



PRETERM BIRTH INITIATIVE

PROGESTERONE USE FOR THE PREVENTION OF PRETERM BIRTH

PURPOSE AND BACKGROUND

Preterm birth, defined as delivery before 37 weeks of gestation, is the leading cause of neonatal mortality and morbidity and also longer term consequences in later life, worldwide¹ It is multifactorial in origin, with approximately two-thirds of all preterm births occurring spontaneously, with the other third being so-called indicated preterm births, where there is maternal or fetal indication for early delivery.² In Australia, 7% of pregnancies resulted in deliveries before 37 weeks during 2002, with approximately 3% births before 34 weeks of gestation. Although this is a small proportion of total births in Australia, it accounts for almost 70% of the total perinatal mortality.³

The purpose of this guideline is to provide evidence-based information to practitioners on the use of progesterone for reducing the risk of spontaneous preterm birth and aid in clinical decision-making.

This guideline (unless stated otherwise) is for the use of natural Progesterone (available as vaginal preparation) only.

MECHANISM OF ACTION AND SAFETY DATA OF PROGESTERONE^{4, 5}

- Although the exact mechanism of action of progesterone in preventing PTB is unknown, several possibilities have been proposed.
- It is thought to enhance quiescence of the uterus by inhibiting uterine contractions.
- In general, the evidence seems to favour two mechanisms: an anti-inflammatory effect that counteracts the infection/inflammation sequence leading to PTB, and a local increase in progesterone in gestational tissues that acts against the functional decrease in progesterone leading to PTB.⁶⁻¹⁰
- Regarding safety, most of the studies have focused on the safety profile of 17-OHPC, the synthetic progesterone. Several studies failed to detect any long-term effect from the intra-uterine exposure of the fetus to pharmacologic progestogen, even when given in the first trimester.¹¹
- Follow up studies to look into long term effects revealed no differences in several parameters at the age of 4 years, in children exposed to 17-OHPC when compared to the control group.^{12, 13}
- The micronized form of progesterone available for use as vaginal pessary or gel is considered to be safe as it is the natural form of progesterone.

The role of progesterone in the prevention of preterm birth has been extensively evaluated by several randomized controlled trials in the last decade, both for:

- The subgroup of women with a previous history of PTB

- Asymptomatic short cervix at the time of routine mid-trimester ultrasound.

A recent meta-analysis of all these studies has confirmed that progesterone reduces the risk of preterm birth in both the above subgroups.

It is important that women diagnosed as having a short cervix during a mid-trimester ultrasound have had the examination done by a proper standardized technique.

Evidence and Recommendation for Use of Progesterone for Prevention of PTB in Singleton Gestations with no prior PTB and with unknown cervical length (CL)

- 17-OHPC use in this context has been studied in a small group of women with no beneficial effect. No RCT has evaluated the effect of vaginal progesterone in this population.
- In summary, there is insufficient evidence to determine the beneficial role of progesterone in this subgroup and hence is not recommended.¹⁴

Evidence and Recommendation for Use of Progesterone for Prevention of PTB in Singleton Gestations with no prior PTB, but a short cervix at 18-23 weeks

- A short cervix detected using a standardized technique of transvaginal ultrasound in the mid-trimester is a powerful predictor of spontaneous preterm birth.^{4, 15}
- Several large RCTs have confirmed a significant risk reduction of PTB among asymptomatic women administered progesterone following the diagnosis of a short cervix.^{15, 16}
- The largest trial included women with a sonographic CL between 10 and 20 mm¹⁶ and a recent IPD meta-analysis demonstrated 50% reduction in the risk of PTB when progesterone was given to women with a cervix measuring 25 mm or less.¹⁷ There is significant reduction in composite neonatal morbidity and mortality and admission to NICU with treatment.¹⁷
- Two cost effectiveness analyses, published so far, looking into the benefits of universal cervical length screening to identify women with short cervical length and then treating with progesterone have reported the benefits of this strategy.^{18, 19}
- In summary, there is strong evidence for use of progesterone in this group.
- It is recommended that cervical length be confirmed using a standardized technique (if not already done). If cervical length is confirmed to be 25 mm or less, at ≤ 24 weeks, vaginal progesterone should be offered for prevention of PTB.
- There is insufficient evidence regarding the appropriate vaginal preparation or dose. A daily dosage of 90-100mg of progesterone gel has a similar effect to a daily dosage of 200mg of progesterone, in both the reduction of PTB and composite neonatal morbidity and mortality.¹⁷ Further, no differences were shown in the effect of progesterone as a function of cervical length in women with a short cervix (less than 25 mm) for the prevention of preterm birth or

reduction of neonatal morbidity and mortality (as determined by a test of interaction).¹⁷

- There is no role of 17-OHPC (IM) in this setting.

Evidence and Recommendation for Use of Progesterone for prevention of PTB in Singleton Gestations with prior PTB

- Systematic review and meta-analysis of five RCTs in women with a history of spontaneous preterm birth, suggest a significant risk reduction in preterm birth, perinatal mortality and major morbidity among women receiving progesterone.²⁰⁻²⁵
- However, there is significant heterogeneity between study findings and this could be attributed to the fact that spontaneous preterm birth is multifactorial in origin. In addition, some studies have looked into the role of vaginal progesterone in this setting²⁶⁻²⁸ while some have used 17-OHPC.^{29, 30}
- Cervical length surveillance is recommended in this group of women.
- If a short cervix is identified then further management is dictated by the degree of shortening, other risk factors and also patient and clinician preferences. These decisions are difficult, and should be individualised and made at a senior level.

Evidence and Recommendation for Use of Progesterone for Prevention of PTB in Singleton Gestations with prior PTB and short CL

- The optimal management of patients with progressive cervical shortening despite progesterone therapy remains uncertain.
- There are no RCT'S comparing vaginal progesterone and cervical cerclage directly for the reduction in risk of delivering preterm.
- An indirect meta-analysis of several RCT's, comparing the role of vaginal progesterone vs placebo, and cerclage vs expectant management in this group of women was performed. It was concluded that the efficacy of both interventions was similar in reducing the risk of preterm birth and adverse perinatal outcomes. There is some evidence to favour cerclage when cervical length is <15mm.³¹

Evidence and Recommendation for Use of Progesterone for Prevention of PTB in Multiple Gestations

- Three recent RCTs have explored the use of vaginal progesterone in prevention of preterm birth in this high-risk group (without considering cervical length) and all were negative for any beneficial effect.³²⁻³⁴
- A sonographic short cervix is a powerful predictor of preterm birth in twin gestations and the risk is much higher in twins than in singleton pregnancy for the same cervical length.^{35, 36}
- In one individual patient meta-analysis, a subgroup analysis of women with twin gestation and cervical length < 25 mm was performed. Vaginal progesterone was associated with a non-significant trend in reduction of PTB and a significant reduction in composite neonatal morbidity and mortality. It is important to note that the observations are based upon a small number of patients.¹⁷



- Recent systematic analysis and Cochrane review report insufficient evidence of benefit.^{24, 25}
- It is recommended that patient management be individualized and discussed with an MFM consultant or a consultant in the Preterm birth clinic

Evidence and Recommendation for Use of Progesterone for Prevention of PTB in patients presenting with PPROM

- At this time, there is no role for progesterone to reduce the risk of preterm birth in women with PPROM.
- A single recent study has looked into the question of whether women with PPROM would benefit from weekly progesterone (IM). No evidence of benefit was found.³⁷
- SMFM clinical guidelines state that it is reasonable to continue 17OH-P treatment in a woman who has been receiving this for the indication of prior PTB, once membranes have ruptured.⁵
- No RCT has evaluated the effect of vaginal progesterone in this subgroup of women.
- The decision to continue with vaginal progesterone in a woman who has been receiving this to reduce the risk of PTB and has presented with PPROM, should be individualized and also be made at a consultant/senior level.

Evidence and Recommendation for Use of Progesterone for Prevention of PTB in women presenting in preterm labour

- There have been several small trials looking into the role of progesterone for primary, adjunctive, and maintenance tocolysis.
- There is inconsistent evidence, with some trials reporting a minor benefit and others reporting none, when intramuscular progesterone was given for maintenance tocolysis (after arrested threatened PTL).³⁸⁻⁴⁰
- In a small number of women with singleton gestation, still pregnant after successful tocolysis for PTL, vaginal progesterone 400mg daily until delivery was associated with longer latency until delivery, compared to no such treatment.⁴¹
- In summary, there is currently insufficient evidence to recommend progesterone for primary, adjunctive, or maintenance tocolysis.

IDEAL ROUTE OF ADMINISTRATION, TIMING OF INITIATION AND CESSATION, AND CORRECT DOSAGE

- Vaginal pessaries of progesterone are available and have the potential advantage of high uterine bioavailability and few systemic side effects. In some patients, vaginal irritation and/or vaginal discharge can be problematic and seems to be more common with gel than suppository use.²⁷
- Optimal dosage for this route of administration is not clearly established, although a recent meta-analysis showed no difference in effect between 90-100 mg and 200 mg progesterone for women with a short cervix.¹⁷
- Timing of therapy has also varied between studies, starting as early as 16 weeks of gestation in women with a previous history of PTB, and in some trials starting between 16-24 weeks of pregnancy when a short cervix is diagnosed on an ultrasound scan. Smaller studies have not shown any difference in the



efficacy when progesterone was started at 16-20 weeks as compared to 20 – 26 weeks.^{42, 43}

- It is recommended to continue the treatment until 36-37 weeks, as early cessation has been associated with an increased risk for preterm delivery.⁴⁴
- In summary, a dose of either 100-200mg micronized progesterone capsule / pessaries, vaginally, nightly, to be started from 16-24 weeks and continued until 36-37 weeks is recommended.

CONCLUSIONS AND RECOMMENDATIONS

1. In women with singleton gestations, no prior PTB and short TVU CL (under 25 mm), at < 24 weeks, vaginal progesterone is associated with reduction in PTB and perinatal mortality and morbidity.
2. There is insufficient evidence to recommend the use of progesterone in singleton gestations with no prior PTB and unknown CL.
3. In singleton gestations with prior PTB, vaginal progesterone starting at 16 weeks and continue until 36 weeks, is recommended. In these women, if on cervical length surveillance the CL shortens to less than 25 mm at less than 24 weeks, continuing with only vaginal progesterone therapy is an option. The second intervention which can help is cervical cerclage (see guideline). If CL =< 15 mm, cervical cerclage may be a better intervention.
4. Progesterone has not been associated with prevention of PTB in multiple gestations, arrested / threatened PTL, or PPROM. There is insufficient evidence to recommend the use of progesterone in women with any of these risk factors, with or without a short CL.

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REFERENCES (STANDARDS)

As Above

Guidelines adapted from:

1. Royal Australian and New Zealand College of Obstetricians and Gynecologists (RANZCOG) guidelines
2. SMFM guidelines

National Standards – 12- Service Delivery

Legislation - NIL

Related Policies - Nil

Other related documents – <http://www.thewholeninemonths.com.au/>
[The Whole Nine Months](http://www.thewholeninemonths.com.au/)

RESPONSIBILITY

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