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SUPPLEMENT ARTICLE

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FIGO Good Practice Recommendations on the use of progesterone in the management of recurrent first-trimester miscarriage

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1 | EXECUTIVE SUMMARY

Recurrent miscarriage, which affects 1% of couples trying to conceive, is defined as the loss of three or more consecutive pregnancies from the time of conception up to 24 completed weeks of gestation.[1] However, for this review the definition is restricted to the first trimester up to 12 completed weeks of gestation. Professional bodies differ in their recommendations regarding the definition of recurrent miscarriage, with some requiring two or more clinical pregnancies with ultrasound or histological confirmation of pregnancy loss, whereas others require three or more losses after a positive pregnancy test with no specification of the need for clinical confirmation.[1,2]

Many factors have been studied as possible causes of recurrent miscarriage, such as anatomical, endocrine, immunological, genetic, and thrombophilia (inherited and acquired) disorders. Endocrine abnormalities include thyroid disorders, polycystic ovarian syndrome, and possibly progesterone deficiencies. Numerous studies have been conducted to assess the use of progesterone in the management of pregnancy loss; however, there is variation in the type and dose of progesterone used and in the methodology of these studies, which has resulted in inconclusive findings.

Progesterone is essential for secretory transformation of the endometrium that permits implantation and maintenance of early pregnancy. Luteal phase insufficiency is one of the reasons for implantation failure and is considered to be responsible for miscarriage.[3] In addition to its well-known role in preparation of the endometrium for implantation, endometrial decidualization, and inhibition of uterine contractility, progesterone also has an immunomodulatory effect by suppression of T-cell activation[4,5] and controlling cytokine production during pregnancy.[6] These characteristics have led to its current widespread use in managing recurrent miscarriage. Therefore, support with progesterone may help to establish a sufficient immune response in early pregnancy and prevent miscarriage.[7]

Progestogens available on the market are classified as either natural or synthetic.[8,9] Synthetic progestogens (progestins) do not correlate with natural progesterone and are artificially manufactured in a laboratory. Natural progesterone suppresses myometrial contractility, unlike the progestin 17-alpha hydroxyprogesterone caproate (17-OHPC) which does not have this effect and at high concentration may stimulate myometrial contractility.[10] No trial has reported long-term follow-up of the use of progesterone for recurrent miscarriage, therefore the safety of progesterone supplementation is still not well known.[11] However, there is no evidence that progesterone causes anatomical or physiological abnormalities in the fetus.

This article highlights agreements based on current research on the use of progesterone in recurrent first-trimester miscarriage and the areas that need more research to provide further evidence to support recommendations. The purpose of this article is to provide a comprehensive summary of available evidence along with practical recommendations concerning the use of progesterone supplementation in women with recurrent first-trimester miscarriage. To achieve these goals, FIGO brought together international experts to review and summarize current knowledge of the subject. These Good Practice Recommendations are directed at multiple stakeholders, including healthcare providers, healthcare delivery organizations and providers, FIGO member societies, and professional organizations. Recognizing the variation in the resources and expertise available for the management of recurrent first-trimester miscarriage in different countries or regions, this article attempts to take into consideration the unique aspects of first-trimester pregnancy care in low-resource settings (labelled "LRS" in the recommendations). This was achieved by collaboration with authors and FIGO member societies from low-resource settings such as India, Sub-Saharan Africa, the Middle East, and Latin America.

2 | TARGET AUDIENCE

This article is directed at multiple stakeholders with the intention of bringing attention to supplementation of progesterone in women with recurrent first-trimester miscarriage. This article proposes to standardize and provide guidance for the use and supplementation of progesterone in women with three or more consecutive first-trimester miscarriages.

The intended target audience includes:

- Healthcare providers: all those qualified to care for pregnant women (obstetricians, maternal-fetal medicine specialists, general practitioners, midwives, nurses, advance practice clinicians, radiologists, and sonographers).
- Healthcare delivery organizations and providers: governments, federal and state legislators, healthcare management organizations, health insurance organizations, international development agencies, and nongovernmental organizations.
- Professional organizations: international, regional, and national professional organizations of obstetricians and gynecologists, obstetric ultrasound, family practitioners, and worldwide national organizations dedicated to the care of women with a history of recurrent first-trimester miscarriage.

3 | ASSESSMENT OF QUALITY OF EVIDENCE AND GRADING OF STRENGTH OF RECOMMENDATIONS

We evaluated the quality of available and eligible evidence using the GRADE criteria. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach is a systematic and transparent approach for rating the certainty of evidence in systematic reviews and clinical practice guidelines.[12] The certainty of evidence can be rated according to five domains: risk of bias, inconsistency, indirectness, imprecision, or publication bias. The process includes an overall rating of the certainty of evidence for each outcome. Evidence

was evaluated and rated by four co-authors (HS, SD, MZ, and AE) and any disagreements were resolved by consensus of all authors.

4 | LITERATURE SEARCH

4.1 | Inclusion and exclusion criteria

Historically, trials assessing the use of progesterone in early pregnancy had small numbers and significant methodological flaws. More recent good-quality studies, despite some variations in the gestational age, duration of treatment, and type of progesterone used, have not enabled health authorities to draw conclusions and make clinical recommendations.

The authors planned a systematic literature search with the following inclusion criteria:

1. Three or more recurrent miscarriages (consecutive and nonconsecutive).
2. Studies reporting on outcome of first-trimester miscarriage.
3. Randomized controlled trials comparing supplementation of progestogens versus placebo or no treatment.
4. Any type of progestogen, dosage, and route of administration.
5. Publications dating back to 1990.
6. Minimum of 50 cases per arm.

Exclusion criteria were as follows:

1. Threatened miscarriage.
2. Studies that included second-trimester miscarriages or preterm births.
3. Withdrawn publications.

4.2 | Results of literature search

Searches identified 1045 Ovid MEDLINE papers, 40 review articles from the Cochrane Library, 32 publications from ClinicalTr

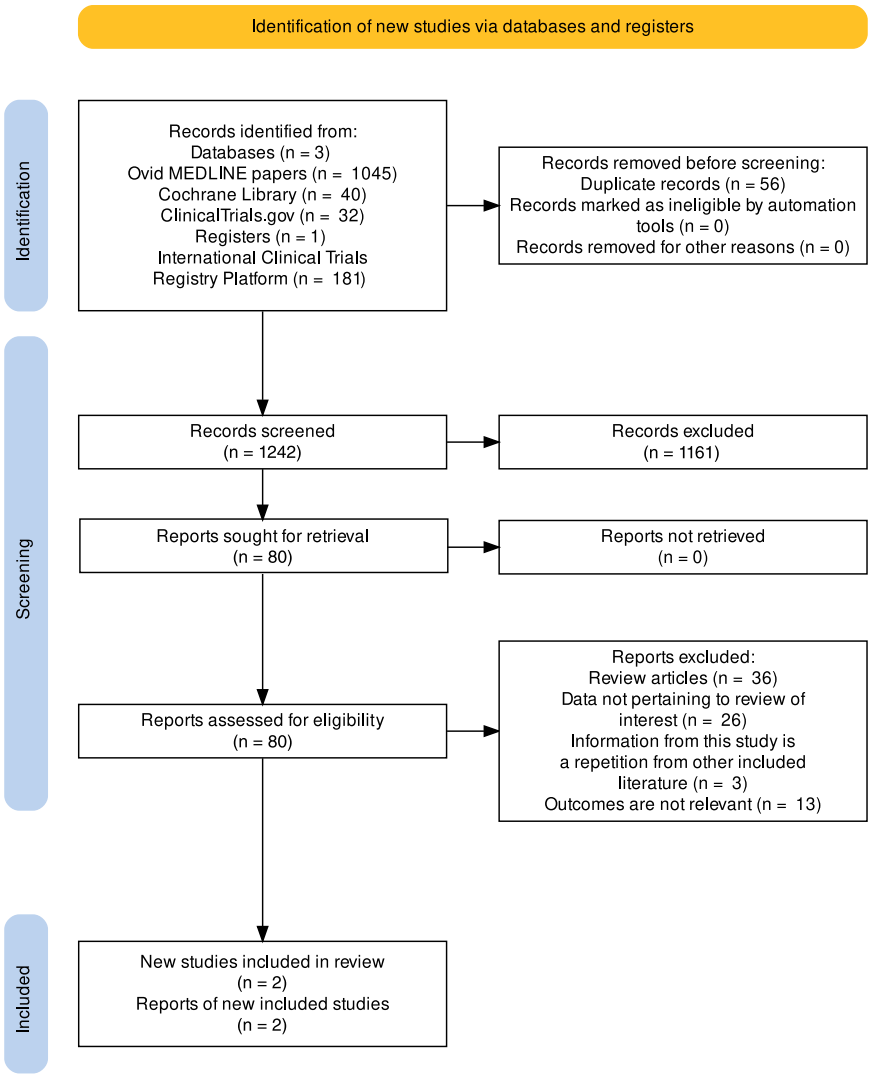

FIGURE 1 Study flow diagram.

ials.gov, and 181 publications from the International Clinical Trials Registry Platform (ICTRP) giving a total of 1298 papers, which were then reviewed. Fifty-six duplicate papers were identified (Figure 1).

After the review process, the following papers qualified for further consideration:

1. A randomized trial of progesterone in women with recurrent miscarriages.[13]
2. Dydrogesterone in the reduction of recurrent spontaneous abortion.[14]

5 | PROGESTERONE SUPPLEMENTATION IN RECURRENT FIRST-TRIMESTER MISCARRIAGE: BACKGROUND, DEFINITION, ETIOLOGY, AND RISKS

5.1 | Background

Recurrent first-trimester miscarriage affects 1% of couples trying to conceive. Professional bodies differ in their recommendations regarding the definition of recurrent miscarriage. Numerous studies have been conducted to assess the use of progesterone in the management of pregnancy loss; however, there is variation in the type and dose of progesterone used and in the methodology of these studies, which has resulted in inconclusive findings.

Progesterone was discovered in the urine of pregnant mares in the 1930s,[15] and over the following decades, natural and synthetic progestogens were introduced into the market in pessary, gel, oral, and injectable preparations.[16] Progesterone is essential for secretory transformation of the endometrium that permits implantation and maintenance of early pregnancy. Luteal phase insufficiency is one of the reasons for implantation failure and is considered to be responsible for miscarriage.[3] In addition to its well-known role in preparation of the endometrium for implantation, endometrial decidualization, and inhibition of uterine contractility, progesterone also has an immunomodulatory effect by suppression of T-cell activation[4,5] and controlling cytokine production during pregnancy.[6] These characteristics have led to its current widespread use in managing recurrent miscarriage. Therefore, support with progesterone may help to establish a sufficient immune response in early pregnancy and prevent miscarriage.[7]

5.2 | Terminology and definitions

Recurrent miscarriage is defined as the loss of three or more consecutive pregnancies from the time of conception up to 24 completed weeks of gestation. However, for this review the definition is restricted to the first trimester up to 12 completed weeks of gestation.

Progesterone is an endogenous steroid and progestogen sex hormone. It belongs to a group of steroid hormones called the progestogens and is the major progestogen in the body. Progesterone is produced by the ovarian corpus luteum during the luteal phase of the menstrual cycle. During pregnancy, progesterone is produced by the corpus luteum and/or the placenta. Progesterone also has antimineralocorticoid and inhibitory neurosteroid activity, whereas it appears to have little or no glucocorticoid or antiandrogenic activity and no androgenic activity.[17] Because of its progestogenic activity, progesterone has functional antiestrogenic effects in certain tissues such as the uterus, cervix, and vagina.[17] In addition, progesterone has antigonadotropic effects due to its progestogenic activity and can inhibit fertility and suppress sex hormone production.[17] Progesterone differs from progestins (synthetic progestogens) such as medroxyprogesterone acetate and norethisterone, with implications for pharmacodynamics and pharmacokinetics as well as efficacy, tolerability, and safety.[17] Route of administration of progesterone can be oral, vaginal, and by injection into muscle or fat, among other routes.[17]

The pharmacokinetics of progesterone is dependent on its route of administration. The medication is approved in the form of oil-filled capsules containing micronized progesterone for oral administration, termed oral micronized progesterone (OMP) or simply oral progesterone.[18] It is also available as vaginal or rectal suppositories, vaginal gels, oil solutions for intramuscular injection, and aqueous solutions for subcutaneous injection, among others.[18,19]

5.2.1 | Consensus-based definition of recurrent first-trimester miscarriage

Recurrent miscarriage, which affects 1% of couples trying to conceive, is defined as the loss of three or more consecutive pregnancies from the time of conception up to 24 completed weeks of gestation.[1] However, for this review the definition is restricted to the first trimester up to 12 completed weeks of gestation.

5.2.2 | Consensus-based definition of progesterone supplementation

There is currently no consensus-based definition of progesterone supplementation.

5.3 | Etiology of recurrent first-trimester miscarriage

Many factors have been studied as possible causes of recurrent miscarriage, such as anatomical, endocrine, immunological, genetic, and thrombophilia (inherited and acquired) disorders. The anatomical causes primarily include major uterine anomalies such as uterine septa; however, it is the authors' view that such causes would mainly contribute to second-trimester losses rather than in the first trimester. Endocrine abnormalities include thyroid disorders, polycystic ovarian

syndrome, and possibly progesterone deficiencies. Immune causes are also thought to contribute to miscarriages, namely natural killer cells, cytokines, thyroid and antinuclear antibodies, lupus, and other immune syndromes. Inherited thrombophilia includes causes such as the presence of factor V Leiden (FVL), prothrombin G20210A mutation (PGM), and antithrombin and protein C and S deficiencies, whereas acquired thrombophilia includes the presence of lupus anticoagulant (LA), anticardiolipin (ACL), and anti-beta 2 glycoprotein antibodies.[20]

5.4 | Possible role of progesterone supplementation

Progestogens available on the market are classified as either natural or synthetic.[8,9] Natural progesterone has chemical structures that are like those produced by the body and is available as a micronized vaginal gel or pessary. Synthetic progestogens (progestins) do not correlate with natural progesterone and are artificially manufactured in a laboratory. Examples of progestins include injectable 17-alpha hydroxyprogesterone caproate (17-OHPC) and oral dydrogesterone. Natural progesterone suppresses myometrial contractility, unlike 17-OHPC which does not have this effect and at high concentration may stimulate myometrial contractility. Although intramuscular progestogens bypass first-pass metabolism in the intestines and liver and achieve very high circulating progesterone levels where the level is maintained for a longer duration compared with vaginally administered progesterone,[21] there is no clear evidence to show improvement in successful pregnancy rate. No trial has reported long-term follow-up of progesterone treatment in recurrent miscarriage; therefore, the long-term safety of progesterone supplementation is still not well known.[11] However, there is no evidence that progesterone causes anatomical or physiological abnormalities in the fetus.

5.5 | Recommendations

A multicenter, double-blind, placebo-controlled, randomized trial of 836 women by Coomarasamy et al.[13] concluded that there was no difference in live births in women with unexplained recurrent miscarriage given vaginal progesterone from positive pregnancy test (65.8%) compared to placebo (63.3%) (RR 1.04; 95% CI, 0.94–1.15).

A recent systematic review and meta-analysis by Saccone et al.[11] which included 10 trials with a total of 1580 women, concluded that the effect of progesterone in reducing pregnancy loss differs by the type of progestogen and that there may be benefit with synthetic progestogens compared to natural progesterone. This meta-analysis is limited because it included old trials that were of low quality and had small numbers; therefore, further direct like-for-like studies need to be conducted to determine the efficacy of progesterone in increasing live births in women with recurrent miscarriage.

Most of the publications reviewed for these Good Practice Recommendations initiated treatment after pregnancy was confirmed; therefore, we cannot address whether progestogens could be more effective if administered during the luteal phase of the cycle, before confirmation of pregnancy. There may also be a role for synthetic progestogens in reducing recurrent pregnancy loss; however, until such evidence is available on the type, timing, and duration of progesterone supplementation, the current recommendations are based on the largest most recent randomized controlled trial available to date.[13]

Conclusion: There is insufficient evidence to recommend the use of progesterone to improve live birth rate in women with recurrent miscarriage.

Recommendation: Commencing natural vaginal progesterone at positive pregnancy test is not recommended in asymptomatic women with a history of unexplained recurrent miscarriage. However, there may be a role for synthetic oral progesterone, but large placebo-controlled trials addressing timing, dosage, and duration are needed.

6 | PROGESTERONE SUPPLEMENTATION IN GENERAL

Progesterone has an important role in maintaining a healthy pregnancy. It is produced by the granulosa lutein cells of the corpus luteum in the latter half of the menstrual cycle and, if a pregnancy is achieved, during the early weeks it continues to be produced from the corpus luteum and from the placenta. Progesterone also has a vital role in preparing the endometrium for implantation of the embryo. If this occurs, the corpus luteum continues to help sustain the pregnancy until about 8–12 weeks of gestation, whereby after this time the placenta takes over the vast proportion of progesterone production and continues this role for the duration of the pregnancy.[22]

The exact role of progesterone in maintaining a pregnancy is not fully understood. However, it has been shown that progesterone deficiency may result in an increase in inflammatory mediators.[23] These include cyclo-oxygenase-2, proinflammatory interleukin 8 (IL-8), and monocyte chemoattractant protein-1, which have been shown to have a role in destabilizing the endometrium.[24] It is therefore thought that regulation of these inflammatory mediators is essential to achieving a successful pregnancy and progesterone in speculated to have a role in this.[25]

The physiological importance of progesterone in the early part of pregnancy has prompted researchers to evaluate the role and effect of progesterone treatment in the first trimester of pregnancy in women with a history of recurrent miscarriage.

Research dating back to 1972 was first to demonstrate the vital role of progesterone in maintaining pregnancy.[26] This study showed that the total removal of luteal tissue before 7 weeks of gestation resulted in a fall in progesterone concentration and subsequent pregnancy loss. Successive studies have shown the association between low serum progesterone concentrations and recurrent miscarriage.[27,28] However, despite strong evidence of an association between low progesterone levels with miscarriage in general, and recurrent miscarriage to be

specific, the few robust studies that have evaluated the use of progesterone treatments to reduce recurrent pregnancy loss have produced widely disparate and variable results. This has made it challenging to formulate a conclusive assessment on its effect on recurrent miscarriage. Furthermore, the variability in the results may also be attributed to the diversity in study parameters, including the use of different progestogens, doses, delivery routes, and protocols.

6.1 | Does progesterone supplementation during pregnancy in general have a beneficial impact on first-trimester recurrent miscarriage?

Numerous studies in the past have investigated the effect of progesterone treatment in patients with recurrent miscarriage, dating as far back as 1953.[29] However, these studies were small, had weak methodological protocols, did not meet the recommended inclusion criteria, or used different types of progestogens. This has led to unreliable results, which has made it difficult for governing bodies and decision makers to provide clear, evidence-based recommendations on the use of progesterone for the treatment of this patient group.

In this review only two studies met the inclusion criteria.[13,14] Of these, the highest quality study was a large multicenter, double-blind, randomized controlled trial of 838 women with unexplained recurrent miscarriage that were treated with vaginal micronized progesterone or placebo.[13] Treatment began from the time of a positive pregnancy result until the end of 12 weeks of gestation. This did not show a significantly higher rate of live births among women with a history of unexplained recurrent miscarriage.

In the other randomized controlled trial that included patients with unexplained recurrent miscarriage, 82 received dydrogesterone (an orally active progestogen that is like endogenous progesterone) and 48 patients had no additional treatment.[14] Treatment began from confirmation of pregnancy and continued until the 12th week of gestation. Results showed that there was a reduction in subsequent miscarriage but live birth outcomes were not reported.[14]

A recent systematic review and meta-analysis by Saccone et al.[11] which included the Coomarasamy et al.[13] publication and nine other trials with a total of 1580 women, concluded that the effect of progesterone in reducing pregnancy loss differs by the type of progestogen and that there may be benefit with synthetic progestogens compared to natural progesterone. This meta-analysis is limited because it included old trials that were of low quality and had small numbers; therefore, further direct like-for-like studies need to be conducted to determine the efficacy of progesterone in increasing live births in women with recurrent miscarriage.

In a recent Cochrane review published in 2018, 13 trials (2556 women) met the inclusion criteria.[29] Nine of the trials compared treatment with placebo while the remaining four trials compared progestogen administration with no treatment. The trials were a mix of multicenter and single-center trials. In six trials women had had three or more consecutive miscarriages and in seven trials women had suffered two or more consecutive miscarriages. Routes, dosage, and duration of progestogen treatment varied across the trials, with most trials at low risk of bias for most domains. The meta-analysis of all women suggests that there is probably a reduction in the number of miscarriages for women given progestogen supplementation compared to placebo/controls (average risk ratio 0.69; 95% CI, 0.51–0.92, 11 trials, 2359 women, moderate-quality evidence). A subgroup analysis comparing placebo-controlled versus nonplacebo-controlled trials and different routes of administration showed no differences between subgroups for miscarriage. On the other hand, there appears to be a subgroup difference for miscarriage between women with three or more prior miscarriages compared with women with two or more miscarriages, with a more pronounced effect in women with three or more prior miscarriages. However, it should be noted that there was high heterogeneity in the subgroup of women with three or more prior miscarriages, making it difficult to conclude any statistical significance to recommend routine supplementation of progesterone.

Another cohort study by Hussain et al.[30] investigated 206 women with recurrent miscarriage found to have subnormal early pregnancy progesterone secretion defined by measuring serum progesterone on the day of positive pregnancy test and 48 hours later. The patients were treated with natural progesterone vaginal pessaries. There was no control group and data were compared with similar historical data. No statistically significant reduction in subsequent miscarriage rates in women with three previous miscarriages was found, while for women with four previous miscarriages the results suggested a possible statistically significant reduction in the subsequent miscarriage rate. There were numerous concerns regarding the results of this study including the lack of a clear control group and the results not showing a comparison between live birth rates between the two groups, making it difficult to extrapolate any beneficial conclusions. Furthermore, the study only included a selected group of patients based on their progesterone levels and therefore cannot be generalized to the overall recurrent miscarriage patient group.[30]

Following a comprehensive review of the literature, only two studies met the inclusion criteria set by the expert panel.[13,14] Collectively, these studies do not show whether progesterone can reduce the risk of miscarriage and increase the rate of live births. There may be a role for oral progesterone treatment, however its use is not recommended at present until more robust placebo-controlled trials are conducted.

6.2 | Is there evidence of any fetal abnormalities with progesterone supplementation in pregnancy (oral/injectable/vaginal/rectal and type)?

Evaluation of the long-term effects of progesterone treatment during pregnancy, especially during the first trimester, is

extremely difficult primarily due to confounding factors and loss to follow-up. To date, no studies have reported any long-term outcomes according to progesterone or progestogens given in the first trimester.[31] Of the studies included in the present review, Coomarasamy et al.[13] showed no statistical difference in congenital anomalies between the progesterone group and the placebo group. Furthermore, to date, no evidence supports or suggests that dydrogesterone, used in the study included in this review (El-Zibdeh[14]), is associated with a risk of fetal congenital anomalies.[31]

6.3 | Is there evidence of safety of progesterone supplementation in pregnancy (oral/injectable/vaginal/rectal and type)?

To the best of our knowledge, no publications have specifically studied the effect of progesterone on safety in patients with recurrent miscarriage; however, evidence of its safety in other areas including reproductive medicine, reproductive endocrinology, and infertility is well documented where progesterone is considered innocuous. This is based on a wealth of experience and its use in a large number of patients over the years.[31]

6.4 | Does a particular progesterone dose have a beneficial impact on first-trimester recurrent miscarriage?

After reviewing all the identified papers and particularly the two publications included in this review, there was no clear evidence of benefit of a particular dose in any of the routes administered to patients with recurrent miscarriage. The individual routes of administration are discussed in the sections that follow.

6.5 | Does a particular progesterone type have a beneficial impact on first-trimester recurrent miscarriage?

Micronized progesterone administered via the vaginal route was used in the study by Coomarasamy et al.[13] although the results did not show that this treatment had a beneficial impact on women with recurrent miscarriage.

In the other study included in the present review, oral dydrogesterone was given. This active progestogen is considered similar to endogenously produced progesterone in its molecular structure and also has a high affinity for progesterone receptors.[14] Dydrogesterone may have a beneficial effect on women with recurrent miscarriage to improve pregnancy outcome; however, to date, no properly designed randomized studies have addressed this. Robust well-designed trials are required to help make a clear recommendation.

6.6 | Does a particular progesterone supplementation route have a beneficial impact on first-trimester recurrent miscarriage?

After reviewing all the identified papers and particularly the three included in this review, there was no clear evidence of benefit of a particular route administered to patients with recurrent miscarriage.

Recommendation	Quality of evidence	Strength of recommendation
6.1. Progesterone supplementation during pregnancy in general is not recommended as no beneficial impact on first-trimester recurrent miscarriage has been shown	⊕⊕⊕⊕	**Strong**
6.2. As there is no clear evidence of any fetal abnormalities with progesterone supplementation in pregnancy (oral/injectable/vaginal/rectal and type), prescribing it on an empirical basis or as part of research trials is not contraindicated	⊕⊕	**Weak**
6.3. As there is no clear evidence of safety concerns regarding progesterone supplementation in pregnancy (oral/injectable/vaginal/rectal and type), prescribing it on an empirical basis or as part of research trials is not contraindicated	⊕⊕	**Weak**
6.4. As there is no clear evidence that a particular progesterone dose has a beneficial impact on first-trimester recurrent miscarriage, prescribing any dose of progesterone on an empirical basis or as part of research trials is not contraindicated	⊕⊕	**Weak**
6.5. As there is no clear evidence that a particular progesterone type has a beneficial impact on first-trimester recurrent miscarriage, prescribing any type of progesterone on an empirical basis or as part of research trials is not contraindicated	⊕⊕	**Weak**
6.6. As there is no clear evidence that a particular progesterone supplementation route has a beneficial impact on first-trimester recurrent miscarriage, prescribing progesterone through any route on an empirical basis or as part of research trials is not contraindicated. It is the authors' view that injectable progesterone may not be considered in LRS due to cost and storage requirements	⊕⊕	**Weak**

Only two studies met the inclusion criteria for this review. Vaginal progesterone was used in one study and this did not show any beneficial effect on patients with recurrent miscarriage.[13] The other study used oral progesterone.[14] This supports a role for oral progesterone treatment in women with recurrent miscarriage. However, after thorough review of this study, it cannot be conclusively recommended at present until more robust placebo-controlled trials are conducted.

7 | ORAL PROGESTERONE SUPPLEMENTATION

Progesterone supplementation given via the vaginal, rectal, and parenteral routes of administration provides higher bioavailability; however, the oral route is likely to be more acceptable as it is noninvasive and it is easier to administer progesterone via this route.[32] Of the two studies included in this review, only one involved the supplementation of progesterone via the oral route in women with recurrent pregnancy loss.[14] This study will be looked at in more detail in subsequent sections.

7.1 | Does oral progesterone supplementation during pregnancy have a beneficial impact on first-trimester recurrent miscarriage?

In 2005, El-Zibdeh conducted a three-arm randomized controlled trial involving 180 women. The two treatment arms received either 10 mg oral dydrogesterone twice daily or 5000 IU intramuscular human chorionic gonadotropin every four days from when the pregnancy was confirmed to the 12th week of gestation.[14] The control group received no additional treatment. The miscarriage rate was significantly lower in the dydrogesterone group compared to the control group (13.4% vs 29%; $P \leq 0.05\%$). This difference was not seen when both treatment arms were compared. The methodology in this study had certain irregularities, including a flawed randomization process and the lack of allocation concealment—factors that increase the likelihood of bias.

Of the two studies included in this review, only one involved oral dydrogesterone for the prevention of recurrent pregnancy loss. This highlights the need for more robust studies with sound methodologies to ascertain if there is a beneficial effect of oral progesterone supplementation on recurrent first-trimester miscarriage.

7.2 | Does preconception oral progesterone supplementation have a beneficial impact on first-trimester recurrent miscarriage?

After a comprehensive review of the literature, we could not identify evidence relating to preconceptual progesterone supplementation for prevention of first-trimester recurrent pregnancy loss. It is the authors' view that giving preconceptual oral progesterone may show benefits compared to only starting supplementation at positive pregnancy test.

7.3 | Is there evidence of any fetal abnormalities with oral progesterone supplementation in pregnancy?

Dydrogesterone is a retroprogesterone and its selectivity for the progesterone receptor is very high. It is not known to induce androgenic changes in the fetus and does not affect placental progesterone production.[32–34] In the study by El-Zibdeh,[14] of the women in the dydrogesterone arm whose pregnancies progressed to viability, two (2.8%) fetuses had congenital malformations: one case of nonimmune hydrops and one case of neural tube defect. This was not significant when compared to 2.9% in the control arm.

Recommendation	Quality of evidence	Strength of recommendation
7.1. Oral progesterone supplementation during pregnancy can be considered as there seems to be some beneficial impact on first-trimester recurrent miscarriage	⊕⊕⊕	Weak
7.2. Preconception oral progesterone supplementation is not recommended in the management of first-trimester recurrent miscarriage as there are no evidence-based published studies	⊕⊕⊕⊕	Strong
7.3. As there is no clear evidence of safety concerns or fetal abnormalities regarding use of oral progesterone supplementation in pregnancy, prescribing it on an empirical basis or as part of research trials is not contraindicated	⊕⊕	Weak
7.4. Prescribing a daily dose of 20 mg oral progesterone would appear to be optimal, however the limitations of published trials and the paucity of studies in this regard should be taken into consideration	⊕⊕	Weak

7.4 | Is there an optimum dose that has a beneficial impact on first-trimester recurrent miscarriage, and if yes, what is this dose?

As previously stated, only one randomized controlled trial was identified from the available literature in which oral progesterone supplementation in the first trimester was in the form of dydrogesterone.[14] This study employed a daily dose of 20 mg oral dydrogesterone, which was given as a twice daily dose regime of 10 mg per dose.[14] Therefore, a daily dose of 20 mg would appear to be optimal; however, the limitations of this study and the paucity of studies in this regard should be taken into consideration.

8 | VAGINAL PROGESTERONE SUPPLEMENTATION

NICE recommends offering women 400 mg vaginal micronized progesterone twice daily if they have vaginal bleeding (threatened miscarriage) from an intrauterine pregnancy confirmed by a scan and a history of a previous miscarriage.[35] However, it is important to note that the purpose of these Good Practice Recommendations is to address recurrent miscarriage. The vaginal route was chosen in a trial with the rationale to deliver a greater proportion of the drug to the biologically relevant site (i.e. the uterus). Vaginal administration appears to allow a preferential distribution of progesterone to the uterus, which confirms the existence of the so-called 'first uterine pass effect.[36]

8.1 | Does vaginal progesterone supplementation during pregnancy have a beneficial impact on first-trimester recurrent miscarriage?

The large multicenter, double-blind, randomized trial by Coomarasamy et al.[13] included 836 women with unexplained recurrent miscarriage who were treated with vaginal micronized progesterone or placebo. The treatment was started from the time of a positive pregnancy result until the end of 12 weeks of gestation and showed no difference in live births in women with unexplained recurrent miscarriage given vaginal progesterone. 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 (relative rate 1.04; 95% CI, 0.94–1.15; rate difference 2.5 percentage points; 95% CI, −4.0 to 9.0). There were no significant between-group differences in the rate of adverse events. These results were not in agreement with previous findings of a Cochrane analysis, which suggested a benefit of progesterone therapy in the first trimester of pregnancy.[37] However, that review was based on the results of small studies with methodological limitations. The authors of the trial admitted that the results were based on a dose of 400 mg twice daily, and it is possible that the results with this regimen are not generalizable and may not be confirmed with different doses and preparations.

The cohort study by Hussain et al.[30] which is not included in the present review, showed evidence from 206 women with recurrent miscarriage found to have subnormal early pregnancy progesterone secretion defined by measuring serum progesterone on the day of positive pregnancy test and 48 hours later. The patients were treated with natural progesterone vaginal pessaries. There was no control group included in the study and data were compared with similar historical data. The study showed no statistically significant reduction in subsequent miscarriage rates in women with three previous miscarriages, while for women with four previous miscarriages the results suggested a possible statistically significant reduction in the subsequent miscarriage rate. Concerns regarding the results of this publication are detailed in section 6.1.

8.2 | Does preconception vaginal progesterone supplementation have a beneficial impact on first-trimester recurrent miscarriage?

No study has investigated preconception vaginal supplementation of progesterone. However, a retracted paper by Ismail et al.[38] reported a randomized controlled trial that was conducted to evaluate the effect of periconceptional progesterone, starting early in the luteal phase before confirmation of pregnancy, in preventing miscarriage in women with a history of unexplained recurrent miscarriage. No conclusion could be deduced as the paper was retracted.

8.3 | Is there evidence of any fetal abnormalities with vaginal progesterone supplementation in pregnancy?

Of the studies included in the present review, Coomarasamy et al.[13] showed no statistical difference in congenital anomalies between the progesterone group and the placebo group.

8.4 | Is there an optimum dose that has a beneficial impact on first-trimester recurrent miscarriage, and if yes, what is this dose?

Progestogens available on the market are classified as either natural or synthetic. Natural progesterone has chemical structures that are like those produced by the body and is available as a micronized vaginal gel or pessary. Current literature shows no clear evidence of benefit of a particular dose in any of the routes administered to patients with recurrent miscarriage. In the Coomarasamy et al.[13] trial, participants were randomly assigned in a 1:1 ratio to receive vaginal suppositories containing either 400 mg micronized progesterone (Utrogestan, Besins Healthcare,

Recommendation	Quality of evidence	Strength of recommendation
8.1. Vaginal progesterone supplementation during pregnancy is not recommended as there is no beneficial impact on first-trimester recurrent miscarriage	⊕⊕⊕⊕	Strong
8.2. Preconception vaginal progesterone supplementation is not recommended in the management of first-trimester recurrent miscarriage as there are no evidence-based published studies	⊕⊕⊕⊕	Strong
8.3. As there is no clear evidence of safety concerns or fetal abnormalities regarding the use of vaginal progesterone supplementation in pregnancy, prescribing it on an empirical basis or as part of research trials is not contraindicated	⊕⊕	Weak
8.4. If prescribing vaginal progesterone on an empirical basis or as part of research trials, a daily dose of 400–800 mg would appear to be optimal, however the limitations of published trials and the paucity of studies in this regard should be taken into consideration	⊕⊕	Weak

Chatswood, Australia) twice daily or matched placebo from soon after receiving positive results on a urinary pregnancy test. This study did not show a beneficial impact of the treatment on women with recurrent miscarriage. The dose used (400 mg twice daily) represents a dose at the top end of the therapeutic window. NICE also recommends 400 mg twice daily in patients with threatened miscarriage,[35] but it is the authors' view that there is currently insufficient evidence to recommend the use of vaginal progesterone for recurrent miscarriage.

9 | RECTAL PROGESTERONE SUPPLEMENTATION

Although progesterone can be administered via oral, vaginal, rectal, and intramuscular routes,[39,40] administration of progesterone via the rectal route for the prevention of recurrent first-trimester miscarriage was not identified in the available literature. This notwithstanding, some studies have investigated rectal administration of progesterone for the management or prevention of pregnancy-related complications, including two randomized controlled trials on the prevention of preterm birth using rectally administered progesterone in pregnancy,[39,41] and two randomized controlled trials where rectal progesterone was used as luteal phase support following intracytoplasmic sperm injection and in vitro fertilization.[42,43] Constipation and increased flatulence in addition to tenesmus and rectal itching were associated with the rectal route.[42,43]

9.1 | Does rectal progesterone supplementation during pregnancy have a beneficial impact on first-trimester recurrent miscarriage?

No study was identified in the literature in which rectal progesterone was investigated for prevention of first-trimester recurrent miscarriage.

9.2 | Does preconception rectal progesterone supplementation have a beneficial impact on first-trimester recurrent miscarriage?

From the available literature, there was no evidence of use of rectal progesterone in the preconception period to prevent recurrent first-trimester miscarriage.

9.3 | Is there evidence of any fetal abnormalities with rectal progesterone supplementation in pregnancy?

Although there was no evidence available on the use of rectal progesterone for recurrent first-trimester miscarriage, where it was used as luteal phase support and in investigation of prevention of preterm birth, the occurrence of fetal abnormalities was not documented.[39,41–43]

Recommendation	Quality of evidence	Strength of recommendation
9.1. Rectal progesterone supplementation during pregnancy is not recommended as there is no beneficial impact on first-trimester recurrent miscarriage	⊕⊕⊕⊕	Strong
9.2. Preconception rectal progesterone supplementation is not recommended in the management of first-trimester recurrent miscarriage as there are no evidence-based published studies	⊕⊕⊕⊕	Strong
9.3. As there is no clear evidence of safety concerns or fetal abnormalities regarding the use of rectal progesterone supplementation in pregnancy, prescribing it on an empirical basis or as part of research trials is not contraindicated	⊕⊕	Weak
9.4. As there are no published data on the optimal dose for rectal progesterone supplementation, no dose is recommended when prescribing on an empirical basis or as part of research trials	⊕⊕	Weak

9.4 | Is there an optimum dose that has a beneficial impact on first-trimester recurrent miscarriage, and if yes, what is this dose?

No studies were found from the available literature in this regard.

10 | INJECTABLE PROGESTERONE SUPPLEMENTATION

The bioavailability of progesterone after administration is dependent on the route used for administration. The highest variability in serum concentration is seen with the oral route due mainly to first-pass metabolism in the liver. Vaginal and rectal routes are associated with less variation in serum concentration; however, this is dependent on proper insertion and local factors. With parenteral administration (intramuscular 17-OHPC), there is rapid buildup of serum concentration and increased bioavailability.[40] It is the authors' view that injectable progesterone may not be considered in LRS due to cost and storage requirements.

Regarding prevention of recurrent first-trimester miscarriage, no studies were identified from the available literature that utilized intramuscular progesterone. Studies where intramuscular progesterone was used in cases of threatened miscarriage (when compared to placebo, Nifedipine, or vaginal progesterone) did not show improved pregnancy outcomes with the intramuscular progesterone group.[44–46] A systematic review and meta-analysis by Saccone et al.[47] revealed a significant reduction in spontaneous preterm delivery occurring at less than 34 weeks of gestation in women who received vaginal progesterone compared to those who were administered intramuscular progesterone.

10.1 | Does injectable progesterone supplementation during pregnancy have a beneficial impact on first-trimester recurrent miscarriage?

No study from the available literature utilized this route of administration for prevention of recurrent first-trimester miscarriage.

10.2 | Does preconception injectable progesterone supplementation have a beneficial impact on first-trimester recurrent miscarriage?

No study from the available literature where intramuscular progesterone was used for this purpose was identified.

10.3 | Is there evidence of any fetal abnormalities with injectable progesterone supplementation in pregnancy?

Although there were no studies from the available literature using intramuscular progesterone for prevention of recurrent first-trimester miscarriage, where it was used in threatened miscarriage and prevention of preterm birth, there was no documented increase in the frequency of fetal abnormalities.[44–46,48]

10.4 | Is there an optimum dose that has a beneficial impact on first-trimester recurrent miscarriage, and if yes, what is this dose?

No evidence was found to support this from the literature available for review.

11 | SUMMARY

Progesterone appears to be essential for maintaining a healthy pregnancy by either preparing the endometrium for implantation of the embryo or its role in modulation of the immune system. However, its exact role in maintaining a pregnancy is not fully understood. Evidence on the use of progesterone suggests no noticeable difference in live birth rates compared to placebo. There seems to be emerging positive indication for the use of synthetic oral progesterone. So far, most trials on treatment of recurrent miscarriage with progesterone have used similar study protocols in terms of route and timing of administration. A different type of

Recommendation	Quality of evidence	Strength of recommendation
10.1. Injectable progesterone supplementation during pregnancy is not recommended as there is no beneficial impact on first-trimester recurrent miscarriage. It is the authors' view that injectable progesterone may not be considered in LRS due to cost and storage requirements	⊕⊕⊕⊕	**Strong**
10.2. Preconception injectable progesterone supplementation is not recommended in the management of first-trimester recurrent miscarriage as there are no evidence-based published studies	⊕⊕⊕⊕	**Strong**
10.3. As there is no clear evidence of safety concerns or fetal abnormalities regarding the use of injectable progesterone supplementation in pregnancy, prescribing it on an empirical basis or as part of research trials is not contraindicated	⊕⊕	**Weak**
10.4. As there are no published data on the optimal dose for injectable progesterone supplementation, no dose is recommended when prescribing on an empirical basis or as part of research trials	⊕⊕	**Weak**

progesterone (e.g. oral) as well as timing of administration (e.g. to start in the luteal phase) could prove more effective.

12 | FUTURE RESEARCH DIRECTIONS

- Large adequately powered randomized controlled trials with representative subgroups covering wider demographics to better capture populations with linked causal factors and including, among other parameters, the number of previous miscarriages, may provide more concrete findings on efficacy and safety.
- Comparisons of the different types of progestogens are essential in a future research agenda given the current paucity of such trials. There is a need for evidence on direct comparisons among different progestogens, such as dydrogesterone or 17-hydroxyprogesterone, the different routes of administration, such as oral, and the onset, timing, and duration of administration.
- A core outcome measure set would aid future clinical effectiveness and reporting, resulting in high-quality meta-analyses and evidence synthesis.
- Further research is required on the role of progesterone on endometrial defects which appear as part of causation of higher-order miscarriages. Additionally, studies on disease modelling may aid the development of diagnostic approaches, including screening for luteal phase defects. Development of endometrial tests may identify women who may benefit from progesterone treatment. Development and validation of tests, and therapeutic trials to determine the efficacy of luteal phase progesterone and other potential interventions, are needed.
- Robust, well-designed, placebo-controlled, luteal phase (preconception) progesterone supplementation trials in general and in low-resource settings.

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