Progesterone in Pregnancy: Evidence-Based Strategies to Reduce Miscarriage and Enhance Assisted Reproductive Technology

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The incidence of miscarriage in early pregnancy, between 5-20 weeks, is common, with a prevalence of between 5-22% of all pregnancies. Miscarriage can have physical, social, and mental health impacts on women and their families. In societies such as Taiwan, where the birth rate is falling and life expectancy is increasing, there is concern that factors that reduce birth rates will have detrimental economic and societal effects. Progesterone has a significant role in maintaining early and successful pregnancy to term. Evidence from preclinical and clinical research on the roles of progesterone has supported recent clinical guidelines in obstetrics and gynecology to reduce rates of early miscarriage and improve methods of assisted reproductive technology (ART). This article aims to present an evidence-based review of current recommendations for the use of progesterone in early pregnancy to reduce miscarriage rates and in luteal phase support for ART, including embryo transfer.

Keywords: **Abortion, Spontaneous • Early Pregnancy Factor • Practice Guideline Progesterone • Reproductive Techniques, Assisted • Review**

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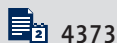
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Background

Evidence from preclinical and clinical research on the roles of progesterone has supported recent clinical guidelines in obstetrics and gynecology to reduce rates of early miscarriage and improve methods of assisted reproductive technology (ART) [1-4].

The basis for understanding the roles of progesterone in the maintenance of pregnancy and modern ART began more than half a century ago. In 1972, Csapo and colleagues discovered that removing the corpus luteum before adequate placental development induced spontaneous miscarriage [5]. This early study showed that progesterone, secreted by the corpus luteum, is crucial for maintaining pregnancy before placental progesterone release [5]. The monthly duration of the corpus luteum is relatively stable at 12-14 days, with 11-17 days being acceptable [6-8]. Progesterone is released in pulses under the effect of luteinizing hormone (LH), but release from the corpus luteum is determined by the increase in levels of human chorionic gonadotropin (hCG) levels following implantation [9]. Failure of the hCG levels to increase sufficiently results directly in corpus luteum failure and a decline in progesterone levels [9]. The release of progesterone in pulses causes its level to fluctuate between 5 ng/mL to 40 ng/mL within a short period, making it difficult to identify progesterone deficiency by taking a single measurement [10,11]. Therefore, the dynamic changes in progesterone levels have recently been recognized as important factors in female fertility [11].

The incidence of miscarriage in early pregnancy, at 5-20 weeks, is common, with a prevalence of 5-22% of all pregnancies [12]. Miscarriage can have physical, social, and mental health impacts on women and their families [13]. In societies such as Taiwan, where the birth rate is falling and life expectancy is increasing, there is concern that factors that reduce birth rates will have detrimental economic and societal effects [14]. There has been growing interest in the role of progesterone in early pregnancy, maintaining successful pregnancy to term, and in ART. Recent preclinical and clinical research has resulted in the development of new clinical guidelines for obstetricians and gynecologists who aim to reduce the rates of miscarriage and improve success rates for ART. This article aims to present an evidence-based review of current recommendations for the use of progesterone in early pregnancy to reduce miscarriage rates and in luteal-phase support for ART, including embryo transfer.

Progesterone and the Maintenance of Pregnancy

During the past 50 years, since the early studies on the role of progesterone in the maintenance of pregnancy, there has

been a surprising lack of real-world clinical data from controlled clinical trials. However, in 2015, a systematic review and meta-analysis of 5 randomized controlled trials (RCTs) showed that early clinical luteal-phase support with progesterone increased the maintenance of pregnancy and the rates of live birth (OR=1.77; 95% CI 1.09-2.86; n=642) [15].

Progesterone also plays an important immunological role in pregnancy. Progesterone upregulates the expression of the Th2-type cytokine and inhibits the production of embryotoxic Th1-type and Th17-type cytokines [16]. However, the Th17-type cytokine also benefits the differentiation of Th17/Th1 or Th17/Th2 cells [17,18]. The Th17/Th2 cell supports embryonic implantation and pregnancy, and the differentiation of Th17 cells into Th17/Th2 cells is also regulated by progesterone [17,18]. In women with unexplained recurrent spontaneous miscarriage, progesterone suppresses the production of Th1-type cytokines and stimulates the production of Th2-type cytokines, supporting a role for progesterone in fetal survival in utero [16].

Routes of Administration of Progesterone

The methods for administration of progesterone have become a recent topic of interest. Oral progesterone agents, vaginal suppositories, and intramuscular or subcutaneous progesterone injections are the most commonly used forms in Taiwan. The most common treatment adverse effects include fatigue, body fluid retention, blood lipid profile changes, irritability, hypercoagulation states, and, most notably, increased androgenic adverse effects [19]. Due to its low bioavailability, oral natural progesterone may be associated with drowsiness and hepatotoxicity when given in high doses [20]. Also, intramuscular progesterone injection can be associated with injection site reactions, including soreness, swelling, itching, and bruising [21]. However, oral dydrogesterone for luteal-phase support is associated with fewer adverse effects and is highly selective for the progesterone receptor but free from the adverse effects associated with estrogen, androgen, and adrenocortical hormones [22].

In 2022, a study by Shaikh and colleagues reported that administering either oral micronized progesterone at 200 mg twice a day for 2 weeks or dydrogesterone at a dose of 10 mg twice a day for 2 weeks had comparable effectiveness in preventing miscarriage [23]. However, women in the micronized progesterone-treated group experienced significantly more adverse effects of drowsiness and giddiness than those in the dydrogesterone-treated group [23]. However, nausea and abdominal bloating were similar adverse effects in both studied groups [23].

In 2022, a systematic review and meta-analysis by Katalinic and colleagues evaluated published safety data on dydrogesterone

to support early pregnancy [24]. The pooled risk ratio analysis findings showed that reported adverse effects for maternal dydrogesterone use and fetal abnormalities showed no significant association (RR=0.96; 95% CI 0.57-1.62) [24].

Progesterone and the Prevention of Threatened Miscarriage

Threatened miscarriage is diagnosed by bloody vaginal discharge or bleeding through the closed cervical opening in the first 20 weeks of pregnancy [25]. Bleeding during early pregnancy can persist for days to weeks and may be associated with suprapubic discomfort, mild abdominal spasms, or pelvic pain [26]. However, bleeding is the main predictive factor for pregnancy loss [26]. Meta-analysis data from published studies up to 2021 shows that 10.3-11.4% of women had experienced 1 pregnancy loss [26]. Even if a threatened miscarriage does not result in a pregnancy loss, the risk of preterm birth remains high [26]. Also, the volume of blood loss is associated with the risk of miscarriage or premature delivery in late pregnancy [27]. When compared with women without bleeding during pregnancy, those with early bleeding in the first pregnancy also had a higher rate of bleeding during their second pregnancy [28].

Meta-analysis data published in 2013 included studies on the use of progesterone to manage the risks of preterm birth, including preterm birth in the previous pregnancy, short cervical length, multiple pregnancies, and premature delivery [29]. The meta-analysis data showed that progesterone reduced the risks of preterm birth when given intramuscularly, orally, or as a vaginal suppository [29]. In 2017, a systematic review and meta-analysis compared different routes of progesterone administration, including oral dydrogesterone, vaginal micronized progesterone, and control treatments [30]. The rate of miscarriage in the oral dydrogesterone-treated group was significantly lower than the control group (11.7% versus 22.6%; OR=0.43; 95% CI 0.26-0.71; P=0.001) [30]. However, in the vaginal administration studies, micronized progesterone 200 mg twice daily and gel 90 mg daily were provided, and the results showed that there was no significant difference between the vaginal administration group and the control group (15.4% versus 20.3%) (OR=0.72; 95% CI 0.39-1.34; P=0.30) [30].

In 2018, analysis of meta-analysis data identified effective results when the progesterone regimen for a threatened miscarriage began from the confirmation of diagnosis and ended at 1-2 weeks after the complete resolution of clinical symptoms [25]. In 2020, a meta-analysis of published studies showed that progesterone increased the live birth rate and reduced the miscarriage rate for women who experienced threatened miscarriage but were limited to the use of oral dydrogesterone

10 mg twice daily or 40 mg ST plus 10 mg twice daily, while the benefits of vaginal progesterone lacked statistical significance [31]. Meta-analysis data published in 2021 by Zhao and colleagues included 59 randomized clinical trials and compared the effects of progesterone administered through different routes in women with threatened miscarriage [32]. Oral dydrogesterone significantly reduced miscarriage rates when compared with placebo (OR=0.42; 95% CI 0.29-0.61; P<0.001) or when compared with the use of vaginal micronized progesterone (OR=0.50; 95% CI 0.34-0.74; P=0.002) [32].

In 2021, Chan and colleagues recruited 406 women in early normal pregnancy, excluding those with recurrent miscarriages and genetic issues in both partners, and conducted a double-blind RCT [33], in which participants were randomly assigned to receive either oral dydrogesterone or a placebo [33]. There were no statistically significant differences between the 2 groups, although this study did not exclude genetic abnormalities in the fetal tissue of the miscarriages [33].

In 2021, Devall and colleagues reported the findings from a meta-analysis of studies of women with threatened and recurrent miscarriages, which concluded that the effectiveness of vaginal micronized progesterone compared with control treatment significantly reduced miscarriage, while intramuscular and oral treatments did not [34]. A recent study by Yatam and colleagues investigated the effectiveness of oral dydrogesterone (10 mg twice daily) versus oral micronized progesterone (200 mg twice daily) in managing threatened miscarriage during the first 12 weeks of pregnancy [35]. Dydrogesterone was more effective than micronized progesterone in reducing pain in the lower abdomen and reducing vaginal bleeding [35]. However, there were no significant differences between the 2 groups regarding spontaneous abortion, preterm delivery, and full-term delivery [35].

Also, in 2022, Nagarkatti and colleagues reported the findings from a real-world study that collected data from 194 obstetricians and gynecologists in India on the use of oral dydrogesterone in 617 eligible patients [36]. The median time for reduction of symptoms from the start of oral dydrogesterone treatment was 3.32 days for the reduction of low back pain, 4.37 days for the cessation of bleeding, and 3.9 days for the reduction of abdominal pain [36]. Miscarriage was reported in 7.29% of patients, which supports that dydrogesterone is not only effective but also safe when used to reduce the incidence of pregnancy loss in women with threatened miscarriages [36].

The method of vaginal pessary administration for threatened abortion has been evaluated in the STOP trial, which found that a nightly 400 mg vaginal progesterone pessary, used from the onset of bleeding until 12 weeks of gestation, did not increase live birth rates in women with threatened miscarriage [37].

Progesterone and Prevention of Recurrent Miscarriage

In 2021, Quenby and colleagues reported that 1.8-2.1% of women experienced 2 miscarriages and 0.5-0.8% experienced 3 or more miscarriages [26]. The American Society of Reproductive Medicine (ASRM), the National Center for Health Statistics, the US Centers for Disease Control and Prevention (CDC), and the World Health Organization (WHO) have defined miscarriage as the expulsion or extraction of a fetus or embryo weighing <500 g, which is equivalent to <20 weeks gestation [38]. Recurrent pregnancy loss (RPL) is defined as 3 or more consecutive miscarriages [38].

Several small clinical trials have reported inconsistent findings for the use of progesterone in the prevention of recurrent miscarriage. Findings from the randomized, double-blind PROMISE trial that included 836 women showed that progesterone administered vaginally at 12 weeks of pregnancy increased the live birth rate by 3% [39], but the findings were not statistically significant (65.8% versus 63.3%; RR=1.04; 95% CI 0.94-1.15) [39]. Meta-analysis data published by Haas and colleagues in 2018 from published studies on recurrent miscarriages showed that progesterone replacement reduced the rate of idiopathic recurrent miscarriages [40]. However, because the route of administration, dose, and duration of treatment differed, the findings did not reach statistical significance [40].

In 2019, Coomarasamy and colleagues published the findings from the PRISM multicenter, randomized, double-blind, placebo-controlled trial that evaluated progesterone compared with placebo in 4153 women from 48 hospitals in the United Kingdom who presented with vaginal bleeding during early pregnancy [41]. In that study, women were randomly assigned to receive either vaginal suppositories containing 400 mg of progesterone or a placebo twice daily at up to 16 weeks of gestation [41]. The primary outcome was the birth of a live baby after at least 34 weeks of pregnancy [41]. However, progesterone therapy administered during the first trimester did not significantly increase the incidence of live births (75% versus 73%; RR=1.03; 95% CI 1.00-1.07; P=0.08) [41]. A subgroup analysis of women with a history of 1 pregnancy loss plus 2 risk factors for bleeding during an ongoing pregnancy showed that patients who received progesterone had a significantly improved live birth rate when compared with those who received the placebo (75% versus 70%; RR=1.09; 95% CI 1.03-1.15; P=0.003) [41]. This benefit was more significant in the subgroup of women with 3 or more pregnancy losses plus experience of bleeding during an ongoing pregnancy (72% versus 57%; RR=1.28; 95% CI 1.08-1.51; P=0.004) [41].

The findings from the PROMISE trial [39], and the PRISM trial [41], have supported the development of clinical recommendations for the use of progesterone in women with recurrent miscarriage [4]. The 2020 recommendations support the use of vaginal administration of 400 mg of micronized progesterone twice daily for women with a history of pregnancy loss and who experience bleeding during early pregnancy [4].

There have been 2 recent studies on the use of 17-hydroxy-progesterone caproate (17-OHPC) by injection for women with recurrent pregnancy loss [21,42]. In 2021, a meta-analysis that included these 2 studies showed that 17-OHPC injection was not recommended to prevent pregnancy loss or recurrent miscarriage [43]. A 2016 study enrolled pregnant women at risk of premature birth and randomized them to receive intramuscular 17-OHPC or vaginal micronized progesterone [44], showing no significant difference between intramuscular 17-OHPC or vaginal micronized progesterone (RR=1.31; 95% CI 0.47-3.66; P=0.59) [44].

In 2021, the Evaluating Progestogens for Preventing Preterm Birth International Collaborative (EPPPIC) group conducted a systemic review of publications on progesterone injection [45]. Meta-analysis of study participant data showed that vaginal progesterone or intramuscular 17-OHPC significantly reduced the premature (<34 weeks) birth rate of single births [45]. However, this statistical significance in the relative treatment effect was not seen between women with shorter cervical lengths (≤25 mm) and those with longer cervical length (>25 mm) [45]. Increased body-mass index (BMI) increased the adverse effects of vaginal progesterone (P<0.001), but this statistical significance was not seen with intramuscular 17-OHPC (P=0.052) [45], and neither intramuscular nor vaginal treatment was significantly beneficial for multiple pregnancies [45]. In 2017, a systematic review and meta-analysis evaluated miscarriage and premature birth of multiple births [46]. For patients with multiple pregnancies and short cervical length, vaginal micronized progesterone significantly reduced the premature birth (<34 weeks) rate (RR=0.71; 95% CI 0.56-0.91) and neonatal mortality (RR=0.53; 95% CI 0.35-0.81) [46].

In studies using progesterone to prevent recurrent miscarriage, the duration of use of progesterone and cessation of its use vary, with 1 study ceasing use at 36 weeks [47] and some at 12 weeks [1,28,48,49]. There is no evidence to support the optimum time of progesterone cessation. However, in 2018, the European Society of Human Reproduction and Embryology (ESHRE) Guideline Group on Recurrent Pregnancy Loss (RPL) supported using dydrogesterone 10 mg twice daily for at least 20 weeks [1]. ESHRE also made 38 recommendations on risk factors, investigations, and approaches to prevent recurrent pregnancy loss and 39 on treatments [1]. Of these recommendations, 60 were evidence-based, 31 were strong recommendations, 29 were conditional recommendations, and 17 were recommended as good clinical practice points [1]. However,

none of these recommendations were based on high-quality evidence [1]. These findings highlight the need for continued controlled clinical studies on the role of progesterone in the prevention of recurrent miscarriage.

Progesterone in Assisted Reproductive Technology (ART)

Primary ART options include intrauterine insemination (IUI) and in vitro fertilization (IVF). IVF is performed as either fresh or frozen-thawed embryo transfer (FET) [50,51]. The 2 main approaches to FET include natural cycles/modified natural cycles and programmed cycles. Although luteal phase support is essential for ART regimens, the best route of progesterone administration remains controversial, which has prompted recent research on this topic [15,50-55].

Progesterone and Luteal-Phase Support for Intrauterine Insemination (IUI)

In 2017, a meta-analysis of 11 studies showed that when compared with control groups, luteal-phase support groups showed a significantly increased clinical pregnancy rate (RR=1.34; 95% CI 1.15-1.57), which was more significant in the groups undergoing gonadotropin ovulation induction and IUI (RR=1.56; 95% CI 1.21-2.02) [51]. Two studies, published in 2015 and 2020, respectively, compared the use of oral dydrogesterone with vaginal micronized progesterone and showed similar pregnancy rates and live birth rates but that the use of an oral agent had greater patient compliance [56,57].

Progesterone and Luteal-Phase Support in Fresh Embryo Transfer (FET)

For FET, in combination with luteal-phase support, the use of exogenous hCG to trigger ovulation and the lack of endogenous LH as luteal support has a direct impact on the release of estrogen and progesterone, which reduces the pregnancy rate and increases the risk of miscarriage [58]. The best time for progesterone supplementation is between oocyte retrieval and embryo transfer (OR=1.31), with 1 day after oocyte retrieval being most beneficial [58]. However, progesterone supplementation up to the third day reduced clinical pregnancy rates compared to supplementation at the onset of oocyte retrieval (OR=0.66; 95% CI 0.50-0.87; $P<0.01$) [3].

In 2015, meta-analysis data published by van der Linden and colleagues compared the effects of progesterone administered via several routes and found no significant difference in effectiveness for FET [15]. Luteal-phase support for FET was

also studied in 2 large clinical trials, LOTUS 1 and LOTUS 2, which compared oral dydrogesterone and vaginal progesterone [22,59]. The LOTUS 1 trial showed that by providing oral dydrogesterone 10 mg 3 times daily and vaginal micronized progesterone 200 mg 3 times daily, starting on the day of oocyte retrieval and continuing until 12 weeks of pregnancy, there was no significant difference between groups in pregnancy rate (37.6% and 33.1%; 95% CI 1.2-10.6) and live birth rate (34.6% and 29.8%; 95% CI -0.8-10.7) [22]. The findings from the LOTUS 2 trial showed that oral dydrogesterone 10 mg 3 times daily and vaginal 8% micronized progesterone 90 mg once daily starting on the day of oocyte retrieval until 12 weeks of pregnancy did not result in a significant difference between the groups in the pregnancy rate (38.7% and 35.0%; 95% CI -2.3-9.7) and live birth rate (34.4% and 32.5%; 95% CI -4.0-7.8) [59].

In 2020, the European Society of Human Reproduction and Embryology (ESHRE) Guideline Group on Ovarian Stimulation for in vitro fertilization (IVF) and intracytoplasmic sperm injection (ICSI) made 84 clinical recommendations [2]. ESHRE also addressed 18 key questions on ovarian stimulation and recommended a non-oral route of progesterone administration to provide luteal support [2]. In 2021, meta-analysis data on progesterone in ART recommended vaginal progesterone as the criterion standard of luteal-phase support in IVF/ICSI [60]. However, meta-analysis data did not identify an optimal route for progesterone administration [60]. An earlier clinical study on luteal-phase support in IVF/ICSI enrolled 210 women who received ICSI and compared oral dydrogesterone 20 mg twice daily and vaginal micronized progesterone 400 mg twice daily [61]. The oral dydrogesterone group had lower progesterone levels, but no statistically significant difference was seen in the pregnancy success rate, miscarriage rates, or adverse effects [61].

Progesterone and Luteal-Phase Support in Natural/Modified Natural Cycle Frozen-Thawed Embryo Transfer (NC-FET/mNC-FET)

In natural and modified natural cycles, the day of ovulation can be determined by blood sample analysis or ovarian ultrasound. Depending on the condition of the endometrium and ovarian follicles, administration of hCG can trigger ovulation. In ART regimens without hCG injection, the use of progesterone is essential. Two NC-FET regimen studies, conducted in 2011 and 2014, respectively, highlighted the benefits of luteal-phase support [62,63]. In 2011, a randomized clinical study compared vaginal micronized progesterone 400 mg twice daily with a placebo and showed that the luteal-phase support group had a significantly higher live birth rate than the control group (30% versus 20%; $P=0.0272$) [62]. In 2014, Kim and colleagues compared the use of vaginal micronized progesterone

gel at 90 mg daily with a placebo and showed that the luteal-phase support group had a significantly lower miscarriage rate than the control group (8.5% versus 24.1%; *P*=0.044) [63].

In 2021, a meta-analysis of data from studies on the use of luteal-phase support in natural/modified natural cycle FET included studies providing vaginal micronized progesterone at 400 mg twice daily or micronized progesterone 200 mg 3 times daily [64]. Even when non-randomized studies were excluded, meta-analysis showed that the luteal-phase support group had a significantly higher live birth rate than the control group (OR=1.67; 95% CI 1.19-2.36) [64]. A 2021 RCT study compared the effectiveness of oral dydrogesterone and vaginal micronized progesterone gel for luteal-phase support during mNC-FET in 134 women under 38 years of age [65]. However, the study found no significant differences in ongoing pregnancy rate, clinical pregnancy rate, or miscarriage rate between the 2 groups, but patients receiving oral dydrogesterone reported better tolerability with fewer adverse effects [65]. The authors concluded that oral dydrogesterone was an effective and well-tolerated option for luteal-phase support in mNC-FET, comparable to vaginal micronized progesterone gel [65].

Some research data show that luteal-phase support should not be provided before the LH surge day plus 3 days [66], which differs from the luteal regimen used in FET. Recently published meta-analysis data from Jiang and colleagues of 4 RCTs involving 1116 participants showed that progesterone supplementation during natural cycle frozen embryo transfer (NC-FET) cycles was associated with a higher live birth rate and clinical pregnancy rate (CPR), particularly in traditional NC-FET (tNC-FET) cycles [67], but no significant association was found in modified NC-FET (mNC-FET) cycles [67]. Also, there was limited evidence that oral dydrogesterone and vaginal progesterone had similar reproductive outcomes in mNC-FET cycles, which warrants further investigation, particularly in tNC-FET cycles [67].

Progesterone and Luteal-Phase Support in Programmed Cycles of Frozen-Thawed Embryo Transfer

The use of programmed cycles inhibits endogenous estrogen. Progesterone is required for endometrial development to achieve luteal transformation, and luteal-phase support is required when the ovarian corpus luteum is absent [68]. In 2021, data from the MIDRONE RCT showed that in programmed cycle for FET, the live birth rates of vaginal micronized progesterone plus oral dydrogesterone and vaginal micronized progesterone alone were 46.3% and 41.3%, respectively (multivariate analysis: RR=1.30; 95% CI 1.01-1.68; *P*=0.042) [69]. The concomitant regimen significantly reduced miscarriage at <12 weeks (3.4% versus 6.6%; RR=0.51; 95% CI 0.32-0.83; *P*=0.009) [69].

Also in 2021, data from another RCT compared the outcomes from using a progesterone vaginal suppository (Cyclogest® 400 mg twice or Endometrin® 100 mg 3 times) and subcutaneous progesterone injection in a programmed cycle for FET [70]. The findings showed that the vaginal progesterone group had a significantly higher pregnancy rate than the subcutaneous progesterone group (28% versus 22.2%; *P*=0.581) [70].

In 2016, a single-blind RCT included 180 infertile women undergoing FET cycles [71]; the study participants were assigned to 3 groups receiving intramuscular progesterone, oral dydrogesterone, or a vaginal progesterone suppository [71]. The study findings showed that all 3 groups had comparable pregnancy and live birth rates, and there was no significant difference in miscarriage rates [71]. These findings indicated that oral dydrogesterone can be used as effectively as either intramuscular or vaginal progesterone supplements for luteal-phase support in an artificial cycle for FET, which is of interest considering the lower cost, ease of use, and patient compliance with oral treatment [71].

In 2017, findings were published from an RCT that compared the pregnancy outcomes from 4 different regimens of luteal-phase support in FET cycles [72]. The 4 regimens included 400 mg vaginal progesterone suppository used twice daily, 10 mg oral dydrogesterone twice daily, 10 mg oral dydrogesterone twice daily combined with injection of 0.1 mg GnRH-alpha, and 10 mg oral dydrogesterone twice daily combined with injection of 1500 IU hCG [72]. The study analyzed 400 FET cycles [72]. The pregnancy rates were significantly lower in the dydrogesterone group than in the other groups [72]; therefore, the authors suggested that the combination of oral dydrogesterone with GnRH-alpha or hCG may be a better alternative to vaginal progesterone for luteal-phase support in FET cycles [72].

However, a 2022 study showed that the use of micronized vaginal progesterone 800 mg/day and oral dydrogesterone 40 mg/day for endometrial preparation in FET cycles had similar reproductive outcomes (*P*=0.196) [73]. In 2021, 2 trials on programmed FET cycles provided a similar conclusion regarding the progesterone level on the day of embryo transfer [54,55]. Even though progesterone is naturally released in pulses, its level on the day of embryo transfer is still one of the predictive factors of successful pregnancy outcomes. In the clinical trial results reported by Gao and colleagues, routine luteal support was provided with oral Femoston twice daily (containing estradiol 4 mg and dydrogesterone 20 mg) and vaginal micronized progesterone 200 mg twice daily [53,54]. Women underwent blood testing on the day of transfer, and those with low progesterone levels (<10.0 ng/ml) were given daily intramuscular progesterone 40 mg to increase the pregnancy rate [53,54]. In the clinical trial results reported by Álvarez and colleagues, routine luteal support was provided with micronized progesterone 200 mg every

Table 1. Evidence-based recommendations for use of progesterone in threatened miscarriage.

Evidence-based recommendations
• Testing of progesterone levels is not required [10,11] • When a threatened miscarriage is confirmed, oral dydrogesterone is recommended at 40 mg, followed by 10 mg twice daily [31] • The above regimen should continue for one to two weeks after the end of clinical symptoms of miscarriage [25]

Table 2. Evidence-based recommendations for use of progesterone in recurrent miscarriage.

Evidence-based recommendations
• Testing of progesterone levels are not required [10,11] • When pregnancy is confirmed, vaginal micronized progesterone is recommended at 400 mg twice daily [4] • The above regimen should continue until the pregnancy reaches 20 weeks of gestation [1]

Table 3. Evidence-based recommendations for use of progesterone in assisted reproductive technology (ART).

Evidence-based recommendations
• Luteal phase support should be provided for intrauterine insemination with oral dydrogesterone (10 mg, three times daily) or vaginal micronized progesterone (200 mg, three times daily), depending on patient preference [2,59,76]

Table 4. Evidence-based recommendations for use of progesterone on fresh embryo transfer, including in patients with natural and modified cycles.

Evidence-based recommendations	
Progesterone for fresh embryo transfer	• Luteal phase support should commence within 3 days of oocyte retrieval [3] • Progesterone can be given by any route, including oral dydrogesterone (10 mg, three times daily), or vaginal micronized progesterone (200 mg, three times daily) [59] • The above regimen should continue until the pregnancy reaches 20 weeks of gestation [22]
Progesterone for natural/modified cycle frozen-thawed embryo transfer	• Luteal phase support should be provided 3 days after the LH surge [66] • Options include vaginal micronized progesterone tablets (400 mg, twice daily) or progesterone gel (90 mg, daily) [62,63]
Progesterone for programmed cycles of frozen-thawed embryo transfer	• The options include vaginal micronized progesterone (400 mg, twice daily) and oral dydrogesterone (20 mg, twice daily) [69] • Blood is sampled to measure progesterone levels. If the progesterone level is <10.6 ng/ml, progesterone is given by intramuscular injection (40 mg) [54] • Or, water-soluble progesterone can be given by subcutaneous injection (25 mg) [55]

8 hours [55]. Patients underwent blood testing on the day of embryo transfer, and the patients with low progesterone levels (<10.6 ng/ml) achieved similar pregnancy outcomes to those with normal progesterone levels after injection of water-soluble 25 mg progesterone [55]. By increasing the dose used for programmed cycles, a higher progesterone level was achieved to facilitate embryo implantation and development [55]. However, evidence for the optimum level of progesterone for FET is still lacking, supporting the need for continued controlled clinical studies on the role of progesterone in ART [74-76].

Conclusions

As shown in Tables **1-4**, evidence-based recommendations are now available for the use of progesterone in threatened miscarriage (**Table 1**), recurrent miscarriage (**Table 2**), ART (**Table 3**), and FET, including in patients with natural and modified cycles (**Table 4**). This review has presented an update from the perspective of obstetricians and gynecologists on the current status of the main studies that have provided evidence to support these recommendations. With increasing concern for

reduced birth rates in many countries, it is hoped that research will continue to provide evidence to support improvements in fertility and successful pregnancy outcomes.

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