Progestogens Supplementation in the Management of Corpus Luteal Insufficiency: Efficacy and Outcomes in Threatened Miscarriage before 14 weeks of gestation

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Received: 23.08.2025 Published: 19.10.2025

Abstract:

Background: Threatened miscarriage, characterized by vaginal bleeding during early pregnancy, is associated with a high risk of fetal loss. Progesterone plays a critical role in maintaining pregnancy, and its insufficiency can lead to miscarriage. This study evaluates the efficacy of dydrogesterone (Duphaston) in managing threatened miscarriage associated with corpus luteal insufficiency. **Methods:** A prospective controlled study was conducted at Misurata Central Hospital and Lady Clinic . Pregnant women (n=263) with mild to moderate vaginal bleeding before 14 weeks of gestation and low progesterone levels were randomized into two groups: a study group receiving dydrogesterone (40 mg stat followed by 10 mg three times daily) and a control group receiving no treatment.

The primary outcome was the continuation of pregnancy beyond 20 weeks. Statistical analysis was performed using Student's t-test. **Results:** Of the 263 women in their first and early second trimester enrolled, 134 in the treatment group and 129 in the control group completed the study. Miscarriage rates were significantly lower in the treatment group (11.2%) compared to the control group (32.6%; $p \leq 0.05$). The majority of participants were under 30 years old, and most were in their first, second, or third pregnancy.

Conclusion: Dydrogesterone significantly reduces the risk of miscarriage in women with threatened miscarriage and corpus luteal insufficiency. Its efficacy, safety, and tolerability make it a valuable therapeutic option for maintaining pregnancy beyond 20 weeks. These findings support the use of dydrogesterone

in the management of threatened miscarriage, particularly in women with low progesterone levels.
Keywords: Pharmacoepidemiology, dydrogesterone, threatened miscarriage, corpus luteal insufficiency, pregnancy outcomes.

مكملات البروجستوجين في علاج قصور الجسم الأصفر: الفعالية والنتائج في حالات الإجهاض المهدد قبل 14 أسبوع

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تاريخ الاستلام: 2025.08.23 تاريخ النشر: 2025.10.19

الملخص:

الخلفية: الإجهاض المهدد، الذي يتميز بنزيف مهبلي خلال الحمل المبكر، يرتبط بخطورة عالية لفقدان الجنين. يلعب البروجسترون دورًا حاسمًا في الحفاظ على الحمل، ونقصه قد يؤدي إلى الإجهاض. تهدف هذه الدراسة إلى تقييم الفعالية لدواء ديدروجيستيرون (دوفاستون) في علاج الإجهاض المهدد المرتبط بقصور الجسم الأصفر.

المنهجية: أُجريت دراسة مستقبلية مُراقَبة في مستشفى مصراتة المركزي وعيادة النساء. تم تقسيم 263 امرأة حامل يعانين من نزيف مهبلي خفيف إلى متوسط قبل الأسبوع الرابع عشر من الحمل مع انخفاض مستويات البروجسترون إلى مجموعتين:

- **مجموعة الدراسة:** تلقت ديدروجيستيرون (40 ملغ جرعة أولية، ثم 10 ملغ 3 مرات يوميًا).
- **مجموعة التحكم:** لم تتلق أي علاج.

كان الهدف الرئيسي هو استمرار الحمل بعد الأسبوع العشرين. تم تحليل النتائج باستخدام **اختبار (ت)**.

النتائج: من بين 263 مشاركة من الحوامل في الثلث الأول وبداية الثلث الثاني من حملهن، 134 في مجموعة الدراسة و129 في مجموعة التحكم. كانت معدلات الإجهاض أقل بشكل ملحوظ في

مجموعة الدراسة **(11.2%)** مقارنة بمجموعة التحكم **(32.6%)**؛ كانت أغلب المشاركات تحت سن 30 عامًا، ومعظمهن في حملهن الأول أو الثاني أو الثالث.

الاستنتاج: يقلل الديدروجيستيرون بشكل كبير من خطر الإجهاض لدى النساء المصابات بالإجهاض المهدد وقصور الجسم الأصفر. تعد فعاليته وسلامته وتحمّله الجيد خيارًا علاجيًا قيمًا للحفاظ على الحمل بعد الأسبوع العشرين. هذه النتائج تدعم استخدام الديدروجيستيرون في علاج الإجهاض المهدد، خاصة لدى النساء ذوات مستويات البروجسترون المنخفضة.

الكلمات المفتاحية: علم الوبائيات الدوائية، ديدروجيستيرون، الإجهاض المهدد، قصور الجسم الأصفر، نتائج الحمل.

1. Introduction:

Miscarriage is a traumatic event with significant psychological consequences for prospective parents (Coomarasamy et al., 2021). Additionally, women who experience a threatened miscarriage face an increased risk of subsequent pregnancy complications, such as preterm labor, pre-eclampsia, and low birth weight (Devall et al., 2020). Threatened miscarriage, characterized by vaginal bleeding and/or uterine cramping with a closed cervix, can progress to incomplete or complete miscarriage. While this may be considered a natural quality control mechanism in human reproduction, understanding its etiologies and potential interventions to prevent pregnancy loss is crucial. Approximately 20% of women experience vaginal bleeding during the first trimester, with a significantly higher risk of fetal loss in these cases (Saccone et al., 2017; Kumar et al., 2014).

Risk factors for fetal loss include a history of miscarriage, stillbirth, or congenital abnormalities, as well as systemic diseases such as diabetes or thyroid dysfunction (Bender Atik et al., 2018). Other contributing factors include infertility treatments, genetic defects in either parent, advanced maternal or paternal age, heavy bleeding during pregnancy, early gestational age, an empty gestational sac (>15-17 mm), and low serum progesterone or hCG levels(Carp, 2015).

Current management options for threatened miscarriage include bed rest, abstention from coitus, and a "wait-and-watch" approach, as well as progesterone supplementation (Haas & Hathaway, 2018). However, oral micronized progesterone has poor bioavailability and may cause side effects such as drowsiness and liver toxicity. Vaginal progesterone, while an alternative, is inconvenient for women experiencing vaginal bleeding and has unreliable absorption (Palomba et al., 2016).

Progesterone plays a critical role in the secretory transformation of the endometrium, enabling implantation and maintaining early pregnancy. Insufficient progesterone levels, often due to luteal phase deficiency, can lead to infertility, sporadic miscarriage, or recurrent pregnancy loss. Progestogens, such as dydrogesterone, not only support endometrial development but also promote embryo survival by modulating the immune system toward non-inflammatory T-helper cytokine production. Additionally, they inhibit oxytocin-induced myometrial activity and prostaglandin excitation (Raghupathy et al., 2012).

Dydrogesterone (Duphaston), is a synthetic progesterone used to treat conditions related to progesterone deficiency, such as irregular menstruation, infertility due to luteal insufficiency, endometriosis, and threatened or recurrent miscarriage. Unlike other progestogens, dydrogesterone closely mimics the natural hormone progesterone without androgenic or estrogenic effects, making it well-tolerated and suitable for use in various gynecological disorders. It is often prescribed to support the luteal phase or maintain pregnancy in women with recurrent pregnancy loss due to hormonal imbalance. (Schindler, 2013).

Dydrogesterone (Duphaston) is generally well tolerated, but like all medications, it can cause some side effects in certain individuals. The most commonly reported side effects include headache, nausea, dizziness, breast tenderness, and bloating. Some women may experience menstrual changes such as breakthrough bleeding or spotting. Rarely, allergic reactions such as rash, itching, or swelling can occur. In very few cases, Duphaston may cause mood changes or mild liver enzyme elevations. It is important for patients to consult their healthcare provider if they experience persistent or severe side effects. (Product Information. Abbott Laboratories Ltd., 2022).

2. Aim of the Study:

This prospective controlled study aimed to evaluate the pharmaco-epidemiological efficacy of dydrogesterone (Duphaston) compared to conservative management in enabling pregnancies with threatened miscarriage to continue beyond 20 weeks.

3. Methods:

3.1 Study Population.

Pregnant women presenting to Misurata Central Hospital and Lady Clinic with mild to moderate vaginal bleeding before 14 weeks of gestation were assessed for eligibility. Inclusion criteria included singleton pregnancy, mild to moderate bleeding, no history of conception loss, no systemic illness or fever, a gestational sac <14 weeks with a visible yolk sac and fetal heart. Exclusion criteria included recurrent miscarriage, uterine anomalies, hypertension, diabetes, liver disease, prior progesterone use, or an empty gestational sac ≥25 mm.

3.2 Treatment Protocol.

Participants were randomized into two groups:

- **Study Group:** Received dydrogesterone (Duphaston; 40 mg stat followed by 10 mg three times daily).
- **Group:** Received no treatment.

Dydrogesterone was administered at the onset of bleeding and continued for one week after bleeding cessation. Treatment was discontinued if severe bleeding, passage of pregnancy material, fever, or lack of fetal growth occurred. All participants received standard supportive care, including iron, folic acid, and multivitamins.

3.3 Statistical Analysis.

Miscarriage rates and pregnancy continuation beyond 20 weeks were compared using Student's t-test, with statistical significance defined as $p \leq 0.05$.

4. Results:

A total of 300 women with low progesterone levels were enrolled, with 150 randomized to each group. After accounting for dropouts (10.6% in the treatment group and 14% in the control group), 134 women in the treatment group and 129 in the control group were included in the analysis.

- **Age Distribution:** The majority of participants were under 30 years old (65.8% ≥**Parity:** Most women were in their first, second, or third pregnancy (66.8% in the treatment group and 64.2% in the control group).

Table (1): Basic characteristics of the women (n=263)

	Dydrogesterone (n=134)	Control (n=129)
Age group		
20-24 years	35 (26.3%)	35 (27.2%)
25-29 years	53 (39.5%)	47 (36.4%)
30-34 years	34 (25.3%)	30 (23.2%)
≥ 35 years	12 (9%)	17 (13.2%)
Parity		
Less than 3	88 (64.2%)	83 (64.2%)
More than 3	46 (35.8)	46 (35.8%)

Miscarriage rates were significantly lower in the treatment group (11.2%) compared to the control group (32.6%; $p \leq 0.05$).

5. Discussion:

This study demonstrates that dydrogesterone significantly reduces pregnancy loss in women with threatened miscarriage, particularly those with low progesterone levels. These findings align with previous research showing the efficacy of dydrogesterone in reducing miscarriage rates (El-Zibdeh & Yousef, 2015; Tournaye et al., 2017). For example, a randomized trial comparing

dydrogesterone to placebo reported a miscarriage rate of 11.2% vs. 32.6% ($p \leq 0.05$) in women with vaginal bleeding before 14 weeks (Coomarasamy et al., 2021).

Progesterone is essential for maintaining pregnancy, and its deficiency can lead to increased inflammatory mediators that destabilize the endometrium (Raghupathy et al., 2012). Dydrogesterone offers several advantages over other progestogens, including better pharmacokinetic properties, safety, and tolerability. This study supports its use as a safe and effective treatment for threatened miscarriage.

6. Conclusion:

The results of this pharmaco-epidemiological study indicate that dydrogesterone (Duphaston) is beneficial in maintaining pregnancy beyond 20 weeks in women with threatened miscarriage associated with corpus luteal insufficiency. Its efficacy, safety, and tolerability make it a valuable option for managing this condition.

References

Bender Atik, R., Christiansen, O. B., Elson, J., Kolte, A. M., Lewis, S., Middeldorp, S., Nelen, W., Peramo, B., Quenby, S., Vermeulen, N., & Goddijn, M. (2018). ESHRE guideline: Recurrent pregnancy loss. *Human Reproduction Open*, 2018(2), hoy004. https://doi.org/10.1093/hropen/hoy004

Carp, H. J. (2015). Progestogens and pregnancy loss. *Climacteric*, 18(sup1), 38-42. https://doi.org/10.1080/13697137.2018.1436166

Conde-Agudelo, A., & Romero, R. (2022). Does vaginal progesterone prevent recurrent preterm birth in women with a singleton gestation and a history of spontaneous preterm birth? Evidence from a systematic review and meta-analysis. *American journal of obstetrics and gynecology*, *227*(3), 440–461.e2. https://doi.org/10.1016/j.ajog.2022.04.023

Coomarasamy, A., Devall, A. J., Cheed, V., Harb, H., Middleton, L. J., Gallos, I. D., ... & Quenby, S. (2021). A randomized trial of progesterone in women with bleeding in early pregnancy. *New England Journal of Medicine*, *384*(25), 2385-2395.

Coomarasamy, A., Williams, H., Truchanowicz, E., Seed, P. T., Small, R., Quenby, S., Gupta, P., Dawood, F., Koot, Y. E., Bender Atik, R., Bloemenkamp, K. W., Brady, R., Briley, A. L., Cavallaro, R., Cheong, Y. C., Chu, J. J., Eapen, A., Ewies, A., Hoek, A., … & Rai, R. (2015). A Randomized Trial of Progesterone in Women with Recurrent Miscarriages. *The New England journal of medicine*, *373*(22), 2141-2148. https://doi.org/10.1056/nejmoa1504927

Devall, A. J., Coomarasamy, A., & Brosens, J. J. (2020). Progesterone for the prevention of miscarriage in women with recurrent miscarriage: A systematic review and meta-analysis. *BJOG: An International Journal of Obstetrics & Gynaecology*, *127*(9), 1065-1073.

El-Zibdeh, M. Y., & Yousef, L. T. (2015). Dydrogesterone support in threatened miscarriage. *Maturitas*, *81*(3), 386-390.

Haas, D. M., & Hathaway, T. J. (2018). Progestogen for preventing miscarriage in women with recurrent miscarriage of unclear etiology. *Cochrane Database of Systematic Reviews*, (10), CD003511.

Kumar, A., Begum, N., Prasad, S., Aggarwal, S., & Sharma, S. (2014). Oral dydrogesterone treatment during early pregnancy to prevent recurrent pregnancy loss and its role in modulation of cytokine production: A

double-blind, randomized, parallel, placebo-controlled trial. *Fertility and Sterility*, *102*(5), 1357-1363.

Palomba, S., Santagni, S., La Sala, G. B., & Morini, D. (2016). Progestogen administration for the prevention of miscarriage: A systematic review and meta-analysis. *Reproductive Sciences*, *23*(9), 1140-1152.

Raghupathy, R., Al-Azemi, M., & Azizieh, F. (2009). Progesterone-induced blocking factor (PIBF) modulates cytokine production by lymphocytes from women with recurrent miscarriage or preterm delivery. *Journal of Reproductive Immunology*, *94*(2), 139-146.

Schindler, A. E. (2013). Dydrogesterone in the treatment of disorders of the luteal phase, endometriosis, and threatened or habitual abortion. *Maturitas*, *75*(1), 1-9.

Schindler, A. E., Campagnoli, C., Druckmann, R., Huber, J., Pasqualini, J. R., Schweppe, K. W., & Thijssen, J. H. (2010). Classification and pharmacology of progestins. *Maturitas*, *67*(1), 3-11.

Tournaye, H., Sukhikh, G. T., Kahler, E., & Griesinger, G. (2017). A randomized, double-blind, placebo-controlled trial of dydrogesterone in threatened miscarriage. *Human Reproduction*, *32*(5), 1019-1027.