The role of progesterone in prevention of preterm birth

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Abstract: Preterm birth continues to provide an enormous challenge in the delivery of perinatal health care, and is associated with considerable short and long-term health consequences for surviving infants. Progesterone has a role in maintaining pregnancy, by suppression of the calcium–calmodulin–myosin light chain kinase system. Additionally, progesterone has recognized anti-inflammatory properties, raising a possible link between inflammatory processes, alterations in progesterone receptor expression and the onset of preterm labor. Systematic reviews of randomized controlled trials evaluating the use of intramuscular and vaginal progesterone in women considered to be at increased risk of preterm birth have been published, with primary outcomes of perinatal death, preterm birth <34 weeks, and neurodevelopmental handicap in childhood. Eleven randomized controlled trials were included in the systematic review, involving 2714 women and 3452 infants, with results presented according to the reason women were considered to be at increased risk of preterm birth. While there is a potential beneficial effect in the use of progesterone for some women considered to be at increased risk of preterm birth, primarily in the reduction in the risk of preterm birth before 34 weeks gestation, it remains unclear if the observed prolongation of pregnancy translates into improved health outcomes for the infant.

Keywords: progesterone, preterm birth, systematic review, randomized trial

The extent of preterm birth
Preterm birth, is defined by the World Health Organisation as birth prior to 37 completed weeks of gestation, and continues to provide an enormous challenge in the delivery of perinatal health care, estimated to affect approximately 13 million births annually worldwide. The incidence of preterm birth is variably reported between 5% and 11% of all births, and its prevention continues to remain elusive, with many reports indicating an increase in the prevalence of preterm birth over recent years. Many factors have been implicated, including an increase in maternal age and use of assisted reproductive techniques, with resultant increases in the risk of multiple pregnancy, increasing maternal body mass index and the influence of obesity, continued maternal smoking during pregnancy, and infection. However, recent reports from Denmark and Australia demonstrate an increase in the occurrence of spontaneous preterm birth among women considered to be at low risk of 22% and 12% respectively.

Health consequences of preterm birth
Infants born preterm are over 40 times more likely to die during the neonatal period than are term infants, and while the risk is greatest for infants born at earlier gestational
ages, this increased risk of mortality persists even for infants born between 32 and 36 weeks gestation. While preterm birth contributes a relatively small proportion of total births, it is associated with in excess of 70% of the total perinatal mortality in developed countries, when excluding deaths related to congenital anomalies.8,12,17

For surviving infants, there are significant health implications, particularly in relation to immature lung development, with respiratory distress syndrome being a major consequence of preterm birth,19 and the most significant cause of early neonatal mortality and morbidity.16 Infants often require respiratory support, with a significant proportion requiring mechanical ventilation. Up to 20% of surviving infants remain dependent on oxygen therapy 28 days after birth, with 25% diagnosed with chronic lung disease.19 Other well-documented health complications include intraventricular hemorrhage and periventricular leukomalacia, with implications for ongoing cerebral dysfunction,20 infectious morbidity,21 and specific neonatal conditions associated with prematurity, including retinopathy of prematurity22 and necrotising enterocolitis.23 Infants continue to be at increased risk of hospitalization in the first year of life.24,25 In the longer-term, children have ongoing risks of motor and sensory impairment,26,27 and subsequent handicap, including cerebral palsy.28 Additionally, infants born preterm have well recognized learning difficulties,29–33 behavioral problems,32,34–36 and continue to be at an educational disadvantage that persists into adulthood.37,38

Economic costs of preterm birth
The immediate and longer-term monetary costs related to preterm birth and neonatal intensive care unit admissions are considerable. Figures from the United States in 1990, estimated a weekly cost of approximately SUS10,000 per preterm baby, increasing considerably with earlier gestational age at birth.39 More recent US figures suggest the annual cost of preterm birth has escalated to in excess of US$26 billion,4 with the costs being greatest for infants born at earlier gestational ages.40

These figures relate primarily to intensive care unit costs, without consideration of costs related to ongoing care. Using data from Oxfordshire and West Berkshire, United Kingdom, Petrou and colleagues have compared the cumulative use and cost of hospitalisation to age 5 years, according to gestational age at birth.25 The duration of hospital admissions for infants born prior to 28 weeks gestation was 85 times greater when compared with infants born at term, with an adjusted mean cost difference of SUS22,789 per infant over the first 5 years of life.25 Infants born between 28 and 31 weeks gestation had 16 times longer duration of hospitalisation, with an adjusted mean cost difference of SUS18,654 per infant over the first 5 years of life.25

Clements and colleagues have conducted population-based estimates of the costs related to infant and toddler development services utilised by preterm infants in the first three years of life.41 Total programme costs approached SUS 66 million, with the mean cost per infant SUS857.41 Costs varied considerably with gestational age at birth, increasing from SUS725 per infant born at term, to SUS1,578 per infant born between 32 and 36 weeks gestation, to SUS5,393 per infant born between 24 and 31 weeks gestation.41

These economic estimates relate primarily to intensive care unit costs, without consideration of costs related to ongoing care, or of the enormous emotional and personal costs for families and individuals who are born preterm.

Recurrence of preterm birth
The “cause” of preterm birth is multifactorial, with social, psychological, and biological factors playing a role.42–45 The most significant and consistently identified risk factor for preterm birth is a woman’s history of previous preterm birth.36–54 Estimates suggest the rate of recurrent preterm birth in this group of women is 22.5%,55 a 2.5 times increased relative risk when compared with women with no previous spontaneous preterm birth.56 For women with a history of a single preterm birth, the recurrence risk in a subsequent pregnancy is approximately 15%, increasing to 32% where there have been two previous preterm births.57 Approximately 30% of women who give birth between 20 and 31 weeks gestation will birth prior to 37 weeks in a subsequent pregnancy,47 and for approximately 10% of these women, the preterm birth will occur at a similar gestational age.47,54,58 In up to 50% of cases of preterm birth, the cause is spontaneous onset of labor or preterm premature rupture of membranes (PPROM).47,59,61

The role of progesterone in preterm labor
The exact mechanism of the onset of both term and preterm labor in humans is a complex interaction of many different hormonal pathways, culminating in co-ordinated uterine contractile activity, mediated by the production of prostaglandins.62–64 Before birth, coordinated uterine activity is associated with connective tissue changes resulting in cervical ripening and dilatation.64 Progesterone has an essential role in maintaining pregnancy,65–67 primarily through...
establishing uterine quiescence.\textsuperscript{58,60} This is achieved through suppression of the calcium-calmodulin-myosin light chain kinase system, reducing calcium flux and altering the resting potential of smooth muscle.\textsuperscript{64,66}

There is considerable debate about the relationship between progesterone withdrawal\textsuperscript{70} and the onset of labor.\textsuperscript{71} In humans, the progesterone receptor (PR) has two major subtypes PR-A and PR-B. Binding of progesterone to PR-A, the short form of the receptor, not thought to be associated with intra-cellular pathway mechanisms, prevents the actions of progesterone mediated by PR-B.\textsuperscript{71} An increase in the myometrial PR-A to PR-B expression ratio occurs at the onset of labor at term, resulting in an increase in myometrial PR-A, and in effect a functional withdrawal of progesterone,\textsuperscript{71,72} with increasing sensitivity to contractile stimuli.\textsuperscript{65,67,73,74}

Prostaglandins produced prior to the onset of labor, also act to increase the PR-A/PR-B expression ratio, and therefore the potential to initiate a functional withdrawal of progesterone.\textsuperscript{67}

In many animals the onset of labor is associated with a decrease in progesterone concentrations,\textsuperscript{62,64,65,75} but this has not been shown to occur in women before term or preterm birth, with no apparently detectable changes to circulating steroid hormone levels evident.\textsuperscript{64,65,67,76,77}

**Progesterone as an anti-inflammatory agent**

In both term and preterm labor, there is evidence of an increase in inflammatory markers tumor necrosis factor (TNF) -alpha, interleukin-1 (IL-1) and interleukin-6 (IL-6), and down-regulation of the anti-inflammatory interleukin-10 (IL-10).\textsuperscript{78,79} Inflammatory cytokines may alter enzyme expression, increasing prostaglandin production prior to the onset of labor.\textsuperscript{78,79} These maternal inflammatory mediators may then interact at the feto-placental unit, precipitating preterm birth.\textsuperscript{80} In particular, inflammatory cytokines interleukin-1 and TNF-alpha act to increase prostaglandin production, while both IL-10 and progesterone have a negative effect on prostaglandin production.\textsuperscript{63}

It is in this context that progesterone may exert its anti-inflammatory properties, raising a possible link between inflammatory process, alterations in progesterone receptor expression and the onset of preterm labor.\textsuperscript{81} While it has been postulated that the effect of progesterone on preterm birth is related to its anti-inflammatory properties, the specific mechanism of action remains unclear. A number of investigators have developed models of inflammation in pregnant animals and examined the effect of pre-treatment with progesterone on inflammatory mediators.

Elovitz and colleagues have developed a mouse model of intra-uterine inflammation with intrauterine injection of lipopolysaccharide (LPS).\textsuperscript{82-84} In these experiments, pre-treatment with progesterone was associated with suppression of activation of contraction-associated genes and inflammatory mediators, as well as prevention of the cervical ripening response to intrauterine inflammation.\textsuperscript{82}

Pre-treatment with progesterone was associated with a reduction in preterm labor and preserved fetal viability in the mouse.\textsuperscript{82,83} In a subsequent experiment, the influence of progesterone on Toll-like receptors was evaluated.\textsuperscript{84}

Toll-like receptors are involved in both the initiation and modulation of the inflammatory response, and regulation of these receptors may be one mechanism whereby intrauterine inflammation mediates the onset of labor, and therefore modifiable by the administration of progesterone.\textsuperscript{84}

Pre-treatment of mice with progesterone prior to the creation of an intra-uterine inflammatory environment, was associated with a decrease in the LPS induced up-regulation of receptors in both the cervix and placenta.\textsuperscript{86} The authors concluded that this may be a potential mechanism whereby progesterone acts to reduce the risk of preterm birth.\textsuperscript{82-84}

Other investigators\textsuperscript{85,86} have evaluated the anti-inflammatory effect of progesterone at the feto-placental unit. Placental chorionic plate arteries were exposed to either lipopolysaccharide alone or in combination with progesterone. Exposure to LPS alone was associated with an increase in the production of the inflammatory cytokine IL-6.\textsuperscript{85,86} Pre-treatment of the arteries with progesterone was associated with reduced production of IL-6 after LPS exposure, although there was no demonstrable effect on the concentrations of TNF-alpha or IL-10.\textsuperscript{85,86} Similarly, exposure to progesterone was associated with a reduction in both fetal and maternal mononuclear cell expression of IL-6 after exposure to LPS, again suggesting these cell populations as possible targets for the anti-inflammatory effects of progesterone, and a potential mechanism for the observed reduction in preterm birth following progesterone.\textsuperscript{85,86}

**Pharmacokinetics of progesterone by route of administration**

Current information about the pharmacokinetics of progesterone relates to its use in assisted reproduction,\textsuperscript{87-90} in menopausal\textsuperscript{91} and post-menopausal women,\textsuperscript{88,92} and in women with endometrial carcinoma.\textsuperscript{93} These studies indicate blood progesterone concentrations following vaginal administration to be lower than after intramuscular administration.\textsuperscript{89,90} There are few data available to inform the optimal route of administration.\textsuperscript{89,90}
administration in women in later pregnancy. For 100 mg vaginal progesterone pessaries the peak blood concentrations are obtained 3 to 8 hours after vaginal administration, due to avoidance of first pass hepatic metabolism. In blood, progesterone is 96% to 99% protein bound, mainly to albumin. While there may be advantages in the use of intramuscular progesterone in terms of increased blood concentrations, such preparations are not available in many countries world-wide.

**Safety of progesterone**
Natural progesterone has been used in pregnancy without demonstrated effect on fetal development or on the risk of congenital anomalies.94,95 Information from animal studies suggests that progesterone influences fetal behavior in sheep,96 with increased concentrations suppressing activity and arousal states.97,98 Much of the information relating to childhood outcomes dates to more than 30 years ago, utilising a variety of progestogenic agents.99–102 Recognized maternal side-effects related to progesterone therapy include headache, nausea, breast tenderness, and coughing.

**Is there clinical evidence to suggest a role for progesterone in preventing preterm birth?**
The administration of progesterone as a therapeutic agent for the prevention of preterm birth dates to the early 1960s,103 with considerable renewed interest in its use following recent reports of randomized controlled trials published first in 2003.104,105

There have been several systematic reviews of randomized controlled trials evaluating the use of both intramuscular and vaginal progesterone in women considered to be at increased risk of preterm birth published,106–111 in addition to many narrative reviews.112–115

In considering the effects of progesterone for preterm birth, the most recent systematic reviews will be considered in more detail.108,109 The prespecified primary outcomes were perinatal death, preterm birth <34 weeks, and neurodevelopmental handicap in childhood.108,109 Eleven randomized controlled trials were included in the systematic review, involving 2714 women and 3452 infants, with results presented according to the reason women were considered to be at increased risk of preterm birth.108,109 Characteristics of these studies are presented in Table 1.

For women with a past history of spontaneous preterm birth, progesterone was associated with no significant difference in perinatal death (3 studies, 1114 participants, relative risk [RR] 0.65, 95% confidence interval [CI] 0.38 to 1.11); but a reduction in preterm birth prior to 34 weeks (1 study; 142 women; RR 0.15; 95% CI 0.04 to 0.64; number needed to treat [NNT] 7; 95% CI 4 to 17) (Table 2).108,109 While there was a significant reduction in the risk of infant birth-weight less than 2500 g (2 studies, 501 infants, RR 0.64, 95% CI 0.49 to 0.83), there were no other differences identified between the two treatment groups for secondary neonatal outcomes. It is important to bear in mind that the combined sample size of 1329 infants is underpowered to reliably detect differences of clinical relevance in markers of neonatal morbidity and mortality. The report by Northen116 details the 2 year follow-up of 278 participants from the Meis randomized trial.105 While only 60% of infants were available for follow-up, this study did not identify statistically significant differences between the progesterone and placebo treatment groups in the risk of childhood developmental delay (RR 0.97; 95% CI 0.55 to 1.73).108,109

Information about the optimal route of progesterone administration is insufficient. Of particular note, the largest study to date using vaginal progesterone gel identified no benefit for women with a previous preterm birth.117 However, the results of ongoing randomized trials assessing the role of intramuscular118 and vaginal119,120 progesterone in women with a history of spontaneous preterm birth will contribute information about the role of progesterone in this group of women (Table 3).

For women considered to be at increased risk of preterm birth due to the identification of a short cervix on ultrasound, progesterone was associated with no significant difference in perinatal death (1 study, 274 participants, RR 0.38, 95% CI 0.10 to 1.40); but a significant reduction in preterm birth before 34 weeks (1 study; 250 women; RR 0.58; 95% CI 0.38 to 0.87; NNT 7; 95% CI 4 to 25).108,109 While the study reported a significant reduction in the risk of neonatal sepsis,112 the sample size of 250 is underpowered to reliably detect differences in neonatal outcomes. There is a single registered randomized trial evaluating the use of intramuscular122 progesterone in nulliparous women with a short cervix identified on transvaginal ultrasound and this will contribute important information when completed.

The role of progesterone to prevent preterm birth in women with a multiple pregnancy is far less certain. Two randomized trials were included evaluating the use of progesterone in women with a multiple pregnancy.123,124 The primary outcome for the Rouse study124 was a composite of birth before 35 weeks gestation or death, with no statistically significant differences identified between the
<table>
<thead>
<tr>
<th>Study</th>
<th>Setting</th>
<th>Methods</th>
<th>Participants</th>
<th>Intervention</th>
<th>Primary outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Da Fonseca</td>
<td>Sao Paulo, Brazil</td>
<td>Randomization: Random number table</td>
<td>157 women considered to be at increased risk of preterm birth (prior preterm birth, presence of cervical suture, uterine malformation)</td>
<td>Vaginal administration</td>
<td>Preterm birth less than 37 weeks; preterm birth less than 34 weeks</td>
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<tr>
<td></td>
<td></td>
<td>Allocation concealment: Identical appearing treatment packs</td>
<td></td>
<td>Nightly 100 mg progesterone vs placebo from 24 to 28 weeks gestation</td>
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<td></td>
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<td>Blinded outcome assessment: Yes Follow-up: 15/157 (&lt;1%) post-randomization exclusions</td>
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<tr>
<td>O’Brien</td>
<td>S3 centers world-wide</td>
<td>Randomization: Random number table</td>
<td>659 women with a history of spontaneous preterm birth</td>
<td>Vaginal administration</td>
<td>Preterm birth less than 32 weeks</td>
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<tr>
<td></td>
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<td>Allocation concealment: Identical appearing treatment packs</td>
<td></td>
<td>Nightly 90 mg progesterone gel vs placebo</td>
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<td></td>
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<td>Blinded outcome assessment: Yes Follow-up: 48/659 (7.3%) lost to follow-up</td>
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<tr>
<td>Meis</td>
<td>Maternal Fetal Medicine Network, USA</td>
<td>Randomization: 2:1 Computer generated random number sequence Allocation concealment: Identical appearing treatment packs Blinded outcome assessment: Yes Follow-up: No losses to follow-up; 2-year follow-up evaluated 278 (60%) infants</td>
<td>463 women with a history of spontaneous preterm birth</td>
<td>Intra-muscular Administration Weekly</td>
<td>Preterm birth less than 37 weeks</td>
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<td>Blinded outcome assessment: Yes Follow-up: 48/659 (7.3%) lost to follow-up</td>
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<td>250 µg 17-OHP vs placebo (castor oil) from 16–20 weeks until 36 weeks gestation</td>
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<td>Johnson</td>
<td>Baltimore, USA</td>
<td>Randomization: Stated to be “random, double blind fashion” Allocation concealment: Identical appearing treatment packs Blinded outcome assessment: Yes Follow-up: No losses to follow-up; 7/50 (14%) post-randomization exclusions</td>
<td>50 women with history of previous preterm birth</td>
<td>Intra-muscular Administration Weekly</td>
<td>Preterm birth less than 37 weeks</td>
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<td>Blinded outcome assessment: Yes Follow-up: 48/659 (7.3%) lost to follow-up</td>
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<td>250 µg 17-OHP vs placebo (castor oil) from “booking” until 24 weeks gestation</td>
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<tr>
<td>Fonseca</td>
<td>United Kingdom, Brazil, Chile, Greece</td>
<td>Randomization: Not stated Allocation concealment: Central telephone process; identical appearing treatment packs Blinded outcome assessment: Yes Follow-up: No losses to follow-up</td>
<td>250 women undergoing trans-vaginal ultrasound where cervical length identified to be $\leq$ 15 mm</td>
<td>Vaginal administration</td>
<td>Spontaneous preterm birth less than 34 weeks</td>
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<td></td>
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<td>allocation concealment: Central telephone process; identical appearing treatment packs Blinded outcome assessment: Yes Follow-up: No losses to follow-up</td>
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<td>Nightly 200 mg progesterone vs placebo from 24 weeks to 33 + 6 weeks gestation</td>
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<tr>
<td>Hartikainen-Sori</td>
<td>Finland</td>
<td>Randomization: Stated to be “placebo controlled and double blind” Allocation concealment: Not stated Blinded outcome assessment: Yes Follow-up: No losses to follow-up</td>
<td>77 women with a multiple pregnancy</td>
<td>Intra-muscular Administration Weekly</td>
<td>Perinatal death</td>
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<td>Allocation concealment: Central telephone process; identical appearing treatment packs Blinded outcome assessment: Yes Follow-up: No losses to follow-up</td>
<td></td>
<td>250 µg 17-OHP vs placebo (castor oil) from 28 weeks until 37 weeks gestation</td>
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<tr>
<td>Rouse</td>
<td>Maternal Fetal Medicine Network, USA</td>
<td>Randomization:“Urn” method of randomization Allocation concealment: Identical appearing treatment packs Blinded outcome assessment: Yes Follow-up: 6/661 (1%) loss to follow-up</td>
<td>661 women with a multiple pregnancy</td>
<td>Intra-muscular Administration Weekly 250 µg 17-OHP vs placebo (castor oil) from 16 – 20 + 3 weeks gestation until 34 weeks gestation</td>
<td>Composite of death or delivery before 35 weeks</td>
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<td>Study</td>
<td>Setting</td>
<td>Methods</td>
<td>Participants</td>
<td>Intervention</td>
<td>Primary outcome</td>
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<tr>
<td>Borna[12]</td>
<td>Iran</td>
<td>Randomization: Random number table</td>
<td>70 women presenting between 24 and 34 weeks gestation with symptoms or signs of threatened preterm labor, where the acute symptoms were arrested following the use of tocolytics</td>
<td>Vaginal administration Daily 400 mg progesterone vs no therapy</td>
<td>Randomization to birth interval</td>
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<td>Allocation concealment: Unclear</td>
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<td>Blinded outcome assessment: No</td>
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<td>Follow-up: Complete</td>
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<tr>
<td>Facchinetti[13]</td>
<td>Italy</td>
<td>Randomization: Random number table</td>
<td>60 women presenting between 25 and 33 + 6 weeks gestation with symptoms or signs of threatened preterm labor, where the acute symptoms were arrested following the use of tocolytics</td>
<td>Intra-muscular Administration Every 4 days, 341 µg 17-OHP vs placebo until 36 weeks gestation</td>
<td>Cervical length by trans-vaginal ultrasound</td>
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<td>Allocation concealment: Randomization list managed by senior midwife; allocation to progesterone or placebo</td>
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<td>Blinded outcome assessment: No</td>
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<td>Follow-up: Complete</td>
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<td>Papiernik[18]</td>
<td>France</td>
<td>Randomization: Unclear Allocation concealment: Unclear</td>
<td>99 women with “High preterm risk score”</td>
<td>Intra-muscular Administration Every 3 days, 250 µg 17-OHP vs placebo from 28 until 32 weeks gestation</td>
<td>Preterm birth less than 37 weeks</td>
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<td></td>
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<td>Blinded outcome assessment: Yes</td>
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<td>Follow-up: Complete</td>
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<tr>
<td>Hauth[19]</td>
<td>Texas, USA</td>
<td>Randomization: Stated to be “randomized, double blind intervention”</td>
<td>168 women on active military duty (Lackland Airforce Base)</td>
<td>Intra-muscular Administration Weekly 1000 µg 17-OHP vs placebo from 16 to 20 weeks until 36 weeks gestation</td>
<td>Preterm birth less than 37 weeks</td>
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<td></td>
<td></td>
<td>Allocation concealment: Not stated</td>
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<td>Blinded outcome assessment: Yes</td>
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<td>Follow-up: Complete</td>
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progesterone and placebo groups. The only pre-specified primary outcome was perinatal death, with no significant differences identified (1 study, 154 participants, RR 1.95, 95% CI 0.37 to 10.33). While the use of progesterone was associated with a reduction in the use of antenatal tocolysis,\textsuperscript{2,14} there were no differences identified for other secondary infant and maternal health outcomes. The role of intramuscular\textsuperscript{23,125–127} and vaginal\textsuperscript{128–131} progesterone in women with a multiple pregnancy is the subject of several ongoing randomized studies.

Two studies were included in the systematic review where women presenting following treatment for threatened preterm labor received progesterone therapy for the remainder of their pregnancy,\textsuperscript{132,133} but none of the pre-specified primary outcomes were reported.\textsuperscript{108,109} Neither study utilized a placebo, and outcome assessors were not blinded, increasing the potential for bias. An ongoing trial assessing the role of vaginal progesterone\textsuperscript{134} in women presenting with symptoms or signs of threatened preterm labor will contribute information in the future.

For women with “other” risk factors that were considered to increase the risk of preterm birth, progesterone was not associated with a significant difference in perinatal death (2 studies, 264 participants, RR 1.10, 95% CI 0.23, 5.29).\textsuperscript{108,109} No other statistically significant differences were identified for the outcomes reported.

While there is information available from randomized trials suggesting that progesterone therapy may be beneficial for some women considered to be at increased risk of preterm birth, for some pregnancy outcomes, there is more limited information available relating to neonatal and infant health outcomes. In particular, there is little information about the benefits and harms of progesterone in relation to long-term infant outcomes. Information is available from the follow-up of a single randomized trial related to long-term infant and childhood health outcomes.\textsuperscript{116} While this report indicates no statistically significant differences in health and developmental assessment at 2 years of age, only 60% of participants were available for assessment.\textsuperscript{116} Therefore, the longer-term follow-up of participants in randomized trials remains a priority.

Maternal outcomes after antenatal progesterone therapy have to date been poorly reported, including treatment side-effects, preferences of mode of administration and satisfaction with their pregnancy care. Further information is required on these important issues.\textsuperscript{135,136}

Similarly, there is insufficient information available to date to be able to make valid recommendations about the optimal dose, route of administration, and gestational age at which to commence progesterone therapy, with utilisation of both vaginal and intramuscular preparations. There is considerable variation in the dose of progesterone administered, ranging from 90 mg daily\textsuperscript{117} to 400 mg daily\textsuperscript{132} when administered vaginally, and from 250 \(\mu\)g weekly,\textsuperscript{105,123,124,137} to 250 \(\mu\)g every 3 days,\textsuperscript{138} 341 \(\mu\)g every 4 days,\textsuperscript{133} up to 1000 \(\mu\)g weekly.\textsuperscript{139} The optimal time to commence therapy also varies considerably across studies, as does the duration of treatment. While the majority of studies commenced therapy in the mid-late second trimester at 24 to 28 weeks gestation,\textsuperscript{104,117,121,123,132,133,138} others commenced in the first trimester at the time of antenatal “booking”\textsuperscript{137} and still others from 16 weeks gestation.\textsuperscript{105,124,139} Similarly, there may be differences in the mechanism of action of natural progesterone (administered vaginally), compared

<table>
<thead>
<tr>
<th>Reason at risk of preterm birth</th>
<th>Outcome</th>
<th>Number of studies</th>
<th>Number of participants</th>
<th>Relative risk</th>
<th>95% confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Previous preterm birth</td>
<td>Perinatal death</td>
<td>3</td>
<td>1114</td>
<td>0.65</td>
<td>0.38 to 1.11</td>
</tr>
<tr>
<td></td>
<td>Preterm birth less than 34 weeks</td>
<td>1</td>
<td>142</td>
<td>0.15</td>
<td>0.04 to 0.64</td>
</tr>
<tr>
<td></td>
<td>Childhood developmental delay</td>
<td>1</td>
<td>275</td>
<td>0.97</td>
<td>0.55 to 1.73</td>
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<td>Ultrasound identified short cervix</td>
<td>Perinatal death</td>
<td>1</td>
<td>274</td>
<td>0.38</td>
<td>0.10 to 1.40</td>
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<tr>
<td>Multiple pregnancy</td>
<td>Perinatal death</td>
<td>1</td>
<td>250</td>
<td>0.58</td>
<td>0.38 to 0.87</td>
</tr>
<tr>
<td>Following symptoms or signs of threatened preterm labor</td>
<td>Nil primary outcomes reported</td>
<td>1</td>
<td>154</td>
<td>1.95</td>
<td>0.37 to 10.33</td>
</tr>
<tr>
<td>“Other” reason</td>
<td>Perinatal death</td>
<td>2</td>
<td>264</td>
<td>1.10</td>
<td>0.23 to 5.29</td>
</tr>
</tbody>
</table>
Table 3 Ongoing studies evaluating progesterone for the prevention of preterm birth

<table>
<thead>
<tr>
<th>Contact</th>
<th>Title</th>
<th>Participants</th>
<th>Intervention</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rozenberg</td>
<td>Efficacy of 17 alpha hydroxy-progesterone caproate for the prevention of preterm delivery. NCT00331695</td>
<td>Women with either presentation in threatened preterm labor, history of prior preterm birth, or multiple pregnancy (twin)</td>
<td>Intra-muscular administration 17-OHP vs placebo</td>
<td>Randomization to birth interval</td>
</tr>
<tr>
<td>Crowther</td>
<td>Progesterone for the prevention of neonatal respiratory distress syndrome (The PROGRESS Study) ISrCTN20269066</td>
<td>Women with a history of spontaneous preterm birth</td>
<td>Vaginal administration progesterone vs placebo</td>
<td>Neonatal lung disease</td>
</tr>
<tr>
<td>Perlitz</td>
<td>Prevention of recurrent preterm delivery by a natural progesterone agent. NCT00329316</td>
<td>Women with a history of spontaneous preterm birth</td>
<td>Vaginal administration progesterone vs placebo</td>
<td>Not stated</td>
</tr>
<tr>
<td>Grobman</td>
<td>RCT of progesterone to prevent preterm birth in nulliparous women with a short cervix. NCT00439374</td>
<td>Nulliparous women with a short cervix identified on trans-vaginal ultrasound</td>
<td>Intra-muscular administration 17-OHP vs placebo</td>
<td>Preterm birth less than 37 weeks</td>
</tr>
<tr>
<td>Bruinse</td>
<td>17 alpha hydroxyprogesterone in multiple pregnancies to prevent handicapped infants (The AMPHIA Study)</td>
<td>Women with a multiple pregnancy</td>
<td>Intra-muscular administration 17-OHP vs placebo</td>
<td>Composite outcome of neonatal morbidity</td>
</tr>
<tr>
<td>Maurel</td>
<td>17OHP for reduction of neonatal morbidity due to preterm birth in twin and triplet pregnancies. NCT00163020</td>
<td>Women with a twin or triplet pregnancy</td>
<td>Intra-muscular administration 17-OHP vs placebo</td>
<td>Composite of adverse neonatal outcomes</td>
</tr>
<tr>
<td>Nassar</td>
<td>Prevention of preterm delivery in twin pregnancies by 17 alpha hydroxyprogesterone caproate. NCT00141908</td>
<td>Women with a twin pregnancy</td>
<td>Intra-muscular administration 17-OHP vs placebo</td>
<td>Preterm birth</td>
</tr>
<tr>
<td>Norman</td>
<td>Double blind randomized placebo controlled trial of progesterone for the prevention of preterm birth in twins. ISrCTN35782581</td>
<td>Women with a twin pregnancy</td>
<td>Vaginal administration progesterone vs placebo</td>
<td>Preterm birth less than 34 weeks</td>
</tr>
<tr>
<td>Rode</td>
<td>Does progesterone prevent very preterm delivery in twin pregnancies? NCT00329914</td>
<td>Women with a twin pregnancy</td>
<td>Progesterone vs placebo</td>
<td>Preterm birth less than 34 weeks</td>
</tr>
<tr>
<td>Serra</td>
<td>Natural progesterone and preterm birth in twins. NCT00480402</td>
<td>Women with a twin pregnancy</td>
<td>Vaginal administration progesterone vs placebo</td>
<td>Preterm birth less than 34 weeks</td>
</tr>
<tr>
<td>Wood</td>
<td>Vaginal progesterone versus placebo</td>
<td>Women with a multiple pregnancy</td>
<td>Vaginal administration progesterone vs placebo</td>
<td>Preterm birth less than 37 weeks</td>
</tr>
<tr>
<td>Martinez de Tajada</td>
<td>Vaginal progesterone to prevent preterm delivery in women with preterm labor. NCT00536003</td>
<td>Women presenting with symptoms and signs of preterm labor, and evidence of cervical change or positive fetal fibronectin testing</td>
<td>Vaginal administration progesterone vs placebo</td>
<td>Preterm birth less than 37 weeks</td>
</tr>
</tbody>
</table>
with the 17-hydroxypregesterone caproate which has been most commonly administered to date as an intramuscular preparation.

**Conclusion**
Preterm birth remains a significant problem in obstetric care, affecting women and babies world-wide. There are considerable health consequences for infants born preterm, as well as economic consequences for the health care system, individuals, and their families. Improving health outcomes for preterm infants requires improvements in care for infants who are born preterm, or developing effective strategies that can reduce the chance of an infant being born preterm.

While the precise mechanism of both term and preterm labor remains unclear, progesterone plays an important role in the maintenance of pregnancy through the maintenance of uterine quiescence. Increasingly, there is information suggesting that progesterone may potentially mediate a woman’s risk of preterm birth acting as an anti-inflammatory agent.

Interest in the use of progesterone as a therapeutic agent to reduce the risk of preterm birth dates back to the 1960s. Recent randomized trial reports have re-ignited the interest in progesterone for this indication. Evidence from randomized controlled trials and systematic reviews indicates a potential beneficial effect in the use of progesterone for some women considered to be at increased risk of preterm birth, primarily in the reduction in the risk of preterm birth before 34 weeks gestation. However, it remains unclear if the observed prolongation of pregnancy translates into improved health outcomes for the infant, as to date there is more limited information available about neonatal and longer-term infant health. Ongoing randomized trials, and in particular follow-up of participants into childhood, will contribute valuable information, and over time, help to establish the precise role of progesterone for women considered to be at increased risk of preterm birth.

**Disclosures**
The authors report no conflicts of interest.

**References**


Dodd and Crowther


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