REVIEW PAPERS

Progesterone in the prevention of recurrent miscarriage – up-to-date review

Progesteron w prewencji poronień nawracających – aktualny przegląd

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KEYWORDS:

- recurrent miscarriage
- pregnancy loss
- luteal phase deficiency
- bleeding in early pregnancy
- vaginal micronized progesterone

ABSTRACT

Progesterone plays a crucial role in female reproductive system regulation. As a result, many of its indications in obstetrics and gynecology have been discovered over the years. This narrative, up-to-date review aims to summarize current reports on the significance of progesterone in the prevention of recurrent miscarriage. It was mainly based on the latest guidelines, the most recent review articles and large, high-quality trials with well-chosen methodology, providing results of unquestionable value. All studies are available in PubMed, Medline, Embase, The Cochrane Library and the research was done by looking through phrases as follows: recurrent miscarriage, pregnancy loss, luteal phase deficiency, bleeding in early pregnancy, micronized vaginal progesterone. Selected studies have demonstrated that there is still no sufficient evidence for the benefits of progesterone administration in miscarriage prevention among symptom-free women with recurrent miscarriage. On the other hand, there are some reports of its positive impact in women struggling with both- recurrent miscarriage and bleeding in early pregnancy. It is reasonable to assume that in this group of women, all factors associated with pregnancy loss, including luteal phase defect (LPD), are more frequent. More research is needed for better identification of women with LPD, because (precisely) in these patients progesterone application may have the most relevant effect in recurrent miscarriage prevention.

SŁOWA KLUCZOWE:

- poronienia nawracające
- utrata ciąży
- niedomoga lutealna
- krwawienie we wczesnej ciąży
- dopochwowy mikronizowany progesteron

STRESZCZENIE

Progesteron odgrywa kluczową rolę w regulacji funkcji kobiecego układu rozrodczego. W związku z tym na przestrzeni lat odkryto wiele jego zastosowań w położnictwie i ginekologii. Niniejszy artykuł ma na celu podsumowanie aktualnych doniesień na temat znaczenia progesteronu w zapobieganiu poronieniom nawracającym. Opiera się na najbardziej aktualnych wytycznych, najnowszych artykułach przeglądowych i dużych, wysokiej jakości badaniach z adekwatną metodologią, dostarczających wyniki o niekwestionowanej wartości. Wszystkie artykuły dostępne są w PubMed, Medline, Embase, The Cochrane Library, a ich selekcję przeprowadzono przez wyszukiwanie następujących fraz: poronienia nawracające, utrata ciąży, defekt fazy lutealnej, krwawienie we wczesnej ciąży, mikronizowany progesteron dopochwowy. Wybrane badania wykazały, że nadal nie ma wystarczających dowodów na korzyści z podawania progesteronu w ramach prewencji poronień wśród bezobjawowych kobiet z poronieniami nawracającymi. Istnieją jednak doniesienia o pozytywnym wpływie progesteronu u kobiet zmagających się zarówno z nawracającymi poronieniami, jak i krwawieniem we wczesnej ciąży. Uzasadnione jest zatem założenie, że w wymienionej wyżej grupie kobiet wszystkie czynniki związane z utratą ciąży, w tym defekt fazy lutealnej (LPD), występują częściej. Potrzebne są dalsze badania w celu lepszej identyfikacji kobiet z LPD, ponieważ to właśnie u tych pacjentek stosowanie progesteronu może mieć największą skuteczność w zapobieganiu poronieniom nawracającym.

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Introduction

Progesterone is a steroid hormone that has always been associated with the female reproductive system (1). Due to the vital role of progesterone in the early stages of pregnancy, it is justifiable to postulate that progesterone deficiency may be responsible for some miscarriages, including recurrent miscarage. Consequently, there have been many clinical studies on progesterone supplementation in women who may have a high risk of miscarriage. The main challenge is to identify the risk factors and the target group that could receive the greatest benefits from this kind of treatment (2). Last but not least, this should result in the issuance and implementation of adequate, worldwide consistent guidelines.

Progesterone as an important female hormone

The molecular formula of progesterone was originally described by Allen in 1933. However, progesterone production did not begin until the mid-1940s. It was initiated by Russell Marker, who used diosgenin as a substrate (3). In the human body progesterone is synthesized from cholesterol. It is secreted mainly by the corpus luteum of the ovary and the placenta during pregnancy, and to a lesser extent by the adrenal cortex (1). Progesterone influences estrogen-dependent secretory transformation of the endometrium, allowing nesting and nourishment of the blastocyst, and is therefore essential for maintaining pregnancy (3, 4). Further it is responsible for relaxing the enlarging uterus and inhibiting its contractions by reducing sensitivity to oxytocin and the production of prostaglandins. Just as significantly, progesterone modifies the mother's immune response preventing fetal rejection (5). It is also relevant outside the reproductive system. It takes a part in the preparation of the mammary gland for breastfeeding. In addition, progesterone is important for the appropriate functioning of the central nervous system, cardiovascular system and bones (3).

Definition of recurrent miscarriage

The term "miscarriage" refers to the spontaneous demise of a pregnancy before the fetus is able to function independently (6, 7, 8). While the current scientific literature encompasses within this definition all pregnancy losses occurring from the time of conception up to the 22nd week of gestation, the referenced articles consistently establish the 24th week of gestation as the definitive cutoff point (7, 8). Among miscarriages, recurrent miscarriage constitutes a distinct clinical entity, which is defined in many different ways depending on the study, authors and country. According to the Royal College of Obstetricians and Gynaecologists (RCOG), recurrent miscarriage represents 3 consecutive pregnancy deprivations until 24 weeks. On the other hand, the American Society for Reproductive Medicine (ASRM) defines it as a two first trimester consecutive miscarriages confirmed by ultrasonography or histopathological examination. Other research mentions three pregnancy forfeitures, including biochemical pregnancies (6). Another definition is provided by the European Society of Human Reproduction and Embryology (ESHRE), specifying the term "recurrent pregnancy loss" (RPL). It describes loss of two or more pregnancies, but does not include ectopic pregnancy and molar pregnancy (7, 8). However, regardless of a definition, this kind of scenario affects approximately 1% of couples striving to conceive (6, 9, 10, 11).

Causes of recurrent miscarriage

The most common causes of miscarriages in general are undoubtedly various numerical chromosome abnormalities with trisomy at the top which, not coincidentally, correlate with the advanced maternal age. Altogether, aneuploidies are responsible for around one half of all miscarriages, including recurrent pregnancy losses (2). It is pertinent to emphasize the outcomes of a retrospective analysis of Nagoya City University Medical Hospital. Miscarriages that are results of chromosomal aberrations occur randomly,

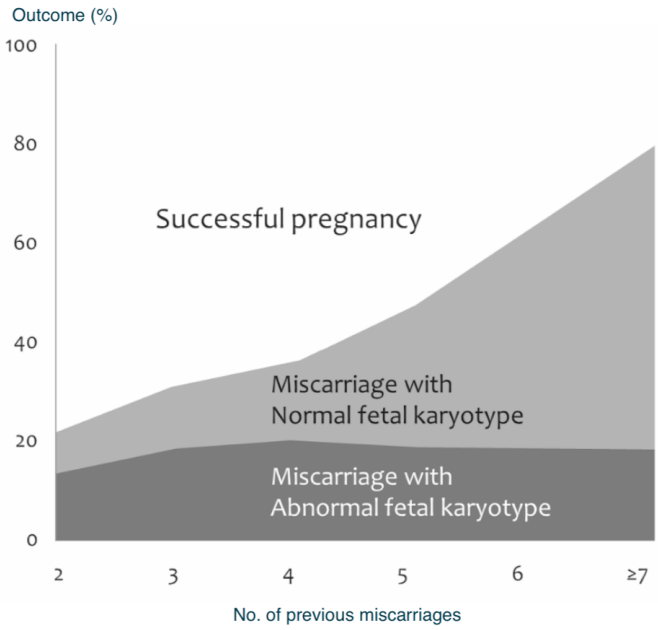

Figure. 1 Miscarriage risk by the number of previous miscarriages (own elaboration).

Table 1. Maternal high evidence level factors of recurrent miscarriage (6).

Type of factors	High evidence level factors
hormonal factors	luteal phase deficiency
epidemiological factors	advancing maternal age
	number of previous miscarriages
	women with BMI<19 or BMI>25 kg/m²
	excess caffeine consumption
acquired thrombophilia	antiphospholipid antibodies
anatomical factors	congenital uterine anomalies
endocrine factors	thyroid autoantibodies

Table 2. Subgroup analysis (13).

Subgroup	The incidence of live births	
	progesterone group	placebo group
women with no previous miscarriages (relative rate, 0.99; 95% CI, 0.95 to 1.04)	74%	75%
women with one or two previous miscarriages (relative rate 1.05; 95% CI, 1.00 to 1.12)	76%	72%
women with three or more previous miscarriages (relative rate, 1.28; 95% CI, 1.08 to 1.51; P = 0.007)	72%	57%

so the risk of a subsequent miscarriage remains constant. In contrast, the risk of "euploid" miscarriage increases with each (consequent) experienced miscarriage (12).

The aforementioned statements consolidate the underlying causes of recurrent pregnancy loss, attributing them to maternal factors. All potential maternal causes of recurrent miscarriage with high evidence level are summarized in Table 1. However, in nearly 50% of recurrent pregnancy losses still no unequivocal cause can be established (5, 6, 9, 10).

Aim of the article

The inspiration for this article came from the fact that it is very difficult to find consistent information and research results concerning the administration and effectiveness of progesterone in recurrent miscarriage. A similar situation affects recurrent miscarriage itself – there is no explicit directives or even definition. Therefore, the most up-to-date guidelines and research results on the mentioned issue were collected in order to establish a common conclusion and suggestions for clinicians.

Materials and methods of the study

Electronic databases such as PubMed, Medline, and Embase were searched using the following keywords: recurrent miscarriage, pregnancy loss, luteal phase defect, bleeding in early pregnancy, and micronized vaginal progesterone. The search was limited to the latest guidelines, recent review articles, and large, high-quality trials featuring well-defined methodologies that provide results of unquestionable value. All studies included had to be peer-reviewed and published in English. Additionally, publications for which the full text was not accessible were excluded. Relevant studies identified during the review of these articles were also included in the analysis.

Review of current evidence and guidelines

Progesterone in the first trimester of pregnancy among women diagnosed with unexplained recurrent miscarriage

Assuming that one of the causes of euploid miscarriages is a luteal phase deficiency, it is conceivable that progesterone may have a beneficial effect on maintaining pregnancy in women struggling with recurrent miscarriage (2). That has prompted the performance of the PROMISE study conducted by Coomarasamy and co-authors. This multicenter, double-blind, placebo-controlled, randomized trial took place at 36 medical centers in the United Kingdom and nine hospitals in the Netherlands between 2010 and 2013. To be eligible for the study, women had to fit the following conditions: 18-39 years old, natural conception within a year, 3 or more unexplained recurrent miscarriage (after thrombophilia, endocrinopathies, anatomical defects, genetic defects exclusion). Thus, 835 patients were qualified and randomly assigned into two groups: research (404 patients) and control (431 patients). Women in the first group received 400 mg of micronized progesterone (Utrogestan) twice-daily vaginal from the moment of a positive pregnancy test (before 6 weeks of pregnancy) until the 12th week of pregnancy. In contrast, the second group was treated with placebo. The appearance of the drugs, as well as the route and timing of their administration, were identical in both groups. The principal outcome was live birth after 24 completed weeks of gestation. The percentage of patients with accessible data for the primary outcome was 98.8% (826 of 836 women). The rate of live births was 65.8% (262 of 398 women) in the progesterone group and 63.3% (271 of 428 women) in the placebo group [relative rate, 1.04; 95% confidence interval (CI), 0.94 to 1.15; rate difference, 2.5 percentage points; 95% CI, -4.0 to 9.0]. There were no significant between-group differences. As a result, the study found no significant increase in live birth rates with the use of vaginal progesterone in pregnancy among women diagnosed with unexplained recurrent miscarriage (10).

Progesterone in the first trimester of gestation in women presenting with vaginal bleeding in early pregnancy

Progesterone could perform an equally important role in women with bleeding in early pregnancy, as LPD is often manifested precisely by vaginal bleeding (2). The subject was developed in the PRISM study conducted by Coomarasamy et al. This was a multicenter, randomized, double-blind, placebo-controlled study ongoing from 2015 to 2017 in 46 medical institutions located across the United Kingdom. The research included 4153 patients who had experienced vaginal bleeding before the 12th week of confirmed intrauterine pregnancy. Moreover, they were 16-39 years old, had no contraindications to progesterone, and were not using other progesterone preparations. Patients were randomly selected to groups taking placebo (2074 women) or progesterone (2079 women). In this study, 400 mg of micronized progesterone (Utrogestan) was used vaginally or transrectally twice-daily from the onset of bleeding, until 16th week of gestation. Live births after the completed 34th week of pregnancy were defined as the principal aim of the study. The follow-up rate for the primary outcome was 97% (4038 of 4153 women). The frequency of live births after completed 34 weeks of pregnancy was 75% (1513 of 2025 women) in the progesterone group and 72% (1459 of 2013 women) in the placebo group (relative rate, 1.03; 95% CI, 1.00 to 1.07; P = 0.08). There were no substantial between-group differences in the entire analyzed group, but there was one subgroup of participants where a considerable difference in the number of live births according to the number of miscarriages in the medical history was shown. The analysis of the results of this subgroup is illustrated in Table 2. The study revealed that among women with bleeding in early gestation, progesterone administration in pregnancy did not result in a remarkably higher rate of live births in general. There is a suggestion of benefit of progesterone usage among patients who have experienced three or more miscarriages and present reproductive tract bleeding in early pregnancy (13).

Recommendations for practice in the management of recurrent miscarriages

Table 3 presents the most recent recommendations for the prevention of recurrent miscarriage created by the following

Table 3. Recommendations for practice in the management of recurrent miscarriages (5, 6, 8, 11, 14, 15, 16, 17).

Organization	Miscarriage prevention	Miscarriage prevention in women with bleeding in early pregnancy
FIGO -2023- (11)	Preconception progesterone supplementation is not recommended	–
	Progesterone supplementation during pregnancy is not generally recommended	
	Oral progesterone during pregnancy might have a beneficial impact on recurrent miscarriages, more research required	
NICE -2023- (14)	–	It is recommended to offer 400 mg of vaginal progesterone twice daily to women with an ultrasound-confirmed intrauterine pregnancy, accompanied by vaginal bleeding and a history of miscarriage
RCOG -2023- (6)	Considerable caution is recommended in the routine use of progesterone in asymptomatic women with recurrent miscarriage, as studies have shown no significant difference in pregnancy outcomes in these cases	It is worth considering progesterone supplementation in women with recurrent miscarriage if they experience bleeding in early pregnancy (suggested dose: 400 mg of micronized vaginal progesterone twice a day until 16 weeks of pregnancy)
ESHRE -2022- (8)	The administration of progesterone in women with RPL and luteal phase deficiency is not recommended because there is insufficient evidence of its positive influence on the live birth rate in this group of patients	Progesterone administered vaginally may enhance live birth rates in women with 3 or more pregnancy losses and vaginal bleeding in a subsequent pregnancy
The Lancet Series on Miscarriage -2021- (15, 16, 17)	Progesterone supplementation may increase life birth rate for women with a history of recurrent miscarriage	The usage of progesterone may reduce the risk of miscarriage in women with bleeding in early pregnancy and history of recurrent miscarriage
PSGO -2015- (5)	There is lack of evidence on the efficacy of gestagens	There is no sufficient evidence on the effectiveness of gestagens
		According to clinical studies, the usage of vaginal progesterone reduces symptoms and the risk of miscarriage

organizations: Polish Society of Gynecologists and Obstetricians – PSGO (5), Royal College of Obstetricians and Gynaecologists – RCOG (6), European Society of Human Reproduction and Embryology – ESHRE (8), International Federation of Gynaecology and Obstetrics – FIGO (11), National Institute for Health and Care Excellence – NICE (14), The Lancet Series on Miscarriage (15, 16, 17).

Summary

This review of studies and recommendations submitted by a number of reputable organizations determining current trends in the treatment of specific disease entities has shown that the topic of progesterone in recurrent miscarriage remains unclear. To begin with, there is a lack of accuracy when it comes to the exact definition of recurrent miscarriage. The authors are fairly unanimous in their conclusion that there is no evidence of a positive effect of progesterone use in women with recurrent miscarriage but without symptoms. Only a more detailed analysis with subgrouping of study participants showed a correlation between progesterone use and a higher percentage of live births in a group of women with vaginal bleeding and a history of recurrent miscarriages. For this reason, some recommendations advise considering progesterone supplementation in this type of patient. Above conclusion is important because it paves the way for further studies aimed at identifying a target point for progesterone, thereby facilitating better identification of patients who would benefit most from its administration.

Conclusion

Progesterone plays an important role in maintaining pregnancy especially in its early stages. At this moment, there is no thorough evidence of the effectiveness of progesterone usage in miscarriages prevention among asymptomatic women diagnosed with recurrent miscarriage. Therefore, it is generally not recommended in this group of patients. On the other hand, there are some suggestions about beneficial effects of progesterone administration in women who have experienced bleeding in early pregnancy and simultaneously have a history of recurrent miscarriages. This is the reason for considering its inclusion in such a clinical situation. In this group of patients any pathology responsible for pregnancy loss, including LPD, could reasonably be anticipated to be more prevalent. There is still room for improvement in the field of research on meaningful testing for luteal phase defect, and consequently identifying women for whom progesterone supplementation would be the most profitable.

Limitations of the study

The limitations of this article primarily arise from its methodological framework. First and foremost, our objective was to adopt a comprehensive approach to the topic while selecting the most influential studies featuring large, randomized participant cohorts. In fact, the article predominantly relies on the findings of two studies: PROMISE and PRISM. Furthermore, the interpretation of the results inevitably remains subjective, shaped by our understanding and perspective, which may not encompass all conceivable interpretations.

Declaration of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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