias<br>**Selective reporting:** low risk of bias<br>**Other bias:** low risk of bias<br><br>O'Brien 2007<br>**Random sequence generation:** low risk of bias |

| Study details | Participants | Interventions | Methods | Outcomes and Results | Comments |
|---|---|---|---|---|---|
| UK, USA and Turkey<br><br>**Study type**<br>IPD MA<br><br>**Aim of the study**<br>To assess whether vaginal progesterone prevents preterm birth and improves perinatal outcomes in women with a short cervix (≤ 25 mm)<br><br>**Study dates**<br>Searches were done from inception until 30th September 2018<br><br>**Source of funding**<br>National Institutes of Health, Department of Health and Human Services (USA) | Quasi-randomised trials, trials that assessed vaginal progesterone in 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<br>Norman 2016<br>200 mg/day vaginal progesterone; Placebo; 22-24 to 34 | information 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)<br>Vaginal progesterone:10/81<br>Placebo:7/77<br><br>Visual or hearing impairment (age 2 years)<br>Vaginal progesterone: 0/100<br>Placebo:2/87 | **Allocation concealment:** low risk of bias<br>**Blinding of participants and personnel**: low risk of bias<br>**Blinding of outcome assessment**: low risk of bias<br>**Incomplete outcome data:** low risk of bias<br>**Selective reporting:** low risk of bias<br>**Other bias:** low risk of bias<br><br>Cetingoz 2011<br>**Random sequence generation:** low risk of bias<br>**Allocation concealment:** low risk of bias<br>**Blinding of participants and personnel:** low risk of bias<br>**Blinding of outcome assessment:** low risk of bias<br>**Incomplete outcome data:** low risk of bias<br>**Selective reporting:** low risk of bias<br>**Other bias:** low risk of bias<br><br>Hassan 2011<br>**Random sequence generation:** low risk of bias<br>**Allocation concealment**: low risk of bias |

| Study details | Participants | Interventions | Methods | Outcomes and Results | Comments |
|---|---|---|---|---|---|
| (extracted 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- | | | | | **Blinding of participants and personnel:** low risk of bias<br>**Blinding of outcome assessment:** low risk of bias<br>**Incomplete outcome data:** low risk of bias<br>Selective reporting: low risk of bias<br>**Other bias:** low risk of bias<br><br><u>Norman 2016</u><br>**Random sequence generation:** low risk of bias<br>**Allocation concealment:** low risk of bias<br>**Blinding of participants and personnel:** low risk of bias<br>**Blinding of outcome assessment:** low risk of bias<br>**Incomplete outcome data:** low risk of bias for obstetric and neonatal primary outcomes; high risk of bias for childhood primary outcome<br>**Selective reporting:** low risk of bias<br>**Other bias:** high risk of bias<br><br>**Other information**<br><br>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>author and 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<br>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,</td><td>Sample size<br>N=80 (N= 41 randomised to vaginal progesterone and N=39 randomised to placebo)<br><br>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,</td><td>21.7 (20.7-22.6)</td><td>21.6 (20.9-22.7)</td></tr></table></td><td>Interventions<br>Women randomised to the vaginal progesterone group received a vaginal suppository with 200 mg of micronized progesterone (Utrogestan).<br>Women randomised to the placebo group received a vaginal suppository with the same appearance as the progesterone group (Medicaps).<br>Women had to use 1 capsule daily between 22 and 34 weeks gestation.</td><td>Details<br>How gestational age was determined or how was preterm birth defined has not been reported.<br>Cervical length was assessed by a US during the 18 to 22 weeks of gestation.<br>Short cervix was defined as cervical length ≤30 mm measured</td><td>Results<br><u>Preterm birth < 34 weeks</u><br>Vaginal progesterone: 5/41<br>Placebo: 6/39<br><br><u>Infant mortality before discharge</u><br>Vaginal progesterone: 1/41<br>Placebo: 2/39<br><br><u>Proven sepsis</u><br><u>Vaginal progesterone:</u> 0/41<br>Placebo: 0/39</td><td>Limitations<br><u>Methodological limitations assessed using the Cochrane collaboration's tool for assessing risk of bias</u><br><br>Random sequence generation: low risk (computer-generated)<br>Allocation concealment: unclear risk (details not reported)<br>Blinding of participants and personnel: low risk ( double blinded)<br>Blinding of outcome assessment: unclear risk (no details reported)<br>Blinding (performance bias and detection bias): unclear risk (see details above)</td></tr>
</table>

| Study details | Participants | Interventions | Methods | Outcomes and Results | Comments |
|---|---|---|---|---|---|
| Patrick M., Pajkrt, Eva, de 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<br><br>**Ref Id**<br>930538<br><br>**Country/ies where the study was carried out**<br>The Netherlands | median (IQR)<br>Cervical length, median mm (IQR): 26 (23-29); 27 (25-28)<br><br>**Inclusion criteria**<br>Women with a singleton pregnancy and a cervical length ≤30 mm<br><br>**Exclusion criteria**<br>Women <18 years old; cervical cerclage; previous preterm birth <34 weeks gestation age; preterm labour or congenital malformations. | | twice within 2 weeks. Randomisation was web-based, study was double blinded. | | **Incomplete outcome data:** low risk (no drop-outs were reported, ITT analysis)<br>**Selective reporting:** unclear risk (protocol does not appear to have been registered) |

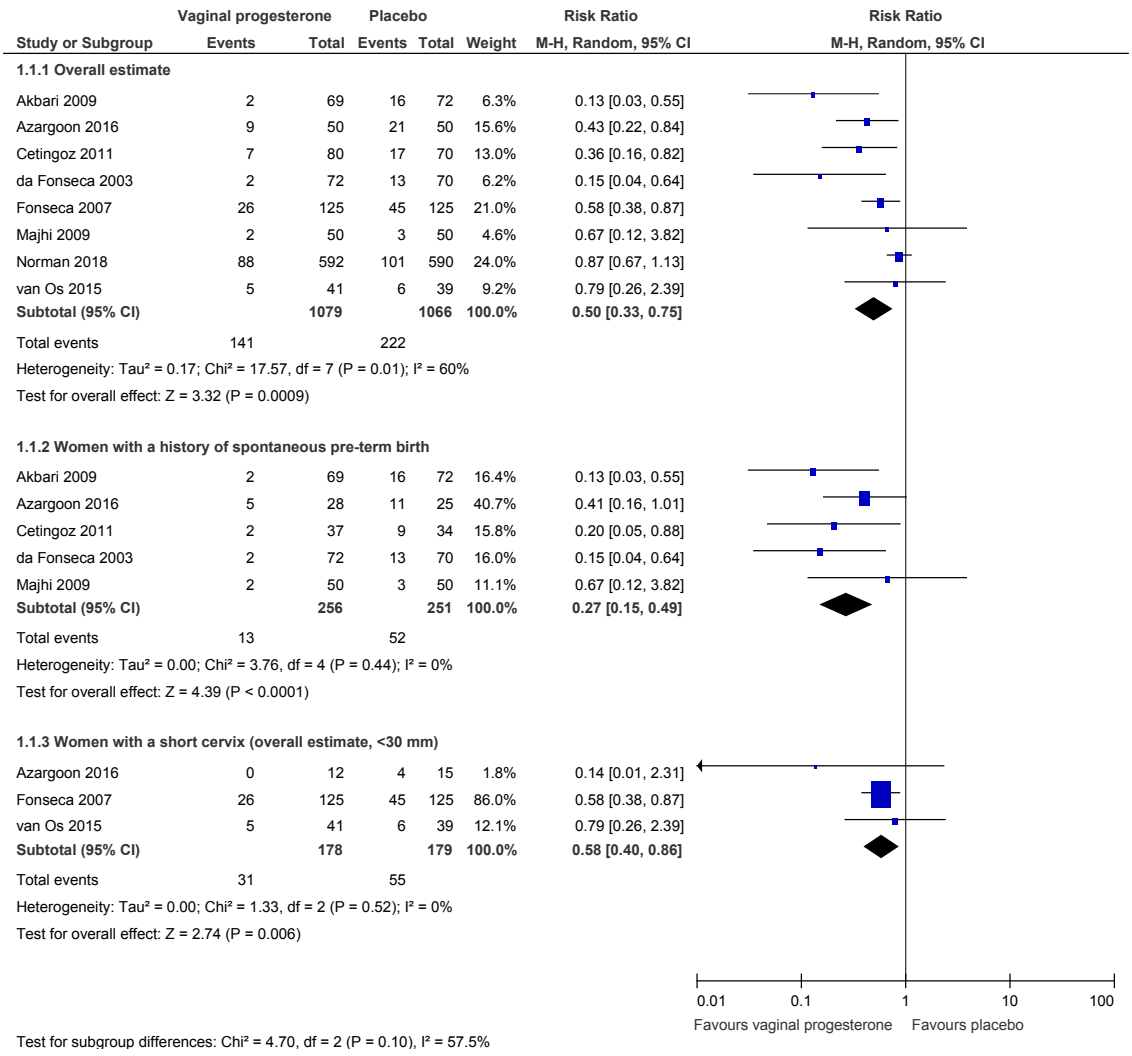
| Study details | Participants | Interventions | Methods | Outcomes and Results | Comments |
|---|---|---|---|---|---|
| **Study type**<br>RCT<br><br>**Aim of the study**<br>To assess whether vaginal progesterone decreases preterm birth rate and neonatal complications in low-risk pregnant women with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

# Appendix E – Forest plots

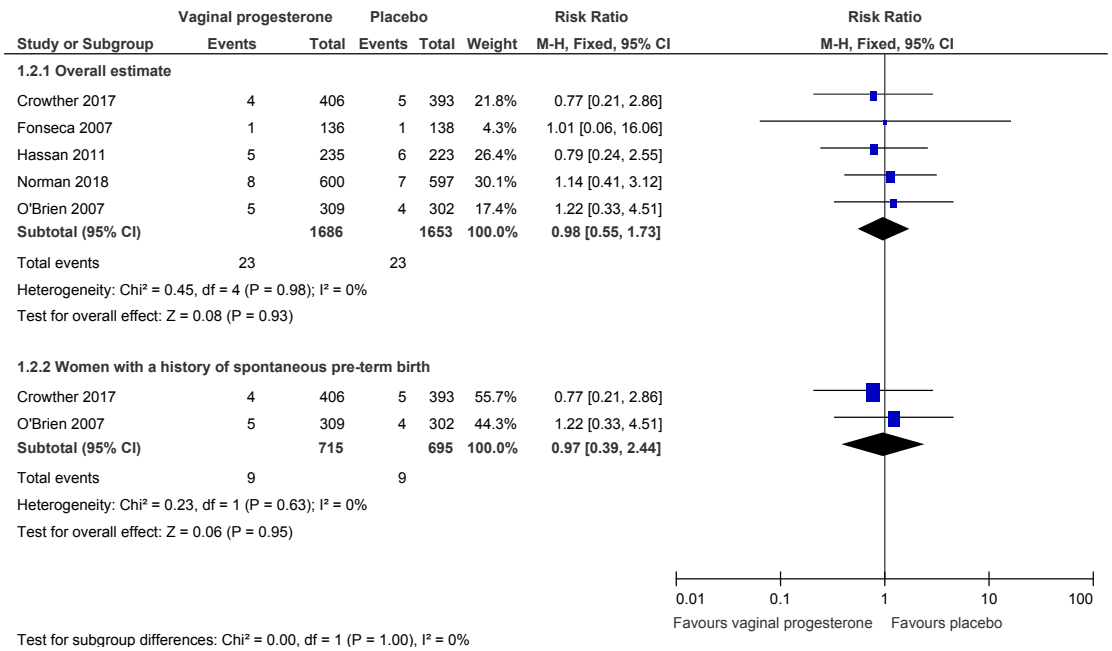
## Comparison 1. Vaginal progesterone versus placebo

### Critical outcomes

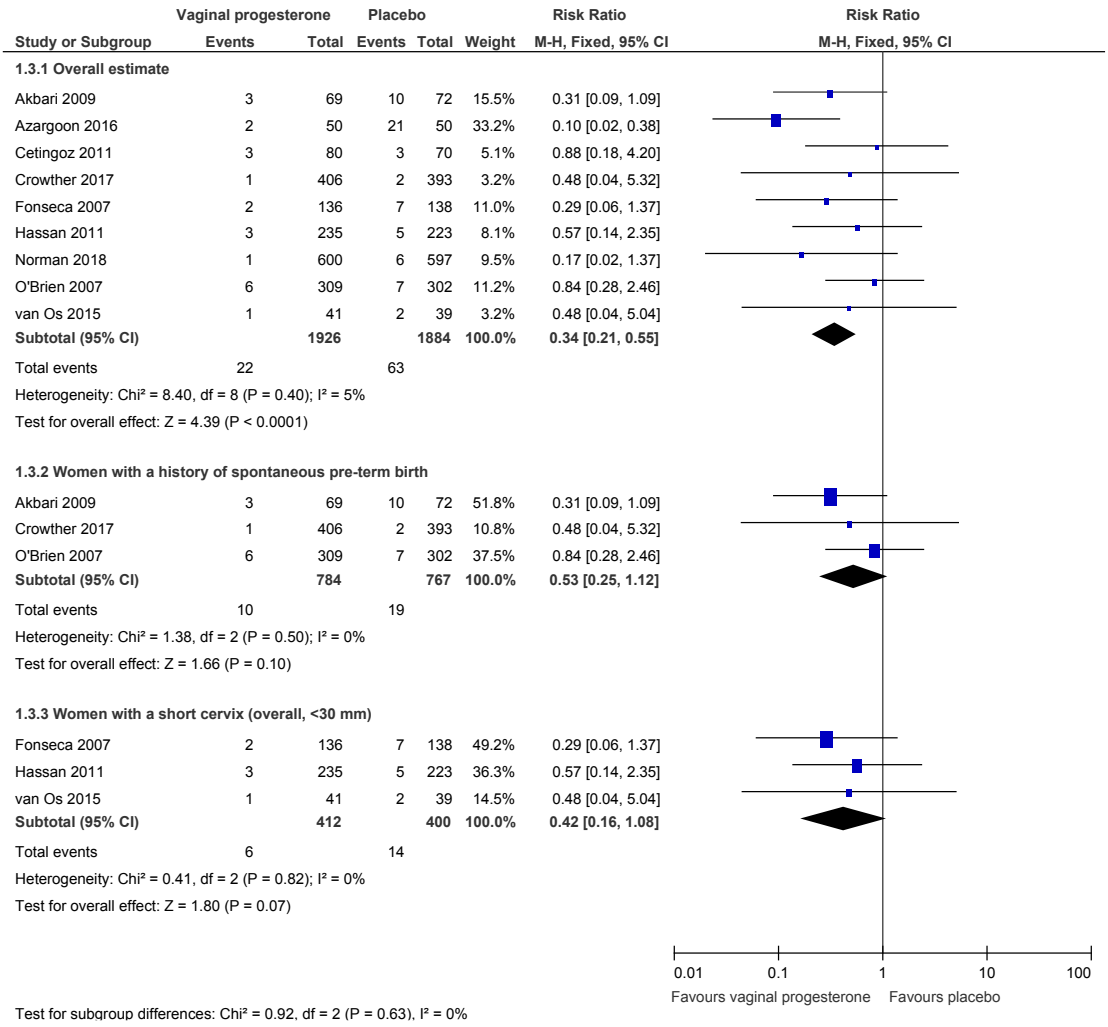
#### Figure 1: Preterm birth <34+0 weeks



## Figure 2: Stillbirth

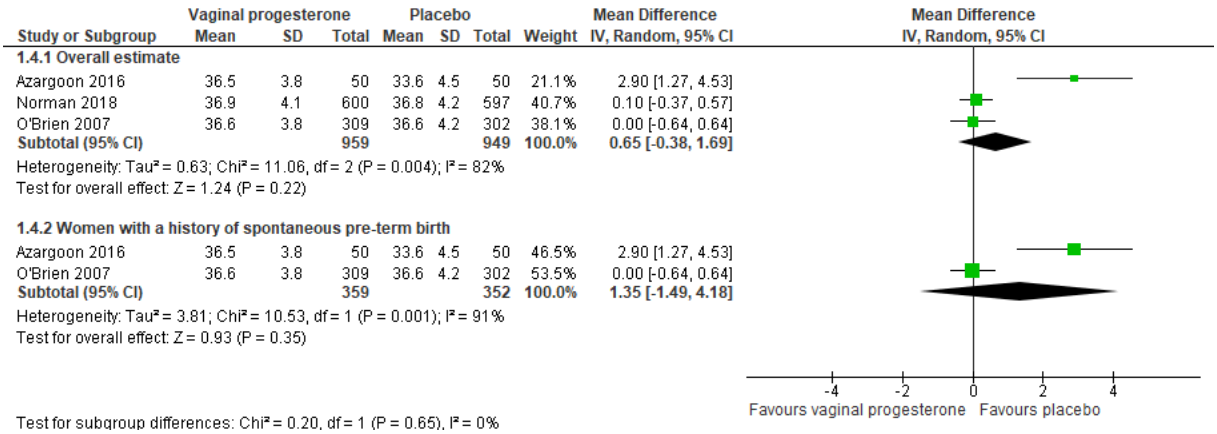


## Figure 3: Infant mortality

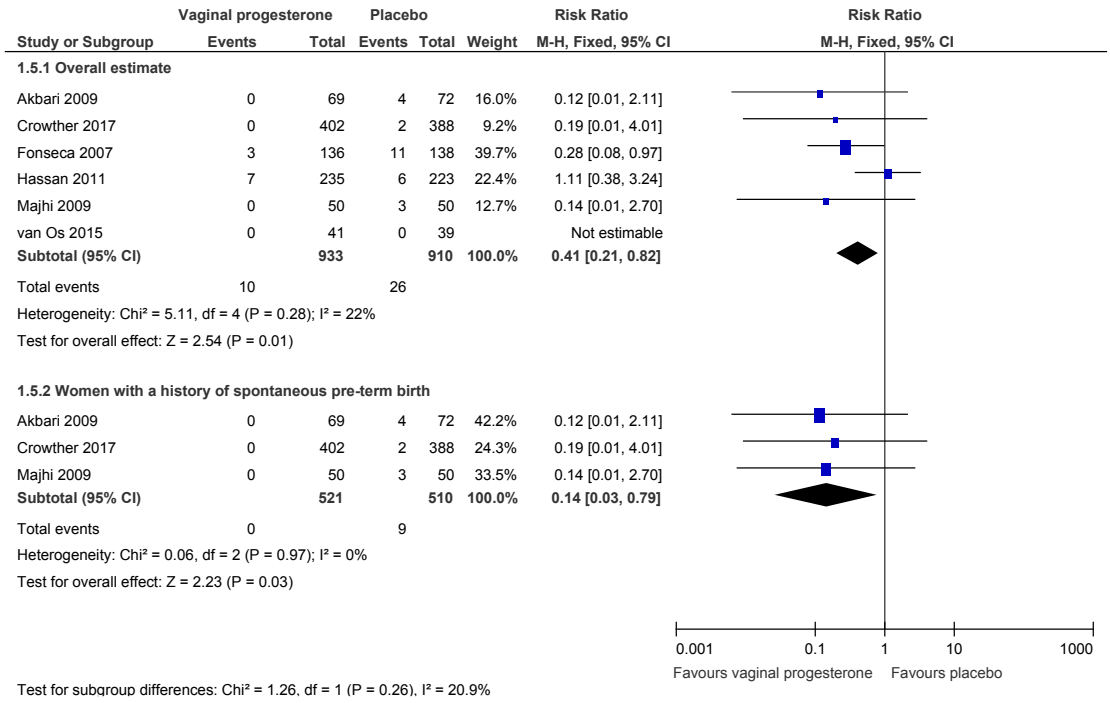



## Important outcomes

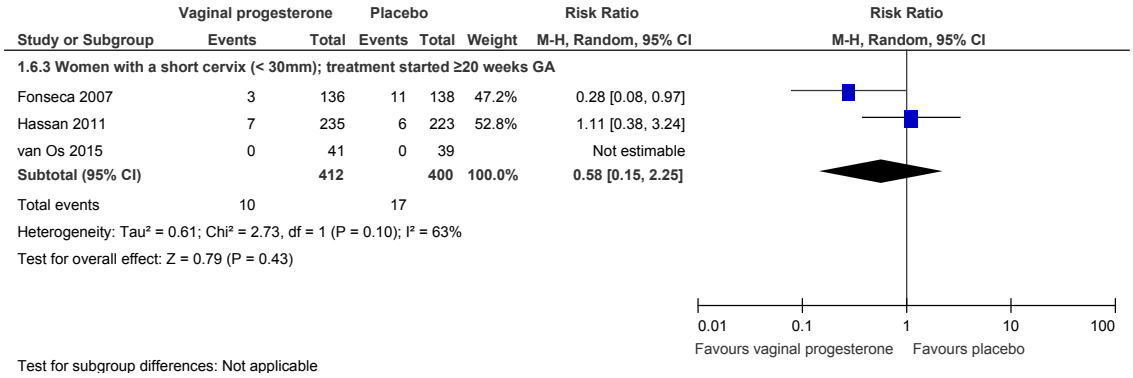
## Figure 4: Gestational age at birth (mean weeks)



## Figure 5: Neonatal sepsis




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

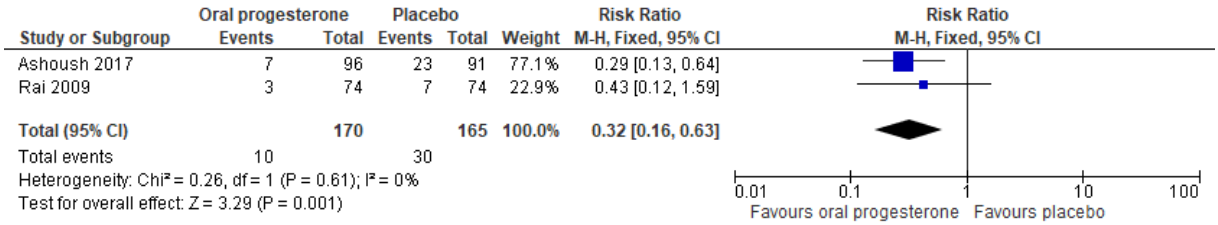



*[This figure is presented separately from figure 5 because a random effects model was utilised due to high heterogeneity for this subgroup]*

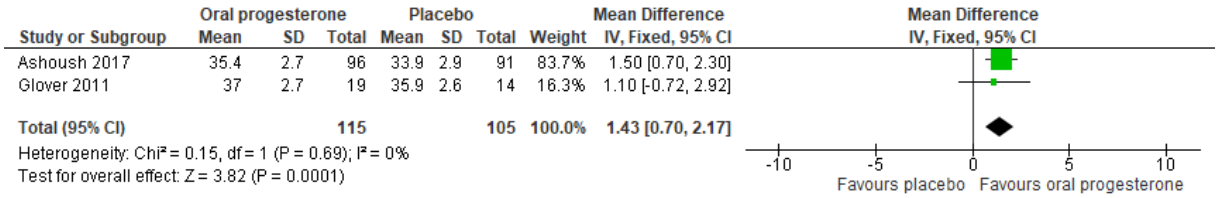
## Comparison 2. Oral progesterone versus placebo

### 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 | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Number of studies** | **Design** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other considerations** | **Vaginal progesterone** | **Placebo** | **Relative (95% CI)** | **Absolute** | **Quality** | **Importance** |
| 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 | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Number of studies | Design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Vaginal progesterone | Placebo | Relative (95% CI) | Absolute | Quality | Importance |
| 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 | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Number of studies | Design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Vaginal progesterone | Placebo | Relative (95% CI) | Absolute | Quality | Importance |
| | | | | | | | | | | 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**

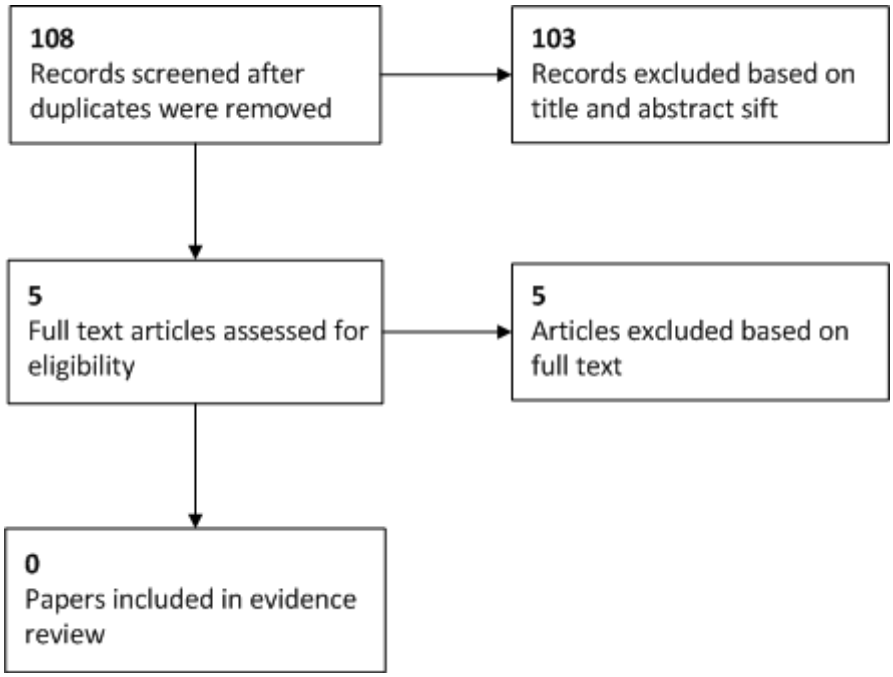
| Quality assessment | | | | | | | Number of patients | | Effect | | Quality | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Number of studies | Design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Oral progesterone | Placebo | Relative (95% 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 |

| Study | Reason for Exclusion |
|---|---|
| Choi, Suk-Joo, Use of progesterone supplement therapy for prevention of preterm birth: review of literatures, Obstetrics & gynecology science, 60, 405-420, 2017 | This systematic review has also considered studies including women with multiple 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) |

| Study | Reason for Exclusion |
|---|---|
| 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 pregnancy, Cochrane Database of Systematic Reviews, 2017, CD012531, 2017 | Protocol |
| 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 | No relevant outcomes have been reported |

| Study | Reason for Exclusion |
|---|---|
| preterm birth in women with threatened preterm labor*, Journal of Maternal-Fetal and Neonatal Medicine, 29, 3223-3228, 2016 | |
| Hermans, Frederik J. R., Schuit, Ewoud, Opmeer, Brent C., Oudijk, Martijn A., Bekker, 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 | Protocol |
| 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 |

| Study | Reason for Exclusion |
|---|---|
| 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., 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 | No relevant population (women were in preterm labour) |

| Study | Reason for Exclusion |
|---|---|
| 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 randomized trials, American Journal of Obstetrics and Gynecology, 213, 438-9, 2015 | Comment letter |
| 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- | The main aim of this study does not match with the main aim of this review |

| Study | Reason for Exclusion |
|---|---|
| analysis, BJOG: An International Journal of Obstetrics & GynaecologyBjog, 20, 20, 2017 | |
| 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 meta-analysis including data from the OPPTIMUM study, Ultrasound in Obstetrics & Gynecology, 48, 308-17, 2016 | Updated by Romero 2018 |
| 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 | Pessary does not contain progesterone |

| Study | Reason for Exclusion |
|---|---|
| controlled trial, BMC Pregnancy and Childbirth, 17, 284, 2017 | |
| 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 months of age, American Journal of Obstetrics and Gynecology, 216, S492, 2017 | Abstract |

**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. |
| Pizzi LT, Seligman NS, Baxter JK, Jutkowitz E, Berghella V. Cost and cost effectiveness of vaginal progesterone gel in reducing preterm birth: an economic analysis of the PREGNANT trial. PharmacoEconomics 32: 467 2014 | Not cost-utility analysis. Cost-effectiveness analysis but of limited applicability because of US setting and definition of key outcome (pre-term birth). |
| Shree R, Page J, Caughey AB, Chandrasekaran S. Vaginal progesterone for preterm birth prevention in women with a short intepregnancy interval: A cost-effectiveness analysis. American journal of obstetrics and gynecology S227 2017 | Available as abstract only |
| Soto Molina H, Diaz-Alvarez O, Sandoval-Avila M, Mejia D, Ramirez A, Rodriguez-Mendoza M M. Complete Economic Evaluation of the Use of Micronized Progesterone By Vaginal Administration for the Prevention of Preterm Birth in Pregnant Patients with Short Cervix in Mexico. Value in Health 21: S144 2018 | Available as abstract only |

*(a) <Insert Note here>*

# 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 |

| Criterion | Explanation |
|---|---|
| Intervention | Use of vaginal progesterone in pregnancy |
| 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<br>• 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. |

| Research question | Does progesterone reduce the risk of preterm birth in women who have a cervical length ≤25mm, but no 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<br>• 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. |

| Research question | At what gestation should treatment with prophylactic vaginal progesterone for the prevention of preterm birth be started and stopped? |
|---|---|
| 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 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<br>o Vaginal progesterone started later in pregnancy (e.g. ≥20 weeks) and stopped at 34 weeks<br>o Vaginal progesterone started later in pregnancy (e.g. ≥20 weeks) and stopped at 36 weeks |
| Outcome | Preterm birth <34 weeks<br>Neonatal outcomes |
| Study design | Randomised controlled trial. |
| Timeframe | Minimum duration of follow up: until discharge from hospital |