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Progesterone therapy in recurrent miscarriages: Evaluating formulations, Administration routes and timing for future insights

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ABSTRACT

Introduction: Miscarriage, an unfortunate outcome of pregnancy, presents significant challenges in reproductive health for individuals and families worldwide. This review highlights the importance of"Progesterone" ahormone vital for the maintenance of pregnancy, in miscarriage.Decreased progesterone levels are associated with increased myometrial contractility, immunologic vulnerability, and endometrial hyperplasia, predisposing individuals to miscarriage and spontaneous abortion. Progesterone supplementation has thus emerged as a promising therapeutic approach to mitigate the risk of miscarriage, yet the optimal formulation, route, and timing of administration remain subjects of ongoing investigation.

Methods: In the context of recurrent and threatening miscarriages, this review investigates various progesterone formulations, delivery routes, and timing protocols including safety and effectiveness profiles of different progesterone formulations, namely oral, vaginal, intramuscular, or subcutaneous, in addition to comparing the disparate studies while analyzing the present literature. We examined the significance of timing in the onset and cessation of progesterone throughout pregnancy, considering preventive and therapeutic approaches.

Conclusion: This study attempts to offer insights into improving progesterone therapy procedures for people at risk of recurrent and threatening miscarriages through a comprehensive synthesis of the available data,ultimately guiding future research directions and informing evidence-based clinical care.

Keywords: Luteal phase deficiency; Pregnancy loss; Progesterone;Recurrent miscarriage; Recurrent spontaneous abortion.

1.INTRODUCTION

Manyhuman conceptions are genetically abnormal and end in miscarriage; this is a common complication of pregnancy.[1]The latest Green-top guideline defines recurrent miscarriage as the loss of 'three or more pregnancies' in the first trimester.[2]Approximately 5% of the couples trying to conceive have at least two consecutive miscarriages.[3]

Progesterone and its derivatives are often prescribed to prevent pregnancy loss.[4]Progestogens can affect implantation, cytokine balance, natural killer cell activity, arachidonic acid release and myometrial contractility. Luteal phase deficiency (LPD) is described as a condition of inadequate progesterone exposure necessary to preserve a regular secretory endometrium and permit healthy embryo implantation and growth. The potential role of progesterone in women with recurrent miscarriage caused due to LPD has been suggested for long but the efficacy is still being tested.[5]A Cochrane review found that progestogens can be used at all stages of pregnancy including supporting the luteal phasebefore pregnancy, threatened miscarriage, recurrent miscarriage, and in prevention of preterm labor. Progestogens were associated with an increased rate of live births or ongoing pregnancy in the progesterone group (odds ratio 1.77, 95% confidence interval (CI) 1.09-2.86). A meta-analysis showed that there was a 28% increase in the live birth rate when progestogens were used for recurrent miscarriage.[6]Another study including 61 patients with recurrent miscarriage found that individualized adjustment of hormone levels including progesterone after ovulation prevents miscarriages and improves the pregnancy success rates.[7]Furthermore, three controlled trials of progesterone treatment in women with recurrent miscarriage have shown small, but not statistically significant, increases in the rates of pregnancies that continue beyond 20 weeks in the treated groups.[8]For the last 30 years progesterone has been used to prevent pre-term labor.[6]

This review aims to discuss the role of progesterone in recurrent miscarriages and the different formulations of progesterone available, routes of administration,and lastly, compare the efficacy of the different routes and the timings of progesterone administration.

2.MATERIALS AND METHODS

This review included studies published from 2010 to 2024, from databases including Google Scholar, PubMed, Springer, and Web of Science using keywords as stated above.Only English-language studies central to the theme were included. The selection process involved a comprehensive literature search using the mentioned databases and keywords to identify potential articles. Search results were carefully screened based on predetermined inclusion and exclusion criteria to ensure alignment with the review's objectives. Factors considered included study design, relevance and research quality. To provide a balanced perspective, the review included articles with varying research methodologies, including experimental studies, clinical trials, and observational studies, published in reputable peer-reviewed journals. Each article's content, methodology, and relevance were critically evaluated and final selection was made by consensus among the authors. The objective was to provide a comprehensive overview and synthesis of current knowledge on the subject matter.

3.Physiological role of progesterone

Progesterone, a steroidal hormone produced by the corpus luteum during the luteal phase, plays a crucial role in establishing and maintaining pregnancy. During the first 10 weeks of pregnancy, progesterone is secreted by the corpus luteum and later by the syncytiotrophoblastof the placenta. Small amounts are secreted by the adrenal cortex.[9]Progesterone is essential for priming the endometrium for embryo implantation, facilitating trophoblast invasion and migration, and supporting steroid hormone biosynthesis.[10]It counteracts estrogen's proliferative effects, activates genes for embryo attachment, and regulates matrix metalloproteinase (MMP) activity to suppress excessive trophoblast invasion. Progesterone's actions are both genomic, through nuclear receptors PR-A and PR-B, and non-genomic, involving rapid cytoplasmic signaling via membrane-bound PRs.[11]In the uterus and ovary, progesterone aids in the release of mature oocytes, supports implantation, and maintains pregnancy by promoting uterine growth and suppressing myometrial contractions. In the mammary gland, it promotes lobular alveolar development for milk secretion while inhibiting milk protein synthesis pre-parturition and preventing bone loss .[12,13]In the brain, progesterone facilitates sexually responsive behavior. It also increases cervical mucus to inhibit sperm penetration. To summarize, progesterone plays crucial physiological roles in various body systems in mammals as shown in Figure 1. Progesterone mediates effects by its receptor, often induced by estrogen, complicating the differentiation of progesterone-specific actions from those of estrogen. During pregnancy, the placenta becomes the primary source of progesterone, with serum levels ranging from 100 to 500 nmol/L.[14]

4.Different formulations of progesterone

A Progestogen is a name given to a class of drugs that induces a progestational effect.The only natural progesterone available is Progesterone(P4) , which is also used as a medication.[15]It is chemically represented as pregn-4-ene-3,20-dione.[16]Progestinis synthetic progesterone.[17]Both synthetic and naturally occurring micronized progesterone (NMP) bind to the classical genomic route, the progesterone receptors (PR), with varying affinities to achieve their biological effects.[11]Various formulations of progestogens have been developed; and their classification based on origin is shown in Figure 2.

4.1. Micronized progesterone

The development of micronized progesterone came about when it was found that upon reducing the particle size of progesterone to less than 10 μm, the available surface area, dissolution rate and intestinal absorptionof progesterone,all improved significantly.[18]

Micronization of the natural progesteroneincreases the half-life of progesterone, with the metabolites, including Allopregnanolone, showing an indirect stimulatory effect on the progesteronereceptor. Unlike synthetic progestins, micronized progesterone has not been shown to affect mood, decrease high-density lipoprotein (HDL) cholesterol levels, or adversely affect pregnancy outcome.[18]It is commonly found in 3 formulations:

a]Oral micronized progesterone

In 1980, oral micronized progesterone (OMP) was introduced, enabling the oral administration of progesterone.[16] The oral route of administering natural progesterone was hindered because of the significant first-pass effect and poor absorption, however the development of the micronized form of the hormone greatly increased its bioavailability. This oral formulation, which consists of a gelatin capsule with natural micronized progesterone(NMP)suspended in oil, was found to further improve the intestinal absorption.[19]However, oral micronized progesterone, due to the active metabolites, has a higher incidence of dizziness, drowsiness and requireshigh doses due to first pass effect.[11, 19]There is currently no information on the effect of oral micronized progesterone on the outcome of a live delivery in women who experience recurrent miscarriages.[20]

b]Sustained release oral micronized progesterone

The sustained-release oral micronized progesterone (NMP SR) formulation bypasses the first-pass metabolism to escape the drawbacks of traditional oral micronized progesterone and produces the intended therapeutic effect with the lowest possible risk of metabolite-related side effects. A hydrophilic matrix polymer is used in the sustained-release formulation to release progesterone micron-sized particles over 16–24 hours in a regulated manner. As a result, this formulation exhibits a long elimination half-life of eighteen hours and strong protein binding capacity (90–99%), with only once daily dosing.[21] By avoiding "Dose Dumping" or abrupt medication release, the "even" release pattern prevents drug loss via hepatic metabolism. Additionally, this lessens drowsiness, one of the dose-related side effects.[18] In a nationwide prescription event monitoring study with 153 patients, prescribing physicians thought oral NMP SR was a clinically feasible option for patients with a bad obstetric history (BOH) and recurrent pregnancy loss, particularly in cases where luteal phase insufficiency was suspected.[22]

c]Vaginal micronized progesterone

There are two preparations of vaginal micronized progesterone: capsule/pessary and gel.[23]Treatment with vaginal micronized progesterone in the form of capsules,400 mg twice a day was found to be associated with increased live birth rates based on the number of previous miscarriages. This finding was reproduced in thePRISM (PRogesterone In Spontaneous Miscarriage) study after it was used in the PROMISE (PROgesterone in recurrent MIScarriagE) experiment.[24]Recently it was discovered that 400 mg of progesterone given vaginally and nightly from the beginning until 12 weeks of pregnancy did not increase the rate of live births in the STOP trial, a double-blind, placebo-controlled randomized control trial(RCT) in women with threatened miscarriage.[25]

4.2 17- alpha-hydroxyprogesterone caproate [17-OHPC]:

17-OHPC, a synthetic progesterone derivative with a long half-life and delayed release, is administered in the form of intramuscular injection.[26] The Food and Drug Administration(FDA) has approved a formulation of 17-OHPC that contains 250 mg of 17-OHPC in 1 mL of castor oil, 46% benzyl benzoate, and 2% benzyl alcohol.[27] It has been demonstrated to be important for luteal phase support and, theoretically, may be considered a viable substitute for intramuscular progesterone in oil form, with the added benefit of less discomfort for patients.[26] Saccone et al. found that synthetic progestogens like weekly IM 17-hydroxyprogesterone caproate, were linked to a lower risk of recurrent miscarriage in contrast with natural progesterone.[28] However, according to the Meis et al. experiment, women administered 17-OHPC had a non-significantly higher rate of stillbirths and miscarriages.[29]

4.3 Dydrogesterone

Dydrogesterone is a syntheticprogesterone commonly available asan oral tablet form. The "bent" shape of progesterone arises from a shift in the spatial orientation of a methyl group at C10 and an additional double bond between C6 and C7shown in Figure 3.[30]Withbetteroral bioavailability of progesterone due to its unique structure, the amount needed clinically is also significantly lower because of its receptor specificity. According to estimates, the oral dosage of progesterone is 10–20 times higher than that of dydrogesterone.[29]Carp et.al found that dydrogesterone treatment was associated with a 47% reduction in the odds of miscarriage, compared to standard care, and an absolute decrease in the miscarriage rate of 11%, even though treatment with progestogens in general and dydrogesterone in particular is somewhat empiric.[31]Dydrogesterone has fewer side effects; there are minimal instances of vaginal bleeding during therapy, and there are no reports of major adverse reactions, including teratogenesis.[29]The reason being, in contrast to other forms of progesterone., dydrogesterone's primary metabolite, 20α-dihydrodydrogesterone, has comparable progestogenic selectivity to the parent molecule.[32]

4.4 Novel Subcutaneous formulations

The use of novel subcutaneous progesterone formulations, in the context of support of luteal phase and its potential impact on miscarriages has been explored through clinical trials. Subcutaneous progesterone formulations are equally effective as vaginal progesterone gel in pregnancy and live birth rates, with similar adverse event profiles. The study highlighted the potential benefits of subcutaneous progesterone, particularly in assisted reproduction, but also mentioned the need for further research to determine its suitability and applicability for large scale patient groups.[33]

4.5 Comparison of the various formulations

Numerous investigations have been carried out that demonstrate the superiority of dydrogesterone over other progesterone formulations for the prevention of recurrent miscarriages.[31, 34, 35] In addition to the decreased adverse reactions, dydrogesterone efficiently lowers the mother's immunological response to embryos, facilitates embryo implantation, and has a positive immunomodulatory effect.[36] It prevents the release of prostaglandins in the endometrium and fosters an environment that is ideal for the development of embryos.[34] Hence, dydrogesterone is safer when treating impending miscarriages resulting from corpus luteum insufficiency when compared to progesterone, indicating that dydrogesterone can greatly enhance the outcome of delivery.[34]

5.Routes of administration of progesterone

The next factor is selecting the best route of administration of progesterone. A few promising routes have been utilized in clinical trials namely: oral, vaginal, rectal, and intramuscular routes of administration as shown in Figure 4. Three of these: vaginal, rectal, and intramuscular routes of supplementation of progesterone provide higher bioavailability whereas the oral route of administration has low bioavailability as it undergoes first-pass metabolism. The oral route is preferred owing to its ease of administration and non-invasiveness. We will look into the details to determine the best and most widely accepted route of administration of progesterone.[13]

5.1 Oral

Administrating progesterone orally has shown positive outcomes in several females with a history of recurrent miscarriages. A recent RCT revealed successful pregnancy outcomes upon oral administration of progesterone.[37]Downsides of oral administration include pre-liver and intra-liver effects of metabolism. To overcome these limitations, patients are prescribed Duphaston, a synthetic form of progesterone known as dydrogesterone.[38]One study showed that oraldydrogesterone exhibited a lower risk of miscarriage than natural progesterone.[39]Another study including two RCTs demonstrated significantly low miscarriage rates ($p < 0.05$) in women receiving oral dydrogesterone than those who received placebo.[40]

Dydrogesterone's selectivity for the receptor of progesterone is very high, and it does not induce androgenic changes in the fetus, leaving placental progesterone production unaffected.[41] To provide further evidence, there is a need for more robust studies evaluating oral dydrogesterone efficacy with assertive methodologies. A well-known study employed a daily dose of 20 mg oral dydrogesterone and such doses can be considered optimal until future trials.[23] Akbar et al. 2017 had concluded a one year RCT comparing oral progesterone supplementation against vaginal progesterone. It was found that the oral route of administration was effective in 90% females compared to 71% effectiveness via vaginal route.[42]

5.2 Vaginal

Vaginal route of progesterone refers to supplementation of progesterone via vagina,a direct path through which progesterone enters the targeted site of the uterus with high bioavailability as it does not have to enter the first-pass metabolism unlike the oral route.[43]

AnRCTconducted in 2019 compared oral and vaginal routes of progesterone supplementation. A total of 136 pregnant women were included and divided into two groups of 68 each. Group A was given 200 mg of oral micronized progesterone twice a day and group B was given 400 mg vaginal progesterone suppository once daily. The course was followed up until 20th week of gestation. Out of 136, only 98 women completed the follow-up; 49 women in each group. It was seen that 13 females out of 49 from group B suffered from miscarriages upon vaginal progesterone, compared to only 4 cases of miscarriagesout of 49 women of group A who were prescribed oral progesterone.[37] Another large, multi-center RCT compared vaginal micronized progesterone, and placebo in 836 women with idiopathic recurrent miscarriages. The study resulted in 65.8% of live births due to vaginal progesterone compared to 63.3% of live births seen in placebo treatment. There was no significant difference between vaginal administration and the placebo group.[44]An RCT study conducted to compare the efficacy of oral dydrogesterone and vaginal progesterone showed positive outcomes in patients with recurrent pregnancy loss. In the study, 200 patients were randomized into two groups of 100 each. One group was supplemented with 600 mg of vaginal progesterone per day whereas the other group was administered 30 mg of oral dydrogesterone per day. The study revealed that 74 patients in the progesterone group had 2 miscarriages compared to 68 patients in dydrogesterone group. The study concludes that oral supplementation of progesterone has better efficacy over vaginal administration.[45]Hence it can be concluded that vaginal route has demonstrated prevention of recurrent miscarriages, but it is less efficacious than the oral route.

5.3 Parenteral

Withparenteraladministration (commonly, intramuscular 17-OHPC), thereis a rapidbuildupofserum concentration and increased bioavailability.[23]A new development in the field is the availability of novel parenteral progesterone preparations that are water-soluble. They can be administered subcutaneously (SC) to reduce patient discomfort.[46]To maintain the clinical efficacy of oil-based preparations, they are to be administered intramuscularly but are often painful and may lead to adverse effects such as inflammation and abscesses.[17]

The outcomes of a pilot study evaluating oral supplementation of progesterone alone versus IM in addition to oral administration of progesterone suggested that there was a decrease of almost 11% in the rate of miscarriages shown in the groups receiving the additional intramuscular progesterone.[47] On the contrary, a systematic review conducted by Saccone et al. revealed a significant reduction in preterm births in women who were administered progesterone via the vagina compared to the intramuscular route of progesterone.[28] However, when comparing parenteral route with vaginally administered progesterone, there are factors to consider such as formation of sterile abscess at the site of injection along with pain and inflammation at the site.[48]In a survey conducted on 58 women, most of them preferred vaginal over IM injections.[49]

5.4 Rectal

The rectal route of administering progesterone has been studied in a few clinical trials evaluating pregnancy-related complications, and prevention of preterm birth, as well as in two controlled trials in which rectal progesterone was indicated for luteal phase support. There is no clear study conducted to demonstrate rectal progesterone supplementation for the prevention of recurrent miscarriages. Hence, there is no way to say whether rectal delivery of progesterone can be considered as an optimum route of administration of progesterone to treat recurrent miscarriages. Moreover, there are incidences of constipation and irritation of the area if administered via rectum, and thereof it is not a preferred route of administration.[50,51]

5.5 Transdermal

There are numerous positive outcomes of administering progesterone through the skin. When progesterone is applied as a cream/gel to the skin, it has the potential to fight off diseases of the uterus. However, it is not accepted as a systemic treatment, as transdermal supplementation of progesterone has no clear evidence to treat recurrent miscarriages.[16,52]

5.6 The preferred route of administration among both, physicians and patients

Oral progesterone has certain limitations such as reduced bioavailability which leads to higher intake that result in various side effects as shown in Table 1. In the case of vaginal administration of progesterone, it has an advantage over oral such that it does not pass through first-pass metabolism hence complete dosage reaches the uterus. Various studies have shown that physicians as well as patients prefer oral supplementation over vaginal administration of progesterone.[30,53]However, according to NICE guidelines (NG126), physicians should prescribe 400 mg vaginal micronized progesterone, twice daily, to pregnant women who had a history of miscarriage and have vaginal bleeding.[54]

Many studies including a meta-analysis of ten RCT revealed that oral progestogen increased the incidence of livebirths, reducing the risk of miscarriages compared to other mentioned routes of progesterone administration.[55] It had been proved that many patients who received oral dydrogesterone had a successful

pregnancy, almost 24 weeks of complete gestation until full term healthy birth.[56, 57] It can be concluded that oral progesterone is the best and most effective route of administration, followed by the vaginal route. Researchers argue that vaginal administration of progesterone is advantageous as it provides targeted delivery to the uterus, improving endometrial receptivity.

The side effects of maternal progestin supplementation includes risk of hypospadias.[18]The current information is insufficient to guarantee the best route of progesterone supplementation. Hence, to provide clear evidence, there is an urgent need for clinical trials with strong methodologies to assess the most optimal route of progesterone administration in women facing recurrent miscarriages.

6.Timing of administration

In recent years, progesterone supplementation has become known for its profound properties in preventing recurring miscarriages.[58, 59, 60]The relevance of its timing of administration has also become an important topic of debate. Originally, progesterone supplementation was administered during early pregnancy, ideally during the first trimester.[61] Studies suggest that decreasing levels of progesterone during the early stages of pregnancy has resulted in miscarriages as implantation fails to occur.[24,62] Delaying administration or progesterone deficiency leads to the breakdown of the endometrium.

According to the updated NICE guidelines, it recommends that progesterone administration should be given from as early as the 9th week of pregnancy until 16 weeks to appreciate the positive results. Another study suggested that the complete action of progesterone concludes by the 12th week and there was no requirement, to wait up to 16th week.[54]Progesterone administration in the first trimester (conception-12weeks) reduces the risk of hypertensive disorders of pregnancy and pre-eclampsia while those administered in second trimester (13-27 weeks) and third trimester (28-40 weeks) doesn't indicate any positive effects or results.[63] According to a recent study, a shift of trend is highlighted by detecting positive patterns in the administration of delayed progesterone supplementation, which is ideally up to the second trimester.[64]A 2019 study found that early intervention with progesterone supplementation immediately after conception or in the early stages of pregnancy following ovulation is associated with high success rates in preventing recurring miscarriages by providing essential hormonal support for fetal protection. [30]

Another study (Muhammad et. al., 2020), proposed that oral progesterone used in first trimester controls the bleeding, and increases birth rates, or leads to a safe pregnancy and live birth.[65]Females with progesterone intake during their first trimester following three recurrent miscarriages showed similar results.[66]Other studies have reported conflicting results on the impact of its timing, for instance, a study (Devall et al., 2021) suggests that progesterone supplementation does not affect live births, however vaginal micronized progesterone may still help in case of recurrent miscarriages and early pregnancy bleeding.[59] Another study states, that even if progesterone was administered right after a positive pregnancy test, it doesn't yield any positive outcome.[64]It was indicated that althoughdydrogesterone has a positive therapeutic impact on pregnancy, patients under administration of progesterone fails to reveal similar results.[67]

Duncan et. al., indicated that the miscarriage in the first trimester is due to other defects, including chromosomal or morphological abnormalities and not due to decreased levels of progesterone levels. Hence, administration of progesterone would show no positive results.[68]

Contrary to previous findings, Shehata et al.'s recent study reports higher live birth rates when progesterone intake starts from the day of a positive pregnancy test [23]. Additionally, early administration of progesterone demonstrated improved results, whereas late administration did not show significant benefits and had no positive effect on pregnancy outcomes.[69]

Another study indicated that late supplementation of progesterone positively supports the fetus during low progesterone levels in the second trimester of pregnancy. This highlights the importance of progesterone administration for women at risk of recurrent miscarriages.[70]

The timing, effects, and mechanism of progesterone administration remain unclear, with most studies suggesting early supplementation—ideally from the first trimester to the end of the 12th week after a positive pregnancy test—as optimal as shown in Table 2. However, conflicting results are found in other studies[71] due to the consideration of various factors including the patient, study design, population, type of progesterone administrated, and the cause of previousmiscarriages, like endocrine disorders, infections, genetic and immune disorders.[72,73]

CONCLUSION

Recurrent miscarriages, defined as the loss of three or more pregnancies, are more prevalent than commonly assumed. While the exact cause is undetermined, genetic abnormalities are often implicated, with risk factors including aging and previous pregnancy outcomes. Progesterone, a plays a crucial role in maintaining the uterus to support pregnancy. This article focuses on progesterone formulations that can help prevent miscarriages, as well as potential novel formulations. Progesterone can be administered through various routes, with vaginal and intramuscular administration being more effective as they bypass the first-pass metabolism. Most studies

indicate that early administration of progesterone in pregnancy yields the best results. However, further research is needed to determine the optimal method and timing of progesterone administration to prevent miscarriages.

Future Prospects and Challenges

Despite significant research on the role of progesterone in preventing recurrent miscarriages, future studies are needed to fill existing knowledge gaps. Tailoring progesterone therapy to individual patient profiles could revolutionize patient outcomes. However, personalized treatment requires extensive studies to explore genetic predispositions and biomarkers. Long-term follow-up studies are essential to assess the impact of progesterone therapy on maternal and fetal outcomes beyond pregnancy. Resolving discrepancies in the literature regarding the optimal timing, dosage, and route of progesterone administration requires rigorous clinical trials and meta-analyses. There is a need to:

- Conduct large-scale RCTs to study the efficacy of 17-OHPC and oral micronized progesterone on recurrent miscarriages.
- Compare various progestogens (dydrogesterone, 17-hydroxyprogesterone) and administration routes for efficacy, timing, and safety.
- Conduct robust studies to address and improve the shortcomings of IM/SC progesterone administration.
- Assess rectal progesterone for recurrent miscarriages, as it has been studied in pre-term birth prevention and IVF.
- Evaluate transdermal progesterone for recurrent miscarriage treatment, as there is no clear evidence yet.
- Although some studies suggest oral progesterone is effective, researchers argue vaginal administration may be superior, supported by the 2023 NICE guidelines recommending it for vaginal bleeding.
- Ensure equitable access to progesterone therapy in resource-constrained settings, overcoming barriers like cost, availability, and healthcare infrastructure through collaborative efforts.
- Continue research on novel progesterone formulations, such as sustained-release or nanoparticle delivery systems, to enhance bioavailability and therapeutic outcomes.
- Investigate progesterone's role in endometrial defects associated with higher-order miscarriages.
- Conduct therapeutic trials to evaluate the effectiveness of luteal phase progesterone and other potential interventions.
- Design well-controlled placebo trials focusing on luteal phase progesterone supplementation, particularly in low-resource settings, to gather comprehensive data on efficacy and applicability.

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None

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TABLES

Table 1: Table comparing different routes of administration of progesterone in recurrent miscarriages.

Studies	Route	Recommended dosage	Advantage	Limitations
Parveen et al.[37]	Oral	200–300 mg daily.	1.Easy intake 2.Widely used.	1.Requires high intake of doses due to reduced bioavailability. 2.Increased side effects: nausea, headaches.
Paulson et al.[49] Coomarasamy et al.[74]	Vaginal	400 mg twice daily.	1.Direct delivery to the uterus improves uterine contraction. 2.Requires low dosage as it avoids first-pass metabolism.	1. Vaginal irritation 2. Vaginal bleeding due to improper administration.
Paulson et al.[49] Beigi et al. [75]	Parenteral	Weekly injections of 250 mg of 17 alpha-Hydroxy-Progesterone Caproate	1.Achieve optimal blood levels as there is direct delivery to the bloodstream. 2.Bypasses gastrointestinal system and liver metabolism.	1.Significant pain and discomfort. 2.Local soreness, abscess formation, severe inflammatory and allergic reactions.
Coomarasamy et al. [24]	Rectal	400 mg twice daily from 2-16 weeks of gestation.	1.Same effect as that of vaginal, when administered.	1.Not recommended as no strong evidence.
Warren et al.[43]	Transdermal	None	-	1. Not applicable for systemic treatment.

Mg milligram, the table illustrates the routes of progesterone administration along with the required dosage, advantages and limitations to administer the best treatment as required.

Table 2: Summarizes the timings of progesterone administration in recurrent miscarriages along with supportive evidence

Studies	Timings	Findings
Coomarasamy et al. [24]	Start of pregnancy- 12 weeks	Women with recurrent miscarriages benefit from the use of vaginal micronised progesterone.
Khan et al. [65]	Start of pregnancy- 20 weeks	Oral progesterone is more effective than vaginal progesterone in treating threatened miscarriage.
Wu et al. [66]	Start of pregnancy- 20 weeks	Administration of oral dydrogesterone is effective.
Devall et al. [59]	Start of pregnancy- 12 weeks	No effect on live birth.
Yan et al. [64]	Start of pregnancy – 12 weeks	Progesterone supplementation did not significantly improve the incidence of preterm and live birth, so progesterone treatment of threatened miscarriage may be unhelpful.
Guo et al.[67]	Start of pregnancy – 12 weeks	No effect
Linehan et al. [61]	Start of pregnancy – 12 weeks	Increase in live birth rate among women with recurring miscarriages.

The table illustrates that the ideal time for progesterone administration is in between the start of pregnancy and 12 weeks.

Figure 1: This figure illustrates the various physiological roles of progesterone in the human body.

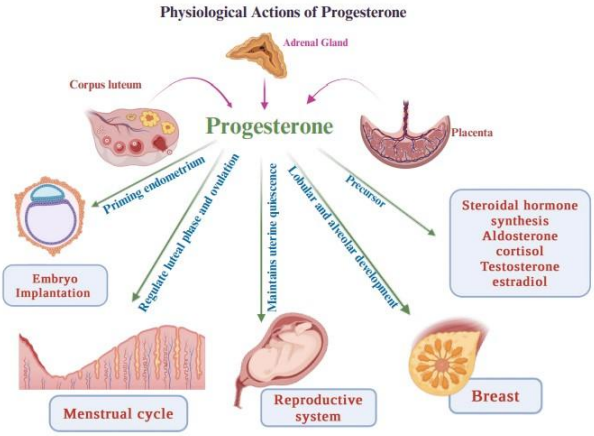

Figure 1: Physiological actions of progesterone

Figure 2: This visualises the types of progesterone and the available category of each type both natural and synthetic.

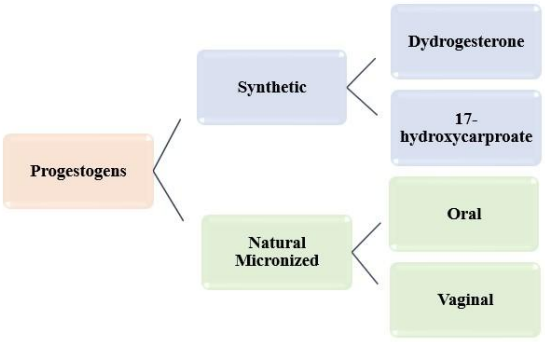

Figure 2: Classification of progesterone

Figure 3: This 3-dimensional diagram shows the chemical arrangement and orientation of progesterone and dydrogesterone structure.

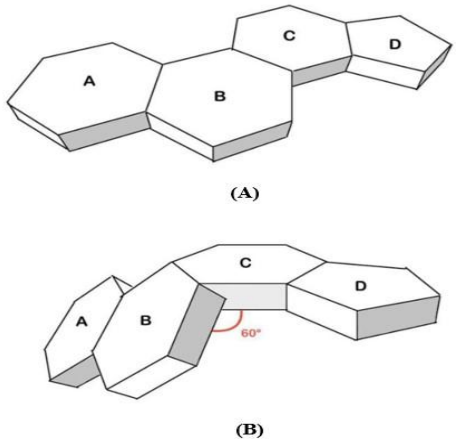

Figure 3: (A) 3D orientation of progesterone, (B) 3D orientation of dydrogesterone.

Figure 4: This classification demonstrates the routes of progesterone administration including transdermal patch, subcutaneous, oral, Intramuscular, intravaginal and intrarectal.

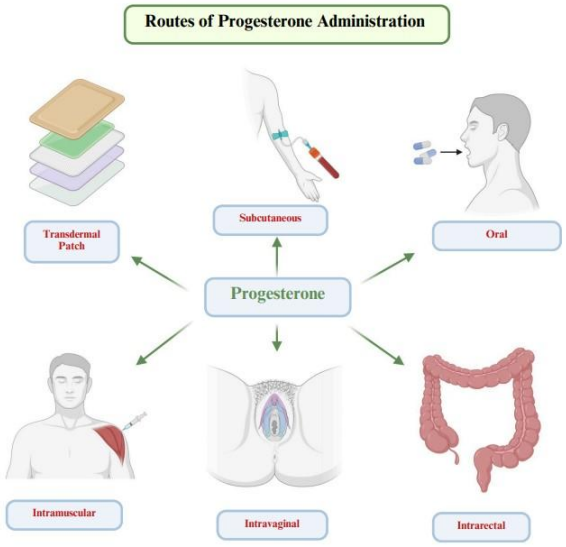

Figure 4: Various routes of administration