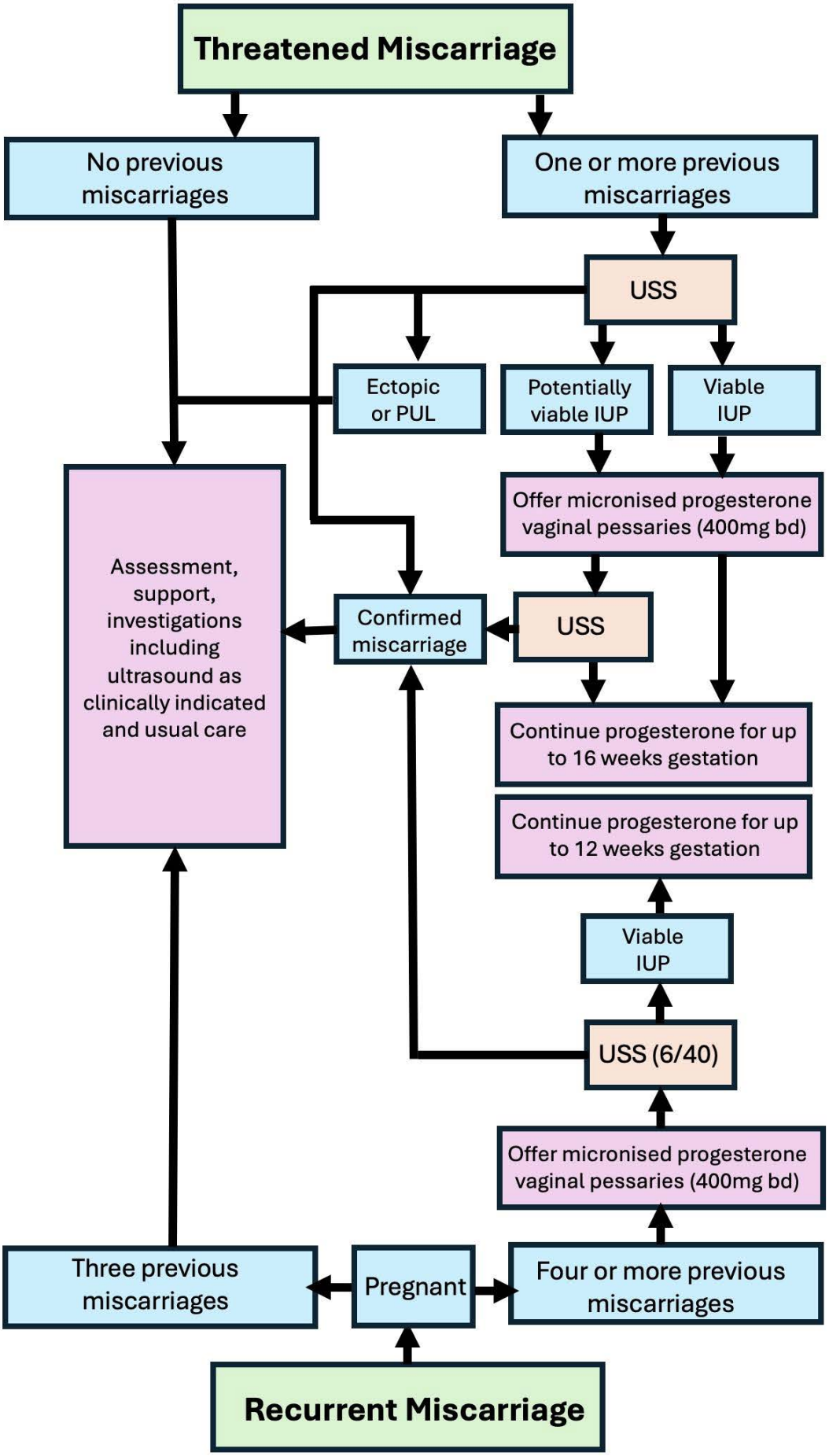
Scottish Government
Riaghaltas na h-Alba

Use of Progesterone in the Management of Threatened Miscarriage and Recurrent Miscarriage

Contents

Summary flow chart



Background

For the purposes of this guideline, we refer to early pregnancy bleeding under 12 weeks' gestation as threatened miscarriage. Threatened miscarriage is defined as an episode of vaginal bleeding in early pregnancy, where the cervical os is closed and the pregnancy is normally sited within the uterus and remains potentially viable. It is one of the most common reasons women attend early pregnancy care. In a large study following up couples trying to conceive who became pregnant (n=4539), 27% of women experienced early pregnancy bleeding. In that cohort more than 85% of women were under 34 years of age and the miscarriage rate was 12%. While the incidence of early pregnancy bleeding and miscarriage in more representative older populations is higher than this, it is still true that most women with early pregnancy bleeding will have a continuing pregnancy. Around 60% of women with vaginal bleeding in the first trimester of pregnancy will have a viable pregnancy.

It is important to remember that vaginal bleeding in pregnancy can be a sign of other pathology such as ectopic pregnancy, molar pregnancy, cervical ectopy or, rarely, cervical malignancy. Early pregnancy unit protocols are designed to ensure that other pathology is not missed. That means that women presenting at less than 12 weeks' gestation with vaginal bleeding should be triaged by staff experienced in early pregnancy care, where possible, to determine the most appropriate management within 24 hours of reporting vaginal bleeding. Assessment usually involves detailed history, ultrasonography +/- speculum examination.

The requirement for a scan before starting treatment with progesterone

The NICE guideline states that progesterone should only be used in women with vaginal bleeding in early pregnancy if they have a confirmed intrauterine pregnancy on ultrasound scan and a history of prior miscarriage. See **Annex A**. This is because progesterone can mask, and potentially worsen, other pathologies such as ectopic pregnancy and molar pregnancy. The requirement for an intrauterine pregnancy to be confirmed before treatment protects women with other pathologies from being prescribed progesterone when it is not clinically appropriate.

Ensuring that a pregnancy is viable or potentially viable

Miscarriage can sometimes be diagnosed on a single ultrasound scan and treatment of a non-viable pregnancy inappropriately with progesterone can unnecessarily delay management of a miscarriage.

This means that only the following scan findings in women with threatened miscarriage and previous miscarriage would be suitable for vaginal micronised progesterone treatment:

- Normally sited pregnancy within the uterus with fetal pole and fetal heart pulsation confirmed.
- Normally sited pregnancy with a fetal pole where the CRL <7mm and no fetal heart pulsation is seen.
- Normally sited pregnancy with a gestational sac and a yolk sac but no fetal pole.
- Where there is a gestation sac (MSD <25mm) but no fetal pole and no yolk sac. However, caution should be exercised because a pseudosac can sometimes be seen in ectopic pregnancy. A gestation sac is eccentrically placed in the uterus with an obvious decidual reaction. Pseudosacs are in the midline with no decidual reaction and may have teardrop rather than smooth edges. If a pseudosac is suspected this is a pregnancy of unknown location and progesterone should not be offered at this stage.

Progesterone should not be offered:

- For women with threatened miscarriage who have no history of previous miscarriage.
- For women with a pregnancy of unknown location (PUL). These women need additional assessment with hCG measurement and repeat scanning.
- For women of previous molar/ectopic pregnancy/PUL alone with no previous miscarriage.
- For women with some clinical conditions and elements of patient history that mean that treatment with progesterone is contraindicated or relatively contraindicated even if they have a history of previous miscarriages, therefore treatment must take individual history into account.

The dose of progesterone

Only vaginal micronised progesterone should be offered. The dose recommended is 400 mg twice a day.

Prometrium is now licenced for use in the prevention of miscarriage in women presenting with bleeding in the first trimester of pregnancy and have a history of recurrent miscarriages. This guideline is therefore recommending the use of this vaginal micronised progesterone for this patient group.

There are other types of vaginal micronised progesterone that are not licenced that are available (e.g. Utrogestan/Cyclogest) with recommended doses and these could be considered as an alternative to Prometrium, particularly if Prometrium is not available. These other unlicenced preparations would be prescribed off-label. Off-label prescribing means the product licence does not cover the indication or age for which the medicine is being prescribed. It is commonly used in some areas of medicine, such as in paediatrics. The General Medical Council (GMC) has published guidance to support the prescribing of unlicensed medicines and medicines off-label. The guidance states that doctors should usually prescribe licensed medicines in accordance with the terms of their licence but they may prescribe medicines off-label where, on the basis of an assessment of the individual patient, they conclude, for medical reasons, that it is necessary to do so to meet the specific needs of the patient. In doing so, doctors must be satisfied that there is sufficient evidence or experience of using the medicine to demonstrate its safety and efficacy and take responsibility for prescribing the medicine and for overseeing the patient's care, monitoring and any follow up treatment. The guidance also advises that if a doctor intends to prescribe a medicine off-label they should explain this to the patient and give the reasons for doing so. Please see the General Medical Council's 'Good practice in prescribing and managing medicines and devices' (Section titled: Prescribing unlicensed medicines) for further information.

The duration of treatment

Vaginal micronised progesterone treatment can be continued until 16 weeks, as per the NICE guideline. See **Annex A**.

Side effects of treatment

Women may experience increased discharge using progesterone pessaries. For information on side effects, cautions, contraindications and interactions please refer to the British National Formulary and Summary of Product Characteristics (SmPC):

Licenced Preparation

- Prometrium 400mg soft vaginal capsules - Summary of Product Characteristics (SmPC) - (emc) (medicines.org.uk)

Unlicenced preparations

- Cyclogest 200mg pessaries - Summary of Product Characteristics (SmPC) - (emc) (medicines.org.uk)
- Cyclogest 400mg pessaries - Summary of Product Characteristics (SmPC) - (emc) (medicines.org.uk)
- Utrogestan Vaginal 200mg Capsules - Summary of Product Characteristics (SmPC) - (emc) (medicines.org.uk)
- Progesterone | Drugs | BNF | NICE

Please ensure that you have checked for any allergies or ingredients that are not suitable for some patients.

Contraindications to treatment with progesterone

Therapeutic progesterone may not be suitable for those with a history of liver tumours or severe hepatic dysfunction, current genital or breast cancer, severe arterial disease, previous history of thromboembolism, jaundice relating to pregnancy, severe itch related to pregnancy, pemphigoid gestationis, acute porphyria or a previous reaction to progesterone.

Follow up after treatment with progesterone is initiated

No extra follow up is required for eligible women who opt to use vaginal micronised progesterone for threatened miscarriage with a history of one or more miscarriages, if they are known to have a viable pregnancy at treatment initiation. Their usual antenatal care booking should proceed as normal. Women should be advised to stop vaginal micronised progesterone treatment by 16 weeks' gestation.

For women using vaginal micronised progesterone who commence treatment when viability of the pregnancy is not certain, it is good practice to repeat an ultrasound scan for viability 1 to 2 weeks after commencement of progesterone.

Effects of progesterone on fetal development

Women should be made aware that there are no current concerns for the mother or unborn baby from existing evidence and as per the NICE guidelines. However, there is overall limited evidence available and there is no evidence on the long-term effects on babies of using progesterone supplementation in the first 16 weeks of pregnancy. The discussion should be documented in the Electronic Patient Record (EPR).

Use in recurrent miscarriage

The PROMISE trial, the largest multicentre Randomised Control Trial to date, which was adequately powered and with a very low risk of bias, showed that routine progesterone supplementation did not result in a significantly higher rate of live births (progesterone 65.8% vs placebo 63.3%, difference 2.5% (95%CI -4.0-9.0)). However, the efficacy seemed to change based on number of previous miscarriages. The livebirth rate was not higher for women with a history of 3 miscarriages (RR 1.01 CI 0.89-1.14, P=0.91). However, there was a trend to a benefit for women with 4 or more miscarriages (63% vs 58%, P=0.07).

Therefore, based on the evidence from the PROMISE trial, and as per the recommendations in the Lancet miscarriage series, it is recommended that vaginal micronised progesterone treatment should be offered for asymptomatic women with recurrent miscarriage with 4 or more miscarriages.

Treatment regimen for recurrent miscarriage

Asymptomatic women with four or more previous miscarriages should be offered vaginal micronised progesterone (400 mg twice daily) from a positive urine pregnancy test until 12 weeks of gestation, where clinically appropriate. This regimen is based on the PROMISE study protocol that informed this document. Women considering treatment should be provided with verbal and written information on available evidence and potential risks/benefits, including that there is no conclusive trial evidence that progesterone reduces the risk of miscarriage including after 4 miscarriages.

As progesterone could be harmful in the event of an abnormally located (ectopic) pregnancy, an ultrasound scan should be provided at 6 weeks' gestation, in order to confirm intrauterine gestation and potential viability. At the time of writing, there is no need to wait for an ultrasound scan prior to commencing vaginal micronised progesterone for asymptomatic women with 4 or more miscarriages.

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Annex A

Evidence Base

Threatened Miscarriage

Progesterone is the naturally occurring hormone that maintains pregnancy. It reduces bleeding, makes the uterus less irritable, lowers inflammation and dampens down the immune system. It was suggested that some women who repeatedly miscarry may have insufficient progesterone or an insufficient response to progesterone. Therefore, the large PRISM randomised controlled trial assessed the efficacy of progesterone treatment in the prevention of miscarriage in those presenting with threatened miscarriage.

The overall findings of the PRISM study showed that progesterone treatment for threatened miscarriage did not result in a statistically significant increase in livebirth. Overall, without progesterone treatment 72% of women in that study had a livebirth (cf 76% with progesterone, P=0.08). However, the study suggested a clinically significant difference with a greater effect seen with increasing number of previous miscarriages. Post-hoc analysis of the PRISM trial found that administrating vaginal micronised progesterone, which is molecularly similar to endogenous progesterone, into the vagina may increase chance of livebirth at 34+ weeks' gestation after bleeding in early pregnancy for women with 1 or more previous miscarriages (70% vs 75% RR 1.09 95%CI 1.03-1.15, P=0.003.

Subgroup analyses showed that women with no previous miscarriages had 1% less livebirth if treated with progesterone (74% vs 75%, RR 0.99, 95%CI 0.95-1.04, P=0.71) which was not statistically significant. However, for women with 1-2 previous miscarriages, there was a non-significant trend for 4% more livebirths in the group treated with progesterone compared to placebo (livebirth rate 76% with progesterone, 72% with placebo, RR 1.05 (95%CI 1.00-1.12), P=0.07). For women with 3 or more previous miscarriages who presented with early pregnancy bleeding, there were 15% more livebirths in the progesterone group compared to placebo (livebirth rate 72% with progesterone, 57% with placebo, RR 1.28 (95%CI 1.08-1.51), P=0.004). A single study has evaluated the cost-effectiveness of progesterone use in this setting, and suggests progesterone is cost-effective for women with a history of previous miscarriage(s).

As a result of this study NICE changed their guidance in 2021. They recommend that vaginal micronised progesterone (400mg twice daily) should be offered to women with an intrauterine pregnancy confirmed by a scan, if they have vaginal bleeding and have previously had a miscarriage. If a fetal heartbeat is confirmed, vaginal micronised progesterone should be continued until 16 completed weeks of pregnancy. The Review of evidence and justification of the recommendation and duration of treatment is available in the NICE guideline (NG126) and can specifically be found in NG126 Evidence review C on page 18.

Recurrent Miscarriage

There have been no NICE recommendations on the use of vaginal micronised progesterone without threatened miscarriage. The RCOG Green-Top Guideline on recurrent miscarriage advised that routine supplementation with progesterone should be used with caution in asymptomatic women with unexplained recurrent miscarriage. Meta-analysis have reported a possible benefit from progestogen supplementation. This document is recommending that vaginal micronised progesterone treatment should be offered for asymptomatic women with recurrent miscarriage with 4 or more miscarriages. This is based on the evidence provided from the PROMISE trial. In that study the livebirth rate was not higher for women with a history of 3 miscarriages (RR 1.01 CI 0.89-1.14, P=0.91). However, there was a trend to a benefit for women with 4 or more miscarriages (63% vs 58%, P=0.07).

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