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ORIGINAL ARTICLE

Dydrogesterone vs. Progesterone: Which is More Effective in Threatened Miscarriage?

Didrogesteron vs. Progesteron: Düşük Tehdidinde Hangisi Daha Etkili?

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ABSTRACT

Background/Aims: Threatened miscarriage, marked by vaginal bleeding during the first 20 weeks of pregnancy, is a frequent complication with potential adverse outcomes. Dydrogesterone and micronized progesterone are commonly prescribed to manage this condition, yet their comparative efficacy remains under debate. This study aims to evaluate the effectiveness and safety of dydrogesterone versus micronized progesterone in treating threatened miscarriage.
Methods: A retrospective case-control study was conducted at Our Hospital, including 123 pregnant women aged 6 to 20 weeks presenting with uterine bleeding. Participants were divided into two groups based on receiving either dydrogesterone (n=56) or micronized progesterone (n=67). Pregnancy outcomes, including miscarriage rates, preterm labor, and mode of delivery, were recorded and analyzed using SPSS software.
Results: The miscarriage rate was slightly higher in the dydrogesterone group (9.6%) compared to the progesterone group (5.9%), though this difference was not statistically significant (p=0.729). Both groups exhibited high rates of successful delivery, with no significant difference between them (p>0.05). Additionally, no significant differences were observed in the incidence of pregnancy complications or mode of delivery between the two groups.
Conclusion: Both dydrogesterone and micronized progesterone are effective in managing threatened miscarriage, with no significant differences in pregnancy outcomes. Further large-scale, randomized trials are needed to confirm these findings and refine treatment guidelines.

Keywords: Dydrogesterone, Miscarriage prevention, Progesterone, Progestin therapy, Threatened miscarriage

ÖZ

Amaç: İlk 20 haftalık hamilelik döneminde vajinal kanama ile belirginleşen abortus imminens, olumsuz sonuçlar doğurabilecek sık karşılaşılan bir komplikasyondur. Bu durumu yönetmek için yaygın olarak dydrogesteron ve mikronize progesteron reçete edilmektedir, ancak bu iki ilacın karşılaştırmalı etkinliği halen tartışılmaktadır. Bu çalışmanın amacı, düşük tehdidini tedavi etmede dydrogesteron ve mikronize progesteronun etkinliğini ve güvenliğini değerlendirmektir.
Yöntemler: Hastanemizde retrospektif vaka-kontrol çalışması yapıldı ve vajinal kanama ile başvuran 6 ila 20 haftalık 123 hamile kadın dahil edildi. Katılımcılar dydrogesteron (n=56) veya mikronize progesteron (n=67) almalarına göre iki gruba ayrıldı. Düşük oranları, erken doğum ve doğum şekli gibi hamilelik sonuçları kaydedildi ve SPSS yazılımı kullanılarak analiz edildi.
Sonuçlar: Düşük oranı dydrogesteron grubunda (%9,6), progesteron grubuna kıyasla (%5,9) biraz daha yüksek olmasına rağmen, bu fark istatistiksel olarak anlamlı değildi (p=0,729). Her iki grup da yüksek başarılı doğum oranları sergiledi ve aralarında anlamlı bir fark bulunmadı (p>0,05). Ayrıca, her iki grup arasında hamilelik komplikasyonları veya doğum şekli açısından anlamlı farklar gözlemlenmedi.
Sonuç: Hem dydrogesteron hem de mikronize progesteron, düşük tehdidini yönetmede etkili olup, hamilelik sonuçlarında anlamlı fark bulunmamıştır. Bu bulguları doğrulamak ve tedavi kılavuzlarını netleştirmek için daha büyük ölçekli, randomize çalışmalara ihtiyaç vardır.

Anahtar Kelimeler: Gebelik, Miyom, Sezaryen miyomektomi, Üçüncül merkez

Introduction

Threatened miscarriage, characterized by vaginal bleeding during the first 20 weeks of pregnancy, is a common complication that can lead to significant anxiety and potential pregnancy loss. The use of progestogens, such as dydrogesterone and micronized progesterone, has been explored as a therapeutic intervention to prevent miscarriage in these cases (1, 2). However, the comparative efficacy of these two treatments remains a subject of ongoing research and debate. A meta-analysis by Devall et al.aligns with previous findings indicating that while progestogens may have limited impact on live birth rates for women with threatened or recurrent miscarriage, vaginal micronized progesterone could potentially increase live birth rates in women with a history of previous miscarriages and early pregnancy bleeding (3). Dydrogesterone, an

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oral retrosteroid with a structure closely related to that of natural progesterone, has been shown to have greater bioavailability and higher selectivity for the progesterone receptor compared to micronized progesterone (4). Several studies have investigated the effectiveness of dydrogesterone in reducing the incidence of miscarriage in women with threatened miscarriage. For instance, a systematic review and meta-analysis demonstrated that dydrogesterone significantly lowers the miscarriage rate compared to placebo, indicating its potential as a beneficial treatment option (5-7). A study is consistent with findings from a randomized controlled trial that found oral dydrogesterone at a dosage of 20 mg/day did not significantly prevent miscarriage in women with threatened miscarriage (8). On the other hand, micronized progesterone, administered either orally or vaginally, is another commonly used progestogen for managing threatened miscarriage. A randomized controlled trial comparing micronized progesterone and dydrogesterone found no significant difference in miscarriage rates between the two treatments, although micronized progesterone led to higher post-treatment serum progesterone levels (1, 9). Additionally, a systematic review highlighted that while both treatments are effective, dydrogesterone may offer advantages in terms of fewer side effects, such as drowsiness and giddiness, compared to micronized progesterone (10).

The choice between dydrogesterone and micronized progesterone for treating threatened miscarriage is a complex process influenced by factors such as patient tolerance, side effect profiles, and individual biochemical responses to treatment. Given the critical role of progesterone in pregnancy maintenance and the uncertainty surrounding the optimal form of administration, this study aims to compare the efficacy and safety of these two widely used forms of the hormone—dydrogesterone and micronized progesterone. By examining the relative benefits and potential drawbacks of these treatments, this research seeks to provide valuable insights that will aid clinicians in making more informed treatment decisions and improve outcomes for women experiencing early pregnancy complications.

Material Methods

This retrospective case control study was conducted at Our Hospital, involving pregnant women with a gestational age of 6 to 20 weeks who presented with uterine bleeding and a closed cervix upon vaginal examination. All participants underwent ultrasound evaluation prior to inclusion in the study. Exclusion criteria included the presence of fetal or uterine abnormalities, absence of fetal heart rate, multiple pregnancies, hydatidiform mole, pelvic inflammatory disease, and underlying conditions such as cardiopulmonary disease, thyroid disorders, renal or hepatic dysfunctions, diabetes, and any history of receiving drug therapy for threatened abortion (TA). Additionally, mothers who did not consent to participate were excluded from the study.

Participants were randomly assigned to one of two study groups using a random number table. Group 1 received 10 mg dydrogesterone tablets (Duphaston® by Abbott Co.) twice daily (every 12 hours), while Group 2 received 200 mg micronized progesterone soft gel (Progestan® by Kocak Farma.) twice daily (every 12 hours). The hormone treatment was administered from the time of admission until two weeks after the cessation of bleeding.

Participants were followed and provided with prenatal care according to national guidelines until the conclusion of their pregnancies. Pregnancy outcomes and any associated complications were recorded and compared between the two groups. Data collection was conducted using a checklist that included demographic information such as age, gestational age, gravidity and parity. Additionally, complications such as, preterm labor, preterm rupture of membrane, ablation placenta and abortion were documented.

This study was approved by the Ethics Committee for Non-Drug and Non-Medical Device Research of KTO-Karatay University with the document date and number: 01.07.2024-87661 and the decision number 2024/64.

Statistical Analysis

Statistical analyses were conducted using SPSS software version 23 (IBM, Chicago, IL, USA). Quantitative variables were presented as mean ± standard deviation (SD), while qualitative variables were reported as frequency and percentage. The normality of the data distribution was assessed using the Kolmogorov-Smirnov test. Pregnancy outcomes between the two groups were compared using independent t-tests, chi-square tests, and Fisher's exact test, with a P-value of less than 0.05 considered statistically significant.

Results

Tables 1 presents a comparative analysis of demographic and clinical characteristics between the Dydrogesterone (n=56) and Progesterone (n=67) groups.

Table 1: Demographic and clinical characteristics of patients

Variable	Dydrogesterone (n=56)	Progesteron (n=67)	p-value
Age, years	28.18 ± 2.19	27.13 ± 2.49	>0.05
Gravida, median	2.34±1.53	2.58±1.88	>0.05
Parity, median	1.07±1.33	1.15±1.29	>0.05
Gestational week mean	7.69 ± 0.38	7.1 ± 0.38	>0.05
Marital Status, n -Single -Married -Other	- 50 (89.2(%) 6 (10.71%)	- 67 (100%) -	>0.05
Educational Status, n -Illiterate -Primary Education -High School -Higher Education	- 10 (17.9%) 39 (69.6%) 7 (12.5%)	- 8 (11.9%) 51 (76.1%) 8 (11.9%)	>0.05
Occupation, n -Employed -Unemployed	17 (30.4%) 39 (69.6%)	28 (41.7%) 39 (58.2%)	0.02
Socioeconomic Status, n -Low -Medium -High	5 (8.9%) 40 (71.4%) 11 (19.6%)	7 (10.4%) 49 (73.1%) 11 (16.4%)	>0.05
Smoking, n -No -Yes	56 (100%) -	65 (97.1%) 2 (2.99%)	>0.05
Alcohol Use, n -No -Yes	56 (100%) -	67 (100%) -	>0.05
Ethnicity, n -Turkish -Asian -African -European	46 (82.1%) 2 (3.57%) 3 85.35%) 5 (8.9%)	57 (85%) 1 (1.49%) 2 (2.98%) 7 (10.4%)	>0.05

The mean age of participants in the Dydrogesterone group was 28.18 ± 2.19 years, slightly higher than the Progesterone group, which had a mean age of 27.13 ± 2.49 years. This difference was not statistically significant ($p > 0.05$). The median number of pregnancies (gravida) was similar between the groups, with the Dydrogesterone group reporting a median of 2.34 ± 1.53 and the Progesterone group reporting 2.58 ± 1.88. The difference was not statistically significant ($p > 0.05$). The mean gestational age at the time of the study was 7.69 ± 0.38 weeks for the Dydrogesterone group and 7.1 ± 0.38 weeks for the Progesterone group. The observed difference was not statistically significant ($p > 0.05$). The ethnic composition of the groups was predominantly Turkish, with no statistically significant differences between the groups ($p > 0.05$).

Table 2 compares maternal and perinatal outcomes between the Dydrogesterone and Progesterone groups.

Table 2: The effect of progestin suppositories on threatened abortion based on maternal and perinatal characteristics

Variable	Dydrogesterone (n=56)	Progesteron (n=67)	Chi-Square	df	p-value
Miscarriage	5 (9.6%)	4 (5.9%)	0.000	0	0.729
Successful delivery	47 (83.9%)	59 (88%)	0.000	0	1.000
Parity -Nulliparous -Multiparous	42 (75%) 14 (25%)	54 (80.5%) 13 (19.4%)	0.279	1	0.597
Pain -Yes -No	14 (25%) 42 (75%)	19 (28.3%) 48 (71.6%)	0.046	1	0.830
Vaginal bleeding -Moderete -Spotting	10 (17.8%) 46 (82.1%)	13 (19.4%) 54 (80.6%)	0.000	1	1.000
Gestational Age (week) ≤8 week 8-16 week ≥16 week	2 (3.6%) 44 (78.6%) 10 (17.9)	7 (10.4) 45 (67.2) 15 (22.4)	2.700	1	0.239
Mode of Delivery, n - Vajinal - Sezeryan	40 (71.4%) 16 (28.6%)	51 (76.1%) 16 (23.9%)	0.148	1	0.701
Congenital Anomalies, n -No -Yes	47 (100%) -	59 (100%) -	-	-	-
Pregnancy complications, n PROM Preterm birth Placental Abruption None	2 (4.25%) 5 (10.6%) 1 (2.1%) 39 (82.9%)	4 (6.78%) 8 (13.6%) 3 (5.08%) 44 (74.6%)	1.319	3	0.725

PROM: premature rupture of membranes

The incidence of miscarriage was 9.6% in the Dydrogesterone group and 5.9% in the Progesterone group. The Chi-Square test revealed no statistically significant difference between the groups ($p = 0.729$). Successful delivery rates were 83.9% in the Dydrogesterone group and 88% in the Progesterone group, with no statistically significant difference ($p = 1.000$). The mode of delivery did not differ significantly between the groups, with similar proportions of vaginal and caesarean deliveries ($p = 0.701$). The incidence of pregnancy complications was slightly higher in the Progesterone group, but this difference was not statistically significant ($p = 0.725$).

Discussion

The management of threatened miscarriage often involves the use of progestogens, with dydrogesterone and micronized progesterone being the most commonly prescribed. The effectiveness of these treatments has been the subject of numerous studies, and the results provide valuable insights into their comparative efficacy and safety. Both dydrogesterone and micronized progesterone show similar efficacy in reducing miscarriage rates in women with threatened miscarriage (9-11)

Several studies have demonstrated that both dydrogesterone and micronized progesterone are effective in reducing the incidence of miscarriage in women experiencing threatened miscarriage. A systematic review and meta-analysis found that the incidence of miscarriage was significantly lower in the total progesterone group compared to the control group, with oral dydrogesterone showing a more pronounced effect than vaginal progesterone (11). Another study confirmed that dydrogesterone significantly reduced the risk of miscarriage compared to conservative management alone (12).

The TRoMaD study, a randomized controlled trial, compared the clinical outcomes of women treated with micronized progesterone (MP) and dydrogesterone (DYD). The study found no significant difference in the rates of miscarriage and resolution of bleeding between the two groups. However, fewer patients treated with DYD reported side effects such as drowsiness and giddiness, suggesting a better tolerability profile for dydrogesterone (10).

Multiple meta-analyses have reinforced the efficacy of dydrogesterone in preventing miscarriage. One such review highlighted a 47% reduction in the odds of miscarriage with dydrogesterone compared to standard care, indicating a substantial treatment effect (5, 6). Another review concluded that dydrogesterone is an essential component in the treatment of recurrent pregnancy loss due to its significant impact on reducing miscarriage rates (13).

The safety profile of dydrogesterone has been well-documented, with minimal adverse effects reported in clinical studies. This makes it a preferable option for many clinicians and patients (4, 14). In contrast, micronized progesterone, particularly when administered vaginally, has been associated with local side effects such as vaginal discharge and irritation (14).

This study has several limitations that should be considered when interpreting the results. Firstly, the retrospective design of the study may introduce selection bias, as the data were collected from medical records rather than through prospective enrollment. This could affect the generalizability of the findings to broader populations.

Secondly, the sample size, while adequate for initial comparisons, was relatively small. This limits the statistical power of the study to detect smaller differences between the groups, particularly in rare outcomes such as specific pregnancy complications or adverse effects.

Thirdly, the study was conducted at a single center, which may limit the external validity of the findings. Variations in clinical practice, patient populations, and healthcare systems across different regions could influence the applicability of the results.

Furthermore, patient adherence to the prescribed medication regimens was self-reported, which could lead to inaccuracies in assessing the true impact of the interventions.

Lastly, the study did not include a placebo or no-treatment control group, which makes it difficult to assess the absolute effectiveness of dydrogesterone and micronized progesterone compared to no treatment.

Future studies with larger sample sizes, prospective designs, and multi-center participation are needed to confirm these findings and further explore the nuances of treatment outcomes in threatened miscarriage.

Conclusion

Both dydrogesterone and micronized progesterone are effective in managing threatened miscarriage. There are no statistically significant differences in most maternal and perinatal outcomes between the Dydrogesterone and Progesterone groups, except for occupation status, where a significant difference was observed. The observed connection between occupation status and the choice of dydrogesterone or progestin use appears to be entirely coincidental, with no underlying causal relationship.The choice between these treatments should be guided by individual patient profiles. Further large-scale, randomized controlled trials are warranted to solidify these findings and optimize treatment protocols for threatened miscarriage.

Conflict of Interest Statement

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References

1.Bolger LA, O'Riordan N, Allen C. A rapid improvement event: progesterone prescribing in prevention of miscarriage. BMJ Open Qual. 2024;13(1).

2.Duncan WC. Did the NICE guideline for progesterone treatment of threatened miscarriage get it right? Reprod Fertil. 2022;3(2):C4-c6.

3.Devall AJ, Papadopoulou A, Podesek M, Haas DM, Price MJ, Coomarasamy A, et al. Progestogens for preventing miscarriage: a network meta-analysis. Cochrane Database Syst Rev. 2021;4(4):Cd013792.

4.Mirza F, Patki A, Pexman-Fieth C. Dydrogesterone use in early pregnancy. Gynecological Endocrinology. 2016;32:106-97.

5.Tetruashvili N, Shih E. Efficacy of Dydrogesterone in Threatened Miscarriage: a Systematic Review and Meta-analysis. DoctorRu. 2022.

6.Carp H. A systematic review of dydrogesterone for the treatment of threatened miscarriage. Gynecological Endocrinology. 2012;28:983-90.

7.Lou C, Wang C, Zhao Q, Jin F. Effect of dydrogesterone and progesterone on threatened miscarriage due to corpus luteum insufficiency. Am J Transl Res. 2021;13(5):4544-52.

8.Kuptarak A, Phupong V. Oral dydrogesterone for prevention of miscarriage in threatened miscarriage: a randomized, double-blind, placebo-controlled trial. J Matern Fetal Neonatal Med. 2024;37(1):2333929.

9.Shayna S, Celene Yan Yan H, Tan T, Allen J, Malhotra R, Truls Ø. Micronized Progesterone Compared With Dydrogesterone for Threatened Miscarriage: A Randomized Controlled Trial [328]. Obstetrics & Gynecology. 2015;125:104.

10.Jia Yun SS, Allen J, Hui CY, Ku CW, Malhotra R, Truls Ø, et al. The randomised controlled trial of micronised progesterone and dydrogesterone (TRoMaD) for threatened miscarriage. European journal of obstetrics, gynecology, and reproductive biology. 2018;228:319-24.

11.Hee-Joong L, Park T, Jae Hoon K, Norwitz E, Lee B. The Influence of Oral Dydrogesterone and Vaginal Progesterone on Threatened Abortion: A Systematic Review and Meta-Analysis. BioMed Research International. 2017;2017.

12.Ramachandhiran Udayar P. Dydrogesterone in threatened miscarriage: a Malaysian experience. Maturitas. 2009;65 Suppl 1.

13.Carp H. Progestogens in the prevention of miscarriage. Hormone Molecular Biology and Clinical Investigation. 2016;27:55-62.

14.Pandya M, Gopeenathan P, Gopinath P, Das S, Meenakshi S, Veena S. Evaluating the clinical efficacy and safety of progestogens in the management of threatened and recurrent miscarriage in early pregnancy- A review of the literature. Indian Journal of Obstetrics and Gynecology Research. 2016;3:157-66.