

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,¹ and continues to provide an enormous challenge in the delivery of perinatal health care, estimated to affect approximately 13 million births annually worldwide.² The incidence of preterm birth is variably reported between 5% and 11% of all births,^{3,4} and its prevention continues to remain elusive, with many reports indicating an increase in the prevalence of preterm birth over recent years.⁵⁻⁷ 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,⁸⁻¹⁰ increasing maternal body mass index and the influence of obesity,¹¹ continued maternal smoking during pregnancy,^{12,13} and infection. However, recent reports from Denmark⁶ and Australia⁷ 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,^{14,15} and while the risk is greatest for infants born at earlier gestational

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ages, this increased risk of mortality persists even for infants born between 32 and 36 weeks gestation.¹⁶ 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,¹⁸ 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 \$US10,000 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,⁵ 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 \$US 22,789 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 \$US18,654 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 \$US 66 million, with the mean cost per infant \$US857.⁴¹ Costs varied considerably with gestational age at birth, increasing from \$US725 per infant born at term, to \$US1,578 per infant born between 32 and 36 weeks gestation, to \$US5,393 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.^{46–54} 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).^{17,59–61}

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.^{68,69} 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.^{64,66}

There is considerable debate about the relationship between progesterone withdrawal⁷⁰ and the onset of labor.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.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,^{71,72} with increasing sensitivity to contractile stimuli.^{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.⁶⁷ In many animals the onset of labor is associated with a decrease in progesterone concentrations,^{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.^{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).^{78,79} Inflammatory cytokines may alter enzyme expression, increasing prostaglandin production prior to the onset of labor.^{78,79} These maternal inflammatory mediators may then interact at the fetoplacental unit, precipitating preterm birth.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.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.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).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.⁸² Pre-treatment with progesterone was associated with a reduction in preterm labor and preserved fetal viability in the mouse.^{82,83} In a subsequent experiment, the influence of progesterone on Toll-like receptors was evaluated.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.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.⁸⁴ The authors concluded that this may be a potential mechanism whereby progesterone acts to reduce the risk of preterm birth.⁸²⁻⁸⁴

Other investigators^{85,86} have evaluated the anti-inflammatory effect of progesterone at the fetoplacental 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.^{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.^{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.^{85,86}

Pharmacokinetics of progesterone by route of administration

Current information about the pharmacokinetics of progesterone relates to its use in assisted reproduction,⁸⁷⁻⁹⁰ in menopausal⁹¹ and post-menopausal women,^{88,92} and in women with endometrial carcinoma.⁹³ These studies indicate blood progesterone concentrations following vaginal administration to be lower than after intramuscular administration.^{89,90} There are few data available to inform the optimal route of

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 vaginal^{119,120} 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,¹²¹ 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 1 Characteristics of randomized controlled trials evaluating progesterone for prevention of preterm birth

Study	Setting	Methods	Participants	Intervention	Primary outcome
Da Fonseca ¹⁰⁴	Sao Paulo, Brazil	Randomization: Random number table Allocation concealment: Identical appearing treatment packs Blinded outcome assessment: Yes Follow-up: 15/157 (< 1%) post-randomization exclusions	157 women considered to be at increased risk of preterm birth (prior preterm birth, presence of cervical suture, uterine malformation)	Vaginal administration Nightly 100 mg progesterone vs placebo from 24 to 28 weeks gestation	Preterm birth less than 37 weeks; preterm birth less than 34 weeks
O'Brien ¹¹⁴	53 centers world-wide	Randomization: Random number table Allocation concealment: Identical appearing treatment packs Blinded outcome assessment: Yes Follow-up: 48/659 (7.3%) lost to follow-up	659 women with a history of spontaneous preterm birth	Vaginal administration Nightly 90 mg progesterone gel vs placebo	Preterm birth less than 32 weeks
Meis ¹⁰⁵					
Northern ¹¹⁶	Maternal Fetal Medicine Network, USA	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	463 women with a history of spontaneous preterm birth	Intra-muscular Administration Weekly 250 µg 17-OHP vs placebo (castor oil) from 16–20 weeks until 36 weeks gestation	Preterm birth less than 37 weeks
Johnson ¹³⁷	Baltimore, USA	Randomization: Stated to be "random, double blind fashion" Allocation concealment: Identical appearing treatment packs Blinded outcome assessment: Yes Follow-up: 7/50 (14%) post-randomization exclusions	50 women with history of previous preterm birth	Intra-muscular Administration Weekly 250 µg 17-OHP vs placebo from "booking" until 24 weeks gestation	Preterm birth less than 37 weeks
Fonseca ¹²¹	United Kingdom, Brazil, Chile, Greece	Randomization: Not stated Allocation concealment: Central telephone process; identical appearing treatment packs Blinded outcome assessment: Yes Follow-up: No losses to follow-up	250 women undergoing trans-vaginal ultrasound where cervical length identified to be ≤ 15 mm	Vaginal administration Nightly 200 mg progesterone vs placebo from 24 weeks to 33 + 6 weeks gestation	Spontaneous preterm birth less than 34 weeks
Hartikainen-Sori ¹²³	Finland	Randomization: Stated to be "placebo controlled and double blind" Allocation concealment: Not stated Blinded outcome assessment: Yes Follow-up: No losses to follow-up	77 women with a multiple pregnancy	Intra-muscular Administration Weekly 250 µg 17-OHP vs placebo from 28 weeks until 37 weeks gestation	Perinatal death
Rouse ¹²⁴	Maternal Fetal Medicine Network, USA	Randomization: "Urn" method of randomization Allocation concealment: Identical appearing treatment packs Blinded outcome assessment: Yes Follow-up: 6/661 (1%) loss to follow-up	661 women with a multiple pregnancy	Intra-muscular Administration Weekly 250 µg 17-OHP vs placebo (castor oil) from 16 – 20 + 3 weeks gestation until 34 weeks gestation	Composite of death or delivery before 35 weeks

(Continued)

Table 1 (Continued)

Study	Setting	Methods	Participants	Intervention	Primary outcome
Borna ¹³²	Iran	Randomization: Random number table Allocation concealment: Unclear Blinded outcome assessment: No Follow-up: Complete	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	Vaginal administration Daily 400 mg progesterone vs no therapy	Randomization to birth interval
Facchinetti ¹³³	Italy	Randomization: Random number table Allocation concealment: Randomization list managed by senior midwife; allocation to progesterone or placebo Blinded outcome assessment: No Follow-up: Complete	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 (atosiban)	Intra-muscular Administration Every 4 days, 341 µg 17-OHP vs placebo until 36 weeks gestation	Cervical length by trans-vaginal ultrasound
Papiernik ¹³⁸	France	Randomization: Unclear Allocation concealment: Unclear Blinded outcome assessment: Yes Follow-up: Complete	99 women with "High preterm risk score"	Intra-muscular Administration Every 3 days, 250 µg 17-OHP vs placebo from 28 until 32 weeks gestation	Preterm birth less than 37 weeks
Hauth ¹³⁹	Texas, USA	Randomization: Stated to be "randomized, double blind intervention" Allocation concealment: Not stated Blinded outcome assessment: Yes Follow-up: Complete	168 women on active military duty (Lackland Airforce Base)	Intra-muscular Administration Weekly 1000 µg 17-OHP vs placebo from 16 to 20 weeks until 36 weeks gestation	Preterm birth less than 37 weeks

Table 2 Summary findings reported in systematic reviews^{105,106} for primary outcomes by reason at risk of preterm birth

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

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,¹²⁴ there were no differences identified for other secondary infant and maternal health outcomes. The role of intramuscular^{125–127} and vaginal^{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,^{132,133} but none of the pre-specified primary outcomes were reported.^{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 progesterone¹³⁴ 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).^{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.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.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.^{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 daily¹¹⁷ to 400 mg daily¹³² when administered vaginally, and from 250 µg weekly,^{105,123,124,137} to 250 µg every 3 days,¹³⁸ 341 µg every 4 days,¹³³ up to 1000 µg weekly.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,^{104,117,121,123,132,133,138} others commenced in the first trimester at the time of antenatal “booking”,¹³⁷ and still others from 16 weeks gestation.^{105,124,139} Similarly, there may be differences in the mechanism of action of natural progesterone (administered vaginally), compared

Table 3 Ongoing studies evaluating progesterone for the prevention of preterm birth

Contact	Title	Participants	Intervention	Outcome
Rozenberg ¹⁸ prozenberg@chi-poissy-st-germain.fr	Efficacy of 17 alpha hydroxy-progesterone caproate for the prevention of preterm delivery. NCT00331695	Women with either presentation in threatened preterm labor, history of prior preterm birth, or multiple pregnancy (twin)	Intra-muscular administration 17-OHP vs placebo	Randomization to birth interval
Crowther ¹⁹ caroline.crowther@adelaide.edu.au progress@adelaide.edu.au	Progesterone for the prevention of neonatal respiratory distress syndrome (The PROGRESS Study) ISRCTN20269066	Women with a history of spontaneous preterm birth	Vaginal administration progesterone vs placebo	Neonatal lung disease
Perlitz ²⁰ yperlitz@poria.health.gov.au	Prevention of recurrent preterm delivery by a natural progesterone agent. NCT00329316	Women with a history of spontaneous preterm birth	Vagina administration progesterone vs placebo	Not stated
Grobman ²² spong@exchange.nih.gov	RCT of progesterone to prevent preterm birth in nulliparous women with a short cervix. NCT00439374	Nulliparous women with a short cervix identified on trans-vaginal ultrasound	Intra-muscular administration 17-OHP vs placebo	Preterm birth less than 37 weeks
Bruinse ²⁵ H.W.Bruinse@umcutrecht.nl	17 alpha hydroxyprogesterone in multiple pregnancies to prevent handicapped infants (The AMPHIA Study)	Women with a multiple pregnancy	Intra-muscular administration 17-OHP vs placebo	Composite outcome of neonatal morbidity
Maurel ²⁶ diana_abril@pediatrix.com	17OHP for reduction of neonatal morbidity due to preterm birth in twin and triplet pregnancies. NCT00163020	Women with a twin or triplet pregnancy	Intra-muscular administration 17-OHP vs placebo	Composite of adverse neonatal outcomes
Nassar ²⁷ an21@aub.edu.lb	Prevention of preterm delivery in twin pregnancies by 17 alpha hydroxyprogesterone caproate. NCT00141908	Women with a twin pregnancy	Intra-muscular administration 17-OHP vs placebo	Preterm birth
Norman ²⁸ Jane.Norman@ed.ac.uk	Double blind randomized placebo controlled trial of progesterone for the prevention of preterm birth in twins. ISRCTN35782581	Women with a twin pregnancy	Vaginal administration progesterone vs placebo	Preterm birth less than 34 weeks
Rode ²⁹ line.rod@rh.dk	Does progesterone prevent very preterm delivery in twin pregnancies? NCT00329914	Women with a twin pregnancy	Progesterone vs placebo	Preterm birth less than 34 weeks
Serra ³⁰ vserra@ivies	Natural progesterone and preterm birth in twins. NCT00480402	Women with a twin pregnancy	Vaginal administration progesterone vs placebo	Preterm birth less than 37 weeks
Wood ³¹ stephen.wood@calgaryhealthregion.ca	Vaginal progesterone versus placebo in multiple pregnancy. NCT00343265	Women with a multiple pregnancy	Vaginal administration progesterone vs placebo	Gestational age at birth
Martinez de Tajada ³⁴ begona.mdt@bluewin.ch	Vaginal progesterone to prevent preterm delivery in women with preterm labor. NCT00536003	Women presenting with symptoms and signs of preterm labor, and evidence of cervical change or positive fetal fibronectin testing	Vaginal administration progesterone vs placebo	Preterm birth less than 37 weeks

with the 17-hydroxyprogesterone 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.

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