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ABSTRACT

Preterm birth occurs in 5-18% of pregnancies, and is the leading cause of neonatal morbidity, mortality, and infant death. Up to 30% of preterm births are for iatrogenic reasons, but the remainder are due to spontaneous onset of labour or pre-labour premature rupture of membranes (P-PROM). During pregnancy the uterus remains quiescent and the cervix remains long and closed. Although the exact mechanisms which lead to spontaneous preterm birth are not fully understood, it is likely that the terminal pathways which are common to term labour are activated prematurely. Despite continued research efforts to develop preventative strategies, there have been no major advances resulting in the reduction in spontaneous preterm birth (sPTB) rates. Progesterone is the most researched prophylactic agent, yet there is a lack of consistency in reported beneficial effects for the prevention of PTB and improvement in neonatal outcome. This is likely to stem from the multifactorial aetiology of sPTB, the varied patient cohorts recruited, as well as the use of different preparations and routes of administration of progesterone. This review summarises the scientific rationale supporting the efficacy of progesterone, the results of major randomised controlled trials and finally emphasizes how targeted studies with more detailed patient stratification are essential if we are to understand which population would benefit.

Keywords: Progesterone, preterm labour, short cervix

PRETERM BIRTH – A GLOBAL PROBLEM

An estimated 15 million babies are born early and one million children die every year due to the complications of preterm birth (1). Preterm birth is now the leading cause of death in children under the age of five (2). Approximately 65-70% of preterm births are spontaneous, with the remainder being indicated for maternal or fetal reasons (3). Despite extensive research into the mechanisms of spontaneous preterm labour, this has not yet translated into a reduction in its incidence (4). There are many challenges the most striking being the lack of our ability to understand the connection between most identifiable risk factors and causality, and a common failure to address the multifactorial nature of preterm birth in randomised controlled trials of intervention, instead considering preterm birth to be a single pathology with an isolated endpoint.

BIOCHEMICAL PROCESSES OF LABOUR

Three processes are required for term labour to occur; uterine contractility, membrane rupture, and cervical dilation. Uterine contractility occurs with the activation of the contraction associated proteins (CAPS): gap junction proteins, oxytocin and prostanoid receptors, cell signalling proteins and prostaglandin synthesis enzymes. Interaction between actin and myosin in the smooth muscle cell leads to myocyte contractility (5). This interaction is regulated by the enzyme myosin light chain kinase (MLCK) (6), which phosphorylates myosin and is activated by calcium and calmodulin (7), and inhibited by myosin phosphatase (MLCP). The control of contractility is proportional to the activity ratio of the MLCK and MLCP as this determines the phosphorylation status of myosin regulatory light chain (8). The CAPs oxytocin and prostaglandin F₂ alpha (PGF_{2α}) alter the activity ratio of MLCK and MLCP which leads to the increase in sensitivity of the contractile unit to calcium (9-11). The connexins (connexin-43, connexin-40 and connexin-45) regulate contractility by controlling the interaction between myocytes for the propagation of action potentials (12, 13). In addition to the endocrine and mechanical stimuli of uterine contractility, a switch to an inflammatory state occurs, with the influx of activated leukocytes releasing cytokines that promote further prostaglandin synthesis (14-16).

Fetal membrane rupture occurs as a result of biochemical and anatomical changes to its structure, with pro-inflammatory cytokines (14), matrix metalloproteinases (17-19), and oxidative stress (20) causing leukocyte infiltration, extracellular matrix degradation and apoptosis. Pro-inflammatory cytokines act to further drive the production of COX-2 and PGE₂ in amnion (21-24). Likewise, cervical ripening and dilation is dependent on leukocyte infiltration (14, 25), pro-inflammatory cytokine, matrix metalloproteinase (26-28), and prostaglandin production. PGE₂ decreases the concentration of collagen (29), increases the synthesis of proteoglycans (30), enhances migration of leukocytes towards the cervix (31) and augments the potency of pro-inflammatory chemokines (32). Taken together, this leads to remodelling and dilation of the cervix.

CAUSES OF PRETERM BIRTH

The pathways described above are physiological processes which act in concert to result in a vaginal delivery at term. Yet these processes can occur prematurely as a result of pathology, leading to either contractility (threatened PTL), membrane activation (PPROM) or cervical dilation (cervical insufficiency) either in isolation or in combination resulting in sPTB.

Inflammation/Infection

The most studied causal factor leading to sPTB is inflammation, with or without evidence of infection. Births at earlier gestations are more likely to be associated with infection, with histologic chorioamnionitis reported in nearly 70% of preterm deliveries between 20 and 24 weeks' gestational age, compared with only 16% of cases delivering at 34 weeks (33). Ascending infection is the most likely source since detectable microorganisms in amniotic fluid is higher in women with P-PROM compared to intact membranes (34, 35), and are most commonly of genital tract origin, for example *Ureaplasma urealyticum*, *Mycoplasma hominis*, *Streptococcus agalactiae*, *Escherichia coli*, and *Gardnerella vaginalis* (36, 37). Microorganisms are recognised by pattern recognition receptors (PRRs), resulting in the production of prostaglandins, cytokines and chemokines, leading to leukocyte infiltration and further enhancement of an inflammatory response and augmentation of the biochemical processes involved in parturition (38, 39).

Immune dysregulation

Preterm labour, in the context of infection could paradoxically be described as a highly regulated immune response. Activation of the primitive innate immune response can be described as a well-designed outcome to expel the fetus and infected fetal membranes from a highly inflammatory environment to aid tissue repair and resolution in order to ensure survival of the mother. To the contrary, the ability of the maternal host to tolerate certain microbes associated with preterm labour, such as *Lactobacillus iners* (40) and *Gardnerella vaginalis* (41), and to deliver at term also reflects a highly regulated immune response which does not cause an inflammatory response in the mother, and neither does it spare the fetus. A dysregulated immune response, whereby inflammation leads to P-PROM, silent dilation of the cervix, an irritable uterus in the absence of labour can place the fetus at risk of the sequelae of the fetal inflammatory response syndrome, and life threatening sepsis in the mother.

Stretch

The higher rates of preterm birth in women with multiple pregnancies, polyhydramnios and uterine anomalies has directed many studies to investigate a role of uterine over-distension and stretch in preterm labour. *In vitro* studies confirm that stretch of both human amniocytes and myocytes can lead to the expression of labour-associated genes such as COX-2, PGE₂, and the oxytocin receptor (42-44).

Cervical insufficiency

Although the incidence of cervical insufficiency is reported to be 1% (45), the incidence is likely to be higher due to the failure to maintain a barrier to ascending infection leading to the misleading attribution of pathology primarily to infection and inflammation. Hormonal and inflammatory mediators contribute to cervical remodelling, which involves disruption of the architecture between cervical cells and the extracellular matrix consisting of collagen, elastin decorin, glycosaminoglycans, proteoglycans and hyaluronic acid (46, 47). Essential to this process are the matrix metalloproteinases produced by cervical and activated immune cells. Studies of 'rescue' or 'emergent' cervical cerclage show a bimodal distribution of outcomes, with one group experiencing early pregnancy loss associated with chorioamnionitis, whilst the other group does well, often going to term. This suggests two mechanisms of preterm cervical dilatation, one 'infection/inflammation' associated which cannot be resolved by cervical cerclage, the other due to genuine mechanical incompetence which does respond to cerclage. Similarly the association between deep cervical conization and preterm birth points to cervical mechanical damage as a potential mechanism.

Vascular disorders

The most common pathological feature of preterm placentas with no signs of inflammation are vascular lesions (48). Vascular lesions in the decidual vessels attached to the placenta are associated

with a mean odds ratio of 3.8 for delivering preterm with intact membranes, and an odds ratio of 4 with premature rupture of membranes (49). Decidual necrosis and haemorrhage can activate labour through the production of thrombin. Thrombin upregulates COX-2 and PGE2 production in amnion (50), causes a dose-dependent increase in myometrial contractility (51) induces an inflammatory response by activating neutrophils, (16), and may enhance cervical ripening by activating matrix metalloproteinases.

SCIENTIFIC RATIONALE SUPPORTING USE OF PROGESTERONE

Progesterone is produced by the corpus luteum in early pregnancy and subsequently by the placenta giving rise to serum concentrations of 10-40ng/mL in the first trimester increasing to 100-200ng/mL by term (52). During pregnancy the uterus remains quiescent under the effect of the 'progesterone block', a paradigm which was first proposed in the 1950's, which refers to the prevention of uterine contractility (53). Progesterone exerts its effect via genomic and non-genomic pathways through interaction with nuclear and plasma membrane progesterone receptors respectively. The major progesterone receptor isoforms PR-A and PR-B account for the genomic actions and act as ligand activated transcription factors modulating the expression of pro- pregnancy and pro- labour genes. In the majority of mammals a reduction in circulating progesterone occurs as a result of regression of the corpus luteum as a precursor to parturition. Rodent studies demonstrate the importance of progesterone for maintenance of pregnancy since loss of systemic progesterone production as a result of ovariectomy or the use of the progesterone antagonist RU486 induces cervical remodelling and leads to preterm labour (54). In contrast to rodents, human labour is not preceded by a decrease in serum progesterone levels but instead results from a 'functional' withdrawal. Alterations in the progesterone receptor isoforms occur in myometrium, cervix and fetal membranes in human parturition whereby there is an increase in the expression of the truncated nuclear PR-A, which has reduced transcriptional activity compared with PR-B (55-57). Furthermore, the progesterone receptor antagonist RU486, mifepristone, is used effectively in humans for cervical ripening, and readily induces abortion if given in early pregnancy (58), providing compelling evidence that progesterone is also required to maintain pregnancy in humans.

Inflammation plays a key role in both term and preterm labour, with the pro-inflammatory transcription factor NF- κ B known to be a key regulatory of both pro-inflammatory cytokines and pro-labour gene expression (59). Substantial evidence exists supporting immunomodulatory mechanisms of progesterone in the maintenance of pregnancy (60). Progesterone inhibits NF- κ B, COX-2, prostaglandin synthesis in amniocytes, thrombin induced IL-11 in term decidual cells, and IL-8 production in amniocytes and myocytes. (61-63). Progesterone also acts directly on immune cells by suppressing the differentiation of the pro-inflammatory T helper 1 cells and enhancing T helper 2 cell differentiation *in vitro* (64). Systemic immunomodulatory effects upon progesterone supplementation in pregnancy reveal a reduction in mRNA of the pro-inflammatory cytokines IL-1 β and IL-8 in peripheral blood leukocytes, and a reduction in CD11b expression (required from transmigration) in circulating neutrophils (65).

Progesterone also contributes to myometrial quiescence, and exhibits direct tocolytic effects on contracting myometrial strips *in vitro* (66). Progesterone increases cyclic AMP, reduces intracellular calcium, and inhibits phosphorylation of myosin required for the calcium-calmodulin-myosin light chain kinase pathway thereby reducing contractility (67, 68). *In vitro* studies demonstrate an inhibition of the contraction associated proteins OTR, connexin-43 and COX-2 via PR-mediated suppression of NF- κ B activation and increased expression of the ZEB1 transcription factor (zinc finger E-box-binding homebox 1) (69-71).

PROGESTERONE PREPARATIONS

With such a strong scientific rationale supporting potential therapeutic benefit of progesterone in the prevention of preterm labour, there have been extensive studies attempting to translate *in vitro* findings with *in vivo* effect. However, it is important to recognise that clinical trials use two forms of progestogens; either natural progesterone (P4) or a synthetic analogue if its metabolite 17-hydroxyprogesterone (17-OHPC), which should be considered as two entirely different compounds. Whilst 17-OHPC is the only progestin approved by the USA Food and Drug Administration (FDA) for the prevention of preterm birth (72), both the National Institute for Health and Care Excellence and the American College of Obstetricians and Gynaecologists (ACOG) recommend the use of vaginal progesterone in women with a short cervix (73, 74). For the purpose of this review we will summarise the evidence for the efficacy of these progestogens for the prevention of preterm birth separately.

17-OHPC

17 α -hydroxyprogesterone caproate (17-OHPC) is a synthetic version of the natural metabolite of progesterone, 17 α -hydroxyprogesterone (17-OHP). Esterification of 17-OHP with caproic acid produces 17-OHPC which increases the half-life to 10 days (75). 17-OHPC is administered by intramuscular injection and is metabolised by the liver. Support for its use by the FDA and the ACOG is based on the results from the National Institute of Child Health (NIH) study by Meis et al in 2003 (76). This was a large randomised controlled trial of 463 women with a singleton pregnancy and a prior history of at least one preterm birth which compared the effects of placebo with weekly 17-OHPC (250mg, i.m.), from 16-20 weeks until 36 weeks or delivery. The study was terminated early because an interim analysis showed a significant reduction in the rate of preterm birth at less than 37, 35 and 32 weeks; 54.9% to 36.3% (OR 0.66, 95% CI 0.54-0.81), 30.7% to 20.6% (OR 0.67, 95% CI 0.48-0.93), and 19.6% to 11.4% (OR 0.58, 95% CI 0.37-0.9) respectively. Based on these statistics its use would translate to an estimated reduction of 9870 preterm births <37 per year in the United States (77).

Interestingly however, the same regime of 17-OHPC does not appear to reduce the rate of preterm birth in women with a short cervix, as defined by <30mm corresponding to the lower 10th centile. A recent randomized controlled trial was halted by the Data Safety Monitoring Board after randomising 657 women, since the interim analysis showed no difference in frequency of preterm birth between both treatment and placebo groups; 25.1% vs 24.2%, $p=0.8$ (with mean cervical lengths of 23.9mm $\pm$ 5.6 and 23.8mm $\pm$ 5.7 respectively) (78).

Several randomised controlled trials have explored the potential for 17-OHPC in women with a multiple pregnancy showing no benefit of its use in this cohort (79-81). A large trial modelled on the Meis 2003 singleton trial randomised 661 women with twins to 250mg of 17-OHPC or placebo from 16-20 weeks to 35 weeks. More of subjects than 90% did not have a history of prior preterm birth, and no cervical length measurements were taken. No difference in preterm delivery rates <35 weeks were seen between both groups; 31.2% with 17-OHPC and 26.1% with placebo, RR of 1.2, 95% CI 0.9-1.5 (79). Similarly in 2011, 240 women with dichorionic twins, >80% of which had no history of previous PTB, were randomised to receive 250mg of 17-OHPC or placebo from 16-24 weeks to 34 weeks, showing no benefit in the treatment group; mean gestational age at delivery 35.3vs 35.9 weeks, $P=0.1$ (80). In addition, no benefits have been demonstrated with 17-OHPC in higher order pregnancies. Two randomised controlled trials of triplet pregnancies reported similar results; with mean gestational age of delivery of 32.4 vs 33.0 weeks with 17-OHPC and placebo respectively

($P=0.527$) in one study a mean gestational age of delivery of 31.9 vs 31.8 weeks ($P = .36$) in the other (82, 83).

When combining two risk factors, a short cervix and twin pregnancy, there is still no reported beneficial effect of 17-OHCP on preventing preterm birth. The rate of preterm birth before 35 weeks was 64.3% vs 45.8% ($P=0.18$) in women with a cervical length <25th percentile (84). In a larger study of twins, with a shorter cervical length cut off and a higher dose of 17-OHPC (500mg i.m.), there was also no difference in sPTL rates <37 weeks, (26% 17-OHPC vs 21 % placebo) (85).

Apart from the data reported in the Meis trial (76), there is a lack of evidence to support the use of 17-OHPC for the prevention of preterm birth, regardless of risk factor. Critics of the Meis trial point out the high rate of preterm delivery in the placebo arm (54.9%), that the rate of PTB in treatment arm (36.3%) is similar to that of a population with a prior history of preterm birth, and to the rates used in power calculations for several trials (86). When considering the biological reasons for the lack of efficacy of 17-OHPC we should recognise that in contrast to natural progesterone 17-OHPC has a lower relative binding affinity of 26-30% to progesterone receptors (87) and does not inhibit uterine contractility (66). Moreover, the vehicle for 17-OHPC is castor oil, which has been reported to have stimulant effects on the uterus with positive effects on the induction of labour in women at term (88-90), and has been shown to induce uterine contractions in mice via activation of the EP₃ receptors (91). Therefore, it is perhaps unsurprising that trials using 17-OHPC have been largely negative.

Natural progesterone (P4)

Natural progesterone (P4) is commonly manufactured from plant extracts. The chemical structure is identical to that of progesterone secreted by the corpus luteum in the first trimester of pregnancy and later by the placenta (92). Natural progesterone can be administered orally, vaginally, rectally or by intramuscular injection. Due to the first pass metabolism of progesterone a 10-fold higher concentration of progesterone can be found in the endometrium with vaginal administration compared with the intramuscular route (93).

In the same year that the Meis trial was published, Da Fonseca et al published a randomised placebo controlled trial of natural vaginal progesterone in 142 women at high risk of PTB in Brazil (94). Women were included if they had a history of prior preterm birth, had a uterine anomaly or had cerclage for cervical insufficiency. This study also demonstrated a reduction in preterm labour. With 100 mg of vaginal progesterone once a day from 24 to 34 weeks preterm delivery rates were reduced from 28.5% to 13.8% ($P=0.03$) and 18.6 % to 2.8% ($P=0.002$) for less than 37 and 34 weeks respectively. More than 90% of women in the trial had a previous preterm birth with up to 5% classed as having cervical insufficiency. However, a larger and more recent study by Crowther et al of women from New Zealand and Australia failed to demonstrate an effect using 100 mg of vaginal progesterone (95). The inclusion criteria was a history of prior preterm birth, with 398 women being randomised to 100mg of vaginal progesterone and 389 to placebo. There was no difference in the PTB rate <37 weeks between the progesterone and placebo groups, (36.5% compared with 37.2%). Similarly, O'Brien et al randomised 659 women with a history of prior preterm birth to placebo or 90mg of vaginal progesterone in the form of a gel from 18+0 and 22+6 weeks until 37 weeks and showed no beneficial effects for PTB <37 or <32 weeks (96). However, women had a mean cervical length of 37mm at the time of recruitment and women with a shortened cervix, who may benefit the most from progesterone supplementation, were excluded from the trial. The vast majority of women included in these studies either had a normal or unknown cervical length, with the latter study excluding women with a short cervix.

Two large multicentre trials exploring the potential for vaginal progesterone in women with a short cervix have demonstrated significant reductions in the rate of preterm labour (97, 98). In both studies roughly 85% of women had no history of prior preterm birth. The first study was by Fonseca et al randomized women with a cervical length (CL) of < 15mm at 20-25 weeks to 200mg of vaginal progesterone or placebo from 24-34 weeks (97). This was associated with a 44% reduction in preterm birth <34 weeks (34% to 19%, RR 0.56, 95% CI 0.36-0.86). The second study randomised 458 women with a cervical length of between 10-20mm from between 20⁺⁰-23⁺⁶ weeks and 36⁺⁶ weeks to 90mg of vaginal progesterone or placebo at centres either in Europe or the USA. This trial also demonstrated a significant reduction in preterm birth <33 weeks from 16.1% to 8.9% with a RR of 0.55, 95% CI 0.31-0.91, (P=0.02). Based on the results of this study the number needed to treat to prevent one preterm birth <33 weeks in women with a cervical length of 10-20mm is 14.

The largest trial of vaginal progesterone to date (the OPPTIMUM study) randomised 618 women to 200mg of uterogestan and 610 women to placebo from 22-24 weeks to 34 weeks gestation (99). The inclusion criteria was a previous preterm birth (78-80% of women), or a cervical length $\leq$ 25mm (34-38% of women) or a positive fetal fibronectin in addition to a risk factor for PTB (27-30% of women). Progesterone had no effect on the rate of delivery < 34 weeks (15% in progesterone and 17% with placebo, odd ratio (OR) of 0.85, 95% CI 0.62-1.15, P=0.29). A subclass analysis of 251 women with a cervical length of $\leq$ 25mm revealed an odds ratio of 0.69, 95% CI, 0.39-1.20, P=0.54) for the obstetric outcome of fetal death or liveborn delivery <34 weeks. These individual patient data of women with a short cervix were included in a recent meta-analysis to determine if vaginal progesterone is effective in women with a short cervix (100). This meta-analysis included five high quality trials of 974 women with a cervical length $\leq$ 25mm and reported a reduction in PTB <33 weeks (relative risk, 0.62; 95% CI, 0.47-0.81; P=0.006).

Unlike the conflicting reports on potential efficacy for vaginal progesterone in singleton pregnancies, there is a consensus that vaginal progesterone has no beneficial effect in the prevention of preterm birth in women with twin pregnancies. The study of progesterone for the prevention of preterm birth in twins (STOPPIT) trial randomised 500 women to 90mg of vaginal progesterone or placebo from 24 weeks to 34 weeks and showed no beneficial effect for the reduction of preterm delivery (OR 1.36, 95% CI 0.89-2.09) (101). A larger study of 677 women with diamniotic twins randomised to a higher dose of 200mg of progesterone also showed no benefits for preterm birth rates with treatment compared with placebo (102). No randomised controlled trials with placebo and progesterone have been performed in triplets (103).

NEONATAL OUTCOME AND SAFETY PROFILE

Whilst reporting on gestational age of delivery as an outcome is essential for studies into the prevention of preterm birth, it must not be forgotten that the main aim of delaying preterm labour is to increase survival and reduce short and long term morbidity to the neonate, and to not cause harm.

The Meis trial reported a significant reduction in low birth weight of <2500g (p=0.003), rate of necrotising enterocolitis (p=0.01), need for supplemental oxygen and intraventricular haemorrhage and a non-significant trend in the reduction of respiratory distress syndrome (76). Of concern however, there was a non-significant increase in fetal death (RR 1.50, 95% CI 0.31-7.34), which was also seen in a large randomised controlled trial in twins (RR 1.4, 95% CI 0.6-3.2) (79). Furthermore supplementation in triplet pregnancies led to a statistically significant increase perinatal mortality (RR 4.7 95% CI 1.0-22.0, p=0.05) (83). Although there are limited data on the long term effects of 17-

OHPC; a follow up at a mean of 4 years of 278 children from the Meis trial revealed no differences in physical examination, the health or performance compared with placebo (104). Despite 17-OHPC being an FDA approved compound to prevent PTB in women with prior history of PTB, its approval is under Subpart H of the Code of Federal Regulations, a regulatory pathway used when the decision is made on the basis of a surrogate endpoint, i.e. delivery <37 weeks gestation (86).

There is however more evidence to support improved neonatal outcomes with the use of natural progesterone. Fonseca et al showed a non-significant reduction in a composite of neonatal morbidity 8.1% vs 13.8%, (RR 0.59, 95% CI 0.26 to 1.25, $p=0.17$) (97). Hassan et al reported on a significant reduction in respiratory distress syndrome (3.0% vs 7.6%; RR, 0.39; 95% CI, 0.17–0.92; $P = 0.03$), any neonatal morbidity or mortality event (7.7% vs 13.5%; RR, 0.57; 95% CI, 0.33–0.99; $P = 0.04$), and birth weight <1500g (6.4% (15/234) vs 13.6% (30/220); RR, 0.47; 95% CI, 0.26–0.85; $P = 0.01$) (98).

Neonatal morbidity or death was reduced with in the progesterone treatment group with as odds ratio of 0.62, 95% CI 0.41 to 0.94, unadjusted $P=0.02$). Specifically, components of neonatal outcome neonatal death and brain injury on ultrasound were both significantly reduced with progesterone treatment, unadjusted $P= 0.0009$ and 0.008 respectively. These benefits were not reproduced in studies of multiple gestations. The STOPPIT trial of 500 cases of twin pregnancies showed no difference in the rate of adverse effects between the progesterone and placebo groups, and the combined proportion of intrauterine death or delivery <34 weeks were similar at 24.7 % in the progesterone group and 19.4% in the placebo groups (OR 1.36, 95% CI 0.89–2.09) (101). Data on long term outcomes of vaginal progesterone supplementation in both singleton and multiple pregnancies are lacking.

SUMMARY AND CONCLUSION

There is a consensus that neither 17-OHPC nor vaginal progesterone are effective in reducing the risk of preterm birth or improving neonatal outcome where the only risk factor is multiple pregnancy (105). A more complex picture arises in determining if progestogens are effective in reducing preterm birth and neonatal outcome in singleton pregnancies. As described in this review, there is substantial support for biological plausibility of natural progesterone by reducing contractility, immunomodulation, and inhibition of labour associated gene expression. There also appears to be no evidence of short term harm, and it is unlikely that there is no long term harm, but rather an indication of improvement in neonatal outcome (97–99). It is well recognised that one of the greatest challenges in researching the prevention of PTB is the heterogeneity of populations studied and the lack of understanding of the pathological processes involved. Given that the majority of studies showing a positive effect are of women with a short cervix, both the NICE and ACOG guidance support the use of vaginal progesterone for the prevention of PTB if women are found to have a short cervix (73, 74). The recommendation for the use of progesterone in women with a prior history of preterm birth is not as heavily supported by RCTs. It is likely that the results from studies of this cohort of women are more heavily affected by the challenges of patient heterogeneity and the multifactorial nature of preterm birth. Other under-researched factors that may influence individualised responses and variation in the results of trials include pharmacogenetics and pharmacokinetics of different progesterone regimes and the geographical and environmental influence on preterm birth risk. Therefore, rather than continued efforts to determine efficacy of progesterone in a heterogenic population, we recommend that we redirect efforts to be able to better stratify patient cohorts at risk of PTB. We also believe that such efforts should also not detract us from a search for much needed alternative novel preventative strategies.

PRACTICE POINTS

- A major challenge in researching preventative strategies for the prevention of preterm birth is the multifactorial nature of its aetiology
- Neither 17-OHPC or vaginal progesterone are effective in reducing the risk of preterm birth or improving neonatal outcome in multiple pregnancies
- There is a consensus that for women who have a short cervix (defined as <25mm) with no prior history of sPTB vaginal progesterone is the progestin of choice
- There are inconstant reports of efficacy of progestogens for the prevention of preterm birth in women with a previous spontaneous preterm birth

RESEARCH AGENDA

- Research into the causes of preterm birth should consider preterm birth as a symptom of many different pathogenic processes rather than one disease entity
- Future research studies on prevention of preterm birth should focus on improved patient stratification for inclusion in RCTs

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Conflicts of interest

The authors have no conflicts of interest.

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