Progestogens in the management of miscarriage and preterm birth

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SUMMARY

Miscarriage affects up to 20% of pregnant women, resulting in substantial psychological repercussions in addition to inherent problems from bleeding and infection. Preterm births constitute about 7-12% of all births but are over represented in terms of perinatal morbidity and mortality. Despite existing trials examining the use of progestogens in both these conditions, there is a dearth of guidelines for the practicing clinician. A systematic review of the literature was performed by an expert panel formed by the Obstetrical & Gynaecological Society of Malaysia from the inception of the databases searched up to February 2020, without language restrictions. The level of evidence and recommendations was determined by the panel and peer-reviewed by local and international experts. The use of progestogens is recommended in women with threatened miscarriages who have experienced previous miscarriage as luteal phase support in women undergoing assisted reproduction and in women with short cervix of <25mm in the midtrimester. In addition, it can be considered in women with recurrent miscarriage, where no other cause is identified. This article reviews the existing evidence including the guideline above and is intended to aid primary care doctors and obstetricians in their prescribing practices when managing these common conditions.

KEYWORDS:
Cervical insufficiency, dydrogesterone, luteal phase, preterm labour, progesterone, recurrent miscarriage

KEY CONTENT

- In women with threatened miscarriage, the use of progestogens is associated with a higher incidence of live birth. This benefit is more apparent in the subgroup of women with previous miscarriages.
- Progestogens may be considered in women with unexplained recurrent miscarriages. There is some evidence of a biological gradient, where the benefit appears to increase with the number of previous miscarriages.
- Progestogens are recommended to support the luteal phase in patients undergoing IVF, although there is no clear evidence to indicate the superiority of any particular type of progestogen, their dose, or route of administration.
- Vaginal progesterone should be considered in singleton and twin pregnancies with a short cervix, regardless of history of prior preterm births (PTB). This benefit cannot currently be extrapolated to women with higher order multiple pregnancies.

LEARNING OUTCOMES

- Be able to compare the use of progestogens in various clinical conditions in early pregnancy, incorporating the latest evidence from well-conducted randomised trials
- Be able to recognise that the benefit of progestogens in women with threatened and recurrent miscarriage is dependent on the number of previous miscarriages experienced
- Be able to effectively use progestogens in the prevention of late miscarriage and preterm birth in women with short cervix

PRACTICE GAPS

- Should progesterone be withheld in women with bleeding in early pregnancy unless they have experienced three or more previous miscarriages, as the evidence is more robust in this subgroup of women?
- Should the practice of giving intramuscular 17-α-hydroxy-progesterone caproate be ceased based on the recent data from PROLONG trial?

INTRODUCTION

Miscarriage is defined as pregnancy loss from the time of conception until 24 weeks of gestation. It is considered as one of the most common complications of early pregnancy, affecting up to 20% of pregnant women.[1] In addition to causing excessive bleeding, infection, and other possible complications related to surgical treatment, miscarriages may also give rise to substantial psychological repercussions, including anxiety, depression, and post-traumatic stress disorder.[2] Approximately 50-70% of miscarriages are associated with chromosomal abnormalities in the conceptus, with autosomal trisomy-especially trisomy 16,

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triploidy, and monosomy X being the predominant chromosomal aberrations reported in the first trimester.[3] A smaller, potentially preventable proportion of miscarriages may be caused by luteal phase deficiency, while in the remainder, the cause is not known.

Progestogen is an umbrella term which encompasses progestins (synthetic progestogens) and naturally occurring progestogen such as progesterone. Progesterone is produced by the corpus luteum in the ovary and is required to prime the endometrium for embryonic implantation. Other postulated protective mechanisms of this hormone include modulation of maternal immune response, suppression of the inflammatory response, reduction of uterine contractility, and improvement of utero-placental circulation.[4]

It is this physiological importance that has prompted the utilisation of progesterone supplementation in early pregnancy to prevent miscarriages, largely in three different circumstances; the first, in women who have started to bleed during early pregnancy in an attempt to preserve the pregnancy, while the second, to prevent further loss in asymptomatic women with previous unexplained recurrent miscarriage. Thirdly, progestogen has also been widely used in patients undergoing assisted reproduction.[5] Beyond the first trimester, progestogen has a more established role in the prevention of preterm births, although the evidence is less robust in women with multiple pregnancies.[6-8]

As progestogens are available in various forms, dosages, and indications, it can be a source of confusion for clinicians, especially since there is a dearth of clinical guidance in prescription. This Continuous Medical Education (CME) article was written as a supplement to the guideline produced by the Obstetrical & Gynaecological Society of Malaysia (OGSM) aimed at increasing prescriber confidence amongst general practitioners, family medicine specialists, and obstetricians alike and will primarily focus on formulations available in the country.

METHODOLOGY

A panel of experts in the field of Obstetrics and Gynaecology was appointed by the society to determine clinical knowledge gaps in the management of miscarriage and to formulate a practice guideline. The experts included general obstetricians and gynaecologists, reproductive medicine, and maternal fetal medicine subspecialists from the Ministry of Health Malaysia, local public and private universities, and private practice. A modified Delphi method was used and the panel of eleven experts, including the chairperson who acted as the moderator, determined that the use of progestogens in miscarriage was a key area to address. A second round of discussion specifically identified threatened miscarriage, recurrent miscarriage, and luteal phase support as areas with clinical gaps that require a practice guideline. As miscarriage and birth around the threshold of viability were considered a continuum, this was expanded to include preterm births.

Systematic review of the literature was performed via Medline, Database of Abstract of Reviews of Effects (DARE), Cochrane Controlled Trials Register (CENTRAL), Cochrane Database of Systematic reviews and Cumulative Index to Nursing and Allied Health Literature (CINAHL) from its inception until February 2020 without language restrictions. The panel was divided into four groups where each member independently extracted data on the allocated subset of miscarriage or preterm birth and assessed the study quality. The panel determined the level of evidence and recommendations. The guideline was produced and peer-reviewed by local and international experts. Proposed changes were revised and when there was no clear consensus, the opinion of the majority, including the chair, was followed.

THREATENED MISCARRIAGE

A Cochrane review updated in 2018 on the use of progestogen for this specific indication included seven trials involving 696 participants, with low to moderate quality of evidence. The results indicated that treatment of threatened miscarriage with progestogens compared to placebo or no treatment probably reduces the risk of miscarriage; (risk ratio (RR): 0.64; 95% confidence interval (95%CI): 0.47, 0.87; 7 trials; 696 women), while treatment with oral progestogen compared to no treatment also probably reduces the miscarriage rate (RR 0.57, 95%CI: 0.38, 0.85; 3 trials; 408 women). However, treatment with vaginal progesterone compared to placebo, probably has little or no effect in reducing the miscarriage rate (RR: 0.75; 95%CI: 0.47, 1.21; 4 trials; 288 women). The review thus concluded that treatment of threatened miscarriage with progestogens compared to placebo or no treatment probably reduced the risk of miscarriage. However, the use of vaginal progesterone probably had little or no effect when compared with placebo.[9]

By far the largest to date, the recently published Progesterone in Women with Bleeding in early Pregnancy (PRISM) trial was a multicentre, randomised, double-blinded, placebo-controlled trial conducted across 48 hospitals in the UK.[10] A total of 12,862 women were eligible, of which 4153 were randomly assigned to receive either 400 mg of vaginal micronised progesterone (2079 women) or placebo (2074 women) twice daily. The rectal route was an alternative to women whom vaginal administration was unacceptable and notably, this was the preferred route in 1% of women, demonstrating a high acceptability of vaginal progesterone.

The trial showed that among women with bleeding in early pregnancy, progesterone therapy administered during the first trimester of pregnancy did not result in a significantly higher incidence of live births at or beyond 34 weeks of gestation (75% vs. 72%, relative rate 1.03, 95%CI: 1.00, 1.07; p=0.08). However, further subgroup analysis showed that progesterone had possible benefits in women with bleeding in early pregnancy and with a previous history of miscarriage. While live birth is the appropriate primary outcome, there was also no significant difference in the incidence of miscarriage with or without the use of progesterone (20% vs. 22%, relative rate 0.91, 95%CI: 0.81, 1.01). This would be a useful parameter to compare with less-well designed studies looking at miscarriage as the primary outcome. Interestingly, of the 12,862 women who were eligible for randomisation, 8709 or two-thirds of women declined to participate. An economic evaluation subsequent to this, using the same

PRISM cohort, found that progesterone was likely to be a cost-effective intervention in women with a previous miscarriage. Despite an additional £76 per patient in the progesterone arm, the cost-effectiveness acceptability curve for the base-case analysis was favorable. The discordance between clinical and health economic outcomes was attributable to the estimation and quantification of the uncertainty around clinical end-points.[11]

A more recent meta-analysis of 10 randomised controlled trials (RCTs) subsequent to the aforementioned Cochrane review included findings from PRISM and specifically re-examined live birth as the primary outcome. The authors found that progestogens increased the incidence of live birth (RR 1.07, 95%CI: 1.00, 1.15; p=0.04; I2=18%) but the benefit was only seen in with oral progestogen (RR 1.17, 95%CI: 1.04, 1.31; p=0.008; I2=0%) and not in vaginal progestogen (RR 1.04, 95%CI ; 1.00, 1.08; p=0.07; I^2=0%;). Similarly, oral progestogen reduced the risk of miscarriage (RR 0.73, 95%CI: 0.59, 0.92), but not when administered vaginally.[12] A small, open-labelled RCT involving 141 women directly investigated the efficacy of oral micronised progesterone compared to dydrogesterone.[13] The authors did not find any difference in the primary outcome of miscarriage prior to 16 weeks of gestation (10.2% micronised progesterone versus 15.2% dydrogesterone; p=0.581) or resolution of bleeding by days 4-10 (89.7% micronised progesterone versus 96.6% dydrogesterone; p=0.272). Significantly more women on oral micronised progesterone complained of drowsiness and giddiness during treatment.

It is also worth noting that commonly dispensed advice such as bed rest, use of human chorionic gonadotrophin (hCG), or uterine muscle relaxants are not recommended in the management of threatened miscarriage.[14,15]

RECURRENT MISCARRIAGE

American Society of Reproductive Medicine (ASRM) and the European Society of Human Reproduction and Embryology (ESHRE) defines recurrent miscarriage as two or more consecutive miscarriages.[16,17] We have chosen to adopt the definition proposed by the ASRM and ESHRE as this is well-supported by a large study which found that the likelihood of detecting an abnormality after two losses was similar to that after three or four or more losses.[18] Approximately 0.5-2% of women experience recurrent loss. While there are some well-defined causes of recurrent pregnancy loss, in almost 50% of cases, the aetiology cannot be determined, and is therefore classified as unknown aetiology or unexplained.[19,20] For the purpose of this document, recurrent miscarriage will refer to recurrent pregnancy losses of unknown aetiology.

A 2013 Cochrane review of randomised or quasi-RCTs compared progestogens with placebo or no treatment, given in an attempt to prevent miscarriage.[21] The reviewers found that while there was no evidence to support the routine use of progestogen in early to mid-pregnancy, there appeared to be improved outcomes in women with a history of three pregnancy losses or more to reduce the risk of miscarriage (Peto OR 0.39; 95%CI: 0.21, 0.72, 4 trials; 225 women). It should be noted that the primary outcome was a risk of miscarriage rather than livebirths and the four trials included were of substantial methodological limitations. A more recent Cochrane review then reanalysed data from trials specific to women with recurrent miscarriages and suggested that there may be a reduction in the number of miscarriages in women given progestogen supplementation, compared to placebo or controls (average RR: 0.73, 95%CI: 0.54, 1.00, 10 trials; 1684 women; moderate quality evidence).[22] A subgroup analysis comparing placebo-controlled versus non-placebo-controlled trials of women with three or more prior miscarriages compared to women with two or more miscarriages and different routes of administration showed no clear differences in rates of miscarriage. Furthermore, there was probably a slight benefit for women receiving progestogen seen in the outcome of live birth rate. It was therefore concluded that for women with unexplained recurrent miscarriages, supplementation with progestogen therapy probably reduces the rate of miscarriage in subsequent pregnancies.

One of the trials included in this most recent Cochrane Review was a randomised double-blinded trial involving 388 patients with recurrent pregnancy loss comparing 20 mg dydrogesterone daily to a placebo. The trial demonstrated that the incidence of a further miscarriage was 2.4 times higher in the placebo group (RR: 2.4; 95%CI: 1.3, 5.9), thereby supporting the use of dydrogesterone to improve pregnancy outcomes.[23]

The Progesterone in Recurrent Miscarriages (PROMISE) in 2015 compared micronised progesterone at a dose of 400mg twice daily to vaginal placebo capsules, soon after a positive urinary pregnancy test (and no later than 6 weeks gestation) until 12 completed weeks, with the primary outcome being live birth after 24 weeks of gestation.[24] A total of 836 women who conceived naturally within one year were randomised. In an intention-to-treat analysis, the rate of live births was 65.8% (262 of 398 women) in the progesterone group and 63.3% (271 of 428 women) in the placebo group (RR: 1.04; 95%CI: 0.94, 1.15; rate difference: 2.5 percentage points; 95%CI: -4.0, 9.0). There were also no significant inter-group differences in the rate of adverse events including the incidence of congenital anomalies and specifically genital anomalies. Based on this finding, ESHRE guideline concluded that vaginal progesterone in early pregnancy was of no benefit in women with unexplained recurrent pregnancy loss. However, it acknowledged that there was some evidence of efficacy when oral dydrogesterone was initiated at the time of confirmation of fetal heart activity.[17]

Another recent systematic review and meta-analyses included 21 RCTs that assessed a myriad of therapeutic options in recurrent pregnancy loss and concluded that treatment with progestogens starting in the luteal phase seemed effective in increasing live birth rate but not when started after conception.[25] No head-to-head RCT has been conducted specifically to compare the various progesterone options, doses, or the modes of administration.

In May 2019, the findings of the PRISM trial, the largest controlled randomised trial of progesterone treatment of threatened miscarriages, were published.[10] A sub-group analysis found that women who had three or more previous miscarriages benefited from progesterone treatment if they presented with bleeding in early pregnancy.

LUTEAL PHASE SUPPORT IN ASSISTED REPRODUCTION

The Practice Committee of the American Society for Reproductive Medicine (ASRM) in 2015 reaffirms the use of progesterone supplementation for luteal phase support in patients undergoing assisted reproductive technology (ART) procedures. This should be distinguished from the treatment of luteal phase deficiency in natural, unstimulated pregnancies, where there is no evidence of benefit in improving pregnancy outcomes.[26] van der Linden reported that progesterone given during the luteal phase was associated with higher rates of live birth or ongoing pregnancy compared with placebo or no treatment. However, the quality of evidence provided by the five RCTs conducted in the late 1980s through 1990s was considered very low quality. Furthermore, when the analysis was restricted to livebirths, there were no differences between both groups.[27] A meta-analysis of eight RCTs comparing oral dydrogesterone and vaginal progesterone found similar efficacy in both drugs for luteal phase support. However, the trials reported surrogates such as on-going pregnancy and miscarriage as the primary outcome, rather than live births.[28]

There is insufficient evidence to recommend a particular type, dose, or route of progesterone administration for luteal phase support and the recommendations in this guideline were based on consensus amongst the expert panel.[27]

PRETERM BIRTH

Preterm birth (PTB) complicates between 7 and 12% of all births yet accounts for more than 85% of all perinatal morbidity and mortality. Its aetiology is multifactorial and pathophysiological mechanisms include intrauterine infection, cervical insufficiency, and increased uterine stretch/distension in the cases of multiple pregnancies.[29] PTB can broadly be classified as spontaneous or medically indicated ("iatrogenic"). A previous PTB is the strongest predictor for a subsequent PTB.[30] However, approximately 20% of preterm deliveries are due to various maternal or fetal indications such as severe preeclampsia or fetal growth restriction. The term medically indicated PTB has been proposed to describe this subgroup. Clearly, progesterone has no role in these women. Cervical shortening is a known risk factor for PTB in both low and high risk populations.[31] The relative risk of PTB was estimated at 6 if <26mm (10th centile), 9 if <22mm (5th centile) and 14 if <13mm (1st centile).[29] The majority of studies on cervical length were performed in midtrimester, coinciding with morphology screening, using thresholds of below 20 mm or 25 mm for intervention and these cut-offs remain the most frequently used in clinical practice.[30] A meta-analysis in 2005 found singleton women with a history of spontaneous PTB, including preterm labour and premature rupture of membranes, who received 250 mg intramuscular 17-α-hydroxy-progesterone caproate (17P) weekly, had lower rates of recurrent PTB (29.3% vs. 40.9%; OR: 0.45; 95%CI: 0.22, 0.93). In addition, subjects allocated to receive 17P had lower rates of birth weight less than 2500g. No differences in rates of hospital admissions for threatened preterm labour or perinatal mortality were noted for subjects receiving progestational agents in general or for those receiving only 17P specifically. Hassan et al.,[32] demonstrated that in a cohort of 458 women, the progesterone group had a lower rate of preterm birth before 33 weeks compared to placebo. Vaginal progesterone was also associated with a significant reduction in the rate of preterm birth before 28 and 35 weeks, respiratory distress syndrome and birth weight <1500g.[33]

A subsequent literature review of all randomised trials between 2003 and 2017 reaffirmed that only two routes of progesterone administration were effective, weekly intramuscular injections of 17P and daily administration of vaginal progesterone suppository of 100-200mg in preventing further PTB, in singleton pregnancies with previous PTB.[34] The purported efficacy of IM 17P and the American College of Obstetricians and Gynecologists (ACOG) recommendation is largely based on data from Meis et al., although the recent trial, 17P to Prevent Recurrent Preterm Birth in Singleton Gestations (PROLONG) has brought us back to the drawing board.[1,35] This trial which recruited four times more women, including women outside of the USA, showed that 17P did not reduce the risk of preterm labour. Of note, the racial and social demographics in the PROLONG study appear to reflect women of a lower risk group.

For a brief period, questions were raised on the efficacy of progesterone after the publication of the Vaginal Progesterone Prophylaxis for Preterm Birth (OPPTIMUM) trial in 2016. The results of that trial showed that vaginal progesterone did not significantly reduce the risk of PTB or perinatal morbidity and mortality in the entire population or in the subgroup of women with a cervical length ≤25mm. Needless to say, this created significant confusion amongst clinicians. A closer look at OPPTIMUM however, revealed that this study had a very broad inclusion criteria, where more than a quarter of women did not even have a short cervix. Furthermore, there were methodological concerns about the interval between diagnosis, randomisation, and starting progesterone in high-risk women. The National Institute for Health and Care Excellence (NICE) in the UK suggests a cut-off of 25mm be used for intervention, with vaginal progesterone again being the first line for women with no prior PTB but a short cervix of <25mm. However, in women with prior PTB, it recommends either vaginal progesterone or cervical cerclage. Cervical cerclage was recommended as a first line in women deemed to be at the highest risk; those with a short cervix of <25mm and either a history of preterm prelabour rupture of membranes (PPROM) or cervical surgery.[36] In addition, OPPTIMUM did in fact find a reduction in neonatal brain injury and neonatal death but these were not given sufficient emphasis compared to the composite primary outcome, which was non-significant.[37] Romero et al., then performed a meta-analysis using individual patient data, including five high-quality trials and OPPTIMUM to resolve this controversy. A total of 974 women (498 allocated to vaginal progesterone, 476 allocated to placebo) with a cervical length ≤25mm were included and it was found that vaginal progesterone was associated with a significant reduction in the risk of PTB <33 weeks of gestation. Moreover, vaginal progesterone significantly decreased the risk of

respiratory distress syndrome, composite neonatal morbidity and mortality, birthweight <1500 and <2500g and admission to the neonatal intensive care unit.[38] Conde-Agudelo et al., showed that vaginal progesterone was as effective as performing a cervical cerclage in women who could be considered at the highest risk of preterm birth.[39] The authors made an indirect comparison meta-analysis in a cohort of women with singleton pregnancy, previous spontaneous PTB, and a short cervix. Five trials that compared vaginal progesterone versus placebo (265 women) and another five that compared cerclage versus no cerclage (504 women) were included. Vaginal progesterone, compared to placebo, significantly reduced the risk of PTB <35 and <32 weeks of gestation, composite perinatal morbidity/mortality, neonatal sepsis, composite neonatal morbidity, and admission to the neonatal intensive care unit. Cerclage, compared to no cerclage, significantly decreased the risk of PTB <37, <32, and <28 weeks of gestation, composite perinatal morbidity/mortality, and birthweight <1500g. Vaginal progesterone and cerclage were found to be comparable in terms of the reduction of PTB and adverse perinatal outcomes.

Evidence from an updated individual patient meta-analysis by Romero et al. showed that progesterone supplementation prolonged gestation and improved perinatal outcomes in women with twin pregnancies and a short cervix.[5] This contradicted earlier clinical trials which did not take into consideration the cervical length when starting progesterone.[6,7] Further studies are required in this area as the outcome of the meta-analysis was significantly influenced by a single study. A trial involving 134 healthy women with triplet pregnancies on the other hand showed that the rate of fetal loss or preterm birth <35 weeks was similar between women assigned to receive 17P and placebo from 16 to 21 weeks through 35 weeks of gestation.40

CONCLUSION

The merits and benefits of progesterone in various scenarios presenting clinically as miscarriage remains in equipoise. The evidence for the use of progesterone is more robust in the prevention of early preterm birth in women with a short cervix.

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ETHICAL CONSIDERATION

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CONFLICT OF INTEREST

None of the guideline committee members were paid honorarium. No pharmaceutical representatives were involved in the discussions, or in providing assistance in any form, in the preparation of this guideline. Neither was their opinion sought.

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ASSESSMENT OF LEARNING
Multiple Choice Questions (MCQ)
Each of the following stem has either a TRUE or FALSE answer.

1. A 28-year-old primigravida at 10 weeks of gestation presents to your general practice with complaints of per vaginal spotting. She has otherwise no abdominal pain and your bedside ultrasound scan showed a singleton live fetus, measuring around 9 weeks of gestation. You do not see any other abnormalities and a speculum examination showed a normal vagina and cervix. She is very worried and requests for medications to stop the bleeding. The appropriate management is
   A. Oral dydrogesterone
   B. Vaginal micronised progesterone
   C. Complete bed rest for the next 3 to 7 days
   D. Reassure

2. A 38-year-old lady at 10 weeks of gestation presents to your general practice as her obstetrician is away. This is her fourth pregnancy and she has had three previous spontaneous first trimester miscarriages. Her obstetrician could not identify the cause of her previous miscarriages but previously advised her to see a doctor as soon as she suspected she was pregnant. She is asymptomatic and your bedside ultrasound scan showed a singleton live fetus, measuring around 9 weeks of gestation. She is understandably worried and requests for medications to help "strengthen her pregnancy". The appropriate management is
   A. Oral dydrogesterone
   B. Vaginal micronised progesterone
   C. Folic acid and supplements containing docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA)
   D. Reassure

3. A 38-year-old lady who is 14 weeks pregnant presents to your general practice as her obstetrician is away. This is an IVF pregnancy and she has had a previous spontaneous first trimester miscarriage. She was given progesterone until a few weeks ago but has read about the importance of luteal phase support in early pregnancy. She is asymptomatic but understandably worried and requests for medications to help "strengthen her pregnancy". The appropriate management is
   A. Oral dydrogesterone
   B. Vaginal micronised progesterone
   C. 8% intravaginal progesterone gel
   D. Reassure

4. A 28-year-old primigravida who is 20 weeks pregnant with a singleton pregnancy has just had a midtrimester anomaly screening and told that her baby was normal. However, the cervical length measured 21mm. She was otherwise asymptomatic. The appropriate management
   A. Oral dydrogesterone
   B. Vaginal micronised progesterone
   C. Repeat cervical length measurement in 1 week
   D. Reassure

5. A 28-year-old primigravida who is 20 weeks pregnant with a dichornionic diamniotic twin pregnancy has just had a midtrimester anomaly screening and told that her babies were normal. However, the cervical length measured 21mm. She was otherwise asymptomatic. The appropriate management
   A. Oral dydrogesterone
   B. Vaginal micronised progesterone 200mg ON
   C. Vaginal micronised progesterone 400mg ON
   D. Repeat cervical length measurement in 1 week