Progesterone use in pregnancy: role in early pregnancy and preventing preterm birth.

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Progesterone supplementation in pregnancy has three evidence-based roles, the first being in luteal phase support, the second is in the management of threatened miscarriage and the third in the prevention of preterm birth. In this article I will briefly review the evidence for its use in threatened miscarriage and prevention of preterm birth and provide references to up-to-date guidelines in how to use it.

Threatened miscarriage

Unfortunately, approximately one in five pregnancies result in miscarriage. This can often have significant impact on individuals and couples, with associated grief, mental health decline and feelings of inadequacy or like "something is wrong with me". Although the most common cause of miscarriage is genetic, and a large proportion of patients will go on to have subsequent successful pregnancies, there is a group of women who will have recurrent miscarriages. These patients should be investigated for underlying medical conditions that may be contributing to recurrent pregnancy loss.

In August 2023 the UK NICE guideline on the management of miscarriage was updated to include recommendation of **offering vaginal micronized progesterone 400mg twice daily** to women with an intrauterine pregnancy confirmed by scan, if they have **vaginal bleeding** and have p**reviously had a miscarriage.** This should be continued until 16 weeks completed gestation. This recommendation is based on a 2021 Cochrane meta-analysis of seven randomized clinical trials assessing progestogen treatment for preventing miscarriage among women with threatened or recurrent miscarriage. The metanalysis revealed that although there was no effect for live birth rates of vaginal progesterone compared to placebo in women with threatened miscarriage (RR1.03 [95% CI 1.00, 1.07]). However, the subgroup analysis of women with a threatened miscarriage and one or more previous miscarriages, showed that vaginal progesterone compared to placebo increased the livebirth rates (RR 1.08) [95% CI 1.02, 1.15] with 36 more livebirths per 1000. It is important to note that the metanalysis did not find benefit of vaginal progesterone in women with recurrent miscarriage without threatened miscarriage in the current pregnancy. The current RANZCOG statement (Cobs-29a) has not been revised since 2018 and does not reflect this evidence and suggests only that "progesterone supplementation until the second trimester in women with a clinical diagnosis of threatened miscarriage may reduce the rate of spontaneous miscarriage and may be considered". This guideline is due for review.

So how do practitioners prescribe progesterone when reviewing a patient with threatened miscarriage in the context of previous miscarriages? Currently you will need to provide the patient with a private script for progesterone capsule, 200mg as it is currently not listed on the Pharmaceutical Benefit Scheme for this indication. Instruct the patient to insert two capsules vaginal twice daily and continue to 16 weeks completed pregnancy. One box contains 42 capsules and will cover the patient for up to 10 days. You may provide up to three repeats. The cost to the patient will be approximately $90 to $100 per month.

Prevention of preterm birth

The leading cause of neonatal morbidity and mortality worldwide is preterm birth, or birth before 37 weeks gestation. Approximately two thirds of all preterm births are spontaneous. It is important to identify women at risk of preterm birth and to refer these women early for obstetric care. Risk factors for preterm birth include, but are not limited to:

- History of pregnancy loss between 16-24 weeks gestation
- Spontaneous preterm birth
- Preterm prelabour rupture of membranes <34 weeks gestation
- Short cervix identified on ultrasound
- Congenital uterine anomalies
- History of uterine surgery e.g. septum resection
- History of cervical surgery e.g. cone biopsy, two or more LLETZ or deep LLETZ (depth >10mm), radical trachelectomy for treatment of cervical cancer.

Often there may be no identifiable risk factors for preterm birth. The current RANZCOG guideline on measurement of cervical length for the prediction of preterm birth (C-Obs 27) recommends measurement of cervical length for all women in the mid-trimester scan, or morphology ultrasound. If the cervical length transabdominally measures less than 35mm, or is not adequately visualised, then a transvaginal (TV) cervical length is indicated. In a singleton pregnancy, a cervical length of less than 25mm on TV scan in a woman who is asymptomatic necessitates referral to an obstetrician. In this case RANZCOG recommends commencing vaginal progesterone therapy (RANZCOG clinical statement C-Obs 29b). This guideline also recommends consideration of treatment with vaginal progesterone for women with a history of preterm singleton birth.

In March 2021, the Evaluating Progesterone for Preventing Preterm Birth International Collaborative (EPPPIC) published the results of an individual participant data meta-analysis including 31 trials. The aim was to assess the effect of progesterone in reducing preterm birth in asymptomatic women at risk of preterm birth (short cervix on mid-trimester scan on history of spontaneous preterm birth). The study showed that progesterone, in various forms including vaginal, oral and intramuscular, reduced the risk of preterm birth before 34 weeks when compared to placebo for women with singleton pregnancies at risk of preterm birth. The effect of vaginal progesterone was a reduction by 22% (RR0.78, CI 0.68, 0.90). The same, however, was not true for women with multifetal pregnancies.

For the **indication of prevention of preterm birth**, vaginal progesterone is listed on the PBS and there is a streamlined authority code: 11835. The patient must have a **singleton** pregnancy, must have EITHER a **short mid-trimester cervix** (<25mm) OR a **history of preterm birth**, and treatment **must not be started before 16 weeks** gestation. You can prescribe progesterone 200mg capsule, quantity of 42 per box with three repeats. Instruct your patient to administer one capsule per vagina each night and continue up to 34 to 36 weeks gestation. The cost to your patient will be approximately $32 and at a standard dose one bow will provide treatment for six weeks. Local guidelines may vary, however, and some practitioners may choose to prescribe two capsules nocte, rather than one.

References

Ectopic pregnancy and miscarriage: diagnosis and initial management. NICE guideline [NG126]. Updated 23 August 2023. https://www.nice.org.uk/guidance/ng126

Devall AJ et al. Progestogens for preventing miscarriage: a network meta-analysis. Cochrane Library 19 April 2021. https://doi.org/10.1002/14651858.CD013792.pub2

Progesterone support of the luteal phase in the first trimeter. RANZCOG Statement C-Obs 29a. Updated March 2018. https://ranzcog.edu.au/wp-content/uploads/2022/05/Progesterone-Support-of-the-Luteal-Phase-and-in-the-First-Trimester.pdf

Measurement of cervical length for prediction of preterm birth. RANZCOG Best Practice Statement C-Obs 27. Updated November 2021. https://ranzcog.edu.au/wp-content/uploads/Measurement-Cervical-Length-Preterm-Birth.pdf

Progesterone: Use in the second and third trimester. RANZCOG Clinical Statement C-Obs 29b. Updated November 2023. https://ranzcog.edu.au/wp-content/uploads/2022/05/Progesterone-Use-in-the-second-and-third-trimester-of-pregnancy-for-the-prevention-of-preterm-birth.pdf

Evaluating Progestogens for Preventing Preterm birth International Collaborative (EPPPIC): meta-analysis of individual participant data from randomised controlled trials. The Lancet. Vol 397, 10280:1183-1194, March 27 2021. DOI: 10.1016/S0140-6736(21)00217-8

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