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Progesterone supplementation in women with threatened miscarriage: narrative review

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ABSTRACT

The effectiveness of progesterone supplementation in treating impending miscarriages is still debatable. This narrative review aimed to evaluate the effectiveness of progesterone for pregnant women who are at risk of miscarriage. The effectiveness of progesterone were obtained from online database publications as PubMed, EBSCOhost, and Google Scholar between 2019 and 2024. The search was conducted by entering keywords in the database. Then by screening titles, abstracts, and contents, the search result obtained 15 articles. The outcomes were miscarriage, preterm birth, and live birth. Eight RCTs, 1 cohort, 5 meta-analyses, and 1 systematic review were included in this narrative review. The RCTs reviewed, revealed several journals which mention that oral, vaginal, and placebo progesterone have not significantly differed in preventing miscarriage. However, there were RCTs journal mention that oral dydrogesterone, vaginal and oral progesterone are effective in preventing miscarriage. In contrast, a meta-analysis research indicated that oral progesterone, vaginal progesterone, and dydrogesterone were all effective in reducing miscarriage. Progesterone supplementation may be effective in women at risk of miscarriage. The recommended route of progesterone treatment to threatened miscarriage is still controversial, but based on this narrative review, the vaginal route of progesterone is more effective and safer than oral route.

ABSTRAK

Efikasi suplementasi progesteron dalam pengobatan wanita yang terancam keguguran masih kontroversial. Ulasan naratif ini bertujuan mengevaluasi efektivitas suplementasi progesteron dalam mencegah wanita hamil yang terancam keguguran. Data efektivitas progresteron diperoleh dari database daring seperti PubMed, EBSCOhost, dan Google Scholar yang diterbitkan dari 2019-2024. Kata kunci dimasukkan ke dalam database pada proses pencarian jurnal. Kemudian dengan menyaring judul, abstrak, dan isi, hasil pencarian diperoleh 15 artikel. Hasil yang diukur adalah keguguran, kelahiran prematur, dan kelahiran hidup. Delapan RCT, 1 kohort, 5 meta-analisis, dan 1 ulasan sistematik dimasukkan dalam ulasan naratif ini. Ulasan hasil RCTs mengungkapkan beberapa jurnal yang menyebutkan bahwa progesteron oral, vaginal, dan plasebo tidak berbeda secara signifikan dalam mencegah keguguran. Namun, ada jurnal RCT yang menyebutkan bahwa didrogesteron oral, progesteron vaginal dan oral efektif dalam mencegah keguguran. Di sisi lain, sebuah meta-analisis melaporkan progesteron oral, progesteron vaginal, dan didrogesteron ditemukan efektif dalam mencegah keguguran. Suplementasi progesteron mungkin efektif pada wanita yang berisiko keguguran. Rute pengobatan progesteron yang direkomendasikan untuk keguguran terancam masih kontroversial, tetapi berdasarkan tinjauan naratif ini, rute vaginal progesteron lebih efektif dan aman daripada rute oral.

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INTRODUCTION

Threatened miscarriage is defined as vaginal bleeding before the 20th week of pregnancy, with or without abdominal pain. It is a prevalent problem affecting around one in every five pregnant women.[1] Current guidelines for managing miscarriage involve a combination of targeted treatments for identified causes and supportive care for unexplained cases.[2] Pharmacological interventions include aspirin and heparin for antiphospholipid syndrome, levothyroxine for thyroid dysfunction, and bromocriptine for hyperprolactinemia, among others.[2] Non-pharmacological approaches may involve lifestyle modifications, genetic counseling for chromosomal abnormalities, or surgical correction of uterine abnormalities.[2] While treatments like preimplantation genetic testing and progesterone supplementation are considered in select cases.[2] Specifically for progesterone supplementation, some opinions state that low progesterone levels have been proposed as an underlying cause of impending miscarriage because they play an important role in preserving pregnancy by promoting uterine quiescence. There has been a lot of interest in using progesterone supplementation to prevent miscarriage in women experiencing early pregnancy hemorrhage.[2] However, the efficacy of this medication has been clinically debated and not supported by data.[2]

Randomized controlled trials (RCT) evaluating progestogens for threatened miscarriage have produced inconsistent results, with previous systematic reviews and meta-analyses indicating potential benefits but being limited by small sample sizes and a lack of emphasis on live birth rates, the most important clinical outcome. The American College of Obstetricians and Gynecologists[3] has indicated that conclusive evidence supporting the use of progestins in cases of threatened early pregnancy loss is lacking. A significant trial published in 2019 further challenged the efficacy of progesterone, finding no substantial increase in live birth rates compared to placebo.[3] This narrative review aims to update and synthesize current evidence, incorporating the latest research, to evaluate whether progesterone supplementation is associated with improved benefits for women experiencing threatened miscarriage.

MATERIAL AND METHODS

This is a narrative review aimed to identify and summarize the previous study article, avoid research duplication, and investigate the new under-researched fields.[4] The article investigation method was carried out in the literature database of PubMed, EBSCOhost, and Google Scholar with the keywords ”Pregnancy”, “Threatened Miscarriage”, “Dydrogesterone”, and “Progesterone”.

The criteria of article inclusion were based on (i) a literature review of progesterone usage in pregnancy with miscarriage-threatened which was published in 2019-2024 (ii) the research subjects are women with first and second-trimester pregnancy, (iii) types of article designs are case-control, case report, cohort, randomized controlled trials (RCTs), systematic review and meta-analysis (iv) the article can be fully accessed and written in English. The article exclusion criteria are as follows: (i) research studies on the use of progesterone in third-trimester pregnancy; (ii) research studies on in vivo and in vitro; and (iii) the article contains expert comments that are not supported by research studies. The result measured in this narrative review is any occurrence of miscarriage, preterm birth, and live birth.

RESULTS AND DISCUSSION

Study selection

The initial results of the articles achieved were 127 articles, 76 articles from PubMed, 42 articles from EBSCOhost, and 10 articles from Google Scholar. After the duplication of the exclusion process was conducted there are 125 articles obtained. Then, the title and abstract screening were done, yielding 64 articles. After the screening with the criteria of inclusion and full-text reading, there are 15 articles which consist of 8 articles of RCT, 1 cohort article, 5 meta-analysis articles, and 1 systematic review article. Those 15 articles used to discuss the effectiveness of progesterone in miscarriage-threatening comprehensively which then became the basis for determining which progesterone therapy is most effective in preventing miscarriage in the 1st and 2nd trimesters of pregnancy. The stages of investigation, selection, and the result of the investigation are presented in the diagram below (FIGURE 1).

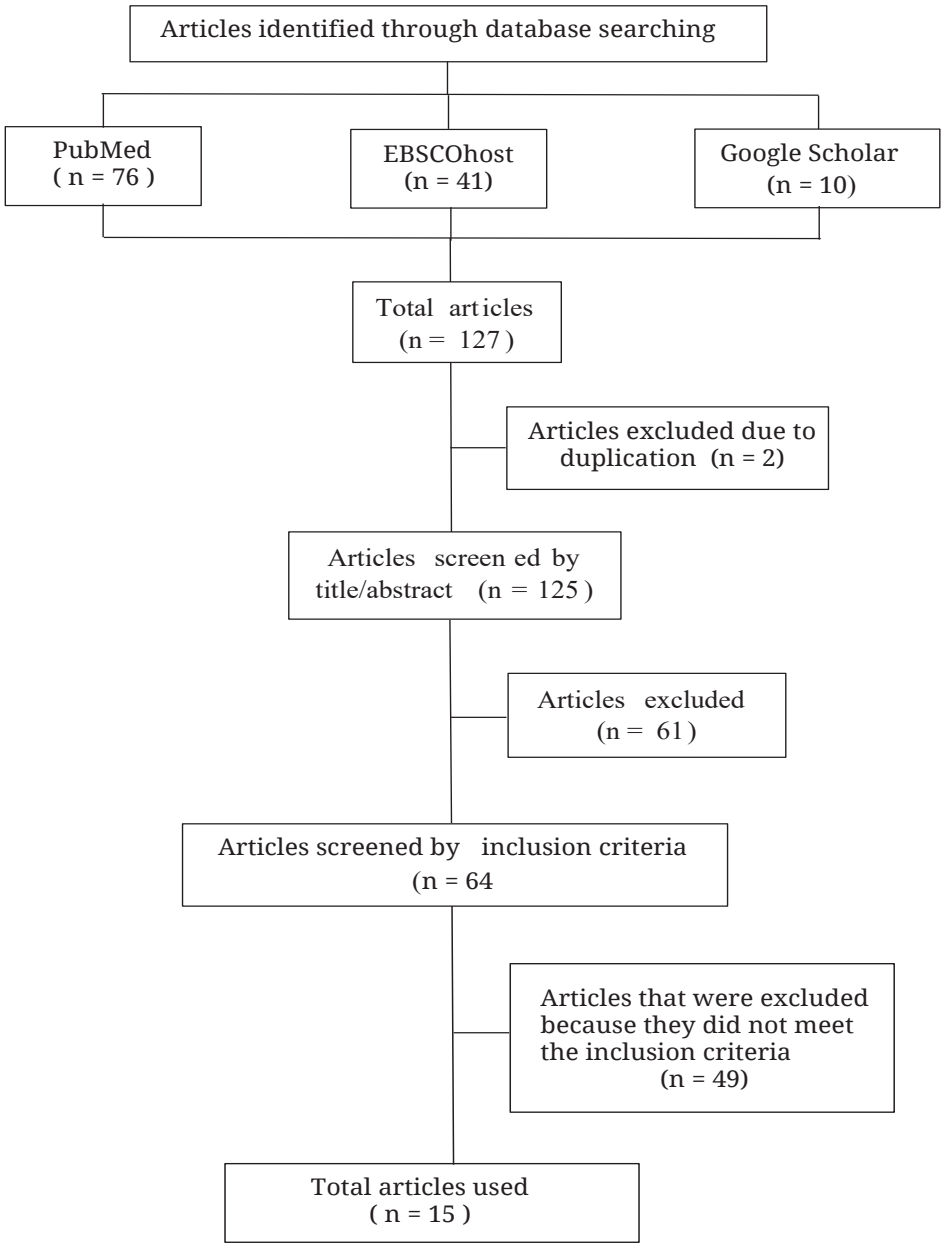

FIGURE 1. Article Search Process

Study characteristic

The baseline characteristics of the studies are depicted in TABLE 1 and 2. TABLE 1 consists of nine studies with eight RCTs and 1 cohort showing 10.810 women enrolled. Among nine studies, there are five studies[1-3,6,7] used a placebo and controlled treatment, and four studies[4,5,8,9] used controlled treatment. From nine studies in TABLE 1, three studies[1,3,6] reported live birth, two studies[5,9] reported miscarriage prevention, and three studies[4,7,8] reported the continuation of pregnancy, one study[2] reported miscarriage rate.

TABLE 2 contains six studies consisting of 5 meta-analyses and 1 systematic review showed 26.571 women enrolled. Among six studies, four studies[1,2,3,6] used placebo and controlled treatment, and two studies[4,5] used controlled treatment. There are also six studies in which three studies[2,5,6] reported miscarriage and live birth, one study[1] reported miscarriage, one study[3] reported pregnancy success rate, one study[4] reported miscarriage, preterm birth, and live birth.

TABLE 1. Study characteristics (RCT and cohort)

Reference	Type of study	Study location	Population characteristic				Intervention	Outcome
			Total patients	Age (yr)	Gestational age (wk)	Pregnancy history		
Coomarasamy *et al.*[5]	RCT	UK	4153	16-39	<12	Vaginal bleeding	Vaginal progesterone, placebo	Live birth
Chan *et al.*[6]	RCT	Australia	406	18-40	1-12	Threatened miscarriage, vaginal bleeding	Dydrogesterone, placebo	Miscarriage rate
Coomarasamy *et al.*[7]	RCT	UK	4153	16-39	<12	Vaginal bleeding	Vaginal progesterone, placebo	Live birth
Kale *et al.*[11]	RCT	India	200	28-35	<12	Recurrent miscarriage, bleeding	Vaginal progesterone, oral dydrogesterone	Stoppage of bleeding, continuation of pregnancy
Parveen *et al.*[9]	RCT	Pakistan	136	18-45	<12	Vaginal bleeding	Oral & vaginal micronized progesterone	Miscarriage prevention
McLindon *et el.*[10]	RCT	Australia	269	>18	<10	Threatened miscarriage, bleeding	Vaginal progesterone, placebo	Live birth
Kuptarak,[11]	RCT	Thailand	100	18-45	6-20	Threatened miscarriage	Dydrogesterone, placebo	Continuation of pregnancy
Shinwari *et al.*[12]	RCT	Pakistan	108	16-40	<12	Recurrent miscarriage	Dydrogesterone, vaginal micronized progesterone	Vaginal bleeding, Continuation of pregnancy
Lou *et al.*[13]	Cohort	China	1285	27	6-10	Threatened miscarriage	Dydrogesterone, progesterone	Miscarriage prevention

TABLE 2. Characteristics of the study (systematic review & meta-analysis)

Reference	Type of study	Total of studies included	Population characteristic			Intervention	Outcome
			Total patients	Gestational age (wk)	Pregnancy history		
Haas *et al.*[14]	Meta-analysis	12	1856	<20	Recurrent miscarriage	Natural progesterone, synthetic progesterone (dydrogesterone), placebo	Miscarriage
Devall *et al.*[15]	Meta-analysis	7	5682	<24	Vaginal bleeding, previous miscarriage	Micronized progesterone, dydrogesterone, 17-α-hydroxyprogesterone, placebo	Miscarriage, live birth
Guo *et al.*[16]	Meta-analysis	13	2454	-	Recurrent spontaneous abortion	Dydrogesterone, progesterone, human chorionic gonadotropin (hCG), placebo, active immunization	Pregnancy success rate
Yan *et al.*[17]	Meta-analysis	9	4907	<20	Recurrent miscarriage, vaginal bleeding	Micronized progesterone, dydrogesterone	Miscarriage, preterm birth, live birth
Zhao *et al.*[18]	Meta-analysis	15	6616	<20	Recurrent miscarriage	Micronized progesterone, dydrogesterone, 17-OH progesterone caproate (17-OHPC)	Miscarriage, live birth
Li *et al.*[19]	Systematic review	10	5056	<20	Threatened miscarriage	Progesterone, placebo	Miscarriage, live birth

Main findings

This review covers eight randomized controlled trials, one cohort study, five meta-analyses, and one systematic review that studies progesterone is used to prevent miscarriage in pregnant women. The progesterone used is natural progesterone and dydrogesterone, a synthetic progesterone. Progesterone can be given through oral or vaginal. This review will discuss the effectiveness in precaution of miscarriage and to compare the use of progesterone based on its type and how the way it is given.

Comparisons of progesterone based on type and route

A randomized double-blind controlled trial by Kuptarak dan Phupong,[11] evaluated the effectiveness of progesterone usage in precaution of miscarriage to women who have potential of it. The progesterone used is synthetic oral dydrogesterone which is compared to placebo. The result of the study shows that the number of pregnancies that ongoing until 20 weeks of pregnancy in the group of dydrogesterone (90%) has no difference significantly to the group of placebos (86%) (RR=1.19; 95%CI: 0.71-2.02; p=0.538). In addition, there is no significant difference in both groups in the number of live births (90% dydrogesterone group and 86% placebo group, RR=1.19; 95%CI: 0.71-2.02; p=0.538). This research is in line with the previous study conducted by Chan *et al.*[6] The research compares the occurrence of miscarriage to the patient who received dydrogesterone with a placebo. The result of the study showed that miscarriage before 20 wk of pregnancy in the group of progesterone (12.8%) and placebo (14.3%) has no difference significantly (RR=0.897; 95%CI: 0.548-1.467; p=0.772).

Lou *et al*.,[13] investigate the efficacy and safety of oral dydrogesterone and oral progesterone for women with the risk of miscarriage due to corpus luteum insufficiency. Corpus luteum insufficiency can trigger miscarriage which is caused by the insufficient number of progesterone secretion therefore it was ineffective in hampering the uterus contraction frequency and immune refusal to embryonic antigen.[18,20] The result of the study indicates that miscarriage prevention in the oral dydrogesterone group (87.22%) and oral progesterone group (86.13%), has no significant difference (RR=1.01; 95%CI:0.97-1.06; p=0.566). However, the research conducted by Shinwari *et al*.,[12] with the method of Progesterone administration through the vaginal indicates different results. Oral dydrogesterone (88.9%) is more effective in preventing miscarriage repeatedly compared to vaginal progesterone (66.7%) especially in women with age 20-30 yo with the incident of miscarriage with the previous occurrences of miscarriage less than four times (p=0.03). Based on the study by Kale *et al*.,[8] dydrogesterone is also faster in stopping the bleeding compared to vaginal progesterone (53.90 ± 9.09 vs 94.60 ± 7.29 hr, sequentially, p<0.0001). Nevertheless, there is no significant difference in both groups towards ongoing pregnancy until 24 weeks (p=0.5267) and until full-term pregnancy of 37 wk (p=0.5267).

A RCT conducted by McLindon *et al*.,[10] identified the role of progesterone and placebo via vaginal administration in women with a history of at least one-time bleeding and miscarriage previously toward normal and preterm birth. Progesterone intervention did not significantly result when compared with the group who received placebo (RR=0.98; 95%CI: 0.88-10.9; p=0.683) on the rate of live birth, preterm birth (RR=1.38; 95%CI: 0.69-2.78, p=0.361), and birth with miscarriage history previously (RR=0.95; 95%CI: 0.82-1.11; p=0.55). It was aligned with the study conducted by Coomarasamy *et al*.[7] showed that progesterone usage did not have any significant effect on the birth compared with placebo (RR=1.03; 95%CI: 1-1.07; p=0.07).

A study by Parveen *et al*.,[9] reported that evaluated the administration of progesterone via vaginal and oral. The study resulting that the use via oral was statistically had success in pregnancy at 91.8% (n=45) and 9.2% (n=4) experiencing a miscarriage, then compared to a group that received vaginal administration showed success in pregnancy at the rate of 73.5% (n=36) and miscarriage for about 26.5% (n=13; p=0.0164), thus progesterone via oral has better effectiveness than via vaginal in decreasing the risk of miscarriage.

Comparisons with other studies

The use of progesterone through oral in increasing the success of pregnancy has been confirmed in a systematic review and meta-analysis. Li *et al*.,[19] reported that identified the use of progesterone with placebo or without any medication for women with pregnancy threat in 10 meta-analysis articles (n= 5056 participants). The use of progesterone increasing birth occurrences statistically significant (RR=1.07; 95%CI:1-1.15; p=0.04) and can improve the rate of birth better than placebo (RR=1.17; 95%CI: 1.04-1.13; p=0.008) and via vaginal has a statistically insignificant value compared to placebo (RR=1.04; 95% CI:1.00–1.08; p=0.07).

Eight of nine studies in the meta-analysis conducted by Yan *et al*.,[17] showed the effect of progesterone in preventing miscarriage. The finding indicates that progesterone supplementation can reduce the rate of miscarriage compared to placebo (RR=0.70; 95%CI: 0.52-0.94; p=0.13). This outcome is consistent with the research

conducted previously by Haas *et al.*,[14] from twelve inclusion experiments, ten experiments showed that progesterone (27.5%) possibly can reduce the rate of miscarriage compared to placebo or control (20.1%) (RR=0.73; 95%CI: 0.54-1.00). The meta-analysis also indicated that the administration of progesterone via different administration way did not show any significant difference in preventing miscarriage (p=0.27).

Devall *et al.*,[15] arranged a meta-analysis to see the effectiveness of progesterone and dydrogesterone in preventing miscarriage. Micronized progesterone which is administered via vaginal can decrease the rate of miscarriage if compared with placebo (RR=0.90; 95% CI:0.80-1.01). Dydrogesterone showed the effectiveness than the placebo (RR=0.90; 95% CI:0.55-1.47). Progesterone vaginal was compared with dydrogesterone, resulting no significant difference between those two (RR=1.00; 95% CI:0.60-1.66). A meta-analysis by Guo *et al.*,[16] was conducted to investigate dydrogesterone efficacy compared with another intervention progesterone, human chorionic gonadotropin (hCG), placebo, and active immunization. The analysis indicates that the success rate of pregnancy and avoidance of miscarriage in the experiment group is significantly higher compared with the control group (OR =4.26; 95% CI:2.59–7.00; p=0.000). The meta-analysis by Zhao *et al.*,[18] discusses the effectiveness of progesterone on pregnant women who have a high risk of miscarriage and a history of miscarriages. The resulting study indicates that the use of progesterone is effective in preventing miscarriage by increasing the number of live births (RR=1.04; 95% CI:0.99-1.10).

Mechanism of progesterone on preventing miscarriage

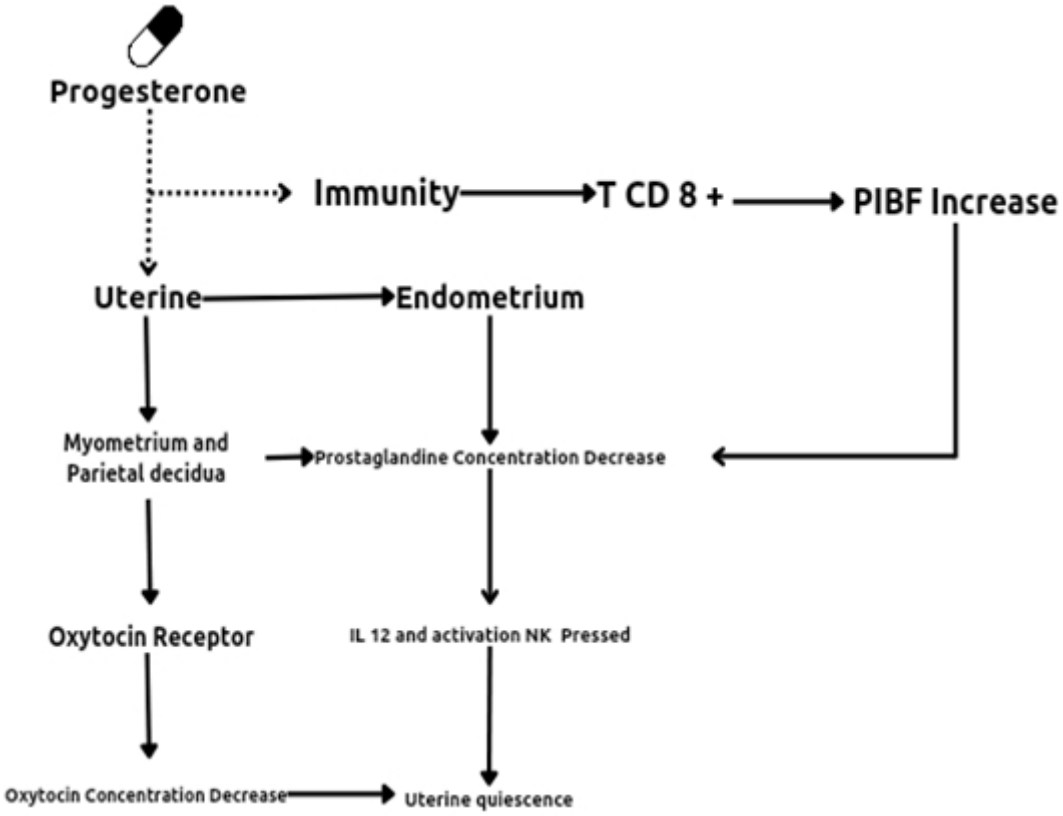

FIGURE 2. Mechanism of progesterone on preventing miscarriage

The uterus is calmed by the direct method of progesterone action through modifications in PGR-B isoform by activating the PAQR5, PAQR7, and PAQR8 receptors. This is accomplished by deregulating GJA1, oxytocin, and prostaglandins.

Progesterone also works by competing with oxytocin receptors in the parietal decidua and myometrium to reduce oxytocin production and preserve uterine relaxation during pregnancy. This method involves the closure of the Ca2+ ion pathway, which is known to produce contractions when the cytoplasmic concentration is high.[21] Progesterone also interacts with CD8+ T cells, which lower interleukin 12 and inhibit the activation of Natural Killer cells, hence reducing uterine contractions, according to another immune system mechanism.

In order to suppress NK activity and several cytokines, which lowers the concentration of prostaglandins produced in the endometrium and myometrium, and to suppress the production and sensitivity of cell receptors, which prevent contractions, progesterone-induced blocking factor (PIBF), which is increased by the interaction between progesterone and T CD8+, can inhibit T helper 1 cells and increase the activity of T helper 2 cells. The concentration of progesterone-induced blocking factor (PIBF) in pregnant women's urine indicates that this mediator rises at the start of pregnancy and falls when the baby is born.[21,22]

Gestational age towards miscarriage occurrences

In this study, gestational age does not play a significant role in miscarriage occurrences. It is known that the causes of miscarriage are related to the history of bleeding during pregnancy or having experienced at least one miscarriage previously. The bleeding during pregnancy observed occurred from the first to the second trimester.

Interpretation

In this review, the administration of natural progesterone or synthetic (dydrogesterone) supplementation might be beneficial in decreasing the miscarriage occurrences for women with bleeding risk and/or who have a miscarriage history. Dydrogesterone from synthetic progesterone has the same molecule structure as progesterone but has significantly higher bioavailability 5.6 times greater than progesterone 12 therefore, even with a small dose, it can already produce a clinical response.[23] During pregnancy, progesterone helps to inhibit the release of cytokines from cells T that result in uterine contractions. Progesterone binds to receptors on T cells, which are activated by antigens in response to the changes in the uterus, the administration of progesterone contributes to the thickening of the endometrium after fertilization for strengthening the attachment of the fetus and supporting the fulfillment of fetus nutrition through the blood vessels.[24,25] The administration of progesterone via different routes either vaginal or oral, has different effectiveness. Progesterone administration via vaginal has better absorption compared to the oral route. This is because the oral route will go through liver metabolism or first-pass effect for about 12% to become pregnanediol and its metabolites which are conjugated with glucuronic acid for excretion through urine which can reduce the drug's bioavailability.[26] Progesterone administration via the vaginal route is more effective in supporting the formation of the corpus luteum and is preferred by patients due to ease and comfort usage.[27] This is consistent with the result of meta-analysis and systematic reviews in this study, which show a significant difference

between vaginal and oral progesterone in preventing miscarriage. However, different outcomes were found in reviews of randomized controlled trials and cohort studies, it demonstrated that oral delivery outperformed the vaginal method in terms of effectiveness.

Progesterone as an intervention to prevent pregnancy is significantly harmful. The potential side effects are generally mild, such as headaches, dizziness, bloating, nausea, and breast pain.[7,28] These effects usually arise after oral progesterone usage. Meanwhile, vaginal progesterone may cause side effects such as dysmenorrhea and vaginal irritation due to local application.[11,29] Patients with liver function abnormalities, such as cholestasis, or cardiovascular conditions should utilize progesterone with caution.[28] The development of advanced formulations to improve oral bioavailability and reduce side effects could enhance its clinical application. Research on personalized approaches, considering genetic, hormonal, and medical factors, may further optimize progesterone therapy in preventing miscarriage.

Limitation

This review has several weaknesses such as the participants who have different baseline characteristics in every study (including gestational, history of pregnancy, and miscarriage history), intervention given (including kinds of progesterone, dose, route, and duration of administration) also definition of outcomes. Because of this, it is challenging to suggest the progesterone dosage and route that would be most helpful for women who are at risk of miscarriage.

CONCLUSION

Progesterone supplements may be beneficial for women who are at risk of miscarriage. From the result of this study, the recommended route of progesterone administration via the vaginal is more effective and safer compared to oral. A clinical study needs to be conducted on the participants with more homogenous baseline characteristics to minimize the bias of the study that can affect the validity of the research result.

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