Main editor

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Publishing Tips

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Summary of recommendations

1 - Background
2 - Objectives
3 - Progesterone for women with history of preterm birth

<table>
<thead>
<tr>
<th>Weak Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>In women with a singleton pregnancy and history of preterm birth before week 37, without an obvious course such as uterine malformation or conization, the administration of progesterone, might be considered in order to reduce the risk of a repeated preterm birth before week 33-35. Progesterone should be initiated before week 24 either vaginally or intramuscularly. The uncertainty of whether there is a possible risk for rare but severe neurological dissability in the offspring due to progesterone treatment, must be taken into consideration.</td>
</tr>
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4 - Progesterone for women with a short cervix

<table>
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<tr>
<td>In women with a singleton pregnancy before week 25 and a short cervix below 25 mm, vaginal progesterone administration should be considered in order to reduce risk for preterm birth before week 33-35. The uncertainty of whether there is a possible risk for rare but severe neurological dissability in the offspring due to progesterone treatment, must be taken into consideration.</td>
</tr>
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5 - Methods
6 - Description of studies
7 - Discussion
8 - Authors' conclusions
9 - Contributions of authors
10 - Declarations of interest
11 - Author group
1 - Background

Preterm birth
Preterm birth refers to a delivery occurring before 37 completed weeks of gestation (WHO) [1]. It is the leading cause of infant mortality and morbidity worldwide. The risk of perinatal morbidity is highly related to the gestational age at birth, and survival increases from less than 10% before 24 weeks to more than 95% by 32-33 weeks of gestation [2][3][4]. Correspondingly, the risk of having a severe functional impairment is inversely related to gestational age at delivery among surviving infants born very prematurely [5]. Immaturity affects most organ systems, and severe neonatal complications related to preterm birth include respiratory distress syndrome, bronchopulmonary dysplasia, retinopathy of prematurity, intraventricular haemorrhage, necrotizing enterocolitis, sepsis, and patent ductus arteriosus [4][6][7]. In childhood and early adolescence, abnormalities of neuromotor function and slow mental development have been shown to be more frequent in children that were born preterm compared to children born at term [5][8][9][10]. The incidence of preterm birth varies from 5 to 18% worldwide with the highest incidence in the low-income countries [1]. In the Nordic countries, 6% of all pregnant women deliver prior to 37 weeks of gestation [11]. Approximately one third of the cases of preterm birth are iatrogenic due to maternal or fetal complications such as preeclampsia, intrauterine growth restriction and placental abruption, whereas the remaining two thirds constitute spontaneous preterm onset of labour or preterm rupture of membranes. Although significant improvements in standard of living and medical science have been obtained, preterm birth rates have remained mainly unchanged [11].

Prediction and prevention of PTB
Due to a very diverse etiology of preterm birth, prediction and prevention of the condition is complicated. The two best predictors of preterm birth have been shown to be measurement of the cervical length at mid-gestation and information on the woman’s history of previous preterm birth. The cervical length, which can be assessed during pregnancy by vaginal ultrasonography [12], will remain relatively unchanged in uncomplicated pregnancies until the beginning of the last trimester, where a progressive shortening takes place [13][14]. Second-trimester cervical length measurements can be used in the prediction of preterm birth, where the risk of spontaneous birth ≤34 weeks decreases from approximately 70% at a cervical length of 5 mm at 23 weeks’ gestation to 0.5% at 50 mm in singleton pregnancies [15]. Similar results are found in twin pregnancies, where the risk of delivery before 33 weeks gradually increases from 2.5% at 60 mm to 12% at 25 mm and 80% at 8 mm [16]. However, it seems that finding a short cervix during the second trimester ultrasound scan seems to be very rare in the Nordic counties [17][18]. Information on women’s obstetric history is important since the risk of spontaneous preterm birth has been shown to increase progressively with decreasing gestational age at previous births [19]. Correspondingly, it has been shown that women with previous births after 37 weeks of gestation have decreased risk of spontaneous preterm birth in a subsequent pregnancy [20]. Combining obstetric history and cervical length measurement has been shown to enhance prediction of preterm delivery in singleton pregnancies [21] but not in twin gestations where cervical length performs the best without improvements in prediction by addition of obstetric history [22].

Progesterone for prevention of PTB
Progesterone supplementation is mainly administered intramuscularly or vaginally due to a first-pass hepatic metabolism effect if administered orally [23]. Vaginal progesterone treatment, as gel, pessaries or tablet, is often considered more convenient and easier to administer compared to intramuscular treatment. Reported side effects to vaginal progesterone treatment are local irritation and vaginal discharge, whereas side effects such as injection site pain, itching, and swelling have been reported for intramuscular treatment. Progesterone plays an important role throughout pregnancy, and progesterone supplementation in the first weeks after assisted reproduction technology has been used for luteal phase support for several decades [24]. It may be given as a natural or synthetic progesterone supplementation, where micronized progesterone is identical to the form produced by the placenta and, therefore, is regarded as a natural progesterone, as opposed to the synthetic 17α-hydroxyprogesterone caproate [23]. As early as the 1950ies, it was suggested that progesterone supplementation could prevent preterm birth [25]. Since then several studies have examined the effect of progesterone treatment during the second and third trimester to prevent preterm birth in high-risk singleton pregnancies, defined as women with a short cervical length at midgestation and/or a history of previous preterm birth. Although the precise mechanism for the suggested preventive effect of progesterone on preterm birth is not fully elucidated, the hormone has been proposed to decrease the risk of preterm uterine contractions potentially through an inhibitory effect of progesterone on the amount of gap junctions in the myometrium as well as by suppressing gene transcription for calcium channels and oxytocin receptors [26]. Furthermore, progesterone might have an anti-inflammatory effect and inhibit cervical ripening through suppression of proinflammatory cytokines leading to a reduction in the concentration of prostaglandins in the cervix [27]. The effect of progesterone has also been explored in women presenting with established or threatened preterm birth (regular contractions and cervical dilation less than 3 cm). A Cochrane review from 2104 found insufficient evidence to advocate progestational agents as a tocolytic for women presenting with preterm labour [73].

Why it is important to do this review
Pregnant women of Nordic origin have a lower risk of preterm birth compared to the populations examined in the majority of the published randomized controlled trials. This review was undertaken to provide recommendations for pregnant women at risk in a Nordic setting.
2 - Objectives

The aim of this review was to provide recommendations for progesterone supplementation for the prevention of preterm birth in pregnant women with either a history of preterm birth or a short cervix. The recommendations should be suitable for Nordic obstetrical units.
3 - Progesterone for women with history of preterm birth

Progesterone for prevention of preterm birth

1 History of preterm birth: Vaginal progesterone vs placebo/NT

1.1 Preterm birth before week 33-36

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Vag. Progesterone</th>
<th>Placebo/NT</th>
<th>Risk Ratio</th>
<th>Risk of Bias</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Events</td>
<td>Total</td>
</tr>
<tr>
<td>Azargoon 2016</td>
<td>5</td>
<td>28</td>
<td>11</td>
<td>25</td>
</tr>
<tr>
<td>Cetinkaz 2011</td>
<td>2</td>
<td>37</td>
<td>9</td>
<td>34</td>
</tr>
<tr>
<td>Fonseca 2003</td>
<td>2</td>
<td>72</td>
<td>13</td>
<td>70</td>
</tr>
<tr>
<td>Hassan 2011</td>
<td>6</td>
<td>38</td>
<td>7</td>
<td>34</td>
</tr>
<tr>
<td>Malhi 2009</td>
<td>2</td>
<td>50</td>
<td>3</td>
<td>50</td>
</tr>
<tr>
<td>Norman 2016</td>
<td>74</td>
<td>406</td>
<td>82</td>
<td>437</td>
</tr>
<tr>
<td>O’Brien 2007</td>
<td>70</td>
<td>309</td>
<td>80</td>
<td>302</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>1000</td>
<td>952</td>
<td>100.0%</td>
<td>0.66 [0.46, 0.93]</td>
</tr>
<tr>
<td>Total events</td>
<td>161</td>
<td>205</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Tau² = 0.08, Chi² = 11.12, df = 6 (P = 0.06), I² = 46%
Test for overall effect: Z = 2.36 (P = 0.02)

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F)Selective reporting (reporting bias)
(G) Other bias

Progesterone for prevention of preterm birth

2 History of preterm birth: Intramuscular progesterone vs placebo/NT

2.1 Preterm birth before week 33-36

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Progesterone</th>
<th>Placebo/NT</th>
<th>Risk Ratio</th>
<th>Risk of Bias</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Events</td>
<td>Total</td>
</tr>
<tr>
<td>Meis 2003</td>
<td>63</td>
<td>306</td>
<td>47</td>
<td>153</td>
</tr>
<tr>
<td>Saghafi 2011</td>
<td>8</td>
<td>50</td>
<td>18</td>
<td>50</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>71</td>
<td>356</td>
<td>203</td>
<td>100.0%</td>
</tr>
<tr>
<td>Total events</td>
<td>71</td>
<td>356</td>
<td>203</td>
<td>100.0%</td>
</tr>
</tbody>
</table>

Heterogeneity: Tau² = 0.00, Chi² = 1.01, df = 1 (P = 0.31), I² = 1%
Test for overall effect: Z = 3.05 (P = 0.002)

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias
Weak Recommendation

In women with a singleton pregnancy and history of preterm birth before week 37, without an obvious course such as uterine malformation or conization, the administration of progesterone, might be considered in order to reduce the risk of a repeated preterm birth before week 33-35. Progesterone should be initiated before week 24 either vaginally or intramuscularly. The uncertainty of whether there is a possible risk for rare but severe neurological disability in the offspring due to progesterone treatment, must be taken into consideration.

Practical Info

When to initiate the progesterone supplementation?
The included studies initiated the treatment before gestational week 24. As we want to prevent not to treat, early intervention makes sense. Therefore, most obstetricians initiate the treatment in the early second trimester or even in the first trimester of pregnancy.

When to stop the progesterone supplementation?
The included studies stopped the treatment between 34 and 37 weeks gestation. Some obstetricians might recommend continuation until 37 gestational weeks, due to Csapo’s progesterone block theory [25], i.e. fear of labour contractions as a result of progesterone withdrawal.

How to administer the progesterone?
Concerning the reduction of the risk of preterm birth before 34 gestational weeks the two administration forms seem equivalent; a) weekly intramuscular injection of synthetic 17α-hydroxyprogesterone caproate (17OHPC) and b) daily vaginal administration of micronized progesterone.
The two studies with the highest weight in the meta-analysis used one daily administration of either 90 or 200 mg progesterone vaginally. In order to achieve a more even diurnal progesterone level, some obstetricians prescribe 100 mg twice a day.

In the Nordic countries, vaginal administration is standard, whereas intramuscular administration is used in other parts of the world. We found no difference in effect related to administration route. In a meta-analysis (data not shown) combining the 9 studies using either vaginal and intramuscular administration, we found the same effect for reducing risk or preterm birth before week 33-35 (RR 0.66 (0.51-0.85 95%CI). The vaginal administration is easy to use but has the side effect of vaginal discharge and discomfort. In these cases, some obstetricians accept rectal administration. The effect of this administration, however, has never been studied. The intramuscular administration has side effects related to injection site with local skin reactions such as pain, itching and swelling.

Key Info

Benefits and harms

Preterm birth
In women with a history of preterm birth, there is only an expected small effect due to the low risk of unexplained preterm birth in a Nordic population. It is especially preterm birth before week 34 that is associated with an increased risk of morbidity and mortality, and these cases may be the ones most likely to benefit from progesterone treatment [74]. We did not find studies evaluating whether there might be an additive effect for reducing late preterm birth by continuing progesterone treatment until week 37.

Long-term (2 years) mortality and morbidity in infants, including cerebral palsy
- Primary outcome: Only one placebo-controlled randomized trial (The OPPTIMUM study) included long-term childhood outcome as one of their primary outcomes [29]: a composite outcome of death or moderate to severe neurodevelopmental impairment at two years of age. This outcome favored placebo (12% risk) over progesterone (17%). However, the difference was not statistically significant: OR of 1.45 (95% CI 0.98 – 2.15; p = 0.064). Thus, this study indicates that progesterone does not improve this long-term outcome, in fact it might even worsen the outcome.
- Secondary analysis: Secondary analysis of the Meis study [30], where children underwent a physical examination at a mean follow-up of 48 months of age, showed no difference between the progesterone and placebo group with regard to health status, physical examination or neurophysiological development evaluated by the Ages and Stages Questionnaire.
- Twin studies: Secondary analyses of two twin studies did not find evidence of neither benefit nor harm of second and third trimester progesterone exposure regarding neurophysiological development at up to 6 years of age [83][31][32].

Serious maternal adverse effects, including cancer

Small net benefit, or little difference between alternatives
Rationale

The majority of the studies includes women with a history of preterm birth before week 37. There is only one study including women with a history of preterm birth before week 34, the Norman study [29]. The authors of this metaanalysis find it mainly clinically relevant to prevent preterm birth before week 34 and therefore the Norman study was set as comparator in the metaanalysis (see Table 1 below).

Based on the dots given in the section "Practical information", we give a weak recommendation in favor of treatment with progesterone in women with a history of preterm birth.

- Preterm birth before week 33-35 (weight 7) favored treatment with both vaginal progesterone (RR 0.66; 95%CI 0.46-0.93) and intramuscular progesterone (RR 0.63; 95%CI 0.46-0.85). As the risk of publication bias was high, we recalculated the RR including only the two publications with the highest weights and the lowest risks of bias (RR 0.85; 95%CI 0.70 – 1.04; 12.0% [29][58]). Furthermore, one of these two studies were also characterized by preterm birth rates closer to the 8.6% found in a Swedish population with a history of preterm birth before week 34, and a repeated preterm birth before week 34 (Table 1). We conclude, that in a Nordic population the risk reduction of preterm birth before week 33-35 is more likely to be 15% as estimated by the two largest included studies, covering one study in a Nordic population, than the 34% risk reduction found by the meta-analysis of all seven studies.

- Adverse long-term effects for the offspring (weight 9) favored placebo (RR 1.35; 95%CI 0.98 – 1.93). However, the evidence was very low. We conclude that this result is of concern.

- Maternal adverse effects including cancer (Weight 8): Progesterone may increase the risk of breast cancer in menopausal women. This question has not been addressed in pregnant women in whom we know the progesterone level is already high. We conclude that we cannot ignore this potential risk.

Table 1. Prevalence of preterm deliveries in the second pregnancy given the gestational duration in the first pregnancy.

Table presents the fraction of women who experienced preterm delivery (delivery before 34th or 37th week of gestation) in the second pregnancy given the duration of the first pregnancy. Analyses are based on the data retrieved from the Swedish Medical Birth Register (MFR), on two cohorts. One cohort, includes singletons, both induced and spontaneous deliveries, and cover the births that occurred over the years 1973 – 2012. Second cohort is restricted to spontaneous deliveries, and cover the singleton births that occurred over the years...
1990 – 2012. Analyses were run using the best estimate of gestational age provided in the MFR (*The Swedish Medical Birth Register - A Summary of Content and Quality*, n.d.).

<table>
<thead>
<tr>
<th>First child*</th>
<th>Term</th>
<th>Second child*</th>
<th>Preterm</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&gt;= 37 weeks</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>n (%)</td>
<td>&lt; 34 weeks</td>
<td>&lt; 37 weeks</td>
</tr>
<tr>
<td></td>
<td></td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td><strong>Years 1973 – 2012, induced and spontaneous deliveries, n = 2 433 820 births (two consecutively born singletons) in n = 1 216 910 mothers.</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>First child*</td>
<td>Term</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>&gt;= 37 weeks, 1 150 814 (100)</td>
<td>1 116 181 (97.0)</td>
<td>7 582 (0.7)</td>
</tr>
<tr>
<td></td>
<td>&lt; 34 weeks, 15 280 (100)</td>
<td>11 590 (75.9)</td>
<td>1 321 (8.6)</td>
</tr>
<tr>
<td></td>
<td>&lt; 37 weeks, 66 096 (100)</td>
<td>55 133 (83.4)</td>
<td>2 774 (4.2)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>First child*</th>
<th>Term</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&gt;= 37 weeks, 440 848 (100)</td>
<td>431 492 (97.9)</td>
<td>1705 (0.4)</td>
</tr>
<tr>
<td></td>
<td>&lt; 34 weeks, 4 002 (100)</td>
<td>2847 (71.1)</td>
<td>366 (9.1)</td>
</tr>
<tr>
<td></td>
<td>&lt; 37 weeks, 21 718 (100)</td>
<td>18 247 (84.0)</td>
<td>747 (3.4)</td>
</tr>
</tbody>
</table>

* order of the child was assessed based on the cleaned/revised variable of parity (included child of 1\(^{st}\) and 2\(^{nd}\) parity)
** the mode of the delivery (induced / spontaneous) has been registered in the MFR since the year 1990

Clinical Question/ PICO

**Population:** Women with a singleton pregnancy and a history of spontaneous abortion/preterm birth between 16+0 and 37 weeks unless explained by twins, placental abruption, trauma, conization or similar.

**Intervention:** Progesterone, vaginal (100, 200 and 400 mg), before week 24

**Comparator:** Placebo/NT

### Outcome Table

<table>
<thead>
<tr>
<th>Outcome Timeframe</th>
<th>Study results and measurements</th>
<th>Absolute effect estimates</th>
<th>Certainty of the Evidence (Quality of evidence)</th>
<th>Plain text summary</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Preterm birth before week 33-35 Weeks</strong></td>
<td>Relative risk 0.66 (CI 95% 0.46 - 0.93) Based on data from 1,952 patients in 7 studies.¹ (Randomized controlled)</td>
<td>Relative risk 0.66</td>
<td>Low</td>
<td>Vaginal progesterone for women with history of preterm birth probably reduces risk of preterm birth before week 33-35. Due to serious publication bias. Due to serious indirectness.</td>
</tr>
<tr>
<td><strong>Long-term effect for offspring 2 years</strong></td>
<td>Relative risk 1.38 (CI 95% 0.98 - 1.93) Based on data from 818 patients in 1 studies.³ (Randomized controlled)</td>
<td>Relative risk 1.38</td>
<td>Low</td>
<td>We are uncertain whether vaginal progesterone improves or worsens long-term outcomes for offspring. Due to serious inconsistency and imprecision.</td>
</tr>
<tr>
<td><strong>Maternal adverse effects, including cancer 5 Years</strong></td>
<td>Relative risk</td>
<td>Relative risk</td>
<td>Low</td>
<td>We found no randomized controlled trials examining short-term and long-term serious adverse effect.</td>
</tr>
</tbody>
</table>
serious. Publication bias: Serious. There is some concern regarding the problem area 'commercially funded', but as this is not stated in the publications, we did not downgrade this. Also the small studies here are more likely to be a result of publication bias. The large studies have a different RR (0.85) than the small. This made us downgrade due to serious concerns for publication bias.;

3. Primary study [29]. Baseline/comparator:: Primary study.

4. Inconsistency: Serious. Point estimates vary widely; Indirectness: No serious. Imprecision: Serious. Only data from one study; Publication bias: No serious.

5. There are no randomized controlled trials with long term follow up on women treated with progesterone compared to no treatment.

References


[38] Progesterone for prevention of preterm birth. 2018;

### Clinical Question/ PICO

**Population:** Women with a singleton pregnancy and a history of spontaneous abortion/preterm birth between 16+0 and 37 weeks unless explained by twins, placental abruption, trauma, conization or similar.

**Intervention:** Progesterone, intramuscular, before week 24

**Comparator:** Placebo/NT

<table>
<thead>
<tr>
<th>Outcome Timeframe</th>
<th>Study results and measurements</th>
<th>Absolute effect estimates</th>
<th>Certainty of the Evidence (Quality of evidence)</th>
<th>Plain text summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preterm birth before week 33-35 Weeks</td>
<td>Relative risk 0.63 (CI 95% 0.46 - 0.85) Based on data from 559 patients in 2 studies. (^1) (Randomized controlled)</td>
<td><strong>320</strong> per 1000 <strong>202</strong> per 1000</td>
<td>Low Due to serious indirectness, Due to serious imprecision, Due to serious imprecision (^2)</td>
<td>Intramuscular progesterone for women with history of preterm birth probably reduce risk of preterm birth before week 33-35.</td>
</tr>
<tr>
<td>Long-term effect for offspring 2 years</td>
<td>Relative risk 1.38 (CI 95% 0.98 - 1.93) Based on data from 818 patients in 1 studies. (^3) (Randomized controlled)</td>
<td><strong>122</strong> per 1000 <strong>168</strong> per 1000</td>
<td>Low Due to serious inconsistency, Due to serious imprecision (^4)</td>
<td>We are uncertain whether progesterone improves or worsen long-term effect for offspring.</td>
</tr>
<tr>
<td>Maternal adverse effects, including cancer Years</td>
<td>Relative risk</td>
<td>CI 95%</td>
<td>We found no randomized controlled trials examining serious short or long term adverse effects.</td>
<td></td>
</tr>
</tbody>
</table>

1. Systematic review \(^3\) with included studies: Meis 2003, Sagha\(f\)i 2011. **Baseline/comparator:** Control arm of reference used for intervention \(^2\). History: Women with a singleton pregnancy and a history of spontaneous abortion/preterm birth between 16+0 and 37 weeks unless explained by twins, placental abruption, trauma, conization or similar.
2. **Risk of bias: No serious**. Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias in one study but due to the weighting of only 16.6% we did not downgrade. **Inconsistency: No serious. Indirectness: Serious**. Differences between the population of interest and those studied. Nordic countries have a baseline risk of preterm birth much lower than in the published studies. **Imprecision: Serious**. Due to one study weighing 84% of the estimate. **Publication bias: No serious**.

3. Primary study [29]. We included the study by Norman here, despite the fact, that the study uses vaginal progesteron, as we expect the effect of progesterone on the offspring will be independent of administration route. **Baseline/comparator:: Primary study**.

4. **Inconsistency: Serious**. Point estimates vary widely. **Indirectness: No serious. Imprecision: Serious**. Only data from one study; **Publication bias: No serious**.

5. There are no randomized controlled trials with long term follow up on women treated with progesterone compared to no treatment.

**References**


[38] Progesterone for prevention of preterm birth. 2018;
4 - Progesterone for women with a short cervix

4 Short cervix: Vaginal progesterone vs placebo/NT

4.1 Preterm birth before week 33-35

In women with a singleton pregnancy before week 25 and a short cervix below 25 mm, vaginal progesterone administration should be considered in order to reduce risk for preterm birth before week 33-35. The uncertainty of whether there is a possible risk for rare but severe neurological dissability in the offspring due to progesterone treatment, must be taken into consideration.

Practical Info

- We included studies on women with a short cervix (< 25 mm before week 25) with or without a history of preterm birth.
- We excluded studies including women with symptoms of preterm birth (contractions and bleeding).
- In the primary PICO we wanted to explore the effect of progesterone in women with no symptoms, no history and so on. However, no studies fulfilled these criteria. Furthermore, we do not recommend screening for short cervix in the general population due to low prevalence of asymptomatic short cervix (see Table 2 below) and low prevalence of preterm birth before week 34 in the Nordic countries (see Table 1 in Rationale for “Progesterone for women with history of preterm birth”).
- The primary outcome was initially set as “delivery before 34 weeks”. However, we included studies with information on preterm delivery from 33 +0 to 35 +0 weeks due to lack of studies only addressing delivery before 34 weeks gestation.

Table 2. Summary of studies on cervical length

<table>
<thead>
<tr>
<th>Study</th>
<th>Cut off (mm)</th>
<th>Week for cervical screening</th>
<th>Location</th>
<th>Number of women screened</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>To [22]</td>
<td>&lt;15</td>
<td>22-24</td>
<td>UK, Europe, South America</td>
<td>47 143</td>
<td>1.1%</td>
</tr>
<tr>
<td>Fonseca [40]</td>
<td>20-25</td>
<td>20-23</td>
<td>UK, South America</td>
<td>24 620</td>
<td>1.7%</td>
</tr>
<tr>
<td>Hassan [41]</td>
<td>10-20</td>
<td>20-23</td>
<td>UK, Europe, 10 countries</td>
<td>32 091</td>
<td>2.3%</td>
</tr>
<tr>
<td>Heath [15]</td>
<td>22-23</td>
<td>22-23</td>
<td>London</td>
<td>2 713</td>
<td>8.1%</td>
</tr>
<tr>
<td>Goya [42]</td>
<td>18-22</td>
<td>18-22</td>
<td>Spain</td>
<td>11 518</td>
<td>6.4%</td>
</tr>
<tr>
<td>Taipale [17]</td>
<td>19-21</td>
<td>19-21</td>
<td>Finland</td>
<td>3 694</td>
<td>0.2%</td>
</tr>
<tr>
<td>Wulff [43]</td>
<td>16-23</td>
<td>16-23</td>
<td>Sweden</td>
<td>3 334</td>
<td>0.8%</td>
</tr>
<tr>
<td>Kuusela [18]</td>
<td>18-22</td>
<td>18-22</td>
<td>Finland</td>
<td>3 694</td>
<td>0.2%</td>
</tr>
<tr>
<td>Wulff [43]</td>
<td>19-21</td>
<td>19-21</td>
<td>Denmark</td>
<td>3 334</td>
<td>0.8%</td>
</tr>
<tr>
<td>Kuusela [18]</td>
<td>16-23</td>
<td>16-23</td>
<td>Sweden</td>
<td>2 122</td>
<td>0.5%</td>
</tr>
</tbody>
</table>
When to initiate the progesterone supplementation?
The included studies initiated the treatment before gestational week 25 in case of cervix length below 25 mm.

When to stop the progesterone supplementation?
The included studies stopped the treatment between 34 and 37 weeks gestation. Some obstetricians might recommend continuation until 37 gestational week, due to Csapo’s progesterone block theory [25], i.e. fear of labour contractions as a result of progesterone withdrawal.

Key Info

Benefits and harms

Vaginal administration of progesterone is associated with reversible side effects as outlined in the background section.

Preterm birth

Vaginal administration of progesterone in women with a short cervix is associated with a net benefit of reducing the risk of preterm birth (RR 0.63; CI 95% 0.48 - 0.83).

Long-term (2 years) mortality and morbidity in infants, including cerebral palsy

We refer to key info for "Progesterone for women with history of preterm birth" in section 3 for elaboration of the possible benefits and harms on the offspring.

Serious maternal adverse effects, including cancer

We refer to key info for "Progesterone for women with history of preterm birth" in section 3 for elaboration of this subject as we do not expect any difference in benefits and harms related to indication for treatment (history or short cervix).

Certainty of the Evidence

Overall study quality of the included trials was judged as fair to good. However in some cases sufficiently detailed information for deciding on study quality was not available.

Preference and values

No substantial variability expected

Resources and other considerations

In this guideline, we did not compare progesterone-treatment with alternatives including vaginal cerclage, abdominal cerclage, and relief from physical activities. However, several studies indicate a positive effect of cerclage for selected cases [46], especially when the cervix is very short.

For further consideration - see section 3, Key info for "Progesterone for women with history of preterm birth".

Rationale

The majority of studies includes women with a history of preterm birth before week 37. There is only one study including women with a history of preterm birth before week 34, the Norman study [29]. We find it mainly clinically relevant to prevent preterm birth before week 34 and therefore the Norman study was set as a comparator in the meta-analysis.
Clinical Question/ PICO

**Population:** Pregnant women with a singleton pregnancy and a short cervix below 25 mm; no uterine malformation and no cerclage.

**Intervention:** Vaginal progesterone (100, 200 and 400 mg) before week 24

**Comparator:** Placebo/NT

<table>
<thead>
<tr>
<th>Outcome Timeframe</th>
<th>Study results and measurements</th>
<th>Absolute effect estimates</th>
<th>Certainty of the Evidence</th>
<th>Plain text summary</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Preterm birth before week 33-35 Weeks</strong></td>
<td>Relative risk 0.63 (CI 95% 0.48 - 0.83) Based on data from 885 patients in 4 studies. (Randomized controlled)</td>
<td>244 per 1000</td>
<td>Moderate Due to serious Indirectness</td>
<td>Vaginal progesterone probably reduces risk for preterm birth before week 33-35 in women with short cervix.</td>
</tr>
<tr>
<td><strong>Long-term effect for offspring 2 years</strong></td>
<td>Relative risk 1.38 (CI 95% 0.98 - 1.93) Based on data from 818 patients in 1 studies. (Randomized controlled)</td>
<td>122 per 1000</td>
<td>Low Due to serious inconsistency, Due to serious imprecision</td>
<td>We are uncertain whether progesterone improves or worsens long-term outcomes for the offspring.</td>
</tr>
<tr>
<td><strong>Maternal adverse effects, including cancer Years</strong></td>
<td>Relative risk</td>
<td>CI 95%</td>
<td></td>
<td>We found no randomized controlled trails examining serious short or long term adverse effects.</td>
</tr>
</tbody>
</table>

2. **Inconsistency:** No serious . **Indirectness:** Serious . Differences between the population of interest and those studied. Low risk of short cervix in a Nordic country ; **Imprecision:** No serious . **Publication bias:** No serious .
3. **Inconsistency:** Serious . **Point estimates vary widely:** Indirectness: No serious . **Imprecision:** Serious . Only data from one study ; **Publication bias:** No serious .

**References**
[38] Progesterone for prevention of preterm birth. 2018;
5 - Methods

Criteria for considering studies for this review

Types of studies
To reach a broad consensus on all elements of the PICO for this review, i.e. which participants, interventions, comparisons and outcomes to include, a Delphi process (REF) was undertaken [47]. A Delphi-panel was created, constituting 35 experts of relevant professions (obstetricians, neonatologists, midwifes, researchers and one oncologist) from the Nordic countries. Three rounds of internet-based questionnaires were answered anonymously. In the first round the panel was asked to give free suggestions regarding PICO’s. In the second and third round the panelists rated the suggested variables on a Likert scale (1 to 5), and had the opportunity to comment and add new suggestions. The response rate in the first round was 25/35 (71%), in the second 16/35 (46%) and in the third 17/35 (49%). The PICO described below was the result of an agreement rate with a cut-off at 4 defining consensus. We only included published randomized controlled studies investigating progesterone for prevention of preterm birth in pregnant women at high risk according to obstetric history or finding of a short cervix.

Types of participants
Women with a singleton pregnancy and increased risk of preterm birth due to:
1. Prior pregnancy with a spontaneous abortion or preterm birth between gestational week 16+0 and 37+0, not explained by multiple pregnancy, abruption of placenta, trauma or cervical conization
2. Actual pregnancy with a cervical length < 25 mm as measured by ultrasound at < 25+0 gestational weeks and no other risk factors for preterm birth, i.e. a preterm birth or threatening preterm birth in a previous pregnancy or labor contractions, bleeding or positive fibronectin test in current pregnancy.

Types of interventions
Administration of vaginal progesterone (100, 200 or 400 mg) or intramuscular progesterone versus no progesterone or placebo.

Types of outcome measures
Primary outcomes
1. Birth before gestational week 33+0-35+0 (spontaneous or iatrogenic)
2. Long term (2 years) mortality and morbidity in infant, including cerebral palsy
3. Serious maternal adverse effects, including cancer.

There was a difference between the protocol and the review. In the protocol we wanted to set a cut off at gestational week 34 for the primary outcome “preterm birth”. However, only few studies used a cutoff at week 34. To be able to include more studies we used either week 33 or 35, if data for week 34 was not available.

Secondary outcomes
None

Search methods for identification of studies
A systematic literature search was carried out. Only articles in English were included.

Electronic searches
The following databases were searched:
Cochrane database of systematic reviews
Using the following search words:
birth birthweight clinical controlled gestagen gestonorone hydroxyprog* lbw low matur* pre pre-matur* preemie preemies prematur* premie premies preterm progestagen progesterone progestin* progestogen randomi$ed rct term trial vlbw weight

And for PubMed:
A literature search was carried out in Medline 31. May 2018 with the following search string: (((((premature) OR preterm) OR premature birth[MeSH Terms])) AND ((((((progestagen) OR progestogen) OR progestins) OR progestational agent) OR progesterone) OR progesterone[MeSH Terms])) AND (((randomized controlled trials as topic[MeSH Terms]) OR randomized controlled trial[Publication Type]) OR randomized controlled trial) OR controlled clinical trial) OR controlled clinical trial[Publication Type]) resulting in 336 articles.

Searching other resources
We contacted two trialists for data on preterm birth <34 weeks ([48] and [49]), and one responded ([48]) but did not have data for preterm birth <34 weeks.

Data collection and analysis
We used the standard methods of The Cochrane Collaboration [50]. Members of the guideline group independently assessed trials for inclusion in the review and extracted the data. All the articles were also discussed in sessions with the co-authors. The methodology used to assess risk of bias of studies included in the review is described in the Cochrane Handbook for Systematic Reviews of Interventions [50]. Each article was reviewed by two independent authors and later discussed in the guideline panel. We conducted data management and analysis using RevMan software (5.3).

Selection of studies
The guideline panel assessed all the potential studies identified as a result of the search strategies. Any disagreement on whether to include a study was resolved through discussion. No third author was consulted. Only data from full text articles were included and if only an abstract was available, study was not included.

Data extraction and management
All authors took part in the data extraction procedure according to the above.

Assessment of risk of bias in included studies
Assessment was defined by the guideline panel and validated by all authors afterwards. The methodology used to assess risk of bias of studies included in the review is described in the Cochrane Handbook for Systematic Reviews of Interventions [50]. For each included study we stated details regarding assessment of bias risk.

(A) Random sequence generation (checking for possible selection bias)
For each included study the method was assessed as being at:
• Low risk of bias: defined as a randomized process
• High risk of bias: defined as a non-random process
• Unclear risk of bias

(B) Allocation concealment (checking for possible selection bias)
For each included study the method used to conceal allocation was assessed as being at:
• Low risk of bias: defined as allocation by telephone or central randomization procedure, consecutively-numbered sealed opaque envelopes or similar methods
• High risk of bias: defined as methods such as open random allocation, unsealed or nonopaque envelopes, date of birth or similar methods
Unclear risk of bias

(C) Blinding of participants and personnel (checking for possible performance bias)
For each included study the methods used to blind participants and personnel from knowing which intervention a participant received was assessed as being at:
- Low risk of bias: defined as blinding - or if lack of blinding, this was considered unlikely to affect results
- High risk of bias: defined as non-blinding – or if lack of blinding, this was considered likely to affect results
- Unclear risk of bias

(D) Blinding of outcome assessment (checking for possible detection bias)
For each included study the methods used to blind outcome assessors from knowing which intervention a participant received was assessed as being at:
- Low risk of bias: defined as blinding - or if lack of blinding, this was considered unlikely to affect results
- High risk of bias: defined as non-blinding – or if lack of blinding, this was considered likely to affect results
- Unclear risk of bias

(E) Incomplete outcome data (checking for possible attrition bias)
For each included study and outcome, the completeness of data including exclusions from analyses and attrition was assessed, and studies were classified as being at:
- Low risk of bias: defined as e.g. no missing outcome data or missing outcome data balanced across groups
- High risk of bias: defined as e.g. missing outcome data imbalanced across groups
- Unclear risk of bias

(F) Selective reporting (checking for reporting bias)
For each included study the possibility of selective outcome reporting bias was assessed, and studies were classified as being at:
- Low risk of bias: defined as all the study’s prespecified outcomes and all expected outcomes of interest to the current review being reported
- High risk of bias: defined as a lack of reporting of all the study’s prespecified outcomes, one or more reported primary outcomes not prespecified, outcomes of interest were reported incompletely
- Unclear risk of bias

(G) Other bias (checking for bias due to problems not covered by (A) to (F) above)
For each included study any important concerns not included in any of the above-mentioned possible sources of bias was assessed, and studies were classified as being at:
- Low risk of other bias
- High risk of other bias
- Unclear risk of other bias

Measures of treatment effect
For dichotomous data, we presented results as summary risk ratio with 95% confidence intervals. No continuous data included.

Unit of analysis issues
Only randomised studies included, No cluster randomised studies were identified.

Dealing with missing data
Only available data were included.

Assessment of heterogeneity
Heterogeneity was assessed by T2, I2 and Chi2 statistics meta-analysis.
Assessment of reporting biases
A maximum of 9 studies were included with no visual asymmetry. We used funnel plots to investigate reporting bias by assessing asymmetry visually.

Data synthesis
Statistical analysis was performed using RevMan 5.3. Data were analysed according to route of administration (vaginal or intramuscular).

Subgroup analysis and investigation of heterogeneity
No subgroup analysis was performed. For analysis we used random effect.

Sensitivity analysis
The included studies had little drop out and therefore no sensitivity analysis was performed.
6 - Description of studies

Results of the search

The search undertaken in May 2018 identified 25 studies for consideration.

Following studies evaluated the effect of progesterone for women with a history of preterm birth: Akbari 2009 [52], Azargo 2016 [51], Cetingoz 2011 [53], Crowther 2017 [48], Fonseca 2003 [54], Glover 2011 [55], Hassan 2011 [41], Ibrahim 2010 [49], Johnson 1975 [56], Majhi 2009 [57], Meis 2003 [34], Norman 2016 [29], O’Brien 2007 [58], Saghafi 2011 [59].

Following studies evaluated the effect of progesterone for women with a short cervix. Azargo 2016 [51], DeFranco 2007 [60], Fonseca 2007 [40], Grobman 2012 [45], Hassan 2011 [41], Norman 2016 [29], van Os 2015 [44], Winer 2015 [61].

Studies evaluating the effect of progesterone for other reasons: Aboulghar 2012 (after IVF/ICSI) [62], Borna 2008 [63] and Rozenberg 2012 (after tocolysis) [64], Briery 2011 (after preterm rupture of membranes) [65], Caritis 2009 (triplets) [66], Rode 2011 (twins) [83].


Studies with oral progesterone: Glover 2011 [55]

10 studies met the inclusion criteria stated (Azargo 2016 [51], Cetingoz 2011 [53], Fonseca 2003 [54], Fonseca 2007 [40], Hassan 2011 [41], Majhi 2009 [57], Meis 2003 [34], Norman 2016 [29], O’Brien 2007 [58], Saghafi 2011 [59]).

15 studies did not fulfil the inclusion criteria (Akbari 2009 [52], Aboulghar 2012 [62], Borna 2008 [63], Briery 2011 [65], Caritis 2009 [66], Crowther 2017 [48], DeFranco 2007 [60], Glover 2011 [55], Grobman 2012 [45], Ibrahim 2010 [49], Johnson 1975 [56], Rode 2011 [83], Rozenberg 2012 [64], van Os 2015 [44], Winer 2015 [61], Yemini 1985 [67].

There was no information on ongoing studies.

Included studies

Nine studies were included in the analysis of the effect of progesterone to prevent preterm birth in women with a history of preterm birth: Azargo 2016 [51]; Cetingoz 2011 [53]; Fonseca 2003 [54]; Hassan 2011 [41]; Majhi 2009 [57]; Meis 2003 [34]; Norman 2016 [29]; O’Brien 2007 [58]; Saghafi 2011 [59].

Four studies were included in the analysis of the effect of progesterone to prevent preterm birth in women with a short cervix: Azargo 2016 [51]; Fonseca 2007 [40]; Hassan 2011 [41]; Norman 2016 [29].

Three studies evaluated the risk of preterm birth at a cutoff other than 34 weeks: at 33 weeks: Hassan 2011 [41], and at 35 weeks: Meis 2003 [34] and O’Brien 2007 [58].

Excluded studies

Two studies were excluded as full text article in English was not available: Akbari 2009 [52], Yemini M 1985 [67].

Four studies were excluded due to wrong cut off for preterm birth. One study, Johnson 1975 [56], with cut off at 36 weeks, and three studies, Crowther 2017 [48], Ibrahim 2010 [49], Glover 2011 [55], with cut off at 37 weeks. Trialists for two of the studies, Crowther 2017 [48] and
Ibrahim 2010 [49], have been contacted with a request on data on preterm birth before week 34. One main author [48] responded but did not have data on preterm birth at 34 weeks. One main author did not respond [49].

Following studies excluded due to wrong population: The study by Aboulghar 2012 [62], restricted to a population after IVF treatment and included twin pregnancies. Borna 2008 [63] restricted to population after tocolysis, Briery 2011 [65] restricted to a population with preterm rupture of membranes. Caritis 2009 [66] restricted to triplets, DeFranco 2007 [60] was a sub-analysis of the study by O’Brien 2007 [58] on women with short cervix, but as only 9 had cervical length less than 25 mm, the cut off for short cervix was changed to 28. Grobman 2012 [45] and van Os 2015 [44] had a cut off for cervical length at 30 mm. Rode 2011 [83] included only women with twins. Rozenberg 2012 [64] included women after tocolysis. In the study by Winer 2015 [61] 50% had a uterine malformation and a cerclage.

**Risk of bias in included studies**

Overall study quality of the included trials was judged as fair to good. However in some cases sufficiently detailed information for deciding on study quality was not available.

**Allocation (selection bias)**

All trials were stated to be randomized and placebo controlled, but only seven described their method of randomization: Azargoan 2016 [51]; Cetingoz 2011 [53]; Fonseca 2003 [54]; Fonseca 2007 [40]; Hassan 2011 [41]; Meis 2003 [34]; Norman 2016 [29].

Allocation concealment was assessed as low risk of bias in all trials.

**Blinding (performance bias and detection bias)**

Eight studies were double blinded, placebo controlled: Azargoan 2016 [51], Cetingoz 2011 [53], Fonseca 2003 [54], Fonseca 2007 [40], Hassan 2011 [41], Meis 2003 [34], Norman 2016 [29], O’Brien 2007 [58].

Two studies were considered at high risk of performance bias, as the participants were assigned in groups receiving treatment vs. no treatment: Majhi 2009 [57]; Saghafi 2011 [59].

Six studies were considered at low risk of detection bias (Cetingoz 2011 [53], Fonseca 2003 [54], Fonseca 2007 [40], Hassan 2011 [41], Majhi 2009 [57], Norman 2016 [29], Saghafi 2011 [59]) but only in four of these studies, blinding of outcome assessment was evident (Fonseca 2003 [54]; Fonseca 2007 [40]; Hassan 2011 [41]; Norman 2016 [29]).

In four studies there was an unclear risk of detection bias: Azargoan 2016 [51]; Meis 2003 [34]; O’Brien 2007 [58]; Saghafi 2011 [59].

**Incomplete outcome data (attrition bias)**

Four studies had no losses to follow up: Fonseca 2007 [40], Azargoan 2016 [51], Majhi 2009 [57], Saghafi 2011 [59].

Four studies reported a loss to follow up between 1 and 16%: Cetingoz 2011 [53], Fonseca 2003 [54], Hassan 2011 [41], Meis 2003 [34].

Two trials were assessed at unclear risk of bias because dropouts were to the minimal but differed by outcome or increased with long-term follow-up (Norman 2016 [29]) or lost to follow up group was not described (O’Brien 2007 [58]).

**Selective reporting (reporting bias)**

In nine studies all expected outcomes were reported and these studies were assessed as being at low risk of bias for selective reporting: Cetingoz 2011 [53]; Fonseca 2003 [54]; Fonseca 2007 [40]; Hassan 2011 [41]; Ibrahim 2010 [49]; Majhi 2009 [57]; Meis 2003 [34]; Norman 2016 [29]; O’Brien 2007 [58]. In one study, it was not possible to determine whether or not selection bias was present: Saghafi 2011 [59].

**Other potential sources of bias**

Three studies were assessed as being at low risk of bias for other potential sources of bias (Fonseca 2007 [40]; Hassan 2011 [41]; Norman 2016 [29].

One study, Saghafi 2011 [59], was assessed to have a high risk of other bias as twins may be included. The percentage given for preterm birth before week 34 does not match an integer of subjects. In the remaining studies, assessment of other sources of bias was not possible: Azargoan 2016 [51]; Cetingoz 2011 [53]; Fonseca 2003 [54]; Majhi 2009 [57]; Meis 2003 [34]; O’Brien 2007 [58].

In Cetingoz 2001 [53] several risk groups were included and the inclusion criteria “previous preterm birth” was not specified.
[40] does not report on the exact numbers of side-effects.
7 - Discussion

Vaginal progesterone was found effective for prevention of preterm birth before week 33-35 in both women with a history of preterm birth and women with a short cervix (<25 mm). For women with a history of preterm birth, intramuscular progesterone was found effective in reducing preterm birth. No randomized controlled trial on intramuscular progesterone for prevention of preterm birth in women with a short cervix met our inclusion criteria. Also we found no randomized controlled trials with progesterone administered as vaginal gel or oral capsule meeting our inclusion criteria for review. In the Nordic countries, the vaginal administration of progesterone is used. Therefore we separated the analysis according to route of administration, both found to reduce the risk of preterm birth in women with a history of preterm birth. A meta-analysis including both studies on vaginal and intramuscular progesterone, did not change the result.

Only one of the included studies were in a Nordic population, which have a lower risk of short cervix and preterm birth [18][43]. We found no studies exploring the response of progesterone treatment according to ethnic genetic background. The PCORI analysis of the EPPPIC study [68] will be published in 2019. The analysis is an independent individual patient meta-analysis that will have an important say in this discussion.

In the decision on whether to treat or not is the costs related to treatment in contrast to costs related to per child born preterm. In Denmark, the treatment with vaginal progesterone from week 16 will cost 400 euro and an admission to the neonatal ward of a child born between 32 to 35 weeks and with an uncomplicated stay will cost 10.000 euro in total.

Overall completeness and applicability of evidence
We do not know if the data are applicable to Nordic women as the population in the included studies have very high prevalence of PTB compared to the Nordic population. This may be due to a low incidence of short cervix [18]. We only have short term data for the mother. We make the assumptions that the effect of progesterone on the mother is independent of multiple gestation, obstetric history or length of cervix.

Potential biases in the review process
In 2016, the NFOG board established a guideline committee. The aim of this initiative was to increase the availability, quality, and impact of clinical guidelines:
Step 1: Publish translations of existing national guidelines into English. These are now available at nfog.org.
Step 2: Elaborate evidence-based common Nordic guidelines, of which this guideline on progesterone for prevention of preterm birth is the first.

The authors were selected from each country by the individual Nordic scientific societies in Obstetrics and Gynecology.
The possibility of introducing bias was present at every stage of the reviewing process. We attempted to minimize bias in a number of ways: two review authors assessed eligibility for inclusion, carried out data extraction and assessed risk of bias. Each worked independently. Nevertheless, the process of assessing risk of bias is not an exact science and includes many personal judgements.

Agreements and disagreements with other studies or reviews
Compared to other reviews and meta-analyses, we have downgraded the degree of recommendation of progesterone both for women with a history of preterm birth and short cervix [74][69][70][71][72]. The main reason for the downgrading is that we have included the long term effect on the offspring as a critical outcome.
8 - Authors' conclusions

Implications for practice
Vaginal progesterone appears to be beneficial in women with PPTB or short cervix for preventing preterm birth before week 33-35. However, these findings need to be put into the Nordic context of the low rate of preterm delivery and low prevalence of short cervix. Many of the vaginal progesterone studies have been performed in populations with a higher risk of preterm delivery and a higher prevalence of short cervical length. Already in the late 1990-ties Taipale [17] reported that short cervix in the mid second trimester was rare and more recent studies have confirmed this [18]/[43]. That means that a cost-benefit analysis for a Nordic population needs to take these Nordic conditions into account.

Implications for research
Studies are need in the Nordic populations.
9 - Contributions of authors

All Authors contributed to the conception and design of study, the analysis and interpretation of data, the drafting of the review, commenting on it critically for intellectual content and the final approval of the document.
10 - Declarations of interest

None of the authors have any financial conflicts of interest. All members work clinically within the area of the guideline, some through several years. Seven authors have declared potential intellectual or academic conflicts of interest as they have published in the field of progesterone and preterm delivery before or been part of other national or international guideline work regarding this topic. However, prior publications or guideline work in the field were not considered a conflict of interest requiring exclusion from the NFOG guideline group.

Bo Jacobsson
- Commented on the Swedish HTA (Swedish Agency for Health Technology Assessment and Assessment of Social Services) report on progesterone.
- Co-author of a published summary/comment on the OPPTIMUM trial
- Member of a research group within EAPM (European Association of Perinatal Medicine) who has authored a paper with recommendations on the use of progesterone (for the prevention of preterm birth and neonatal outcome)

Trond Michelsen
- Main editor of the Norwegian Guideline on preterm labour where progesterone is recommended.

Line Rode
- Coordinating investigator of the PREDICT Trial, which investigated the effect of progesterone treatment in twin pregnancies.
- Co-author of the Danish national guideline on the use of progesterone for prevention of preterm delivery.
- Co-author of the latest version of the Danish national guideline on the use of progesterone for prevention of preterm delivery, although the work is not considered to be complete. The guideline group is awaiting the result of the NFOG GRADE guideline before finalizing the Danish national guideline.

Nils-Halvdan Morken
- Co-author of a published summary/comment on the OPPTIMUM trial
- Published many studies on preterm delivery, but none focused on the use of progesterone.

Niels Uldbjerg
- Published many papers on preterm delivery, but not on the use of progesterone

Helle Folge Bungum
- Co-author of the latest version of the Danish National Guideline on the use of progesterone for prevention of preterm delivery, although the work is not considered to be complete. The guideline group is awaiting the result of the NFOG GRADE guideline before finalizing the Danish national guideline.
11 - Author group

Jeannet Lauenborg 1, Bo Jacobsen 2, Sissel Saltvedt 2, Iben Sundtoft 1, Verena Sengpiel 2, Johanne Rydelius 2, Lone Hvidman 1, Line Rode 1, Hulda Hjartardóttir 3, Hilkka Ijäs 4, Kati Tihtonen 4, Nils-Halvdan Morken 5, Ferenc Macsali 5, Trond Michelsen 5, Helle Folge Bungum 1, Niels Uldbjerg 1

1 Denmark, 2 Sweden, 3 Iceland, 4 Finland, 5 Norway
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