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Review

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Anat J Obstet Gynecol Res 2025;2(3):99-110

The Role of Dydrogesterone in the Management of Threatened Miscarriage: A Systematic Review of Randomized Controlled Trials

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ABSTRACT

Threatened miscarriage affects approximately 20% of pregnancies and results in pregnancy loss in around half. Progesterone therapy is the most commonly applied pharmacological approach. The efficacy and safety of dydrogesterone were systematically evaluated and compared with micronized/vaginal progesterone for management of threatened miscarriage using analysis of randomized controlled trials (RCTs). Following Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines, RCTs published between January 1, 1980, and September 1, 2025, were screened. The inclusion criteria comprised patients diagnosed with threatened miscarriage in the first trimester, use of dydrogesterone or micronized/vaginal progesterone as intervention, and placebo or conservative approach as comparator. Twelve RCTs involving around 6000 participants were included. Miscarriage rates across the studies ranged from 10% to 33.3%. Large-scale, placebo-controlled studies did not show a significant improvement in live birth rate with vaginal/micronized progesterone compared to placebo (e.g., 20% vs. 22% miscarriage rate, $p>0.05$). Similarly, dydrogesterone did not provide significant superiority compared to placebo in large trials (12.8% vs. 14.3%, $p=0.772$). However, smaller studies reported a significant reduction in miscarriage rates compared to conservative approach (e.g., 12.5% vs. 28.4%, $p<0.05$). Some studies showed that dydrogesterone was associated with earlier cessation of vaginal bleeding, while vaginal progesterone reduced pain and uterine contractions. Adverse events were uncommon but sedation occurred more frequently with vaginal or micronized progesterone. Although pharmacovigilance data have suggested possible associations of dydrogesterone with hypospadias and congenital heart anomalies, no such relationship was confirmed in RCTs. RCT evidence regarding progesterone support in threatened miscarriage is heterogeneous and does not demonstrate a consistent effect in increasing live birth in the general population. While dydrogesterone has advantages for symptom control and practical ease of use, its effect on live birth is no different from other management strategies. Progesterone therapy should be individualized considering patient risk profile and clinical characteristics. Future biomarker-guided RCTs with robust methodology may help resolvie uncertainties and defining the specific subgroups that would benefit from personalized treatment.

Keywords: Dydrogesterone, progesteron, miscarriage

INTRODUCTION

Vaginal bleeding that may be accompanied by pelvic pain without cervical dilation before the 20th week of pregnancy is termed threatened miscarriage.[1] Threatened miscarriage affects approximately 20% of pregnancies and miscarriage occurs in approximately half of affected pregnancies.[2,3]

In cases of threatened miscarriage, bed rest, avoidance of sexual intercourse, or a wait-and-see approach may be applied, while the main treatment option is progesterone. Progesterone deficiency in early pregnancy has been reported to lead to miscarriage.[4] Progesterone has a critical role in the continuation of pregnancy. In the luteal phase, it induces secretory changes in the endometrium that facilitate implantation and support early pregnancy.[5] Progesterone plays a role in supporting immune tolerance throughout pregnancy and in the relaxation of uterine smooth muscles.[6,7] Based on these clinical findings, many studies have investigated the efficacy and safety of progesterone in cases of threatened miscarriage, but the results have been inconsistent.[8-11] Oral micronized progesterone has

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low bioavailability and is associated with side effects such as drowsiness, while vaginal progesterone may be difficult to administer in women with bleeding and impaired absorption when bleeding is substantial.[12]

Dydrogesterone is an orally administered progestin with a profile similar to physiological progesterone. High bioavailability, high selectivity, and administration at lower doses prevent the occurrence of progestogenic side effects.[13] A recent study suggested an association between dydrogesterone used in early pregnancy and congenital defects.[14] The present review will examine the role of dydrogesterone in pregnancies under threat of miscarriage based on randomized controlled trials (RCTs).

METHODS

For this systematic review, the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were followed. The protocol for this systematic review was not prospectively registered. However, to ensure transparency and minimize bias, the review process strictly adhered to the PRISMA checklist, and all eligibility criteria and data extraction procedures were defined a priori. Studies conducted with oral micronized progesterone, vaginal micronized progesterone, and dydrogesterone were systematically collected.

Inclusion Criteria

Studies conducted between January 1, 1980, and September 1, 2025, were included according to the population, intervention, comparison, outcome, and study design (PICOS) framework, as follows; (1) Population - women diagnosed with threatened miscarriage in the first trimester (vaginal bleeding and/or pelvic pain + viable pregnancy confirmed by ultrasonography); (2) Intervention - oral micronized progesterone, vaginal micronized progesterone, or dydrogesterone supplementation; (3) Comparison - comparison of dydrogesterone or micronized progesterone with placebo (inert capsules) or conservative management (observation-only/standard care) controls; comparison of vaginal micronized progesterone with oral micronized progesterone or placebo; comparison of oral micronized progesterone with placebo (4); Outcome measure - miscarriage before the 20th week of pregnancy, ongoing pregnancy after the 20th week of pregnancy, or live birth rates (5); Study design - compilation of RCTs conducted on the effects of dydrogesterone, oral micronized progesterone, and vaginal micronized progesterone on threatened miscarriages.

Exclusion Criteria

Non-randomized studies, reviews and meta-analyses, case reports, animal experiments, studies conducted for luteal support in IVF/ assisted reproductive techniques (ART) cycles, and studies conducted with indications other than threatened miscarriage.

Information Sources

Information was obtained from online databases such as Web of Science, PubMed, Cochrane, Embase, and Google Scholar.

Search

A search strategy containing appropriate keywords was created to identify relevant studies in electronic databases and was applied to access articles. Search terms included a combination of medical subject headings (MeSH) and free-text keywords related to progesterone, dydrogesterone, and threatened miscarriage. Boolean operators (AND, OR) were used to refine the results. The full electronic search strategy for PubMed is presented in Supplementary Appendix 1. Manual search (back referencing) was performed in the reference section to find possible articles that automatic search could not find. We also searched clinical trial registries (ClinicalTrials.gov, WHO, International Clinical Trials Registry Platform) to identify ongoing or unpublished trials, but no completed trials meeting the inclusion criteria were found. Gray literature was excluded as per the exclusion criteria.

Study Selection

The screening process was conducted independently by two reviewers to select relevant articles for systematic review. The initial search identified 1245 articles (Figure 1). Then, 315 duplicate articles were removed. In the second step, 930 articles were screened and evaluated for eligibility for the study. Of these, 780 articles were excluded for reasons such as inability to access full text and lack of relevance to the subject. Of the remaining 150 articles examined, 137 were excluded because they were not RCTs. Consequently, a total of 12 RCTs were included in this review-comprising 7 studies on dydrogesterone and 5 on micronized progesterone-as detailed in Table 1.

Data Collection Process

An Excel spreadsheet was used for the data extraction process covering the basic study characteristics described in the data elements subsection. Data extraction and verification were performed by two reviewers. In cases of disagreement, consensus was reached through discussions.

Data Elements

The following data were extracted: Author, year of publication, country, sample size, study design, intervention regimen and dose, comparison group, and primary outcome measures were extracted through a standard form.

Quality Assessment

The methodological quality of included RCTs was evaluated using the Cochrane risk of bias 2 (RoB 2) tool. Randomization, allocation concealment, blinding, completeness of outcome data, selective reporting, and other potential sources of bias were examined.

Data Synthesis

The primary outcome measure was determined as the miscarriage rate occurring before the 20th week of pregnancy. Secondary outcome measures were ongoing pregnancy after the 20th week of pregnancy, live birth, and maternal and fetal side effects. The feasibility of a meta-analysis was assessed

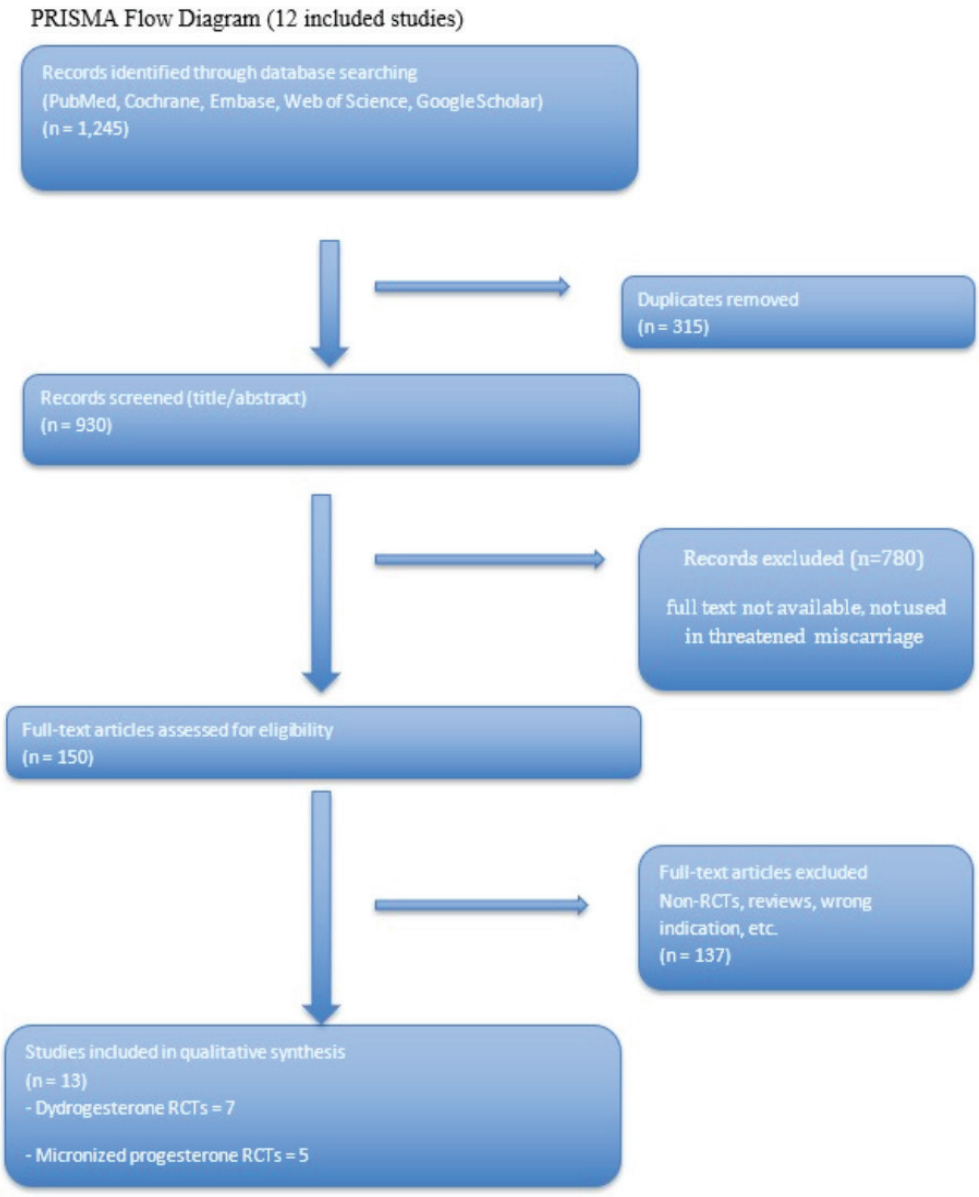


Figure 1. PRISMA flow diagram (12 included studies)

PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses, RCTs: Randomized controlled trials

based on clinical and methodological homogeneity. Specifically, we evaluated the similarity of participants, intervention protocols (dose and route), comparator groups (placebo vs. conservative), and outcome definitions across studies. Due to substantial diversity observed in these domains, a quantitative synthesis was deemed inappropriate to avoid misleading results, and a narrative synthesis was conducted. The risk of bias assessment (RoB 2) was primarily used to guide the interpretation of the findings. Studies judged to have a high risk of bias were discussed cautiously, although none were formally excluded, reflecting the heterogeneous nature of the available evidence.

RESULTS

Included studies opted for different forms of control. Six studies used placebo (Chan et al.,[11] Kuptarak and Phupong[15],

Table 1. RCT findings

Study	Patient number	Group/dose	Miscarriage rate	Statistics	Comment
Chan et al.[11]	406	DYD 40 mg stat +10 mg ×3/day vs. placebo	12.8% vs. 14.3%	RR 0.897, $p=0.772$	Not significant
Kuptarak and Phupong[15]	100	DYD 20 mg/day vs. placebo	10% vs. 14%	$p=0.538$	Not significant
El-Zibdeh and Yousef[16]	146	DYD 10 mg ×2 vs. conservative	17.5% vs. 25%	$p<0.05$	In favor of DYD
Pandian[17]	191	DYD 40 mg loading +10 mg x2/day vs. conservative	12.5% vs. 28.4%	$p<0.05$	In favor of DYD
Siew et al.[18]	118	DYD 10 mg x2/day vs. MP 200 mg x2/day	15.2% vs. 10.2%	$p=0.581$	Not significant
Kale et al.[19]	200	DYD 30 mg vs. 600 mg/day VMP	30% vs. 25%	$p=0.5267$	Not significant
Kumar and Chandersheikhar[20]	90	DYD 10 mg x2/day vs. omp 200 x2/day	11% vs. 11%	Ns	Not significant
McLindon et al.[21] (STOP trial)	278	VMP 400 mg vs. placebo	14.7% vs. 15.8%	0.805	Not significant
Coomarasamy et al.[10]	4153	VMP 400 mg/day vs. placebo	20% vs. 22%	Ns	Not significant
Alimohamadi et al.[22]	160	VMP 400 mg/day vs. placebo	16.9% vs. 14%	Ns	Not significant
Yassaee et al.[9]	60	VMP 400 mg/day vs. placebo	20% vs. 33.3%	$p=0.243$	Not significant
Gerhard et al.[23]	56	VMP 25 mg x2/day vs. placebo	11% vs. 19%	$p>0.05$	Not significant

DYD: Dydrogesterone, VMP: Vaginal micronized progesterone, RCT: Randomized controlled trial

McLindon et al.[21], Coomarasamy et al.[10], Alimohamadi et al.[22], Gerhard et al.[23]), while three studies utilized conservative management/observation only (El-Zibdeh and Yousef[16], Pandian[17], Yassaee et al.[9]) as the comparator.

Regarding the comparison between dydrogesterone and placebo**,** a double-blind study conducted by Chan et al.[11] in Hong Kong included 406 women. Participants had pregnancies with viable embryos at 6-10 weeks with vaginal bleeding. The intervention group received 10 mg dydrogesterone three times daily after an initial dose of 40 mg. The miscarriage rate was 12.8% in the dydrogesterone group and 14.3% in the placebo group (RR 0.897, $p=0.772$). Live birth rate was also similar (81.3% vs. 83.3%). While the strength of the study is the sample size, its limitation is its focus on low-risk patient profile.

In a double-blind RCT conducted by Kuptarak and Phupong[15] in Thailand, 100 patients were included, 50 women were treated with 20 mg dydrogesterone and the other 50 women with placebo. Women who were at 6-12 weeks of pregnancy and in whom a viable embryo was detected were included in the study. The rate of reaching the 20th week of pregnancy was 90% in the dydrogesterone group and 86% in the placebo group ($p=0.538$).

In a trial comparing dydrogesterone with conservative management reported by El-Zibdeh and Yousef[16] in Jordan, 146 patients were evaluated. The study group consisted of women who had previously miscarried and presented with bleeding. The miscarriage rate was 17.5% in the group receiving dydrogesterone, while it was 25% in the control group receiving conservative care ($p<0.05$).[16] The study suggests that dydrogesterone may reduce the miscarriage rate.

In a study conducted by Pandian[17] in Malaysia, 191 patients without a history of recurrent miscarriage were included. The included patients were divided into two groups, the miscarriage rate was 12.5% in the group receiving dydrogesterone and 28.4% in the conservative follow-up group.[17] The ongoing pregnancy rate was significantly higher in favor of dydrogesterone (87.5% vs. 71.6%; $p<0.05$).

A study conducted in Singapore with 118 patients directly compared micronized progesterone and dydrogesterone in threatened miscarriage. No difference was observed between the groups using micronized progesterone and dydrogesterone in terms of miscarriage rate and resolution of vaginal bleeding, but drowsiness was reported to be significantly more common in the group using micronized progesterone.[18] In subgroup analysis according to serum progesterone levels, in women with low progesterone levels, the miscarriage rate was found to be significantly higher, regardless of treatment type.

In a study conducted in India by Kale et al.[19] 200 pregnant women who presented with risk of miscarriage before the 12th week of pregnancy and had previously had >2 miscarriages were included in the study. One hundred pregnant women were assigned to the dydrogesterone group and 100 to the vaginal progesterone group.[19] The women in the dydrogesterone group were given 30 mg/day oral dydrogesterone, and the pregnant women in the progesterone group were given 600 mg/day vaginal progesterone. The time required for cessation of bleeding was significantly shorter in the dydrogesterone group compared to the progesterone group ($p<0.0001$). Furthermore, the number of pregnancies reaching the 24th week was higher in the dydrogesterone group, but the difference was not significant.

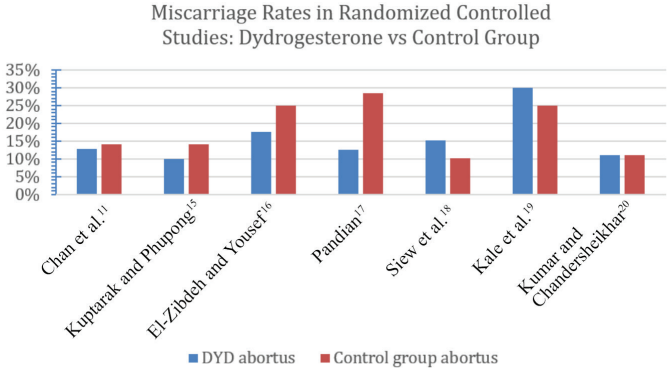
In a small RCT conducted by Kumar and Chandersheikhar[20] in India, 84 patients were included. One group was given 20 mg/day oral dydrogesterone while the other group was given 400 mg/day oral progesterone.[20] Although there was no significant difference between the groups in terms of miscarriage, bleeding ceased earlier in the dydrogesterone group.

Finally, concerning the efficacy of micronized/vaginal progesterone versus placebo, the STOP Trial conducted in Australia compared vaginal progesterone with placebo and 278 pregnant women at <10 weeks were included. However, the study was terminated because miscarriage rates (14.7% vs. 15.8%, $p=0.805$) and live birth rates were similar.[21]

In a study conducted with 836 patients by Coomarasamy et al.[10] to measure the effect of progesterone in recurrent pregnancy losses, it was reported that there was no significant difference in miscarriage and live birth rates (20% vs. 22%) between the group using oral progesterone and the control group.[10]

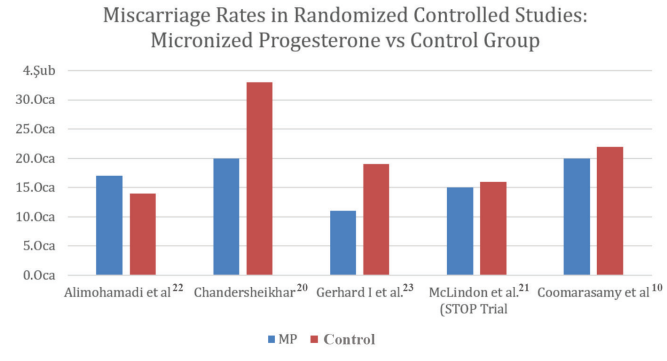
In another single-center RCT conducted in Iran, pregnant women at <20 weeks with threatened miscarriage were included. One group was given 400 mg/day vaginal progesterone while the control group was given placebo.[8] It was reported that there was no difference between the progesterone group and the control group in terms of miscarriage (16.9% vs. 14%), preterm birth, birth weight, and week of delivery.

Another study was conducted in Iran by Yassaee et al.[9] with 60 patients. Of these 30 patients were given 400 mg/day vaginal progesterone while the control group was followed without treatment.[9] The miscarriage rate between the two groups was not different ($p=0.243$).



Graph 1. Miscarriage rates in randomized controlled studies: dydrogesteron vs. control group

DYD: Dydrogesterone



Graph 2. Miscarriage rates in randomized controlled studies: micronized progesterone vs. control group

In a small-scale RCT conducted by Gerhard et al.[23] in Germany, 56 patients were included. Although the study, with its methodological limitations, suggested that vaginal progesterone may be useful in threatened miscarriage, the difference with the control group was not significant.

In terms of safety outcomes, none of the included RCTs explicitly reported cases of hypospadias or congenital heart anomalies in the dydrogesterone or control groups. Maternal adverse events were generally mild; however, drowsiness was reported significantly more frequently in groups treated with micronized progesterone compared to dydrogesterone.

Miscarriage Rates: Visual Comparison

The miscarriage rates in dydrogesterone and control groups are compared graphically in Graphic 1 and Graphic 2.

DISCUSSION

In this systematic review, the efficacy and safety of dydrogesterone and micronized/vaginal progesterone in threatened miscarriage were compared with placebo or conservative approach. In the included RCTs, miscarriage before the 20th week or ongoing pregnancy/live birth rates at ≥24 weeks were mostly used as primary endpoints; secondarily, the duration of improvement of bleeding and pain, side effects, and (in some studies) cytokine profile were evaluated.

When live birth or continuation of pregnancy was evaluated, the superiority of vaginal/micronized progesterone over placebo was not been consistently demonstrated in large and methodologically strong studies.[10,21] When RCTs showing that dydrogesterone was not superior to placebo and studies signaling in favor of dydrogesterone against conservative follow-up are evaluated together, the evidence of efficacy appears heterogeneous. This heterogeneity is thought to arise from differences in patient selection, initial gestational week, timing of treatment initiation, dose/duration, and primary endpoint definitions and the wide time span (1980-2025) of the included studies, which reflects evolving diagnostic and clinical practices.

Some studies showed that bleeding and pain improved more rapidly with dydrogesterone or vaginal/micronized progesterone. However, symptomatic improvement did not reflect a general increase in live birth rates.

Dydrogesterone may have practical advantages with high oral bioavailability, selectivity, and lower sedation profile. However, there was no consistent evidence for increased live birth rate. A similar result was found for vaginal/micronized progesterone. In clinical practice, this suggests that precise definition of indication and the correct combination of timing-dose-duration are important.

Serious adverse events were rare in the included RCTs; both drugs appeared safe for short-term use. Sedation was more frequently reported with vaginal/micronized progesterone. Dydrogesterone is an orally administered active progestin and previous studies have shown that dydrogesterone treatment reduced the risk of miscarriage.[16,24] There is not much research on the relationship between dydrogesterone and adverse pregnancy outcomes. A 2009 review summarized 28 reported

cases of various congenital birth defects; musculoskeletal defects and complex birth defects were the most common types, followed by masculinization, genitourinary defects, neural tube defects, and eye defects.[25] The data did not provide evidence for an association between congenital malformations and dydrogesterone use. In the vigibase study conducted by Henry et al.[14] in 2025, although attention was drawn to the increase in hypospadias and congenital heart anomalies in children of pregnant women using dydrogesterone, the fact that no causality could be established and that the study was only conducted on patients using dydrogesterone for ART should not be ignored even if it is not a proven side effect of dydrogesterone. However, no such association was reported in the RCTs conducted with dydrogesterone that we have examined. However, this highlights the necessity of conducting RCTs with large cohorts on this subject.

In a study conducted by Li et al.[26], exposure to maternal progesterone in the first trimester was found not to increase the frequency of adverse pregnancy outcomes after maternal age and comorbidities were adjusted for. Thus, studies conducted on prevention of threatened miscarriage suggest an importance for, drowsiness and decreased perception caused by progesterone rather than birth defects should be considered.

Study Limitations

Limitations of evidence include high heterogeneity among studies, sample differences, lack of blinding in some studies, and diversity in primary endpoint definitions.

We believe that the clinical implications are that there is no convincing evidence for routine progesterone support to most women with threatened miscarriage. However, individualized use in selected subgroups may be beneficial.

CONCLUSION

RCT evidence regarding progesterone support in threatened miscarriage is mixed and does not demonstrate a consistent effect in increasing live birth. Dydrogesterone may offer advantages for symptom control and ease of use. However, benefits such as increased live birth rate may be limited to selected subgroups. In light of current data, progesterone should be considered in an individualized manner taking into account patient-centered risk profile and symptoms, rther than being prescribed routinely. New, well-designed, biomarker-guided RCTs with adequate power are necessary to define which patients truly benefit and if there are any adverse fetal effects of dydrogesterone.

Footnotes

Author Contributions

Surgical and Medical Practices: K.H., A.Ö., İ.B., Concept: A.Ö., Design: K.H., A.Ö., Data Collection And Processing: K.H., İ.B., Analysis And Interpretation: K.H., A.Ö., Literature Search: K.H., İ.B., Writing: K.H., İ.B.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

REFERENCES

1. Simpson JL. Causes of fetal wastage. Clin Obstet Gynecol. 2007;50(1):10-30.
2. Everett C. Incidence and outcome of bleeding before the 20th week of pregnancy: prospective study from general practice. BMJ. 1997;315(7099):32-34.
3. Weiss JL, Malone FD, Vidaver J, et al. Threatened abortion: a risk factor for poor pregnancy outcome, a population-based screening study. Am J Obstet Gynecol. 2004;190(3):745-750.
4. Palomba S, Santagni S, La Sala GB. Progesterone administration for luteal phase deficiency in human reproduction: an old or new issue? J Ovarian Res. 2015;8:77.
5. Schindler AE. First trimester endocrinology: consequences for diagnosis and treatment of pregnancy failure. Gynecol Endocrinol. 2004;18(1):51-57.
6. Szekeres-Bartho J, Barakonyi A, Polgar B, et al. The role of gamma/delta T cells in progesterone-mediated immunomodulation during pregnancy: a review. Am J Reprod Immunol. 1999;42(1):44-48.
7. Hidalgo A, Suzano RC, Revuelta MP, Sánchez-Diaz C, Baamonde A, Cantabrana B. Calcium and depolarization-dependent effect of pregnenolone derivatives on uterine smooth muscle. Gen Pharmacol. 1996;27(5):879-885.
8. Ali S, Majid S, Niamat Ali M, Taing S, El-Serehy HA, Al-Misned FA. Evaluation of etiology and pregnancy outcome in recurrent miscarriage patients. Saudi J Biol Sci. 2020;27(10):2809-2817.
9. Yassaee F, Shekarriz-Foumani R, Afsari S, Fallahian M. The effect of progesterone suppositories on threatened abortion: a randomized clinical trial. J Reprod Infertil. 2014;15(3):147-151.
10. Coomarasamy A, Williams H, Truchanowicz E, et al. A randomized trial of progesterone in women with recurrent miscarriages. N Engl J Med. 2015;373(22):2141-2148.
11. Chan DMK, Cheung KW, Ko JKY, et al. Use of oral progestogen in women with threatened miscarriage in the first trimester: a randomized double-blind controlled trial. Hum Reprod. 2021;36(3):587-595.
12. Norman TR, Morse CA, Dennerstein L. Comparative bioavailability of orally and vaginally administered progesterone. Fertil Steril. 1991;56(6):1034-1039.
13. Schindler AE, Campagnoli C, Druckmann R, et al. Classification and pharmacology of progestins. Maturitas. 2008;61(1-2):171-180.
14. Henry A, Santulli P, Bourdon M, et al. Birth defects reporting and the use of dydrogesterone: a disproportionality analysis from the World Health Organization pharmacovigilance database (VigiBase). Hum Reprod Open. 2025;2025(1):hoae072.
15. Kuptarak A, Phupong V. Knowledge, attitude, and acceptance of COVID-19 vaccine in pregnant women. Ther Adv Vaccines Immunother. 2024;12:25151355241278832.
16. El-Zibdeh MY, Yousef LT. Dydrogesterone support in threatened miscarriage. Maturitas. 2009;65(Suppl 1):S43-S46.
17. Pandian RU. Dydrogesterone in threatened miscarriage: a Malaysian experience. Maturitas. 2009;65(Suppl 1):S47-S50.
18. Siew JYS, Allen JC, Hui CYY, et al. The randomised controlled trial of micronised progesterone and dydrogesterone (TRoMaD) for threatened miscarriage. Eur J Obstet Gynecol Reprod Biol. 2018;228:319-324.
19. Kale AR, Kale AA, Yelikar K. A comparative, randomized control trial in patients of per vaginal bleeding comparing efficacy of oral dydrogesterone versus vaginal progesterone in successful pregnancy outcome for patients with recurrent pregnancy loss. J Obstet Gynaecol India. 2021;71(6):591-595.

20. Kumar D, Chandersheikhar. Oral dydrogesterone and micronized progesterone in threatened abortion. Int J Acad Med Pharm. 2023;5(1):14-16.
21. McLindon LA, James G, Beckmann MM, et al. Progesterone for women with threatened miscarriage (STOP trial): a placebo-controlled randomized clinical trial. Hum Reprod. 2023;38(4):560-568.
22. Alimohamadi S, Javadian P, Gharedaghi MH, et al. Progesterone and threatened abortion: a randomized clinical trial on endocervical cytokine concentrations. J Reprod Immunol. 2013;98(1-2):52-60.
23. Gerhard I, Gwinner B, Eggert-Kruse W, Runnebaum B. Double-blind controlled trial of progesterone substitution in threatened abortion. Biol Res Pregnancy Perinatol. 1987;8(1 1ST Half):26-34.
24. Walch K, Hefler L, Nagele F. Oral dydrogesterone treatment during the first trimester of pregnancy: the prevention of miscarriage study (PROMIS). A double-blind, prospectively randomized, placebo-controlled, parallel group trial. J Matern Fetal Neonatal Med. 2005;18(4):265-269.
25. Queisser-Luft A. Dydrogesterone use during pregnancy: overview of birth defects reported since 1977. Early Hum Dev. 2009;85(6):375-377.
26. Li L, Wang K, Wang M, et al. The maternal drug exposure birth cohort (DEBC) in China. Nat Commun. 2024;15(1):5312.

Supplementary Appendix 1: Search strategy (PubMed)

Search date: September 1-5, 2025 **Database:** PubMed

Search string: [“abortion, threatened”(MeSH)] OR [“threatened miscarriage”(title/abstract)] OR [“threatened abortion” (title/abstract)] OR [“vaginal bleeding”(title/abstract)] AND [“dydrogesterone”(MeSH)] OR [“dydrogesterone”(title/abstract)] OR [“Progesterone”(MeSH)] OR [“micronized progesterone”(title/abstract)] OR [“vaginal progesterone”(title/abstract)] OR [“oral progesterone”(title/abstract)]

Explanation of terms:

- **MeSH terms:** Controlled vocabulary (e.g., “abortion, threatened”, “dydrogesterone”).
- **Title/abstract:** Keywords searched within the title or abstract of the articles.
- **Boolean operators:**

OR: Used to combine synonyms (e.g., threatened miscarriage OR threatened abortion).

AND: Used to combine the condition (threatened miscarriage) with the intervention (progesterone/dydrogesterone).

Original Article

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Assessing the Learning Curve of Linear and Wedge Labiaplasty Using the Cumulative Summation (CUSUM) Test

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ABSTRACT

Purpose: To assess and compare the learning curves of linear and wedge labiaplasty performed by trainees with no prior cosmetic gynecology experience using the Learning Curve-Cumulative Summation (LC-CUSUM) method.

Methods: This retrospective study analyzed the first 40 consecutive cases performed by two obstetrician-gynecologist trainees. Trainee 1 performed linear labiaplasty, and Trainee 2 performed wedge labiaplasty. Both trainees had completed a structured two-day training course. Unfavorable outcomes were defined as wound dehiscence, postoperative infection requiring antibiotics, or esthetic dissatisfaction where both surgeon and the patient agree on a revision. The acceptable failure rate (p_0) was set at 3% and the unacceptable rate (p_1) at 10%, with $\alpha=0.05$ and $\beta=0.20$. LC-CUSUM curves were constructed using standard algorithms to identify the point at which each trainee achieved competence (decision limit $h=2.5$).

Results: Patient demographics did not differ significantly between the two groups. Operative time was significantly longer for wedge labiaplasty (98±20 min) compared with linear labiaplasty (74±22 min, $p<0.01$). The overall unfavorable outcome rate was 2.5% for linear and 12.5% for wedge labiaplasty ($p=0.08$). LC-CUSUM analysis indicated that competence was achieved after the eighth case for linear labiaplasty and the thiteenth case for wedge labiaplasty. Both trainees' performance curves remained below the decision limit, suggesting acceptable performance after these thresholds were reached.

Conclusion: The LC-CUSUM test demonstrated that linear labiaplasty requires a shorter learning curve compared with wedge labiaplasty in trainees new to cosmetic gynecology. The wedge technique, while esthetically advantageous, is technically more demanding and associated with a higher early complication rate and longer operative time. These results provide evidence-based guidance for training programs, suggesting that linear labiaplasty should be introduced first in structured cosmetic gynecology curricula. Adoption of LC-CUSUM-based monitoring may enhance patient safety and standardize competence assessment in aesthetic gynecologic surgery.

Keywords: Learning curve, cumulative sum, labiaplasty, cosmetic gynecology, surgical education

INTRODUCTION

Cosmetic gynecologic surgery, particularly labia minora plasty (LMP), has seen a substantial increase in demand globally over the past two decades.[1,2] As the prevalence of these procedures rises, so too does the necessity for structured, objective training protocols to ensure optimal outcomes and patient safety.[3] LMP is considered an esthetic procedure requiring technical precision, a clear understanding of vulvar anatomy, and advanced surgical judgment to achieve satisfactory functional and cosmetic results.[4] Due to high patient expectations and the potential for complications, including wound dehiscence, infection and esthetic dissatisfaction, acquisition of competence by a trainee surgeon should be carefully assessed.[5,6]

The traditional assessment of surgical skill acquisition, which often relies on expert opinion, case volume, or simple complication rates, lacks the statistical rigor needed for modern surgical education.[7] The Learning Curve Cumulative Summation (LC-CUSUM) test provides a powerful, graphical,

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and sequential statistical method for objectively monitoring a trainee's performance and determining the point at which they achieve a predefined standard of competence.[8] Unlike traditional control charts, the LC-CUSUM method is specifically designed to detect sustained shifts in performance metrics and is ideally suited for tracking the learning process in new procedures.[9]

The aim of this study was to apply the LC-CUSUM test to the initial experience of surgical trainees learning two distinct LMP techniques: linear and wedge labiaplasty. By comparing the case volume required for each trainee to reach a predefined level of competence, it was hoped to provide evidence of the relative trajectories of the learning curves of these two common procedures.

METHODS

This retrospective study analyzed the first 40 consecutive cases performed by two obstetrician-gynecologist trainees. Trainee 1 performed linear labiaplasty, and Trainee 2 performed wedge labiaplasty. Both trainees had completed a structured two-day training course. Unfavorable outcomes were defined as wound dehiscence, postoperative infection requiring antibiotics, or esthetic dissatisfaction where both surgeon and the patient agree on a revision. The acceptable failure rate (p_0) was set at 3% and the unacceptable rate (p_1) at 10%, with α=0.05 and β=0.20. LC-CUSUM curves were constructed using standard algorithms to identify the point at which each trainee achieved competence (decision limit h=2.5).

Study Design and Participants

This was a retrospective review of the first 40 consecutive cases performed by two trainee gynecologic surgeons, one performing linear labiaplasty and the other performing wedge labiaplasty. Both trainees were specialists in Obstetrics and Gynecology who had never previously performed cosmetic gynecology procedures, including LMP. The study was conducted two years after the trainees had completed their initial training course. Both trainees provided informed consent for the retrospective use of their de-identified patient data.

Prior to initiating practice, each trainee attended a two-day hands-on live surgery course. On the first day, the participants received four hours of theoretical instruction covering vulvar and lower abdominal anatomy, patient selection, informed consent, and operative techniques for LMP. This was followed by two hours of video demonstrations of multiple techniques, including technical tips and troubleshooting. On the second day, each trainee performed and assisted in four live LMP procedures under expert supervision.

After the course, the trainees returned to their respective clinics and began performing cosmetic gynecological procedures. Their initial cases were reviewed by the same expert surgeon with over 15 years of experience in cosmetic gynecology. Two years after the course, the trainees were contacted and invited to participate in this study. Both agreed to share data from their first 40 consecutive LMP cases each. Ethical approval was obtained from the Tekirdağ Namık Kemal University of Ethics Committee (approval number: 2025.140.07.10, date: 29.07.2025).

Patient Selection and Surgical Techniques

All patients underwent LMP primarily for cosmetic reasons. Labium minus classification was performed based on the degree of protrusion exceeding the labia majora and morphological variations, as previously described.[10] Linear labiaplasty was performed with the patient in the lithotomy position. After surgical preparation, the portion of the labium minus protruding beyond the labia majora was excised, ensuring that a minimum of 1 cm of labium minus tissue remained. Excision was performed using curved scissors or a blade. Hemostasis was achieved using needle-tip electrocautery at 35 watts in spray mode. The labial edges were then approximated using 4.0 or 5.0 rapid absorbable sutures in a continuous or interrupted fashion.[11] Wedge labiaplasty involved a V-shaped excision of the most protuberant portion of the labium minus. The size of the resected wedge depended on the individual patient's anatomy. Resection was planned posterior to the central labial artery, which was identified using a previously described transillumination technique.[12] The technique included either central or inferior wedge resections based on anatomical requirements.[13,14] Postoperative care included hourly 10-minute ice packs, non-steroidal anti-inflammatory drugs, and cephalosporin antibiotic prophylaxis. Patients were advised to abstain from sexual intercourse for four weeks postoperatively. Follow-up included evaluations at one and six months post-operation, including clinical review and photographic assessment.

Outcome Measures and Learning Curve Cumulative Summation Parameters

Unfavorable outcomes (failure) were defined as any of the following occurrences requiring intervention: wound dehiscence; labial infection requiring antibiotics; or patient esthetic dissatisfaction requiring a revision surgery.

Statistical Analysis

Based on a previous study showing a 2.7% complication rate in similar cosmetic genital procedures (72/2597), the acceptable failure rate was set at 3% (p_0=0.03) and the unacceptable failure rate at 10% (p_1=0.10).[15] Type 1 error (α) which is the probability of falsely declaring competence was set at 0.05, and type II error (β) which is probability of falsely rejecting a trainee's competence was set at 0.20. From published LC-CUSUM formulas, the sample weight for success (x=0) was 0.0080043 and for failure (x=1) was -1.38629. The average run length under null hypothesis (ARL_0) was set at 40, representing the expected number of cases before a trainee of acceptable competence (p_0) is falsely declared incompetent (a type I error), with a decision interval (h) of 2.5, which is an established value used in the literature, which corresponds to the defined (ARL_0) of 40 for detecting deviations from the acceptable performance standard.[16-19] The learning curve was considered complete when the LC-CUSUM score dropped back to zero and remained below the decision interval for a sustained period, indicating that an acceptable p_0 had been achieved. Continuous variables were

compared using independent samples t-tests. Categorical variables were compared using the chi-square test or Fisher's exact test where appropriate. Analysis of variance was used to compare continuous variables between operators as two operators were used in this study. Statistical significance was set at $p<0.05$. The statistical analysis for LC-CUSUM was performed using established methods.

RESULTS

The first 40 consecutive cases for each trainee were analyzed (Table 1). Baseline patient demographic characteristics did not differ between the two groups. There was no difference between intervention characteristics with the exception of a significantly longer operative time for wedge labiaplasty (74±22 min vs. 98±20 min, $p<0.01$). The failure rate for Trainee 1 (linear labiaplasty) was 2.5%, while it was 12.5% for Trainee 2 (wedge labiaplasty). Although the difference in the overall unfavorable outcome was not significant ($p=0.08$), the rate was four-fold higher for the wedge technique. Specific adverse events for Trainee 2 included three cases of wound dehiscence and two cases of patient cosmetic dissatisfaction. LC-CUSUM analysis demonstrated that competency was achieved after the eighth procedure for Trainee 1 (Figure 1) and after the thirteenth procedure for Trainee 2 (Figure 2). The maximum LC-CUSUM score reached was 0.5 for Trainee 1 and 1.2 for Trainee 2, remaining well below the decision limit (h=2.5) in both cases, suggesting that the predefined level of unacceptable failure was avoided early in the learning process.

Table 1. Comparison of patient demographic and intervention characteristics for the two surgical techniques

	Trainee 1 - linear labiaplasty (n=40)	Trainee 2 - wedge labiaplasty (n=40)	*p*
Age (years)	29.4±9.2	30.5±8.8	0.50
BMI (kg/m²)	27.5±2.3	28.1±3.2	0.30
Labia minora type 1	12 (30%)	9 (22.5%)	0.50
Labia minora type 2	21 (52.5%)	26 (65%)	0.50
Labia minora type 3	7 (17.5%)	5 (12.5%)	0.50
Operation time (min)	74±22	98±20	<0.01
Overall unfavorable outcome	1 (2.5%)	5 (12.5%)	0.08
Wound dehiscence	0	3 (7.5%)	0.07
Infection	1 (2.5%)	2 (5%)	0.50
Aesthetic dissatisfaction	0	2 (5%)	0.10

BMI: Body mass index

DISCUSSION

In this study, the LC-CUSUM test was used to evaluate the acquisition of competency in two different LMP techniques performed by two trainees with no prior experience in cosmetic gynecology. Our findings demonstrated that competency was achieved after eight and 13 procedures for the linear and wedge techniques respectively. To the best of our knowledge, this is one of the first reports applying LC-CUSUM to cosmetic genital surgery and provides quantitative data on the possible number of cases required to reach an acceptable performance level for each technique.

The LC-CUSUM method has been increasingly used to objectively assess the progression of surgical proficiency in various fields, including hysteroscopy, laparoscopy, and ultrasound-guided procedures. For example, in outpatient hysteroscopy, a third-year trainee was reported to require approximately 56 procedures to reach an acceptable performance threshold.[19] Similarly, in deep infiltrating endometriosis mapping using ultrasonography, the number of cases required to achieve competence ranged from 17 to 44, depending on the lesion location.[20] In pelvic reconstructive surgery, learning curves often extend to 30-50 procedures depending on mesh use before proficiency is reached.[21] Compared with these examples, the present results suggest that LMP may have a relatively shorter learning curve, particularly for the linear technique.

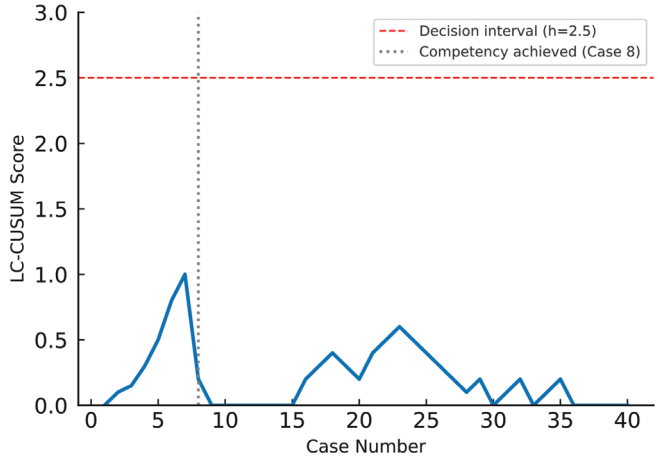

Figure 1. LC-CUSUM Learning Curve - Trainee 1 (linear labiaplasty)
LC-CUSUM: Learning Curve-Cumulative Summation

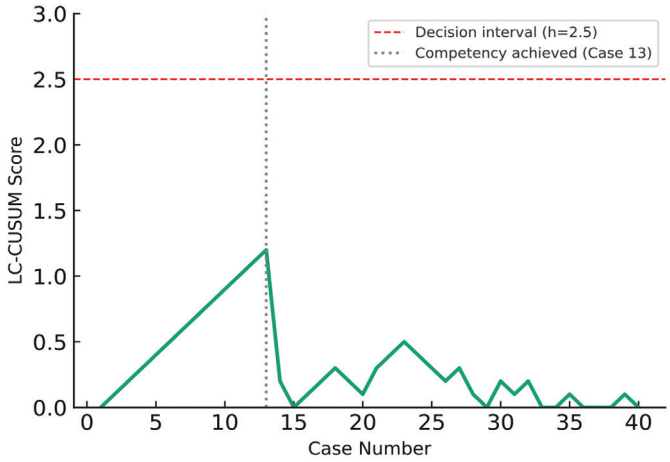

Figure 2. LC-CUSUM Learning Curve - Trainee 2 (wedge labiaplasty)
LC-CUSUM: Learning Curve-Cumulative Summation

The longer operative time and higher failure rate observed for wedge labioplasty in this study are consistent with prior evidence indicating that the wedge method, although esthetically advantageous, is associated with a greater technical challenge. A recent meta-analysis reported that wedge resection was associated with a slightly higher risk of wound dehiscense (3-5%) than edge or linear excision methods.[5] Our findings align with this pattern, showing a 12.5% unfavorable outcome rate for wedge procedures compared with 2.5% for linear resections. This observation highlights the technical complexity of wedge labioplasty and suggests that it may require a longer training phase to achieve similar levels of safety and efficiency. The fact that Trainee 2 eventually met this standard after 13 cases, as evidenced by the LC-CUSUM score returning to the acceptable range, suggested eventual attainment of proficiency for this the procedure with supervision. The eight case requirement for linear labiaplasty was remarkably short, which may indicate this technique as more suited as an entry-level procedure for trainees in cosmetic gynecology. For both trainees, the maximum LC-CUSUM values remained well below the decision interval for unacceptable performance, suggesting that the initial structured training was effective in preventing catastrophic failures early in the learning process, highlighting the importance of structured preparatory training for minimizing patient risks during the initial learning phase.

Study Limitations

This study has several limitations. The small number of trainees is the primary limitation, which restricts the generalizability of our findings. We acknowledge that individual differences in inherent dexterity, prior surgical exposure or learning style could significantly influence the apparent rate of skill acquisition, potentially reflecting personal aptitude rather than technique superiority. However, this study serves as a pilot comparison to provide objective, quantitative data on the learning curve length where previous evidence was lacking. The retrospective design is also a limitation. While the LC-CUSUM method is optimally used in a prospective manner to provide real-time feedback and monitor the acquisition of competence, its retrospective application remains a valid tool for auditing outcomes. Moreover, the definition of failure should be standardized in future studies; including both minor cosmetic dissatisfaction and major complications under the same category may overestimate the failure rate. Patient satisfaction was assessed from clinical documentation and photographic evaluation rather than through a validated scoring system, which may limit the interpretability and comparability of subjective esthetic outcomes. The follow-up period of six months may also be insufficient to capture late complications or patient-perceived outcomes, such as scar satisfaction and sexual function. Furthermore, patient selection bias cannot be excluded, as early cases may have involved less challenging anatomy, potentially accelerating early competence attainment. Lastly, differences in institutional resources or postoperative care could influence outcomes and should be considered in multicenter studies.

Future studies should expand on this work by including a larger number of trainees who perform both techniques, across multiple centers to capture variability in working environments. Incorporating risk-adjusted LC-CUSUM models could allow for the weighting of case complexity, thereby providing more personalized assessments of learning progression. Moreover, integrating patient-reported outcomes such as pain, sexual satisfaction and body image perception would offer a more comprehensive evaluation of surgical competency beyond complication rates alone. Simulation-based training and cadaveric practice should also be explored as tools to accelerate skill acquisition before live patient cases.

CONCLUSION

The application of the LC-CUSUM test to LMP demonstrates that the linear technique may have a significantly shorter learning curve, compared to the more technically demanding wedge resection technique. This study provides objective data to support the strategic planning of surgical training in cosmetic gynecology, suggesting that the linear technique

may be prioritized early in a trainee's experience. Formal training protocols using the LC-CUSUM method may help to objectively define and monitor the achievement of surgical competence, thereby ensuring patient safety and standardized outcomes.

Ethics

Ethics Committee Approval: Ethical approval was obtained from the Tekirdağ Namık Kemal University of Ethics Committee (approval number: 2025.140.07.10, date: 29.07.2025).

Informed Consent: Both trainees provided informed consent for the retrospective use of their de-identified patient data.

Footnotes

Authorship Contributions

Surgical and Medical Practices: E.H.C., G.A., Concept: B.Ü., Design: B.Ü., Data Collection or Processing: E.H.C., G.A., Analysis or Interpretation: B.Ü., Literature Search: B.Ü., Writing: B.Ü.

Conflict of Interest: No conflict of interest was declared by the authors.

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REFERENCES

1. Ortega-Sánchez I, Lucha-López MO, Monti-Ballano S. Motivational factors for labiaplasty: a systematic review of medical research. J Clin Med. 2025;14(8):2686.
2. Triana L, Palacios Huatuco RM, Campilgio G, Liscano E. Trends in surgical and nonsurgical aesthetic procedures: a 14-year analysis of the International Society of Aesthetic Plastic Surgery-ISAPS. Aesthetic Plast Surg. 2024;48(20):4217-4227.
3. Laskowska A, Gronowski P. Female cosmetic genital surgery: complications. J Sex Med. 2022;19(Supplement_2):S213.
4. Buzzaccarini G, Degliuomini RS, De Rosa L, et al. A road map through the multi-faceted world of female genital cosmetic surgical techniques. Int J Gynaecol Obstet. 2025;170(1):49-58.
5. Géczi AM, Varga T, Vajna R, et al. Comprehensive assessment of labiaplasty techniques and tools, satisfaction rates, and risk factors: a systematic review and meta-analysis. Aesthet Surg J. 2024;44(11):NP798-NP808.
6. Sharp G, Mattiske J, Vale KI. Motivations, expectations, and experiences of labiaplasty: a qualitative study. Aesthet Surg J. 2016;36(8):920-928.
7. Berg M, Dahlin LB, Kjellman M. Overview of surgical training and assessment of surgical skills: a narrative review. Front Surg. 2025;12:1605495.
8. St. John AJ, Kim J, Ludeman EM, et al. Charting the future of competency-based surgical education: a systematic review of cumulative sum. Global Surg Educ.2022;1:54.
9. Bolsin S, Colson M. The use of the Cusum technique in the assessment of trainee competence in new procedures. Int J Qual Health Care. 2000;12(5):433-438.
10. Motakef S, Rodriguez-Feliz J, Chung MT, Ingargiola MJ, Wong VW, Patel A. Vaginal labiaplasty: current practices and a simplified classification system for labial protrusion. Plast Reconstr Surg. 2015;135(3):774-788.
11. Girling VR, Salisbury M, Ersek RA. Vaginal labioplasty. Plast Reconstr Surg. 2005;115(6):1792-1793.
12. Kaya AE, Dogan O, Yassa M, Basbug A, Çalışkan E. A novel technique for mapping the vascularity of labia minora prior to labiaplasty: cold light illumination. Geburtshilfe Frauenheilkd. 2018;78(8):775-784.
13. Alter GJ. A new technique for aesthetic labia minora reduction. Ann Plast Surg. 1998;40(3):287-290.
14. Munhoz AM, Filassi JR, Ricci MD, et al. Aesthetic labia minora reduction with inferior wedge resection and superior pedicle flap reconstruction. Plast Reconstr Surg. 2006;118(5):1237-1247.
15. Köle E, Doğan O, Arslan G, Köle MÇ, Aslan E, Çalışkan E. Labiaplasty outcomes and complications in Turkish women: a multicentric study. Int Urogynecol J. 2024;35(5):1045-1050.
16. Dessolle L, Fréour T, Barrière P, et al. How soon can I be proficient in embryo transfer? Lessons from the cumulative summation test for learning curve (LC-CUSUM). Hum Reprod. 2010;25(2):380-386.
17. Biau DJ, Williams SM, Schlup MM, Nizard RS, Porcher R. Quantitative and individualized assessment of the learning curve using LC-CUSUM. Br J Surg. 2008;95(7):925-929.
18. Biau DJ, Resche-Rigon M, Godiris-Petit G, Nizard RS, Porcher R. Quality control of surgical and interventional procedures: a review of the CUSUM. Qual Saf Health Care. 2007;16(3):203-207.
19. Issat T, Beta J, Januszewski M, Jakimiuk AJ. Cumulative summation test for learning curve (LC-CUSUM) in outpatient hysteroscopy. Ginekol Pol. 2017;88(1):9-12.
20. Guerriero S, Pascual MA, Ajossa S, et al. Learning curve for ultrasonographic diagnosis of deep infiltrating endometriosis using structured offline training program. Ultrasound Obstet Gynecol. 2019;54(2):262-269.
21. Wu CJ, Huang KJ, Chang WC, Li YX, Wei LH, Sheu BC. Analyzing the learning curve of vaginal pelvic reconstruction surgery with and without mesh by the cumulative summation test (CUSUM). Sci Rep. 2022;12(1):7025.

Original Article

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Dual Trigger in Poor Responders: Does it Make A Difference in Growth Hormone Supplemented Antagonist Cycles?

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ABSTRACT

Purpose: To compare the clinical and embryological outcomes of dual trigger gonadotropin releasing hormone (GnRH) agonist + human chorionic gonadotropin (hCG) versus hCG-only trigger in POSEIDON group 3 and 4 patients who are characterized by poor ovarian reserve and low prognosis undergoing in vitro fertilization.

Methods: This retrospective study included women diagnosed with poor ovarian response (POSEIDON groups 3 and 4) who underwent controlled ovarian stimulation in GnRH antagonist cycles between January 2020 and January 2024. Patients were divided into two groups: the dual trigger group (DTG) received 0.2 mg triptorelin +250 mcg hCG for final oocyte maturation; the control group (CG) received only 250 mcg hCG. Both groups received growth hormone (GH) co-treatment and luteal phase hormone support. Embryos were frozen when progesterone exceeded 1.5 ng/mL on the trigger day. Outcomes included oocyte yield, embryo transfer rates, and pregnancy outcomes.

Results: The study cohort consisted of 243 women, with 118 in the DTG and 125 in the CG. The DTG had significantly higher gonadotropin consumption and embryo transfer rates (both $p<0.001$), especially day 3 transfers. However, there were no significant differences between the groups in the number of oocytes retrieved, fertilization rates, implantation rates (9.3% vs. 10%, $p=0.8$), clinical pregnancy rates (10.6% vs. 9.9%, $p=0.8$), or live birth rates per transfer (9.7% vs. 8.9%, $p=0.8$).

Conclusion: The dual trigger protocol resulted in increased gonadotropin use and embryo transfer rates but did not improve pregnancy or live birth outcomes. These results suggest that the benefits of dual trigger may be limited by the underlying ovarian reserve, and additional adjuvant therapies, such as GH supplementation, may be required to optimize reproductive outcomes in this challenging patient population.

Keywords: Dual trigger, poor responders, IVF, GnRH agonist, growth hormon

INTRODUCTION

Patients classified as POSEIDON group 3 and 4, typically characterized by diminished ovarian reserve and/or advanced maternal age, represent one of the most challenging populations in assisted reproductive technology (ART). These patients often produce fewer oocytes and embryos with reduced implantation potential, leading to lower pregnancy and live birth rates.[1,2] The POSEIDON criteria were developed to provide a more individualized framework for prognosis and treatment planning in poor-prognosis patients, aiming to improve clinical decision-making and stratification.[3]

Several therapeutic strategies have been explored to improve reproductive outcomes in this population. One such approach is the dual trigger method, combining a gonadotropin-releasing hormone agonist (GnRHa) with low-dose human chorionic gonadotropin (hCG) to induce final oocyte maturation. This method has the aim of mimicking the natural mid-cycle surge of both luteinizing hormone (LH) and follicle stimulating hormone (FSH), potentially enhancing both oocyte maturation and the possibility of embryo development.[4] Some studies have demonstrated improved clinical pregnancy and live birth rates with dual trigger protocols compared with hCG-only triggers, particularly in expected poor responders.[5]

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However, findings remain inconsistent, and additional studies are needed to clarify which patient subgroups benefit most.

Supportive therapies have also gained interest in recent years. Platelet-rich plasma (PRP) has been proposed as a potential tool to enhance follicular activity in women with diminished ovarian reserve, although current evidence remains limited and heterogeneous.[6] Growth hormone (GH) supplementation, on the other hand, has been more widely studied, with suggested benefits on oocyte competence, granulosa cell function, and embryo development.[7] Nevertheless, despite the increasing use of such adjunctive treatments, the optimal approach for final oocyte maturation in POSEIDON group 3 and 4 patients undergoing antagonist protocols is still debated.

In this retrospective comparative study, we aimed to evaluate the effect of dual trigger versus hCG-only trigger on clinical and embryological outcomes in POSEIDON group 3 and 4 patients who received luteal phase GH supplementation within a standardized antagonist protocol. Given the ongoing uncertainty regarding the most effective trigger method for this difficult-to-treat population, we sought to contribute to the existing literature by providing real-world data derived from uniform stimulation, embryo culture, and frozen embryo transfer (FET) procedures.

METHODS

Women diagnosed with poor ovarian response (POR) according to the POSEIDON criteria (groups 3 and 4) were initially evaluated, and women who demonstrated adequate follicular response and qualified for ovulation triggering were included in this retrospective study. The study was conducted between January 2020 and January 2024 in in vitro fertilization centers managed by the Consultant Company, İstanbul, Turkey.

Inclusion Criteria

Patients were included if they fulfilled the following:

1. POSEIDON Group 3 or 4 criteria
2. Age 20-45 years
3. Regular menstrual cycles (24-35 days)
4. Presence of ≥1 antral follicle on baseline ultrasound
5. Undergoing a flexible antagonist protocol with luteal phase GH supplementation
6. Availability of complete stimulation and FET cycle data
7. Demonstrated adequate follicular growth to justify final trigger

Exclusion Criteria

Patients were excluded if they had:

1. Stage III-IV endometriosis
2. Untreated hydrosalpinx
3. Uterine cavity-distorting anomalies (e.g., septate uterus, submucous myoma)
4. Severe male factor infertility requiring surgical sperm retrieval (e.g., testicular sperm extraction)
5. Baseline ovarian cyst >3 cm
6. Uncontrolled endocrine disorders (thyroid, prolactin, Cushing spectrum)
7. Body mass index (BMI) >35 kg/m²
8. Recurrent pregnancy loss (≥3 miscarriages)
9. Use of donor oocytes or preimplantation genetic testing cycles
10. Missing/incomplete cycle documentation
11. Trigger-day progesterone >1.5 ng/mL without availability of freeze-all

Ovarian Stimulation and Trigger Protocol

All patients received luteal phase GH supplementation prior to stimulation, consisting of 36 international unit (IU) GH administered in three divided 12 IU doses every three days. Baseline transvaginal ultrasound was performed on cycle day 2-4. In the presence of antral follicles, stimulation was initiated using:

- 225-450 IU menotropin, or
- **Hybrid protocol:** 150 IU menotropin +150-225 IU recombinant FSH (Gonal-F, Merck)

Follicular assessment was repeated after 5-6 days. Cetrorelix 250 mcg (Cetrotide, Merck) was added when the leading follicle reached 13-14 mm.

Final oocyte maturation was induced using:

- **Dual trigger group:** GnRH agonist +1500 IU hCG
- **hCG-only group:** 6500 IU hCG

In the present study, all embryos were electively frozen and all embryos transfers were performed in frozen -thawed cycles. Progesterone levels exceeding 1.5 ng/mL on the day of trigger have been consistently associated with significantly reduced implantation and clinical pregnancy rates in large prospective studies and meta-analyses. Progesterone elevation above this threshold disrupts endometrial-embryo synchronization, thereby impairing transfer success, and this detrimental effect is independent of embryo quality.[8,9] Therefore, in the present study, a freeze-all strategy was applied when progesterone was >1.5 ng/mL.

Frozen Embryo Transfer Protocol and Embryo Stage Standardization

If menstrual delay exceeded 10 days, micronized progesterone 400 mg/day was administered for withdrawal bleeding. Hormone replacement therapy without GnRH suppression began on day 2-3 of the FET cycle if the endometrial lining measured <5 mm. Estradiol was initiated at 2 mg/day and increased stepwise to 6 mg/day, then up to 8 mg/day once endometrial thickness reached ≥7 mm. Progesterone 50 mg IM daily was added for five days before transfer.

FET outcomes were analyzed on a per-cycle basis, as some patients underwent more than one FET cycle.

To minimize variability in implantation potential, embryo stage at transfer was standardized as follows:

- **Primary strategy:** Blastocyst-stage embryo transfer (day 5/6) whenever blastocyst development was achieved

• **Secondary strategy:** Day 3 embryo transfer only when no blastocyst was available

One or, when available, two embryos were transferred. Estradiol (10 mg/day) and progesterone (50 mg/day) were continued until the pregnancy test and up to 10 gestational weeks if pregnancy occurred.

Statistical Analysis

Continuous variables were initially assessed for normality of statistical distribution by graphical analysis and the Kolmogorov-Smirnov test. The data are presented as the mean value plus or minus the standard deviation. The mean differences between groups were compared by independent samples t test. Categorical variables are presented as frequencies and percentages. Statistical analyses were performed using SPSS, version 28.0 (SPSS-IBM Inc., Chicago, IL, USA). The threshold for statistical significance was established at $p<0.05$.

Due to the lack of data on post-PRP outcomes in cohort studies with adequate sample sizes, we were not able to perform a reliable power analysis before the study commenced.

RESULTS

A total of 243 patients diagnosed with POR according to the POSEIDON criteria were included in the final analysis. Of these, 118 patients underwent a dual trigger protocol, while 125 patients received an hCG-only trigger. Baseline demographic and ovarian reserve characteristics are summarized in Table 1. Patients in the dual trigger group (DTG) were significantly younger and had lower serum AMH levels compared with the control group ($p<0.01$). BMI, antral follicle count, and day-3 FSH levels were comparable between the groups (all $p>0.05$). The proportion of patients classified as POSEIDON group 4 was significantly higher in the control group, whereas POSEIDON group 3 patients were more prevalent in the DTG ($p=0.001$). A higher proportion of patients in the control group had a history of previous failed IVF attempts ($p=0.03$).

Stimulation Characteristics

A total of 243 stimulation cycles were analyzed, including 139 dual trigger cycles and 104 hCG-only cycles. Cycle-based stimulation characteristics are presented in Table 2. The total gonadotropin dose required was significantly higher in dual trigger cycles compared with hCG-only cycles (3540±1303 IU vs. 2844±1110 IU; $p<0.001$). The total number of oocytes retrieved and the number of mature (MII) oocytes were comparable between groups ($p>0.05$). Fertilization rates did not differ significantly between the two protocols.

Embryo transfer was achieved in a significantly higher proportion of dual trigger cycles compared with hCG-only cycles (76.9% vs. 63.4%; $p<0.001$). Among cycles that reached embryo transfer, cleavage stage day-3 embryos were more frequently obtained in the DTG compared with the hCG -only group. (89.7% vs. 77.2%; $p=0.02$).

A freeze-all strategy due to elevated trigger-day progesterone levels was required more often in hCG-only cycles than in dual trigger cycles (33.6% vs. 17.2%; $p<0.001$).

Although mean values of certain stimulation parameters differed between groups, the data ranges largely overlapped, indicating substantial inter-individual variability. Therefore, stimulation characteristics were considered broadly comparable between the dual trigger and hCG-only groups.

Table 1. Baseline demographic variables according to the groups

Variable	Dual trigger group (n=118) n (%)	Control group (n=125) n (%)	*p*
Age (years)	35.7±5.1	38.6±5	<0.001*
BMI (kg/m^2)	25.3±5.8	26.8±4.6	0.02*
Infertility time (years)	7.1±5.1	5.7±4.9	0.03*
AMH (ng/mL)	0.31±0.29	0.41±0.25	0.007*
Antral follicle count (n)	4±1.4	3.8 ±1.3	0.2
Day 3 FSH (mIU/mL)	9.9±5.9	10.3±5.1	0.6
Gravidity			
0	81 (68.6%)	78 (62.4%)	0.5
1	19 (16.1%)	27 (21.6%)	
2 or more	18 (15.3%)	20 (16.0%)	
Previous failed IVF trials ≥1	33 (28.0%)	47 (37.6%)	0.03
Poseidon group			
Group 3	47 (39.8%)	24 (19.2%)	0.001**
Group 4	71 (60.2%)	101 (80.8%)	

*Student t test, statistically significant, ($p<0.05$)
**Chi-square test, statistically significant, ($p<0.05$)
BMI: Body mass index, AMH: Anti-müllerian hormone, IVF: In vitro fertilization

Fertilization and Embryo Development

Fertilization rates were comparable between the dual trigger and hCG-only groups (82.4% vs. 85.4%, $p=0.6$). No statistically significant differences were observed between the groups with respect to early embryological outcomes, in line with previous reports evaluating fertilization efficiency in antagonist cycles using different triggering strategies.[4,5]

Frozen Embryo Transfer Outcomes

Pregnancy outcomes per embryo transfer are summarized in Table 3. Implantation rates were similar between the dual trigger and hCG-only groups (9.3% vs. 10.0%, $p=0.8$). Likewise, no significant differences were observed in biochemical pregnancy rates (2.2% vs. 0.9%, $p=0.4$), clinical pregnancy rates per transfer (10.6% vs. 9.9%, $p=0.8$), or live birth rates per transfer (9.7% vs. 8.9%, $p=0.8$), consistent with findings reported in poor responder populations by Esteves et al.[3] and Hass et al.[10]

Cycle Cancellation and Embryo Availability

Overall cycle cancellation rates were lower in the DTG compared with the hCG-only group; however, this difference did not reach statistical significance (13.5% vs. 19.2%, $p=0.11$). The main reasons for cycle cancellation included inadequate follicular response, fertilization failure, and failure to obtain embryos suitable for transfer, which have also been described as common limiting factors in POSEIDON group 3-4 patients.[1,3]

Adverse Events

No cases of ovarian hyperstimulation syndrome (OHSS) were observed in either group, which was expected given the low follicular response characteristic of POSEIDON group 3 and 4 patients, as previously emphasized by the POSEIDON group and by Esteves et al.[11] Mild post-retrieval discomfort was comparable between groups.

DISCUSSION

In this retrospective comparative study, the impact of dual trigger versus hCG-only trigger in POSEIDON group 3 and 4 patients undergoing antagonist protocols with luteal-phase GH supplementation was compared. Although dual trigger significantly improved blastocyst development, implantation and clinical pregnancy rates were not statistically different between the dual trigger and hCG-only groups ($p>0.05$). Biochemical pregnancy and live birth rates were also comparable between the groups. These results align with emerging evidence suggesting that the addition of a GnRH agonist-induced endogenous LH and FSH surge may enhance oocyte competence and subsequent embryo developmental potential in women with diminished ovarian reserve. However, although dual trigger significantly improved blastocyst development, implantation and clinical pregnancy rates were not statistically different between the dual trigger and hCG-only groups ($p>0.05$). Biochemical pregnancy and live birth rates were also comparable between the groups.

Dual Trigger and Oocyte Maturation in Poor Responders

The significantly higher proportion of mature (MII) oocytes observed in the DTG is consistent with several prior studies reporting enhanced oocyte maturation and meiotic competence. A meta-analysis by Lin et al.[5] showed that dual trigger was associated with a higher MII rate and improved oocyte quality in antagonist cycles, particularly in low-responder cohorts.[12] Similarly, a systematic review by Chen et al.[13] demonstrated that combining GnRHa with hCG increased the odds of retrieving mature oocytes by 28-35% depending on ovarian reserve status.

Table 2. Cycle characteristics of the groups

Variable	Dual trigger cycles (n=139) n (%)	hCG-only cycles (n=104) n (%)	*p*
Total gonadotropin dose used (IU)	3540±1303	2844±1110	<0.001*
Number of oocytes retrieved (n)	3.6±2.8	3.9±2.9	0.5
Number of M2 oocytes retrieved (n)	2.7±2	2.8±2.2	0.7
Empty follicle syndrome, n (%)	8 (5.9)	3 (2.9)	0.2
Number of 2PN (n)	2.2±1.6	2.4±2.2	0.3
Fertilization rate (%)	82.4	85.4	0.6
Cycles with embryos available for transfer, n (%)	107/139 (76.9)	66/104 (63.4)	<0.001**
Cleavage -stage embryos(day 3)	96/107 (89.7)	51/66 (77.2)	0.02**
Blastocyst-stage embryos(day 5)	11/107 (10.3)	15/66 (22.7)	
Embryo transfer single	68/107 (63.5)	45/66 (68.1)	0.5
Double	39/107 (36.4)	21/66 (31.8)	
Freeze-all cycles due to elevated progesterone, n (%)	24/139 (17.2)	35/104 (33.6)	<0.001**

*Student t test, statistically significant, ($p<0.05$)
**Chi-square test, statistically significant, ($p<0.05$)

Table 3. Pregnancy outcomes of both groups

Clinical outcomes (all transfers)	Dual trigger transfers (n=131)	Control transfers (n=101)	*p*
Frozen–thawed embryo transfer, n (%)	131	101	
Embryo transfer day Day 5	131	101	0.4
Pregnancy rate per transfer (%)	17/131 (12.9)	11/101(10.8)	0.6
Biochemical pregnancy, n (%)	3 (2.2)	1(0.9)	0.4
Clinical pregnancy, n (%)	14 (10.6)	10 (9.9)	0.8
Implantation rate,n (%)	16/172 (9.3)	14/140 (10)	0.8
Abortion rate per pregnancy	1/14 (7.1)	1/10 (10)	0.8
Live birth rate per transfer	13 (9.7)	9 (8.9)	0.8
*Chi-square test, statistically significant ($p<0.05$)			

Mechanistically, the addition of GnRHa induces an endogenous surge of both LH and FSH, unlike hCG, which primarily mimics LH activity. The mid-cycle FSH surge is believed to promote cumulus expansion, LH receptor expression, and cytoplasmic maturation, all of which are critical for optimal fertilization and embryo competence.[10,11,14]

These physiological mechanisms likely contributed to the improved blastocyst formation rates observed in our DTG, aligning with prior laboratory models demonstrating enhanced cytoplasmic maturation with exposure to physiological gonadotropin patterns.[15]

Embryo Development and Blastocyst Formation

One of the most interesting findings in the present study was the significantly increased blastocyst formation rate in the DTG. Blastulation is highly sensitive to oocyte competence, and even subtle improvements in maturation can translate into higher blastocyst availability. Our results support previous work by Decleer et al.[16], who reported improved blastocyst formation after dual trigger in both normal and poor responders.

A recent meta-analysis involving over 2,800 cycles further confirmed that dual trigger significantly increases blastulation rates without increasing OHSS risk, making it particularly suitable for diminished ovarian reserve patients who inherently have low follicular numbers.[17]

Frozen Embryo Transfer Outcomes and Endometrial Synchronization

The significantly higher implantation and clinical pregnancy rates after FET in the DTG reinforce the hypothesis that the benefits of dual trigger extend beyond the stimulation phase. Importantly, our study used a standardized freeze-all strategy when progesterone exceeded 1.5 ng/mL, preventing the negative effects of premature luteinization on endometrial receptivity.

Evidence strongly supports this threshold. A large multicenter study by Venetis et al.[18] concluded that progesterone levels >1.5 ng/mL significantly reduced implantation and live birth rates in fresh cycles, independent of embryo quality. A subsequent meta-analysis involving 10 randomized trials confirmed that premature progesterone elevation caused endometrial-embryo asynchrony and lowered pregnancy outcomes by 20-40%.[19] By freezing embryos in these cycles, we minimized this confounding factor and ensured that implantation outcomes were primarily driven by embryo competence thereby reflecting the true biological impact of the trigger strategy.

Role of Growth Hormone Supplementation

All patients in the present study received GH supplementation during the luteal phase before stimulation. GH functions through increased IGF-1 expression, which has been shown to enhance granulosa cell responsiveness, mitochondrial potential, and ultimately oocyte competence. A meta-analysis including 15 controlled studies found that GH supplementation significantly improved MII rate, fertilization, and clinical pregnancy in poor responders.[20]

This standardized use of GH across both groups is an important strength of the present study, as it reduces treatment heterogeneity. Moreover it reduced potential confounders so that differences in outcomes between groups are more likely attributable to the triggering method rather than adjuvant therapy.

Clinical Pregnancy and Implantation Outcomes

Our findings of significantly higher implantation and clinical pregnancy rates with dual trigger are consistent with the cumulative evidence from the literature. A recent randomized controlled trial by Haas et al.[10] demonstrated a 12-15% increase in clinical pregnancy rates with dual trigger compared to hCG alone, particularly in patients with low ovarian response and suboptimal oocyte maturation.[18] Another meta-analysis reported that dual trigger increased the odds of clinical pregnancy by 30%, with similar live birth improvements.[21]

The improvement in pregnancy outcomes observed in our study appears to be driven primarily by enhanced embryo competence, as stimulation parameters, endometrial preparation, and embryo transfer protocols were standardized across groups.

Study Limitations

The strengths of this study include a homogeneous patient population restricted to POSEIDON group 3-4, standardized GH supplementation, consistent stimulation and FET protocols, and embryo-stage standardization prioritizing blastocyst transfer. These design elements minimize common confounders seen in ART research.

Limitations include the retrospective design, lack of randomization, and the absence of live birth data for all cycles at the time of analysis. In addition, while significant differences were observed in several key outcomes, the study may still be underpowered to detect subtler effects, particularly in subgroup analyses, as the two groups were not comparable for several important variables including age, BMI, duration of infertility, anti-müllerian hormone levels, number of previous failed IVF trials and proportion in POSEIDON group 3 or 4.

CONCLUSION

Overall, our findings suggest that dual trigger offers a clinically meaningful advantage over hCG-only trigger in POSEIDON Group 3-4 patients undergoing antagonist cycles with GH supplementation. The improvements in mature oocyte rate, blastocyst development, implantation, and clinical pregnancy outcomes underscore the potential role of dual trigger as a preferred strategy in this difficult-to-treat population.

Future prospective randomized trials are warranted to validate these findings and evaluate long-term reproductive outcomes, including cumulative live birth rates.

Ethics

Footnotes

Authorship Contributions

Surgical and Medical Practices: G.A., Y.C., Concept: G.K., Design: G.K., Data Collection or Processing: G.A., Analysis or Interpretation: N.M.B., R.A.B., Literature Search: G.A., Writing: G.A.

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REFERENCES

1. Zhang J, Wang Y, Mao X, et al. Dual trigger of final oocyte maturation in poor ovarian responders undergoing IVF/ICSI cycles. Reprod Biomed Online. 2017;35(6):701-707.
2. Vaiarelli A, Cimadomo D, Ubaldi N, Rienzi L, Ubaldi FM. What is new in the management of poor ovarian response in IVF? Curr Opin Obstet Gynecol. 2018;30(3):155-162.
3. Esteves SC, Conforti A, Sunkara SK, et al. Improving reporting of clinical studies using the POSEIDON criteria: POSORT guidelines. Front Endocrinol (Lausanne). 2021;12:587051.
4. Griffin D, Feinn R, Engmann L, Nulsen J, Budinetz T, Benadiva C. Dual trigger with gonadotropin-releasing hormone agonist and standard dose human chorionic gonadotropin to improve oocyte maturity rates. Fertil Steril. 2014;102(2):405-409.
5. Lin MH, Wu FS, Hwu YM, Lee RK, Li RS, Li SH. Dual trigger with gonadotropin releasing hormone agonist and human chorionic gonadotropin significantly improves live birth rate for women with diminished ovarian reserve. Reprod Biol Endocrinol. 2019;17(1):7.
6. Simavlı S, Kiyak Caglayan E, Kaygusuz I, Albayrak F, Çalışkan E. Changes in ovarian functions following platelet-rich plasma (PRP) injection and its impact on IVF treatment: a pre-post research. Clin Exp Obstet Gynecol. 2025;52(2):26053.
7. Bender RA, Ozcan C, Aslancan R, Akar B, Caliskan E. The effect of growth hormone addition protocols to poor ovarian responders in in vitro fertilization cycles. Eur Rev Med Pharmacol Sci. 2022;26(15):5503-5508.
8. Bosch E, Labarta E, Crespo J, et al. Circulating progesterone levels and ongoing pregnancy rates in controlled ovarian stimulation cycles for in vitro fertilization: analysis of over 4000 cycles. Hum Reprod. 2010;25(8):2092-2100.
9. Labarta E, Martínez-Conejero JA, Alamá P, et al. Endometrial receptivity is affected in women with high circulating progesterone levels at the end of the follicular phase: a functional genomics analysis. Hum Reprod. 2011;26(7):1813-1825.
10. Haas J, Zilberberg E, Nahum R, et al. Does double trigger (GnRH-agonist + hCG) improve outcome in poor responders undergoing IVF-ET cycle? A pilot study. Gynecol Endocrinol. 2019;35(7):628-630.
11. Esteves SC, Alviggi C, Andersen CY, et al. The POSEIDON stratification of low prognosis patients in ART: an expert consensus. Frontiers in Endocrinology. 2019;10:814.
12. Syam HH, Ritonga MA, Adrianto N. Efficacy of double trigger versus hCG trigger alone in GnRH-antagonist cycles: a systematic review and meta-analysis. Gynecol Obstet Invest. 2025:1-13.
13. Chen CH, Tzeng CR, Wang PH, et al. Dual triggering with GnRH agonist plus hCG versus triggering with hCG alone for IVF/ICSI outcome in GnRH antagonist cycles: a systematic review and meta-analysis. Arch Gynecol Obstet. 2018;298(1):17-26.
14. Gurbuz AS, Gode F, Uzman MS, et al. GnRH agonist triggering affects the kinetics of embryo development: a comparative study J Ovarian Res. 2016;9:22.
15. Kamath MS, Antonisamy B, Selliah HY, La Marca A, Sunkara SK. Perinatal outcomes following IVF with use of donor versus partner sperm. Reprod Biomed Online. 2018;36(6):705-710.
16. Decleer W, Osmanagaoglu K, Seynhave B, Kolibianakis S, Tarlatzis B, Devroey P. GnRH agonist and hCG (dual trigger) versus hCG trigger for final follicular maturation: a double-blinded, randomized controlled study. Human Reproduction. 2014.
17. Hsia LH, Lee TH, Lin YH, Huang YY, Chang HJ, Liu YL. Dual trigger improves the pregnancy rate in fresh in vitro fertilization (IVF) cycles compared with the human chorionic gonadotropin (hCG) trigger: a systematic review and meta-analysis of randomized trials. J Assist Reprod Genet. 2023;40(9):2063-2077.
18. Venetis CA, Kolibianakis EM, Bosdou JK, Tarlatzis BC. Progesterone elevation and probability of pregnancy after IVF: a systematic review and meta-analysis of over 60 000 cycles. Hum Reprod Update. 2013;19(5):433-457.
19. Lawrenz B, Fatemi HM. Effect of progesterone elevation in follicular phase of IVF-cycles on the endometrial receptivity. Reprod Biomed Online. 2017;34(4):422-428.
20. Yang P, Wu R, Zhang H. The effect of growth hormone supplementation in poor ovarian responders undergoing IVF or ICSI: a meta-analysis of randomized controlled trials. Reprod Biol Endocrinol. 2020;18(1):76.
21. Sloth A, Kjølhede M, Sarmon KG, Knudsen UB. Effect of dual trigger on reproductive outcome in low responders: a systematic PRISMA review and meta-analysis. Gynecol Endocrinol. 2022;38(3):213-221.

Original Article

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Investigation of Plasma Metastin Levels in Reproductive-Age Women with Polycystic Ovary Syndrome Diagnosed with Adnexal Masses

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ABSTRACT

Purpose: Metastin has been shown to inhibit metastasis in breast cancer and malignant melanoma and is reported to be elevated in patients with polycystic ovary syndrome (PCOS). We hypothesized that in PCOS patients presenting with an adnexal mass, metastin levels would demonstrate a negative correlation with tumor markers in cases of malignancy. The aim was to evaluate plasma metastin levels and their relationship with tumor markers in PCOS patients in whom adnexal masses were detected.

Methods: This prospective observational case-control study was conducted after obtaining approval from the University of Health Sciences Turkey, Şişli Hamidiye Etfal Training and Research Hospital Ethics Committee (approval no: 742, date: 24.01.2017). Between February and July 2017, women aged 18-49 years who had previously been diagnosed with PCOS and who presented to the gynecology and obstetrics clinic were evaluated. Patients with adnexal masses detected during examination and PCOS patients without adnexal masses were included, while patients who did not meet inclusion criteria or did not wish to participate were excluded. Patients with masses and without masses were included. The number of patients in the groups was determined by power analysis based on previous studies, with 90% power and a 0.05 alpha error. Serum metastin, cancer antigen (CA) 125 (<35 U/mL), CA 19-9 (<37 U/mL), and carcinoembryonic antigen (CEA) (<5.0 ng/mL) levels were measured.

For comparisons between the two groups, Student's t-test was used for normally distributed variables, and the Mann-Whitney U test for non-normally distributed variables. Spearman correlation was used for non-normally distributed variables in correlation analyses. Chi-square test was used for categorical variables. A p value of <0.05 was considered statistically significant, and statistical analyses were performed using SPSS version 25.

Results: A total of 83 patients were included, 40 (48.2%) in the control group and 43 (51.8%) in the case (adnexal mass present) group. The case group had significantly higher mean age and CA-125 values ($p<0.05$). No significant difference was found between groups in levels of metastin, CA-19.9 and CEA, or age at menarche. No significant correlation was found between metastin and tumor markers in the case group.

Conclusion: Although a significantly higher CA-125 value in the case group compared to the control group was expected, the lack of difference in metastin levels between the groups, despite all patients being diagnosed with PCOS, suggested that even if pelvic masses are detected in long-term PCOS patients with high metastin levels, the likelihood of malignancy may be low.

Keywords: Polycystic ovary syndrome, metastin, kisspeptin, adnexal mass

INTRODUCTION

Polycystic ovary syndrome (PCOS) is the most common reproductive endocrinology-related disorder in women of reproductive age and is known to be associated with long-term health risks. PCOS affects approximately 6-8% of women of reproductive age.[1] PCOS is a pathology characterized by oligomenorrhea, hyperandrogenism, and polycystic ovaries detected by ultrasonography.[2] The impaired feedback of steroid sex hormones leads to elevated luteinizing hormone (LH) levels.[3] However, because elevated LH is not observed

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in half of PCOS patients, especially in obese women with PCOS, elevated LH may not be the main cause of PCOS.[3-5] Antagonists of kisspeptin and neurokinin B may reduce gonadotropin releasing hormone (GnRH) pulsatility, normalize LH concentrations, improve folliculogenesis, and induce ovulation in PCOS patients.[6] The classical neuroendocrine dysfunction leading to the ovarian phenotype in women with PCOS is characterized by increased LH pulsatility, decreased follicle stimulating hormone (FSH) secretion, and impaired GnRH secretion, resulting in an altered LH/FSH ratio.[7] Since kisspeptin/*KISS1R* acts as an upstream regulator of GnRH and LH secretion, serum kisspeptin levels are expected to be elevated in women with PCOS. Reproductive age is the period in which adnexal masses are most frequently encountered, although 80-85% of such masses are benign and often ovarian in origin. Functional ovarian cysts are the most common adnexal pathologies and include follicular cysts, corpus luteum cysts and theca lutein cysts (Table 1). The importance of functional cysts stems from the difficulty in clearly differentiating them from true neoplasms. Kisspeptin is a metastasis-suppressor gene product identified by its ability to block metastasis without affecting primary tumor formation. Reduced kisspeptin expression is clinically associated with poor cancer prognosis. Kisspeptin has been proposed to prevent metastasis by inhibiting tumor cell migration and proliferation.[8,9] In a study investigating the effects of Kisspeptin-10 on endothelial cell migration and proliferation, it was shown that Kisspeptin-10 inhibited cell migration and proliferation at high concentrations, while both processes increased at lower concentrations.[10] The present study investigated whether there was a difference in the correlation between tumor markers and metastin levels in PCOS patients diagnosed with adnexal masses compared with PCOS patients without such masses.

METHODS

This prospective observational case-control study was conducted after obtaining approval from the University of Health Sciences Turkey, Şişli Hamidiye Etfal Training and Research Hospital Ethics Committee (approval no: 742, date: 24.01.2017). Women aged 18-49 years who had been previously diagnosed with PCOS and presented to the Obstetrics and Gynecology Clinic between February and July 2017 were evaluated based, on the 2003 Rotterdam ESHRE/ASRM criteria for diagnosis of PCOS:

- oligo- and/or anovulation,
- clinical and/or biochemical signs of hyperandrogenism,
- polycystic ovaries.

Patients who had ≥12 follicles measuring 2-9 mm in a single ovary or ovarian volume ≥10 mL on ultrasound were evaluated, and those with adnexal masses detected during examination were included along with PCOS patients without adnexal masses. After excluding patients who did not meet the inclusion criteria or declined participation, 43 patients with adnexal masses and 40 patients without adnexal masses were included. Sample size was determined using power analysis based on data from previous research (90% power and $\alpha=0.05$).

The age, height, and weight of patients were recorded, and obstetric and medical histories were obtained. For patients in the case group, the size and characteristics of the masses were documented. Patients showing sonographic features suggestive of malignancy[11] (septations, papillary projections, solid nodules, multilocularity, ascites) were referred for oncology consultation, and those who were not taken under oncology follow-up were included. Patients with bilateral masses were excluded.

Venous blood samples for metastin and tumor markers were drawn during the early follicular phase, after overnight fast in the morning, and under the same time conditions for both groups. Samples were centrifuged at +4 °C at 4000 rpm for 10 minutes. Plasma samples were stored at -80 °C until analysis. Plasma metastin, cancer antigen (CA)-125 (normal cut-off <35 U/mL), CA-19.9 (normal cut-off <37 U/mL), and carcinoembryonic antigen (CEA) (normal cut-off <5.0 ng/mL) were measured. Plasma samples were tested using the Human KISS-54 ELISA Kit (Catalog No: E-EL-H5618, www.elabscience.com) and read with a Biotek ELX800 microplate reader using Gen5 software. The detection range was 62.5-4000 pg/mL. All samples were run in duplicate. Tumor markers were analyzed at our hospital laboratory. Exclusion criteria were: hypothalamic hypogonadism; delayed puberty; pregnancy; menopause; known malignancy; congenital adrenal hyperplasia; androgen-secreting tumors; Cushing syndrome; hyperprolactinemia; diabetes; hypertension; oral contraceptive use; and obesity defined as a body mass index >30 kg/m^2.

Statistical Analysis

For statistical analysis, Student's t-test was used for normally distributed data, and the Mann-Whitney U test was used for non-normal data. Spearman correlation was used for evaluating correlations between variables. Categorical variables were analyzed using the chi-square test. Statistical significance was set at $p<0.05$ using SPSS, version 25 (IBM Inc., Armonk, NY, USA).

RESULTS

A total of 83 patients were included in the study. Of these, 40 (48.2%) constituted the control group (PCOS patients without adnexal masses), whereas 43 (51.8%) comprised the case group (PCOS patients with adnexal masses in either ovary). Table 2 shows the age range, tumor marker and metastain results for the whole study cohort.

Table 3 shows the malignancy rate and surgical operation status of the patients in the case group with adnexal mass.

Tables 4-5 shows comparison of the case and control groups for age, age at menarche and the median or mean levels of tumor markers and metastatin.

The mean age of the case group was significantly higher than that of the control group ($p<0.05$) (Figure 1). The median CA-125 value of the case group was also significantly higher than that of the control group ($p<0.05$) (Figure 2). However the median values of CA-125 were within normal limits in both case and control groups. There was no significant difference

Table 1. Causes of adnexal masses in reproductive age[12]

Ovarian causes	Other causes
- Follicular cyst - Corpus luteum - Corpus hemorrhagicum - Theca lutein cyst - Cystadenoma - Endometrioma - Tubo-ovarian complex - Tubo-ovarian abscess - Ectopic pregnancy - OHSS - Hydrosalpinx - Paraovarian cyst - Morgagni cyst	- Pedunculated or intraligamentary myoma - Cecal/sigmoid colon filled with feces or gas - Diverticulitis - Ileitis - Appendicitis - Intra-abdominal hematoma - Pseudocyst (peritoneal inclusion) - Retroperitoneal pathology - Congenital anomalies of the reproductive, gastrointestinal or urinary systems
Neoplastic	
Cystadenoma, cystadenocarcinoma, germ cell tumors	Colorectal tumors, metastases
OHSS: Ovarian hyperstimulation syndrome	

Table 2. Characteristics of the study population

	Age (years)	Age at menarche (years)	CA 125 U/mL	CA 19.9 U/mL	CEA ng/mL	Metastin pg/mL
Mean	29.7	12.83	22.74	15.1	3.75	1992.47
Standard deviation	7.84	0.98	25.02	21.5	22.31	944.73
Median	29	13	15.2	8.8	1.1	1862.3
Minimum	18	10	1.5	0.6	0.1	450
Maximum	46	15	176	156.7	204.4	4000
CA: Cancer antigen, CEA: Carcinoembryonic antigen						

Table 3. Distribution of adnexal masses in the case group

	n	%
Benign mass (operated)	20	24.1
Malign mass (operated	1	1.2
Mass but not operated	22	26.5

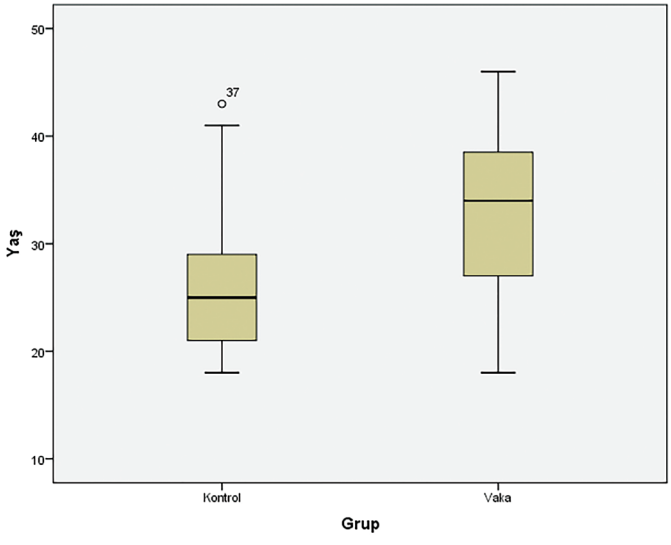

Figure 1. Distribution of case and control groups by age

between the groups in terms of average metastin, (Figure 3), CA 19.9 (Figure 4), CEA levels (Figure 5), or age at menarche. When the relationships between tumor markers in the case group were examined, a moderate positive relationship was found between the three biomarkers CA-19.9, CA-125 and CEA. An increase in one of these tumor markers increases the likelihood of an increase in the other. However, as can be seen in Figures 6 and 7, these relationships are not linear and should be supported by further studies. No significant correlation was found between metastin levels and other tumor markers in the case group. In other words, increases or decreases in metastin levels were independent of CA-19.9, CA-125, and CEA tumor markers. No relationship was found among these markers. In addition, no significant relationship was found between age and metastin levels, CA 19.9, CA 125, and CEA. Although age had a significant effect on adnexal masses, no relationship was observed between age and tumor marker levels. No significant differences were found between the groups with respect to levels of metastin, CA-19.9, CEA levels, or age at menarche. A moderate positive relationship was found between CA-19.9 and CA-125 and CEA in the case group. No significant correlation was observed between metastin levels and other tumor markers in the case group.

DISCUSSION

In women with PCOS, the classical neuroendocrine dysfunction leading to the ovarian phenotype is characterized

Table 4. Comparison of variables between case and control groups

	Case	Control	Levene test	*p*
Mean age (years)	33.09±7.82	26.05±6.08	0.068	**<0.001***
Mean metastin (pg/mL)	1968.3±884.4	2018.43±1016.29	0.270	0.811*
Median age of menarche (years)	13	12.5	-	0.081**
Median CA-125 (U/mL)	17.7	12.95	-	**0.003****
Median CA-19.9 (U/mL)	12.6	7.25	-	0.061**
Median CEA (U/mL)	1.1	1.05	-	0.837**

*Student's t test **Mann-Whitney U test
CA: Cancer antigen, CEA: Carcinoembryonic antigen

Table 5. Correlation between age, age at menarche and tumor markers in the case group

	Age	Menarche age	Metastin	CA 125	CA 19.9	CEA
Age Spearman rho *p* value		0.284 0.065	0.041 0.795	0.266 0.084	-0.036 0.821	0.250 0.105
Menarche age Spearman rho *p* value	0.284 0.065		0.132 0.398	-0.007 0.963	-0.241 0.119	0.130 0.406
Metastin Spearman rho *p* value	0.041 0.795	0.132 0.398		0.067 0.671	0.113 0.469	0.138 0.378
CA 125 Spearman rho *p* value	0.266 0.084	-0.007 0.963	0.067 0.671		0.307 **0.045**	-0.002 0.998
CA 19.9 Spearman rho *p* value	-0.036 0.821	-0.241 0.119	0.113 0.469	0.307 **0.045**		0.484 **0.001**
CEA Spearman rho *p* value	0.250 0.105	0.130 0.406	0.138 0.378	-0.002 0.998	0.484 **0.001**	

CA: Cancer antigen, CEA: Carcinoembryonic antigen

by increased LH pulsatility, decreased FSH secretion, and impaired GnRH secretion, resulting in disruption of the LH-FSH ratio.[7] Since the kisspeptin/GPR54 system is the upstream central regulator that induces GnRH (and LH) secretion, it can be predicted that kisspeptin levels will be higher in women with PCOS.

The reproductive period is the age range in which most adnexal masses are seen; however, 80-85% of these masses are benign and are often of ovarian origin (Table 5).[12] In our study population, 20 patients (24.1%) underwent surgery and were histopathologically benign; 1 patient (1.2%) underwent surgery and was histopathologically malignant; and 22 patients (26.5%) had adnexal masses but were not operated. Considering the patients who were not operated as benign, and given that only one patient was found to be malignant, we detected benign masses at a rate higher than 85%. Of all patients in the case group, only one patient (2.3%) underwent surgery and was confirmed to be malignant.

We initially expected that metastin levels would be lower in cases where the mass was malignant and would show a negative correlation with tumor markers. However, since we had only one malignant case, the sample size was insufficient to interpret the correlation with malignancy.

CA-125, the most commonly used tumor marker in patients with adnexal masses, is synthesized intracellularly, directed

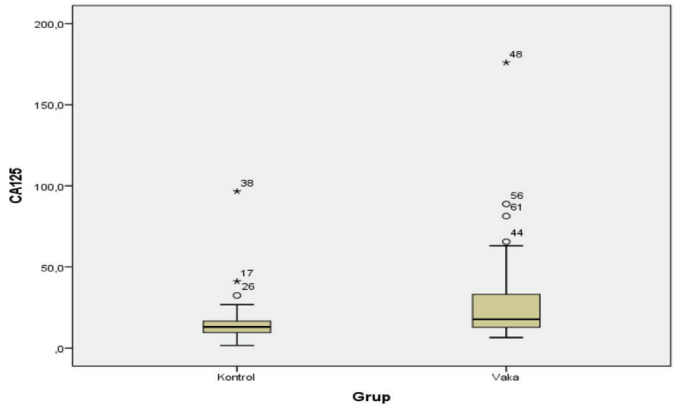

Figure 2. Distribution of case and control groups according to CA-125 levels. Statistically, patient numbers that fall outside the range of values and make a difference

CA: Cancer antigen

toward the luminal surface, and actively secreted into the lumen. Various benign and other causes may also lead to increased levels. The threshold value for CA-125 is 35 U/mL. Since no single screening method is 100% accurate, current screening uses a combination of methods. In our study, the CA-125 value of the case group was significantly higher than that of the control group although only one patient in the case group was proven to have malignant disease.

An elevated CA-125 level in patients with adnexal masses was expected, and in our study, PCOS did not contradict this expectation, and the results were consistent. A moderate positive relationship was found between CA 19.9 and CA 125 and CEA in the case group.[13]

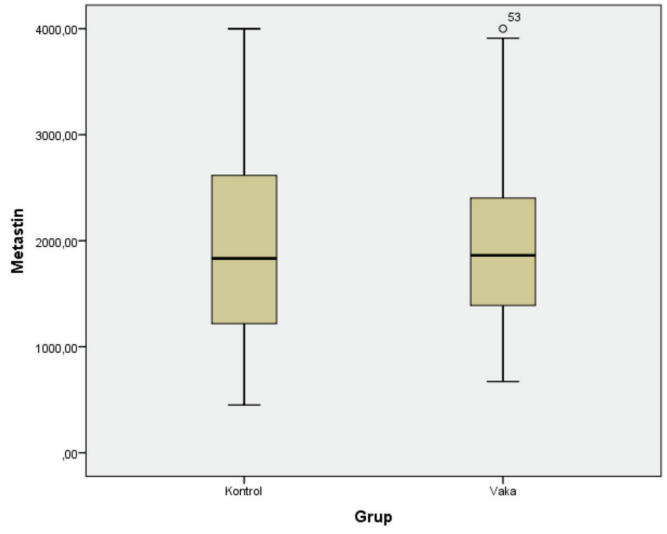

Figure 3. Distribution of case and control groups according to metastin levels

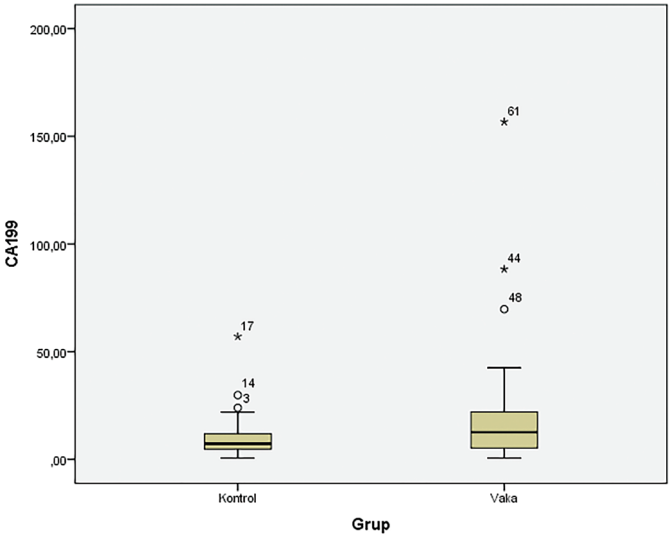

Figure 4. Distribution of case and control groups according to CA-19.9 levels. Statistically, patient numbers that fall outside the range of values and make a difference

CA: Cancer antigen

In studies conducted in 2011 by Redmond et al.[14] and in 2016 by Gottsch et al.[15], *KISS1* directly stimulated LH and FSH secretion in the lateral cerebral ventricle. It is therefore believed to induce puberty via direct action. In our study population, the mean age at menarche was 12.83 (±0.98). Since the age distribution differed between the groups, and because the mean age of the case group was significantly higher than that of the control group, the duration of GPR54 stimulation during the patients' lives varied between the groups and may have influenced our results.

In a study conducted in 2017 by Gorkem et al.[16], serum kisspeptin levels in women with PCOS were found to be significantly higher, and serum kisspeptin levels showed a negative correlation with FSH. Other studies have also

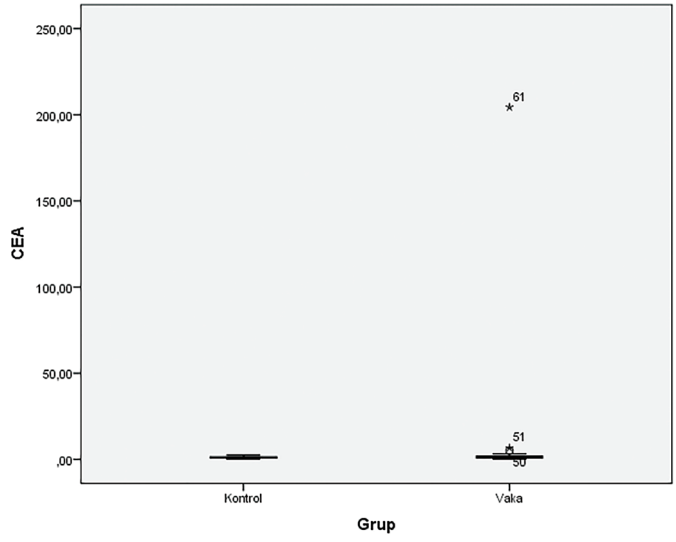

Figure 5. Distribution of case and control groups according to CEA levels (no difference). Statistically, patient numbers that fall outside the range of values and make a difference

CEA: Carcinoembryonic antigen

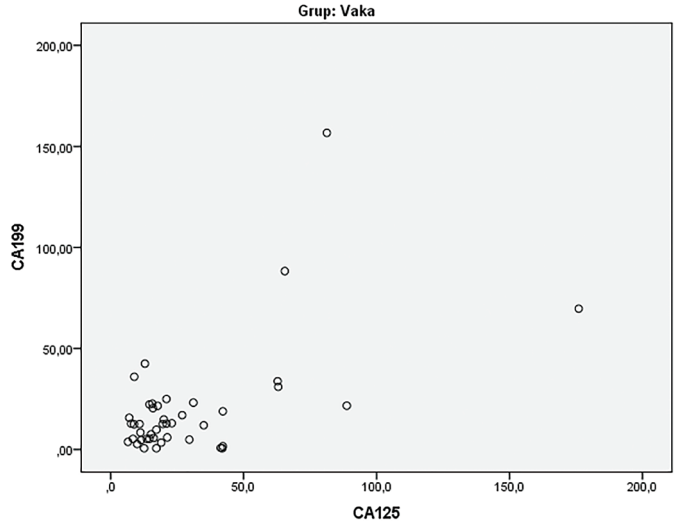

Figure 6. Correlation between CA-19.9 and CA-125 in the case group

CA: Cancer antigen

shown that serum kisspeptin levels are elevated in women with PCOS.[17,18] Since increased LH secretion occurs in PCOS patients, kisspeptin levels were suggested to be higher than in normo-ovulatory women in another study.[19]

Although there was no difference in metastin levels between the control group consisting only of PCOS patients and the case group of women with PCOS and adnexal masses detected, and the detected masses were predominantly benign. When we evaluated the metastin value in the only malignant case, the level was unexpectedly close to the mean and median levels. Since previous studies have shown an association between malignancy and low metastin levels[20,21], this was an unexpected finding.

Cortes et al.[6] showed in 2015, that kisspeptin and neurokinin B antagonists reduced GnRH pulsatility, regulated high LH levels, improved folliculogenesis, and induced ovulation in women with PCOS, and thus metastin levels in PCOS patients are expected to be high. The mean metastin level was 1992.47 (±944.73) in the present study with no significant difference between the groups.

In our study, since both groups consisted of patients with PCOS, the lack of difference in metastin levels between the groups and the proximity of metastin values to the upper limit of the kit used are consistent with findings of previous studies. Including a completely healthy non-PCOS group in future studies would provide more informative results. Studies conducted in 2010 and 2013 showed that kisspeptin exerts anti-metastatic effects in many human cancers, such as melanoma, thyroid, ovarian, bladder, gastroesophageal, pancreatic, lung, and pituitary cancers.[8,22] Clinically, decreased kisspeptin expression is associated with poor prognosis in cancer patients. It has been proposed that kisspeptin prevents metastasis by suppressing cancer cell migration and dissemination.[8]

Although the number of malignant cases was limited, the absence of a significant difference in metastin levels between patients with and without adnexal masses may suggest that high metastin levels in PCOS patients could indicate a lower probability of malignancy even when adnexal masses are detected. The significantly higher CA-125 levels in the case group were expected and align with current diagnostic approaches. In a 2016 study by Cao et al.[20], a prospective analysis of 40 cases with epithelial ovarian cancer showed that the overall survival rate and mean survival time were 28.9% and 38.35±2.84 months, respectively. Furthermore, both residual tumor size and preoperative kisspeptin-1 messenger RNA (mRNA) were significantly associated with prognosis. The same study demonstrated that metastasis and residual tumor size were negatively associated with *KISS1* mRNA, suggesting that patients with low kisspeptin-1 expression were more likely to develop metastasis or residual tumors.[20] Furthermore, kisspeptin-1 was shown to have a significant negative correlation with tumor metastasis and invasion, providing more evidence that it may be a metastasis suppressor molecule in human colorectal cancer.[21]

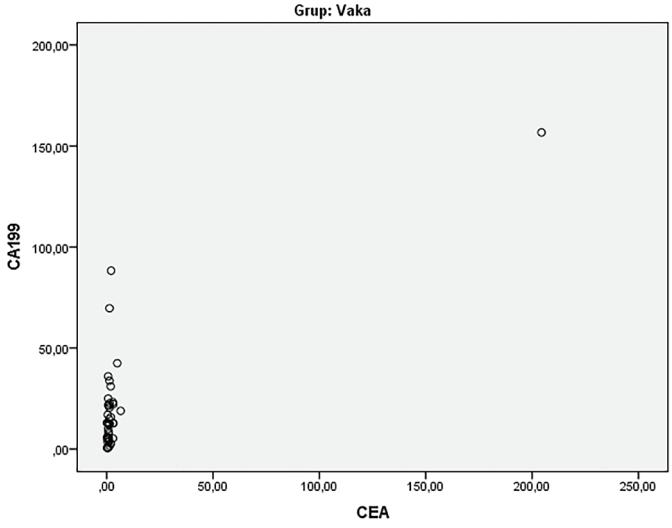

Figure 7. Correlation between CA 19.9 and CEA in the case group
CA: Cancer antigen, CEA: Carcinoembryonic antigen

Study Limitations

Our sample size for evaluating malignancy was too small. Increasing the number of cases and controls and including healthy individuals without a diagnosis of PCOS would strengthen the study.

Hormone levels were not taken on standardized menstrual cycle days and that smokers were not excluded are also limitations. Follow-up of the non-operated patients was incomplete. This may have led to misinterpretation of tumor risk and metastin levels in the group with masses.

The significant age difference between the two groups suggests that the risk of adnexal masses increases with age. Although this difference cannot be eliminated, more homogeneous groups may be formed in future studies.

Blood samples taken on different menstrual days may have altered our values; standardizing the timing of sampling may yield more accurate future results.

CONCLUSION

Measuring metastin levels in completely healthy individuals using the same exclusion criteria may explain the high metastin levels observed in PCOS patients and may provide insight into future research on the etiology of PCOS. Long-term follow-up of PCOS patients may show that, despite high metastin levels, the probability of malignancy may be low even if pelvic masses are detected. Evaluating metastin together with tumor markers in larger future studies and analyzing pathology results may validate the use of metastin as a tumor marker but a great deal of additional data is required. If future studies demonstrate that low metastin levels are associated with malignancy, this relationship may no longer apply in PCOS patients with increased ovarian volume and may be accepted as an exclusion criterion.

Ethics

Ethics Committee Approval: This prospective observational case-control study was conducted after obtaining approval from the University of Health Sciences Turkey, Şişli Hamidiye

Etfal Training and Research Hospital Ethics Committee (approval no: 742, date: 24.01.2017).

Informed Consent: Written informed consent was obtained from all participants.

Authorship Contributions

Surgical and Medical Practices: N.M.E., A.E.Y., Concept: N.M.E., A.E.Y., Design: N.M.E., A.E.Y., Data Collection or Processing: N.M.E., A.E.Y., Analysis or Interpretation: N.M.E., A.E.Y., Literature Search: N.M.E., A.E.Y., Writing: N.M.E., A.E.Y.

Footnotes

Conflict of Interest: No conflict of interest was declared by the authors.

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REFERENCES

1. Goodarzi MO, Quiñones MJ, Azziz R, Rotter JI, Hsueh WA, Yang H. Polycystic ovary syndrome in Mexican-Americans: prevalence and association with the severity of insulin resistance. Fertil Steril. 2005;84(3):766-769.
2. Rotterdam ESHRE/ASRM-sponsored PCOS consensus workshop group. Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome (PCOS). Hum Reprod. 2004;19(1):41-47.
3. Rosenfield RL, Bordini B. Evidence that obesity and androgens have independent and opposing effects on gonadotropin production from puberty to maturity. Brain Res. 2010;1364:186-197.
4. Rosenfield RL. Ovarian and adrenal function in polycystic ovary syndrome. Endocrinol Metab Clin North Am. 1999;28(2):265-293.
5. Rosenfield RL, Mortensen M, Wroblewski K, Littlejohn E, Ehrmann DA. Determination of the source of androgen excess in functionally atypical polycystic ovary syndrome by a short dexamethasone androgen-suppression test and a low-dose ACTH test. Hum Reprod. 2011;26(11):3138-3146.
6. Cortés ME, Carrera B, Rioseco H, Pablo del Río J, Vigil P. The role of kisspeptin in the onset of puberty and in the ovulatory mechanism: a mini-review. J Pediatr Adolesc Gynecol. 2015;28(5):286-291.
7. Norman RJ, Dewailly D, Legro RS, Hickey TE. Polycystic ovary syndrome. Lancet. 2007;370(9588):685-697.
8. Cvetković D, Babwah AV, Bhattacharya M. Kisspeptin/KISS1R system in breast cancer. J Cancer. 2013;4(8):653-661.
9. Smith SC, Theodorescu D. Learning therapeutic lessons from metastasis suppressor proteins. Nat Rev Cancer. 2009;9(4):253-264.
10. Golzar F, Javanmard SH. The effects of kisspeptin-10 on migration and proliferation of endothelial cell. Adv Biomed Res. 2015;4:41.
11. DePriest PD, Gallion HH, Pavlik EJ, Kryscio RJ, van Nagell JR Jr. Transvaginal sonography as a screening method for the detection of early ovarian cancer. Gynecol Oncol. 1997;65(3):408-414.
12. Fleischer, A. C., J. A. Cullinan, and D. M. Kepple. "Color Doppler sonography of pelvic masses." Sonography in Obstetrics and Gynecology. Principles and Practice, 5th edition, AC Fleischer, FA Manning, P. Jeanty, R. Romero, editors, Stamford, CT, Appleton & Lange. (1996):791-813.
13. Dede M, Ercan C.M. Tümör Markerları. In: Ayhan A (Eds). Jinekolojik Onkoloji. 1.Baskı. Ankara, Güneş Kitabevi, 2013; 9: 81-89.
14. Redmond JS, Macedo GG, Velez IC, Caraty A, Williams GL, Amstalden M. Kisspeptin activates the hypothalamic-adenohypophyseal-gonadal axis in prepubertal ewe lambs. Reproduction. 2011;141(4):541-548.
15. Gottsch ML, Cunningham MJ, Smith JT, et al. A role for kisspeptins in the regulation of gonadotropin secretion in the mouse. Endocrinology. 2004;145(9):4073-4077.
16. Gorkem U, Togrul C, Arslan E, Sargin Oruc A, Buyukkayaci Duman N. Is there a role for kisspeptin in pathogenesis of polycystic ovary syndrome? Gynecol Endocrinol. 2017;34(2):1-4.
17. Chen X, Mo Y, Li L, Chen Y, Li Y, Yang D. Increased plasma metastin levels in adolescent women with polycystic ovary syndrome. Eur J Obstet Gynecol Reprod Biol. 2010;149(1):72-76.
18. Jeon YE, Lee KE, Jung JA, et al. Kisspeptin, leptin, and retinol-binding protein 4 in women with polycystic ovary syndrome. Gynecol Obstet Invest. 2013;75(4):268-274.
19. Witchel SF, Tena-Sempere M. The Kiss1 system and polycystic ovary syndrome: lessons from physiology and putative pathophysiologic implications. Fertil Steril. 2013;100(1):12-22.
20. Cao F, Chen L, Liu M, et al. Expression of preoperative KISS1 gene in tumor tissue with epithelial ovarian cancer and its prognostic value. Medicine (Baltimore). 2016;95(46):e5296.
21. Ji K, Ye L, Ruge F, Hargest R, Mason MD, Jiang WG. Implication of metastasis suppressor gene, Kiss-1 and its receptor Kiss-1R in colorectal cancer. BMC Cancer. 2014;14:723.
22. Beck BH, Welch DR. The KISS1 metastasis suppressor: a good night kiss for disseminated cancer cells. Eur J Cancer. 2010;46(7):1283-1289.

Original Article

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Quality and Reliability Assessment of Turkish YouTube Videos Related to Polycystic Ovary Syndrome: A Cross-Sectional Study

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ABSTRACT

Purpose: The aim of this study is to evaluate the content quality and reliability of information shared in Turkish YouTube videos about polycystic ovary syndrome (PCOS).

Methods: In May 2025, a search was conducted on the YouTube platform using the keywords "PCOS," "polycystic ovary treatment," and "what is PCOS." The top 100 most-viewed videos from each search were recorded, and after removing duplicate and exclusion criteria-meeting videos, 144 unique videos were included in the analysis. The overall quality of the videos was assessed using the global quality scale (GQS), and the level of reliability was assessed using the modified DISCERN (mDISCERN) scale. Mann-Whitney U and Kruskal-Wallis tests were used in the statistical analysis.

Results: 84.0% of the videos (n=121) were classified as useful, and 16.0% (n=23) were classified as misleading. The median GQS and mDISCERN scores of useful videos were significantly higher than those of misleading videos, mDISCERN ($p<0.001$). The median duration of useful videos (6.8 minutes) was longer than that of misleading videos (2.3 minutes) ($p=0.003$). However, the median number of views for misleading videos was significantly higher than that for useful videos ($p=0.041$). While 65.3% of the videos were uploaded by physicians, 34.8% of the misleading videos were shared by patients or influencers.

Conclusion: The popularity of misleading content increases the risk of patients being exposed to misinformation. There is a need to increase scientifically accurate content on digital platforms and improve digital health literacy.

Keywords: Digital health, GQS, DISCERN, polycystic ovary syndrome, YouTube

INTRODUCTION

Polycystic ovary syndrome (PCOS) is the most common endocrine disorder affecting women of reproductive age, with an estimated global prevalence of 6-13%.[1] PCOS may present with a heterogeneous clinical picture defined by the presence of at least two of the following findings, based on the Rotterdam criteria, revised in 2003: oligo-ovulation; hyperandrogenism (clinical and/or biochemical); and polycystic ovary morphology on ultrasound.[2,3] PCOS not only causes reproductive health problems, such as irregular menstrual cycles, infertility, and hirsutism, but is also a significant risk factor for serious metabolic complications, such as insulin resistance, type 2 diabetes, dyslipidemia, obesity, and cardiovascular disease.[4,5] Its complex and chronic nature necessitates lifelong management and follow-up for patients, and it is estimated that nearly 70% of affected women remain undiagnosed.

The internet and social media have become the primary sources individuals turn to when seeking health-related information.[6] YouTube, a video-based social media platform, has become a popular source of information for patients because of its ability to present complex health topics in a simplified visual and auditory format.[7] However, the majority of content on YouTube is published without undergoing any scientific or peer review process raises concerns about the quality and reliability of the information on the platform.[8,9] In conditions such as PCOS, where management relies heavily on lifestyle changes and patient education, patients' access to accurate, reliable, and up-to-date information has a direct impact on their treatment compliance and health outcomes. Incorrect or incomplete information can lead patients to ineffective or potentially harmful treatments, cause health anxiety, and damage the physician-patient relationship.[10] Therefore, the aim of this study was to systematically evaluate the content quality, reliability, and demographic

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characteristics of information shared in Turkish YouTube videos about PCOS.

METHODS

Ethical Approval

This study was conducted as a content analysis of videos published on YouTube, a publicly accessible digital platform. It did not involve human or animal subjects, did not collect personal data, and used an observational method. Therefore, it did not require ethical committee approval. This study was conducted in accordance with the principles of the Declaration of Helsinki.

This cross-sectional study was conducted on the YouTube platform in May 2025. The search was performed using three different Turkish keywords: "polikistik over sendromu (polycystic ovary syndrome)," "polikistik over tedavisi (polycystic ovary treatment)," and "PCOS nedir? (what is PCOS)" using the default "relevance" filter, the top 100 most-viewed videos for each search (300 videos in total) were recorded.

After removing duplicate videos (n=122), the remaining 178 unique videos were reviewed according to exclusion criteria. Videos not in Turkish (n=34) were excluded from the analysis. At the end of this process, 144 videos were included in the study (Figure 1).

For each video, data such as duration, number of views, number of likes, upload date, uploader type (physician, university/institution, media organization, patient/influencer), and target audience (patient, healthcare professional) were recorded in an electronic spreadsheet.

Video Evaluation Scales

The quality and reliability of the videos were assessed by a gynecologist (Ç.A) using the following scales. To ensure the reliability of the assessment, a second gynecologist (M.B) independently reviewed all videos and confirmed this assessment. For videos in which the two evaluators disagreed, a consensus meeting was held to reach a final decision. The scales used are described below.

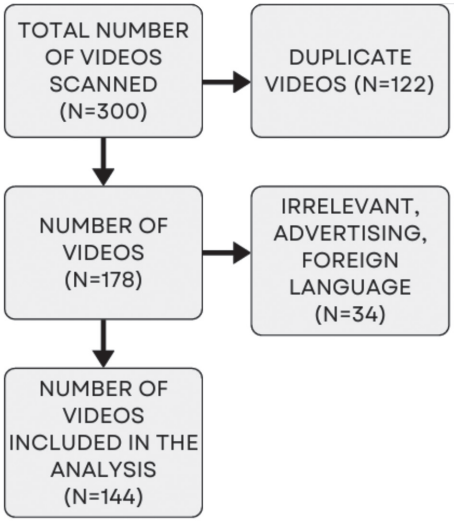

Figure 1. Flowchart for selecting videos included in the study

Global Quality Scale

The global quality scale (GQS) is a 5-point Likert scale measuring the overall fluency, accuracy of information, and educational value of the videos.[11] Each video was scored on a scale of 1-5 according to the following criteria:

1 point: Low quality, contains misleading or incorrect information,

2 points: Generally low quality, contains limited information,

3 points: Moderate quality, contains some useful information but has shortcomings,

4 points: Good quality, mostly accurate and useful information,

5 points: Excellent quality, provides comprehensive, accurate, and balanced information.

Modified DISCERN

The modified DISCERN (mDISCERN) is a measure developed to assess the reliability of health information.[11] This scale allows for a total score of 0-5 to be obtained by evaluating each of the following five criteria as "yes" (1 point) or "no" (0 points):

- Are the information sources clear and reliable?
- Is the information presented balanced and unbiased?
- Are additional information sources or references provided?
- Are areas of uncertainty or controversial topics addressed objectively?
- Are treatment options clearly explained, along with their risks and benefits?

Video Classification

As a result of the evaluation, videos were divided into two groups based on their GQS and mDISCERN scores:

- Useful videos: GQS ≥3 and mDISCERN ≥3 (both criteria must be met)
- Misleading videos: GQS <3 or mDISCERN <3 (failing to meet one criterion was sufficient)

This classification, consistent with similar studies in the literature, considers quality and reliability scores above the mid-range to be "useful".[12,13]

Statistical Analysis

Statistical analyses were performed using SPSS, version 27.0 (IBM Inc., Armonk, NY, USA). Continuous variables are presented as medians (minimum-maximum), and categorical variables are presented as numbers and percentages (%). The Mann-Whitney U test was used to compare two independent groups, and the Kruskal-Wallis test was used to compare more than two groups. Statistical significance was set at $p<0.05$.

RESULTS

The details and quality characteristics of the 144 videos included in this study are summarized in Table 1. Of the videos 84.0% (n=121) were classified as useful, while 16.0% (n=23) were classified as misleading.

The median GQS score of videos classified as useful [3.9 (3-5)] was found to be statistically significantly higher than that of misleading videos [2.7 (2-3)] ($p<0.001$). Similarly, the median mDISCERN score of useful videos [3.6 (2-5)] was significantly higher than the median score of misleading videos [1.8 (1-2)] ($p<0.001$).

The median duration of useful videos was significantly longer at 6.8 min compared to the median duration of misleading videos at 2.3 min ($p=0.003$). In contrast, the median number of views for misleading videos (3,720) was significantly higher than the median number of views for useful videos (1,580) ($p=0.041$) (Table 1).

Regarding the sources of the videos, 65.3% of the videos were uploaded by physicians, 6.3% by universities/institutions, 11.2% by media organizations, and 17.4% by patients or social media content creators. When quality scores were examined according to uploader source, videos uploaded by physicians and universities had significantly higher GQS and mDISCERN scores than those uploaded by patients and influencers ($p=0.024$).

Content analysis showed that videos most frequently addressed treatment options (50.0%), definitions and general information (34.0%), and diet/lifestyle recommendations (25.0%) (Table 2).

DISCUSSION

This study presents a comprehensive analysis evaluating the quality and reliability of videos about PCOS available on Turkish YouTube. Our findings reveal that the majority of videos on the platform (84%) generally contain useful information, but a significant minority (16%) are misleading or of low quality. A more concerning finding was that videos with low-quality and misleading content were significantly more popular than high-quality and useful videos (Table 1). This suggests that patients and individuals seeking information are at risk of being exposed to popular content that lacks scientific accuracy.

Our study found a strong correlation between video quality and source. Videos produced by physicians and academic institutions scored highest on both the GQS and mDISCERN scales, emerging as the most reliable sources of information. In contrast, content created by patients or "influencers" had significantly lower quality scores and a higher likelihood of containing misleading information. These results are consistent with those of other studies. For example, studies examining YouTube videos on various medical conditions such as endometriosis,[12] gestational diabetes,[13] cervical cancer,[14] and rheumatoid arthritis[15] similarly reported that content produced by healthcare professionals was of higher quality and reliability, while videos based on personal experiences or commercial purposes were generally misleading and of lower quality.[16,17]

The finding that misleading videos tend to be shorter and have higher view counts can be explained by modern digital content consumption habits. Users often gravitate toward information that is quick, has been viewed by many other people, is visually appealing, and easy to understand.[18]

Table 1. Quality and reliability characteristics of videos

Variable	Useful (n=121)	Misleading (n=23)	*p* value
Duration (minutes)	6.8 (0.9-28.2)	2.3 (0.6-7.4)	0.003
Views (number)	1,580 (45-200,000)	3,720 (500-42,000)	0.04
GQS score	3.9 (3-5)	2.7 (2-3)	<0.001
DISCERN score	3.6 (2-5)	1.8 (1-2)	<0.00
Uploading source (doctor/patient)	65.3%/11.7	17.4%/34.8	0.024

GQS: Global quality scale

Table 2. Content distribution of YouTube videos

Content heading	N (%)
Definition and general information	49 (34.0)
Symptoms and signs	29 (20.1)
Risk factors	25 (17.4)
Diagnostic methods	24 (16.7)
Treatment options	72 (50.0)
Diet and lifestyle recommendations	36 (25.0)
Infertility relationship	20 (13.9)
Complications	8 (5.6)
Personal experience/vlog	6 (4.2)

However, this can lead to the oversimplification of complex and chronic conditions, such as PCOS, and the omission of important details, resulting in misunderstandings. For example, short videos that focus solely on "cysts" or offer unproven "miracle cures" may negatively impact patients' health management by disregarding the syndrome's metabolic and long-term risks.

The findings of this study are consistent with those of Bakkaloğlu et al.[19] who compared YouTube and Instagram reels content related to PCOS. Both studies show that content produced by healthcare professionals is more reliable, but popularity is not always proportional to quality. This situation emphasizes the importance of digital health literacy. It is important for patients to be able to question the source, purpose, and evidence-based nature of online health information.[20] Thus patients need to be educated and cautioned by healthcare professionals about potentially poor quality infomation available online.

Study Limitations

This study had some limitations. Only the YouTube platform was examined; other popular social media channels such as TikTok and Instagram were not included. Furthermore, as popularity rankings at the time of search may change over time, the results reflect a snapshot of the situation. Although two gynecologists independently assessed the videos, the primary evaluation was conducted by one researcher (Ç.A), with the second evaluator (M.B) performing confirmatory reassessment rather than fully independent blinded scoring. A more robust methodology would have involved two obstetricians independently watching and scoring all videos without knowledge of each other's assessments. Furthermore, while social media content regulation for healthcare professionals exists, monitoring content uploaded by non-professional users remains challenging. Future research could explore whether healthcare professionals uploading high-quality videos in shorter segments with varied verbal and visual materials might help accurate content reach wider audiences and compete with misleading short videos. Finally, we did not analyze viewer comments on frequently viewed low-quality videos, which could provide valuable insights into how audiences interpret and respond to misleading health information. However, a strength of our study is that a large pool of videos (n=144) was evaluated using systematic and validated scales.

CONCLUSION

The Turkish YouTube platform has the potential to be a valuable resource for patients seeking information about PCOS but it contains significant differences in terms of content quality and reliability. The high popularity of misleading and low-quality videos poses a risk to public health. Therefore, physicians, healthcare institutions, and scientific associations should be encouraged to play a more active role on social media by producing evidence-based, understandable, and engaging content. Furthermore, it is critically important to develop educational programs aimed at improving patients' digital health literacy and raising awareness of how to distinguish reliable sources of information.

Ethics

Ethics Committee Approval: The study material was obtained from publicly available YouTube content and does not require ethics committee approval as it does not involve individual intervention or contain identifying data.

Informed Consent: Informed consent was not required due to the use of publicly available YouTube content.

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Footnotes

A Turkish abstract version of this study was presented as an oral presentation at the 2nd Aegean Women's Health Congress, held on October 25-26, 2025, in İzmir, Turkey.

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REFERENCES

1. Gao X, Zhao S, Du Y, et al. Data-driven subtypes of polycystic ovary syndrome and their association with clinical outcomes. Nat Med. 2025;31(12):4214-4224. Erratum in: Nat Med. 2025;31(12):4314.
2. Christ JP, Cedars MI. Current guidelines for diagnosing PCOS. Diagnostics (Basel). 2023;13(6):1113.
3. Rotterdam ESHRE/ASRM-sponsored PCOS consensus workshop group. Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome. Fertil Steril. 2004;81(1):19-25.
4. Sanchez-Garrido MA, Tena-Sempere M. Metabolic dysfunction in polycystic ovary syndrome: pathogenic role of androgen excess and potential therapeutic strategies. Mol Metab. 2020;35:100937.
5. Chen W, Pang Y. Metabolic syndrome and PCOS: pathogenesis and the role of metabolites. Metabolites. 2021;11(12):869.
6. Madathil KC, Rivera-Rodriguez AJ, Greenstein JS, Gramopadhye AK. Healthcare information on YouTube: a systematic review. Health Informatics J. 2015;21(3):173-194.
7. Kuru T, Erken HY. Evaluation of the quality and reliability of YouTube videos on rotator cuff tears. Cureus. 2020;12(2):e6852.
8. Mueller SM, Jungo P, Cajacob L, Schwegler S, Itin P, Brandt O. The absence of evidence is evidence of non-sense: cross-sectional study on the quality of psoriasis-related videos on YouTube and their reception by health seekers. J Med Internet Res. 2019;21(1):e11935.
9. Li HO, Bailey A, Huynh D, Chan J. YouTube as a source of information on COVID-19: a pandemic of misinformation? BMJ Glob Health. 2020;5(5):e002604.
10. Suarez-Lledo V, Alvarez-Galvez J. Prevalence of health misinformation on social media: systematic review. J Med Internet Res. 2021;23(1):e17187.
11. Hu Y, Yang Y, Chen N, Pang Z, Zhong X, Sun J. How to select high-quality health educational short videos on social media? insights from youtube and douyin. BMC Med Educ. 2025;25(1):1418.
12. Lee KN, Tak HJ, Park SY, Park ST, Park SH. YouTube as a source of information and education on endometriosis. Medicine (Baltimore). 2022;101(38):e30639.

13. Cai QY, Tang J, Meng SZ, Sun Y, Lan X, Liu TH. Quality assessment of videos on social media platforms related to gestational diabetes mellitus in China: a cross-section study. Heliyon. 2024;10(7):e29020.
14. Zhang J, Yuan J, Zhang D, et al. Short video platforms as sources of health information about cervical cancer: a content and quality analysis. PLoS One. 2024;19(3):e0300180.
15. Singh AG, Singh S, Singh PP. YouTube for information on rheumatoid arthritis--a wakeup call? J Rheumatol. 2012;39(5):899-903.
16. Wang J, Liu B, Yang G, et al. Assessing the content and quality of GI bleeding information on Bilibili, TikTok, and YouTube: a cross-sectional study. Sci Rep. 2025;15(1):14856.
17. Zhou Y, Yang L, Luo L, Cao L, Qiu J. Quality assessment of videos about dengue fever on douyin: cross-sectional study. JMIR Infodemiology. 2025;5:e76474.
18. Afful-Dadzie E, Afful-Dadzie A, Egala SB. Social media in health communication: a literature review of information quality. Health Inf Manag. 2023;52(1):3-17.
19. Bakkaloğlu FF, Bakkaloğlu İ, Özer A, Hansu K. Polycystic ovary syndrome and social media content: an evaluation through youtube videos and instagram reels content. Anat J Obstet Gynecol Res. 2025;2(2):75-82.
20. Kim JH, Kim HK. Content and quality of YouTube regarding women's health: a scoping review. Korean J Women Health Nurs. 2023;29(3):179-189.

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Early- vs. Late-Onset Neonatal Sepsis: The Predictive Role of Hemoglobin, Delivery Mode, and Inflammatory Indices

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ABSTRACT

Purpose: To identify maternal, perinatal, and neonatal factors distinguishing early-onset sepsis (EOS) from late-onset sepsis (LOS).

Methods: This retrospective study included 74 neonates with sepsis (April 2022 and April 2025) with complete maternal laboratory data. EOS was defined as ≤72 h (n=34) and LOS as >72 h (n=40). Maternal/perinatal variables, neonatal laboratory parameters (including hemoglobin), and inflammatory indices [neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio, systemic immune-inflammation index (SII), systemic inflammation response index, pan-immune-inflammation value] were compared. Predictors were assessed using logistic regression and receiver operating characteristic (ROC) analysis.

Results: Cesarean delivery, in vitro fertilization, and maternal antibiotic use were more frequent in LOS ($p<0.05$). EOS infants had lower gestational age (195.5 vs. 267 days, $p<0.001$) and birth weight (1210 vs. 3200 g, $p<0.001$). Maternal hemoglobin did not differ ($p=0.140$), whereas neonatal hemoglobin was significantly lower in EOS (17.5 vs. 18.7 g/dL, $p<0.001$). CRP, white blood cell count, and neutrophils were higher in LOS. Among indices, only NLR and SII were elevated in LOS ($p=0.025$, $p=0.009$). In multivariate analysis, neonatal hemoglobin [odds ratio (OR)=0.707, 95% confidence interval (CI): 0.553-0.904, $p=0.006$] and vaginal delivery (OR=0.068, 95% CI: 0.007–0.632, $p=0.018$) independently predicted EOS. ROC of neonatal hemoglobin showed moderate discrimination (AUC=0.741) with a cut-off of 17.5 g/dL (sensitivity 82.4%, specificity 50.0%).

Conclusion: Neonatal hemoglobin and delivery mode independently predicted EOS, whereas NLR and SII were higher in LOS. Simple clinical and hematologic parameters may help differentiate sepsis timing.

Keywords: Neonatal sepsis, early-onset, late-onset, hemoglobin, inflammatory indices

INTRODUCTION

Neonatal sepsis remains an important health challenge worldwide and continues to result in poor outcomes, despite considerable advances in intensive care.[1] Clinically, it is typically categorized as early-onset sepsis (EOS), defined as infection within the first 72 hours of life, and late-onset sepsis (LOS), which develops thereafter.[2] EOS is commonly related to vertical transmission from the mother, premature rupture of membranes, or complications occurring around delivery, whereas LOS is generally attributed to hospital-acquired infections, invasive medical procedures, and prolonged stays in neonatal units.[3,4] Recognized risk factors include prematurity, low birth weight, extended rupture of membranes, and maternal infections.[5,6] A wide range of biomarkers including C-reactive protein (CRP), procalcitonin (PCT), and various interleukins, have been extensively investigated for the early detection of sepsis.[7,8] However, most previous studies have focused primarily on differentiating septic neonates from healthy controls, with limited evidence addressing the temporal distinction between EOS and LOS.[9,10]

Recent studies have explored multiple hematologic and inflammatory parameters to improve diagnostic discrimination.[11] Demonstrated that CRP, PCT, and interleukin-6

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levels differ substantially between EOS and LOS, with higher inflammatory responses in LOS. Yin et al.[12] and Eichberger and Resch[13] further showed that indices derived from routine blood counts, including neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR), and the systemic immune-inflammation index (SII) may serve as adjunctive indicators for sepsis subtype differentiation. Similarly, Gatseva et al.[14] reported that the combination of PCT with hematologic ratios improved accuracy in predicting sepsis onset timing. Collectively, these findings highlight growing interest in the use of accessible inflammatory indices for distinguishing sepsis subtypes, although results remain inconsistent and require further validation.

Recent evidence suggests that other hematological parameters may provide additional value. Lungu et al.[15] reported that septic neonates had significantly lower hemoglobin compared to healthy controls. Moreover, in adult sepsis populations, lower hemoglobin has been linked to adverse outcomes.[16] Despite these insights, the predictive role of neonatal hemoglobin and basic obstetric factors, such as mode of delivery in distinguishing EOS from LOS has not been adequately investigated.[17,18] Therefore, the aim of this study was to identify maternal, perinatal, and neonatal predictors that distinguish EOS from LOS in neonates, with particular emphasis on the roles of neonatal hemoglobin levels, delivery mode, and inflammatory indices.

METHODS

Study Design and Population

This study used a retrospective cohort design at Okan University Hospital and involved neonates admitted to the neonatal intensive care unit between April 2022 and April 2025. Newborns diagnosed with sepsis were included. Cases were classified into two groups: (EOS, ≤72 h of life) and (LOS, >72 h of life). Neonates with major congenital anomalies, chromosomal abnormalities, or incomplete medical records were excluded.

Diagnostic Criteria for Sepsis

Sepsis was defined according to clinical signs (respiratory distress, temperature instability, feeding intolerance, lethargy, hypotonia, seizures) combined with at least one abnormal laboratory finding (abnormal white blood cell count, elevated CRP or PCT) and/or a positive blood culture, in line with international consensus definitions.[1,2]

Maternal and Perinatal Data

Maternal variables included age, presence of preeclampsia, gestational diabetes mellitus, in vitro fertilization (IVF) pregnancy, prolonged premature rupture of membranes (≥18 h), and intrapartum antibiotic use. Obstetric characteristics recorded were mode of delivery and gestational age at birth. Inflammatory indices were calculated as follows:

- NLR = neutrophil count / lymphocyte count
- PLR = platelet count / lymphocyte count
- SII = (platelet × neutrophil) / lymphocyte
- Systemic inflammation response index (SIRI) = (neutrophil × monocyte) / lymphocyte
- Pan-immune-inflammation value (PIV) = (neutrophil × platelet × monocyte) / lymphocyte.

Neonatal Data

Neonatal variables included birth weight, Apgar scores, hemoglobin levels, bilirubin, glucose, CRP, and PCT levels at admission. Based on established literature, CRP and PCT thresholds of >5 mg/L and >2 ng/mL, respectively, were considered clinically significant for neonatal sepsis.[7,8]

Outcome Measures

The primary outcome was to identify independent predictors of EOS versus LOS. Secondary analyses included comparison of maternal, neonatal, and inflammatory indices between the two groups.

Ethics Statement

The study was conducted at Okan University Hospital. However, at the time of study initiation, the Okan University Clinical Research Ethics Committee was not yet operational. Therefore, ethical approval was obtained from the Medipol University Non-Interventional Clinical Research Ethics Committee (approval no: 829, date: 17.07.2025) to ensure compliance with ethical standards. Data collection and analysis were entirely performed at Okan University Hospital. The study was conducted in accordance with the Declaration of Helsinki.

Statistical Analysis

All analyses were performed using SPSS, version 27.0 (IBM Corp., Armonk, NY, USA). Continuous variables were assessed for normality using the Kolmogorov-Smirnov test. Data are presented as mean ± standard deviation or median (interquartile range) as appropriate. Continuous variables were compared between EOS and LOS groups using either the Student's t-test or the Mann-Whitney U test, depending on distribution, whereas categorical variables were analyzed with chi-square or Fisher's exact tests.

To assess associations between clinical or laboratory factors and sepsis onset, univariate logistic regression was first applied. Variables meeting a significance threshold of $p<0.10$ were subsequently included in the multivariate regression model. Results are summarized as odds ratios (ORs) with corresponding 95% confidence intervals (CIs). For significant laboratory predictors, receiver operating characteristic (ROC) curve analysis was performed, and the area under the curve (AUC), sensitivity, and specificity are presented. A p-value <0.05 was considered statistically significant.

Sample Size and Power

This retrospective study was based on all eligible cases admitted during the study window; therefore, an a priori sample size calculation was not performed. Instead, we conducted a

post hoc sensitivity analysis to quantify the detectable effect with the available sample (EOS n=34 vs. LOS n=40; total n=74). For a two-sided α=0.05 and 80% power, this available sample provided sensitivity to detect a standardized mean difference of approximately d≈0.65 between groups (e.g., for hematologic variables such as neonatal hemoglobin). In line with our primary model, events-per-variable considerations also support parsimony in multivariable logistic regression (≈34 events for EOS), justifying inclusion of a limited number of independent predictors. We report this as a feasibility-driven retrospective cohort with post hoc sensitivity rather than a priori power (Software: G*Power 3.1.).

RESULTS

Baseline Characteristics

A total of 74 neonates with sepsis were included, of whom 34 (45.9%) had EOS and 40 (54.1%) had LOS. Maternal and obstetric characteristics are presented in Table 1. Cesarean delivery was more frequent in the LOS group compared with EOS (95.0% vs. 76.5%, p=0.037). IVF pregnancies (20.0% vs. 0%, p=0.006) and intrapartum maternal antibiotic use (30.0% vs. 5.9%, p=0.015) were also more common in LOS. Maternal age, preeclampsia, and gestational diabetes did not differ significantly between groups.

Clinical and Laboratory Findings

Blood culture results were available in 56 neonates (75.7%). Among these, 25 (44.6%) had positive cultures. The most commonly isolated microorganisms were *Staphylococcus epidermidis* (n=12), *Klebsiella pneumoniae* (n=8), and *Escherichia coli* (n=5). The remaining 31 culture-negative cases were diagnosed based on compatible clinical and laboratory findings, as per the study criteria. Neonatal clinical and laboratory parameters are shown in Table 2. Median gestational age (267 vs. 195.5 days, p<0.001) and birth weight (3200 g vs. 1210 g, p<0.001) were higher in EOS compared with LOS. White blood cell count (p=0.015) and neutrophil count (p=0.002) were higher in LOS. Neonatal hemoglobin levels were higher in EOS (18.7 vs. 17.5 g/dL, p<0.001). CRP values were higher in LOS (p=0.037). Length of hospital stay was longer in LOS (20 vs. 8 days, p<0.001).

Inflammatory Indices

Among inflammatory indices, NLR and SII were higher in LOS (p=0.025 and p=0.009, respectively), while PLR, SIRI, and PIV showed no significant differences between groups (Table 3).

Multivariate Logistic Regression

Variables entered into the multivariate logistic regression model included gestational age, birth weight, neonatal hemoglobin, and mode of delivery. Neonatal hemoglobin (OR=0.707, 95% CI: 0.553-0.904, p=0.006) and vaginal delivery (OR=0.068, 95% CI: 0.007-0.632, p=0.018) were identified as independent predictors of EOS. Gestational age and birth weight were not significant in the adjusted model. The model accuracy was 86.5% with a Nagelkerke R^2 of 0.595, and the Hosmer-Lemeshow test yielded a p value of 0.018.

ROC Curve Analysis

ROC analysis of neonatal hemoglobin showed an AUC of 0.741 for predicting EOS. The optimal cut-off value was 17.5 g/dL, corresponding to a sensitivity of 82.4% and a specificity of 50.0% (Table 4).

Table 1. Maternal and obstetric characteristics of neonates with early- and late-onset sepsis

Variable	Early-onset (n=34)	Late-onset (n=40)	p value
ASA use, n (%)	2 (5.9)	0 (0)	0.208
Mode of delivery (C/S), n (%)	26 (76.5)	38 (95.0)	0.037*
IVF pregnancy, n (%)	0 (0)	8 (20.0)	0.006**
Preeclampsia, n (%)	2 (5.9)	8 (20.0)	0.097
Gestational DM, n (%)	4 (11.8)	8 (20.0)	0.528
PPROM >18 h, n (%)	4 (11.8)	12 (30.0)	0.088
Maternal antibiotic use, n (%)	2 (5.9)	12 (30.0)	0.015*
Discharge status (exitus), n (%)	6 (17.6)	14 (35.0)	0.119

*p<0.05; **p<0.01. Categorical variables were compared using the χ^2 test or Fisher's exact test, as appropriate
IVF: In vitro fertilization, PPROM: Preterm premature rupture of membranes, DM: Diabetes mellitus, ASA: Acetylsalicylic acid

Table 2. Neonatal clinical and laboratory findings in early- and late-onset sepsis

Variable	Early-onset sepsis (n=34) median (IQR)	Late-onset sepsis (n=40) median (IQR)	*p* value
Gestational age (days)	267 (236-268)	195.5 (182-236)	<0.001*
White blood cell (×10³/μL)	11.4 (9.0-12.1)	13.0 (10.0-17.5)	0.015*
Neutrophil (×10³/μL)	10.9 (8.8-12.0)	13.9 (10.8-17.3)	0.002*
Platelet (×10³/μL)	216.9 (155-278)	218.3 (185-264)	0.862
Maternal hemoglobin (g/dL)	12.4 (10.9-13.0)	11.1 (10.0-12.4)	0.140
Prothrombin time (sec)	14.4 (13.6-15.0)	14.3 (12.8-16.5)	0.811
aPTT (sec)	27.8 (24.9-29.3)	24.7 (22.3-30.3)	0.233
INR	1.11 (1.02-1.20)	1.08 (0.95-1.27)	0.572
Infant weight (g)	3200 (2700-3400)	1210 (1000-2000)	<0.001*
Neonatal hemoglobin (g/dL)	18.7 (17.2-21.5)	17.5 (15.0-19.0)	<0.001*
Fetal bilirubin (mg/dL)	10.0 (6.7-12.1)	7.9 (5.6-11.0)	0.224
Fetal glucose (mg/dL)	56 (45-79)	64 (48-94)	0.460
Fetal CRP (mg/L)	3.7 (0.7-13.7)	10.9 (1.7-25.9)	0.037*
Procalcitonin (ng/mL)	2.8 (1.1-5.9)	2.4 (0.7-6.0)	0.508
Length of hospital stay (days)	8 (6-9)	20 (13-27)	<0.001*

*p<0.05 continuous variables are presented as median (interquartile range) and were compared using the Mann-Whitney U test
CRP: C-reactive protein, aPTT: Activated partial thromboplastin time, INR: International normalized ratio, IQR: Interquartile range

Table 3. Comparison of inflammatory indices between early- and late-onset sepsis

Variable	Early-onset sepsis (n=34) median (IQR)	Late-onset sepsis (n=40) median (IQR)	*p* value
Neutrophil-to-lymphocyte ratio (NLR)	4.5 (3.6-5.3)	8.2 (4.8-11.0)	0.025*
Platelet-to-lymphocyte ratio (PLR)	108.8 (93-132)	130.1 (97-214)	0.108
Systemic immune-inflammation index (SII)	977 (704-1277)	1224.5 (919-2735)	0.009*
Systemic inflammation response index (SIRI)	2.88 (1.8-3.9)	2.25 (1.3-4.8)	0.680
Pan-immune-inflammation value (PIV)	566.4 (372-809)	462.8 (298-811)	0.965

*p<0.05 continuous variables are presented as median (interquartile range) and were compared using the Mann-Whitney U test
IQR: Interquartile range

Table 4. ROC analysis of neonatal hemoglobin for predicting early-onset sepsis

Cut-off (g/dL)	Sensitivity (%)	Specificity (%)	Youden index
14.95	94.1	15.0	0.09
17.15	82.4	45.0	0.27
17.75	76.5	60.0	0.37
18.55	52.9	75.0	0.28

ROC: Receiver operating characteristic

DISCUSSION

By examining a cohort of septic neonates, we identified distinct maternal, perinatal, and laboratory patterns separating EOS from LOS cases. Our findings demonstrate that neonatal hemoglobin and mode of delivery were independent predictors of EOS, while gestational age and birth weight, though significant in univariate analyses, lost predictive value in the adjusted model. In addition, LOS was characterized by higher NLR and SII values, suggesting distinct inflammatory patterns.

The predominance of cesarean delivery in LOS and the association of vaginal delivery with EOS in our study reflect differences in transmission routes. EOS is primarily linked to vertical maternal transmission at birth, whereas LOS typically reflects hospital-acquired infections and the influence of invasive procedures.[19,20] The association between mode of delivery and sepsis onset timing may be explained by differences in exposure pathways. EOS typically results from vertical transmission of maternal microorganisms during vaginal delivery or after membrane rupture, whereas LOS is

more often related to nosocomial pathogens acquired during hospitalization.[20] The higher frequency of cesarean births in the LOS group in our cohort supports this pattern. Previous studies have shown that *Staphylococcus epidermidis*, *Klebsiella pneumoniae*, and *Pseudomonas aeruginosa* are among the most frequent causative agents of late-onset, hospital-acquired sepsis following surgical deliveries and prolonged neonatal intensive care.[21,22] These findings collectively suggest that delivery mode may indirectly influence the timing and microbiological profile of neonatal sepsis.

Neonatal hemoglobin emerged as another key predictor, with lower levels associated with EOS. Lungu et al.[15] recently demonstrated that hemoglobin, together with ferritin and lactate dehydrogenase levels, could serve as predictive markers for neonatal sepsis in general. Our results extend this evidence, showing that hemoglobin also plays a role in distinguishing sepsis timing. In adult critical care, anemia has been consistently associated with poor outcomes in sepsis.[16,23] The mechanisms may involve impaired oxygen delivery, reduced host immunity, and bone marrow suppression. In neonates, lower hemoglobin at birth may reflect intrauterine stress, prematurity, or suboptimal erythropoiesis, all of which predispose to EOS.

Gestational age and birth weight, classical risk factors for sepsis, showed strong associations in univariate analyses but lost significance in multivariate models. This is likely due to collinearity between the two variables, as also reported in previous neonatal sepsis cohorts.[9] Importantly, our model retained high discriminative accuracy (86.5%), suggesting that hemoglobin and delivery mode provide sufficient independent predictive power.

Inflammatory indices, particularly NLR and SII, were elevated in LOS. Similar findings have been described in adult and pediatric sepsis, where elevated NLR and SII are markers of systemic inflammation and worse prognosis.[24,25] In neonates, however, the published evidence is limited, and our study contributes novel evidence linking these indices specifically to LOS. This suggests that LOS may involve a more pronounced systemic inflammatory response, potentially related to prolonged hospital exposure and nosocomial pathogens.

Clinical implications

Our results have several implications. Recognizing hemoglobin levels and delivery route as predictors of EOS underlines the potential of basic, widely accessible parameters for early clinical risk assessment. The ROC-derived cut-off for hemoglobin (~17.5 g/dL), although falling within the normal range, provides a clinically applicable threshold for identifying neonates at higher risk of EOS. Third, the elevation of NLR and SII in LOS suggests that inflammatory indices may have adjunctive value in guiding differential diagnosis once sepsis is established.

Study Limitations

Strengths of this study include the comprehensive evaluation of maternal, perinatal, and neonatal parameters within a single cohort and the use of multiple statistical approaches, including both logistic regression and ROC analyses. However, several limitations should be acknowledged. The retrospective, single-center design and relatively small sample size limit the generalizability of our findings. Furthermore, although the multivariate logistic regression model achieved good discriminative accuracy, its calibration was suboptimal (Hosmer-Lemeshow $p = 0.018$), indicating a potential limitation in model fit. Blood culture confirmation was not available for all cases, and the diagnosis of sepsis was therefore based on a combination of clinical and laboratory findings. Future prospective multicenter studies with larger populations and microbiological validation are warranted to confirm these results.

CONCLUSION

Neonatal hemoglobin level and delivery mode were identified as independent markers distinguishing EOS from LOS in neonates, whereas elevated NLR and SII values characterized LOS cases. These readily available parameters may provide clinicians with preliminary guidance for risk stratification and early management decisions. Nevertheless, given the limited sample size and retrospective design, these findings should be interpreted with caution and validated in larger prospective studies.

Ethics

Ethics Committee Approval: Ethical approval was obtained from the Medipol University Non-Interventional Clinical Research Ethics Committee (approval no: 829, date: 17.07.2025).

Informed Consent: Due to the retrospective nature of the study and the use of anonymized data obtained from routine medical records, the requirement for written informed consent was waived by the Ethics Committee.

Authorship Contributions

Surgical and Medical Practices: G.K., E.C.N.K.Y., Ş.B., Concept: G.K., Design: G.K., E.C.N.K.Y., Data Collection or Processing: E.C.N.K.Y., Ş.B., Analysis or Interpretation: G.K., Literature Search: E.C.N.K.Y., Ş.B., Writing: G.K., E.C.N.K.Y., Ş.B.

Footnotes

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REFERENCES

1. Fleischmann C, Reichert F, Cassini A, et al. Global incidence and mortality of neonatal sepsis: a systematic review and meta-analysis. Arch Dis Child. 2021;106(8):745-752.
2. Kariniotaki C, Thomou C, Gkentzi D, Panteris E, Dimitriou G, Hatzidaki E. Neonatal sepsis: a comprehensive review. Antibiotics (Basel). 2024;14(1):6.
3. Milton R, Gillespie D, Dyer C, et al. Neonatal sepsis and mortality in low-income and middle-income countries from a facility-based birth cohort: an international multisite prospective observational study. Lancet Glob Health. 2022;10(5):e661-e672.

4. Shane AL, Sánchez PJ, Stoll BJ. Neonatal sepsis. Lancet. 2017;390(10104):1770-1780.
5. Simonsen KA, Anderson-Berry AL, Delair SF, Davies HD. Early-onset neonatal sepsis. Clin Microbiol Rev. 2014;27(1):21-47.
6. Puopolo KM, Benitz WE, Zaoutis Te; Committee on Fetus and Newborn; Committee on Infectious Diseases. Management of neonates born at ≥35 0/7 weeks' gestation with suspected or proven early-onset bacterial sepsis. Pediatrics. 2018;142(6):e20182894.
7. Hofer N, Zacharias E, Müller W, Resch B. An update on the use of C-reactive protein in early-onset neonatal sepsis: current insights and new tasks. Neonatology. 2012;102(1):25-36.
8. Stocker M, van Herk W, El Helou S, et al. Procalcitonin-guided decision making for duration of antibiotic therapy in neonates with suspected early-onset sepsis: a multicentre, randomised controlled trial (NeoPIns). Lancet. 2017;390(10097):871-881.
9. Hornik CP, Fort P, Clark RH, et al. Early and late onset sepsis in very-low-birth-weight infants from a large group of neonatal intensive care units. Early Hum Dev. 2012;88(Suppl 2):S69-S74.
10. Dong Y, Speer CP. Late-onset neonatal sepsis: recent developments. Arch Dis Child Fetal Neonatal Ed. 2015;100(3):F257-F263.
11. Cantey JB, Lee JH. Biomarkers for the diagnosis of neonatal sepsis. Clin Perinatol. 2021;48(2):215-227.
12. Yin Q, Yin J, Shen L, Zhou Q, Xu W. The early diagnostic value of neutrophil to lymphocyte ratio and platelet to lymphocyte ratio in neonatal late-onset sepsis. Front Pediatr. 2025;13:1483522.
13. Eichberger J, Resch B. Reliability of interleukin-6 alone and in combination for diagnosis of early onset neonatal sepsis: systematic review. Front Pediatr. 2022;10:840778.
14. Gatseva P, Blazhev A, Yordanov Z, Atanasova V. Early diagnostic markers of late-onset neonatal sepsis. Pediatr Rep. 2023;15(3):548-559.
15. Lungu N, Popescu DE, Manea AM, et al. Hemoglobin, ferritin, and lactate dehydrogenase as predictive markers for neonatal sepsis. J Pers Med. 2024;14(5):476.
16. Vincent JL, Sakr Y, Sprung CL, et al. Sepsis in European intensive care units: results of the SOAP study. Crit Care Med. 2006;34(2):344-353.
17. Wynn JL, Polin RA. Progress in the management of neonatal sepsis: the importance of a consensus definition. Pediatr Res. 2018;83(1-1):13-15.
18. Stoll BJ, Puopolo KM, Hansen NI, et al. Early-onset neonatal sepsis 2015 to 2017, the rise of Escherichia coli, and the need for novel prevention strategies. JAMA Pediatr. 2020;174(7):e200593.
19. Camacho-Gonzalez A, Spearman PW, Stoll BJ. Neonatal infectious diseases: evaluation of neonatal sepsis. Pediatr Clin North Am. 2013;60(2):367-389.
20. Zea-Vera A, Ochoa TJ. Challenges in the diagnosis and management of neonatal sepsis. J Trop Pediatr. 2015;61(1):1-13.
21. Raturi A, Chandran S. Neonatal sepsis: aetiology, pathophysiology, diagnostic advances and management strategies. Clin Med Insights Pediatr. 2024;18:11795565241281337.
22. Özkavaklı A, İmamoğlu EY, Önder N, İmamoğlu S, Ovalı HF. Trends in causative organisms and antimicrobial resistance in late-onset neonatal sepsis. Turk Arch Pediatr. 2024;59(4):375-382.
23. Vincent JL, Baron JF, Reinhart K, et al. Anemia and blood transfusion in critically ill patients. JAMA. 2002;288(12):1499-1507.
24. Forget P, Khalifa C, Defour JP, Latinne D, Van Pel MC, De Kock M. What is the normal value of the neutrophil-to-lymphocyte ratio? BMC Res Notes. 2017;10(1):12.
25. Yang R, Chang Q, Meng X, Gao N, Wang W. Prognostic value of systemic immune-inflammation index in cancer: a meta-analysis. J Cancer. 2018;9(18):3295-3302.

Case Report

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Intramyometrial Ectopic Pregnancy in a Patient with Adenomyosis: A Rare Case Report

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ABSTRACT

Intramyometrial ectopic pregnancy (IMP) is an exceptionally rare form of ectopic gestation, representing <1% of cases. It poses diagnostic challenges as it often mimics leiomyoma or interstitial pregnancy on imaging. A 42-year-old woman with a history of adenomyosis and previous salpingectomy was admitted with acute abdomen and hypovolemic shock. Preoperative laboratory tests revealed hemoglobin (Hb): 9.2 g/dL, hematocrit: 28%, white blood cell: 12,300/mm^3, platelet: 210,000/mm^3, and beta-human chorionic gonadotropin: 65,000 mIU/mL. After emergency laparotomy for ruptured intramyometrial pregnancy, the postoperative Hb level was 7.4 g/dL; however, this value may have been relatively overestimated due to preoperative hemoconcentration. Transvaginal ultrasonography revealed a gestational sac embedded in the uterine fundal myometrium with fetal cardiac activity. Emergency laparotomy revealed a ruptured intramyometrial gestation with massive hemoperitoneum. Estimated intraoperative blood loss was 1800 mL, requiring transfusion of three units of red blood cells and two units of fresh frozen plasma. Total abdominal hysterectomy and salpingectomy were performed. Histopathological analysis confirmed intramyometrial pregnancy associated with adenomyosis. This case highlights the importance of considering IMP in the differential diagnosis of abnormal uterine masses, especially in patients with prior uterine surgery or adenomyosis. Early recognition and prompt surgical intervention are important to prevent catastrophic and potentially life-threatening hemorrhage.

Keywords: Intramyometrial pregnancy, ectopic pregnancy, adenomyosis, hysterectomy

INTRODUCTION

Ectopic pregnancy constitutes approximately 1-2% of all pregnancies, with the vast majority localized in the fallopian tubes. Intramyometrial ectopic pregnancy (IMP), defined as implantation of the gestational sac entirely within the myometrium without communication with the uterine cavity or fallopian tubes, is exceedingly rare (<1%). The pathogenesis, frequency, and natural history of intramural pregnancy, a rare ectopic pregnancy, are not well understood. Treatment varies based on symptom severity, pregnancy location, viability, and stage at diagnosis, with no consensus on ultrasound criteria for identification.[1] The clinical challenge of IMP lies in its diagnostic difficulty, since it can easily be mistaken for degenerating fibroid or interstitial pregnancy. Literature reports fewer than 100 cases worldwide, underlining the rarity of the condition.[2-4] Etiological factors include uterine trauma (dilatation and curettage, cesarean section, myomectomy), assisted reproductive techniques, adenomyosis (as an abnormal niche for implantation), and pelvic inflammatory disease.[2,5,6] Adenomyosis itself is associated with infertility, dysmenorrhea, menorrhagia, and may alter implantation through ectopic endometrial tissue within the myometrium.[6] Diagnostic modalities such as transvaginal ultrasonography (TVUS) and magnetic resonance imaging (MRI) are very helpful for differential diagnosis, as they allow distinction of IMP from fibroid degeneration or interstitial pregnancy.[2,7] Treatment options vary from conservative management (methotrexate, laparoscopic excision, hysteroscopic evaluation) to radical interventions such as emergency hysterectomy in hemodynamically unstable patients.[3,5]

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The objective of this study was to contribute to the scarce literature and highlight the diagnostic and therapeutic challenge of IMP associated with adenomyosis, complicated by rupture and life-threatening hemorrhage.

CASE REPORT

A 42-year-old multiparous woman (G6P4Y4) with a prior right salpingectomy due to ectopic pregnancy and a history of adenomyosis presented to the emergency department with acute abdominal pain, hypotension, and tachycardia. The diagnosis of adenomyosis had previously been made by TVUS due to menorrhagia and dysmenorrhea. She had missed her menstrual period and reported progressive abdominal distension and weakness. On admission, vital signs were: blood pressure 100/72 mmHg, heart rate 100/min, respiratory rate 21/min, and temperature 37.2 °C. Abdominal examination revealed diffuse tenderness, guarding, and rebound. Preoperative laboratory findings were: hemoglobin 9.2 g/dL; hematocrit 28%; white blood cell count 12,300/mm³; platelet count 210,000/mm³; and beta-human chorionic gonadotropin (β-hCG) 65,000 mIU/mL. Renal and liver function tests were normal. Imaging by TVUS showed a gestational sac in the uterine fundus, measuring approximately 46 mm, corresponding to 11+3 weeks, with positive fetal cardiac activity Figure 1. Free fluid with clots (~500 cc) was noted in the Pouch of Douglas and in the perisplenic and perihepatic regions. MRI was not performed due to the emergency clinical condition. Emergency laparotomy revealed 5 × 5 cm ruptured intramyometrial pregnancy localized to the fundus with massive hemoperitoneum Figures 2. Right fallopian tube was absent, left adnexa were normal. Estimated blood loss was 1800 mL. Total abdominal hysterectomy and left salpingectomy were performed, and three units of packed red blood cells plus two units of fresh frozen plasma were transfused intraoperatively. Subsequent histopathological examination confirmed IMP with necrotic decidual tissue and chorionic villi infiltrating the myometrium, alongside adenomyotic foci. The patient was monitored in the intensive care unit for 24 hours, recovered uneventfully, and was discharged on

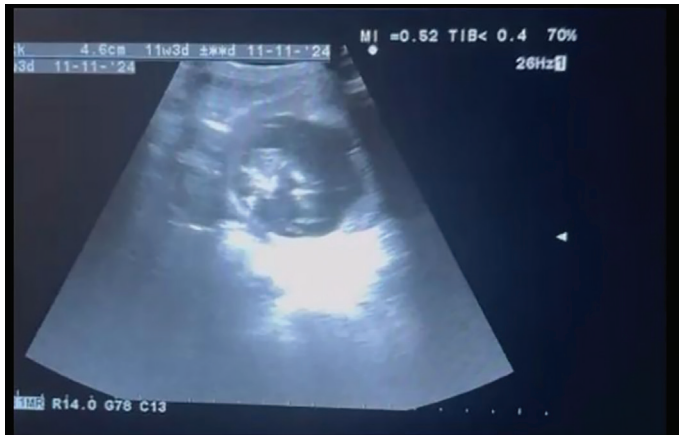

Figure 1. Transvaginal ultrasonographic appearance of an intramyometrial ectopic pregnancy located in the uterine fundus

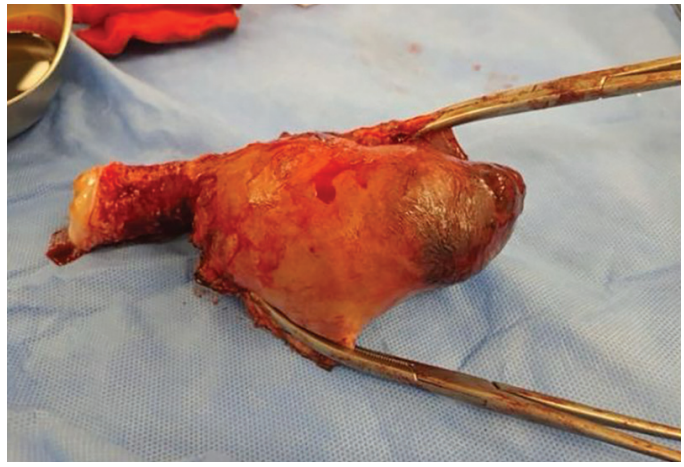

Figure 2. Gross intraoperative view of the ruptured intramyometrial pregnancy specimen following emergency hysterectomy

postoperative day five in a stable condition. Written informed consent was obtained, and institutional University of Health Sciences Turkey, Adana City Training and Research Hospital Ethics Committee approval was secured for publication of this report (approval number: 629, date: 10.07.2025).

DISCUSSION

IMP remains one of the rarest and most diagnostically challenging types of ectopic gestation, with <1% incidence and fewer than 100 reported cases worldwide.[1,2] Because of its rarity, it is frequently misdiagnosed as fibroid degeneration, interstitial pregnancy, or adenomyosis.[3,5,7] The precise etiology of IMP is not fully understood. Well-established risk factors include uterine trauma from prior procedures such as dilatation and curettage, cesarean section, or myomectomy.[1,2] Assisted reproductive technologies, particularly in vitro fertilization and intrauterine insemination, have also been associated with intramyometrial implantation.[4] Pelvic inflammatory disease and perimetrial inflammation have also been implicated.[2,5] Adenomyosis has recently been proposed as a possible predisposing factor Shi et al.[6] suggested that endometrial tissue located within adenomyotic foci can undergo decidualization in response to estrogen and progesterone, thereby creating an abnormal receptive environment for blastocyst implantation deep within the myometrium.[6] Similarly, Aburayyan et al.[2] highlighted adenomyosis as one of the plausible mechanisms predisposing to intramyometrial pregnancy. In the presented patient, histopathological examination confirmed the coexistence of adenomyosis and intramyometrial pregnancy. This observation supports the hypothesis that adenomyotic foci may provide a niche for abnormal implantation. This case may therefore represent one of the first histopathologically confirmed reports of adenomyosis as an etiological factor in IMP. Diagnostic challenges of IMP are as follows. Clinical presentation is nonspecific. Amenorrhea, abdominal pain, and abnormal uterine bleeding are common but overlap with other types of ectopic pregnancy.[3,4] Serum β-hCG levels are variable and have variously been reported as elevated, normal, or declining, thus making them

unreliable.[1,6] Ultrasonography may show a gestational sac embedded in the myometrium with an empty cavity, but misdiagnosis as leiomyoma is frequent.[1,5,7] Three-dimensional ultrasonography and MRI improve accuracy, but intraoperative findings and histopathology remain the gold standard. Management of IMP depends on hemodynamic stability, gestational age, and desire for future fertility. Conservative options include methotrexate therapy and laparoscopic excision with uterine repair.[4,6] In hemodynamically unstable patients, as in the present case, emergency hysterectomy is life-saving.[3] Prognosis for IMP is also variable. Fertility-preserving approaches may be possible in selected and stable patients but risk persistent ectopic tissue. Hysterectomy, although definitive, ensures survival. Early suspicion, individualized treatment, and awareness of adenomyosis as a potential factor may improve outcomes.

CONCLUSION

IMP is a rare but potentially life-threatening condition. The presented case demonstrates that adenomyosis may provide a physiological niche for abnormal implantation, representing a possible new etiological risk factor for IMP. Early diagnosis with TVUS/MRI, awareness of differential diagnoses, and timely surgical intervention are essential to reduce morbidity and mortality. The present case adds novel evidence to the literature and highlights the importance of considering adenomyosis in the pathogenesis of intramyometrial pregnancy.

Ethics

Ethics Committee Approval: The study was approved by the University of Health Sciences Turkey, Adana City Training and Research Hospital Ethics Committee (approval number: 629, date: 10.07.2025).

Informed Consent: Written informed consent was provided by the patient.

Footnotes

Authorship Contributions

Surgical and Medical Practices: S.A., S.Ö.Y., Concept: S.A., S.Ö.Y., Design: S.A., S.Ö.Y., Data Collection or Processing: S.A., S.Ö.Y., Analysis or Interpretation: S.A., S.Ö.Y., Literature Search: S.A., Writing: S.A., S.Ö.Y.

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REFERENCES

1. Memtsa M, Jamil A, Sebire N, Jauniaux E, Jurkovic D. Diagnosis and management of intramural ectopic pregnancy. Ultrasound Obstet Gynecol. 2013;42(3): 359-362.
2. Aburayyan ANMI, Zuhour OMB, Alsalameh BKS, Sabboh M, Jobran AWM. Intramural pregnancy managed by conservative laparoscopic resection:a case report. Case Rep Womens Health. 2024;44:e00653.
3. Yang WX, Wang TT, Zhao S. Persistence of ectopic pregnancy after intramural ectopic pregnancy surgery: a case report. Int J Surg Case Rep. 2025;126:110623.
4. Yamamoto K, Takiuchi T, Kiso K, et al. Intramural pregnancy after intrauterine insemination in a nulligravid patient without previous uterine trauma, complicated by idiopathic thrombocytopenic purpura: a case report. Case Rep Womens Health. 2025;45:e00684.
5. Chen YC, Huang CY. Successful laparoscopic management of a rare intramural ectopic pregnancy. J Minim Invasive Gynecol. 2025:S1553-4650(25)00135-9.
6. Shi J, Wu Y, Li X, et al. Effects of localization of uterine adenomyosis on clinical features and pregnancy outcome. Sci Rep. 2023;13(1):14714.
7. Memtsa M, Jamil A, Sebire N, Jauniaux E, Jurkovic D. Diagnosis and management of intramural ectopic pregnancy. Ultrasound Obstet Gynecol. 2013;42(3):359-362.

Case Report

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Cervical Cancer Diagnosed in the Early Weeks of Pregnancy: A Case Report of Cervical Adenocarcinoma

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ABSTRACT

Cervical cancer diagnosis during pregnancy is the most common type of gynecological cancer. However, cervical adenocarcinoma is rarely seen. A 29-year-old patient, G1P0, presented with vaginal bleeding and a hemorrhagic mass was detected on gynecological examination of the cervix. Ultrasound revealed a 7-week pregnancy. After obtaining written consent regarding the pregnancy and cervical mass, colposcopy revealed a 2 cm diameter cervical mass (FIGO stage IB1) involving the cervical transformation zone, and cold knife conization was performed. The histopathological result was reported as a well-differentiated cervical adenocarcinoma measuring 2 x 1.5 x 0.6 cm, with an invasion depth of 6 mm, positive basal surgical margin, and positive lymphovascular space invasion. Despite being informed about pregnancy and cervical cancer and its risks, the patient refused any intervention and wished to continue her pregnancy. At the follow-up visit, no pathology was detected on pelvic magnetic resonance imaging, control colposcopic examination, or gynecological examination. During the pregnancy follow-up period, a live male infant weighing 3100 g was delivered at 38 weeks. Two months after delivery, the patient consented to surgical treatment and underwent a hysterectomy, bilateral salpingectomy, and pelvic lymph node dissection. After a 2-day follow-up, the patient's condition was stable and she was discharged. Every pregnant woman should be assessed with a gynecological speculum examination. Treatment management can be adapted according to the reproductive desires of patients of childbearing age.

Keywords: Cervical cancer, conization, diagnosis, pregnancy, treatment

INTRODUCTION

Cervical cancer is the second most common cancer diagnosed during pregnancy, occurring in 0.1-12.0 per 10,000 pregnancies.[1] The transformation zone naturally turns outward under the influence of high oestrogen levels; during pregnancy, it is usually easy to reach the squamous-columnar junction.[2] This facilitates diagnosis and treatment during pregnancy. Cervical cancer diagnosed during pregnancy is one of the most problematic diseases because it also affects the pregnant uterus. If possible, standard treatment for cervical cancer is appropriate during pregnancy.[3] Diagnosis of invasive cervical cancer during pregnancy requires a multidisciplinary approach. The aim of cervical cancer treatment during pregnancy is to provide oncological and perinatal care and to ensure fetal survival without risk of morbidity.[4] The purpose of this case report is to present a case of cervical adenocarcinoma diagnosed in the early weeks of pregnancy and describe management and outcome.

CASE REPORT

A 29-year-old G1P0 woman presented with vaginal bleeding. A hemorrhagic mass approximately 2 cm in diameter was detected on gynecological examination of the cervix, and ultrasound revealed a 7-week pregnancy. After informing the patient about the procedure and obtaining her consent, a 2 cm cervical mass, including the cervical transformation zone, was detected during colposcopy. Cold knife conization was performed (Figure 1 shows the front view of the conization specimen, Figure 2 shows the rear view), and the cervix was

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sutured at the 6 and 12 o'clock positions. Following surgery, transvaginal ultrasound revealed a cervical length of over 35 mm. The pathological finding was reported as a well-differentiated cervical adenocarcinoma measuring 2 × 1.5 × 0.6 cm, with a 6 mm invasion depth, positive basal surgical margin, positive lymphovascular space invasion (the black arrow in Figure 3 indicates the endocervical epithelium, while the asterisk indicates the adenocarcinoma portion of the tissue (hematoxylin and eosin stain x25), and as seen in Figure 4, the carcinoma cells were immunopositive for P16 (p16 x 50). The patient was informed about pregnancy, cervical cancer, and all risks (including hysterectomy, bilateral salpingectomy, and pelvic lymph node dissection), but refused surgery and wished to continue her pregnancy. At a follow-up visit approximately three weeks later, pelvic magnetic resonance imaging (MRI) revealed no evidence of parametrial involvement or lymph node involvement. No lesions were detected during the patient's follow-up colposcopic examination and the patient did not receive any chemotherapy during follow-up. During the pregnancy follow-up period, due to breech presentation during labor + intracervical adenocarcinoma, a live male baby weighing 3100 g was delivered at 38 weeks of gestation with an Apgar score of 9-10. Preoperative positron emission tomography/computed tomography (PET/CT) revealed increased focal fluorosdeoxyglucose (FDG) uptake (maximum standard uptake value =6.98) at the level of the cervix uteri, and pelvic MRI showed a 12 mm signal change on the mucosal surface at the level of the cervix uteri and mucosal involvement on contrast-enhanced imaging. The patient

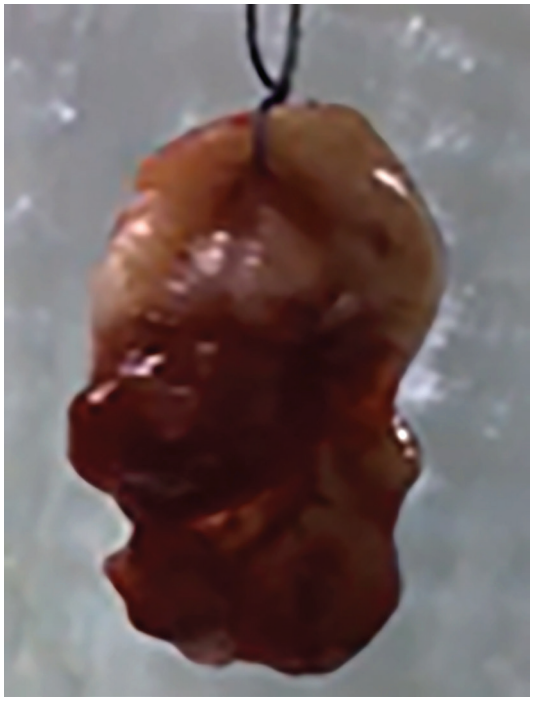

Figure 1. Anterior view of conization specimen of the cervix

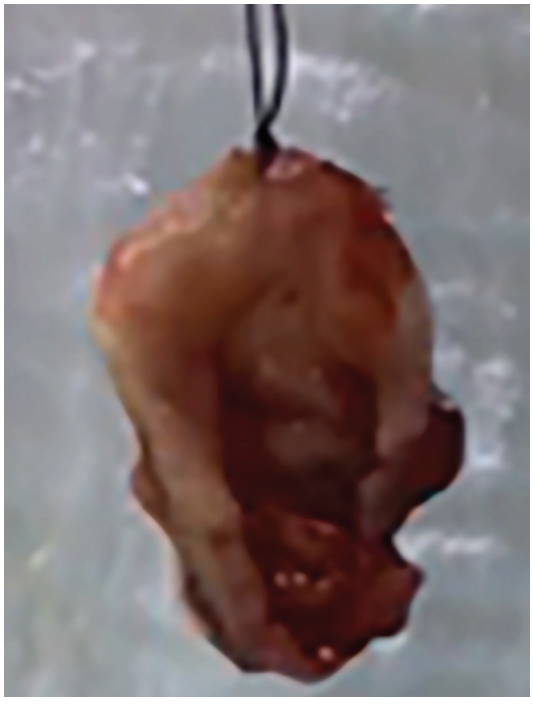

Figure 2. Posterior view of conization specimen of the cervix

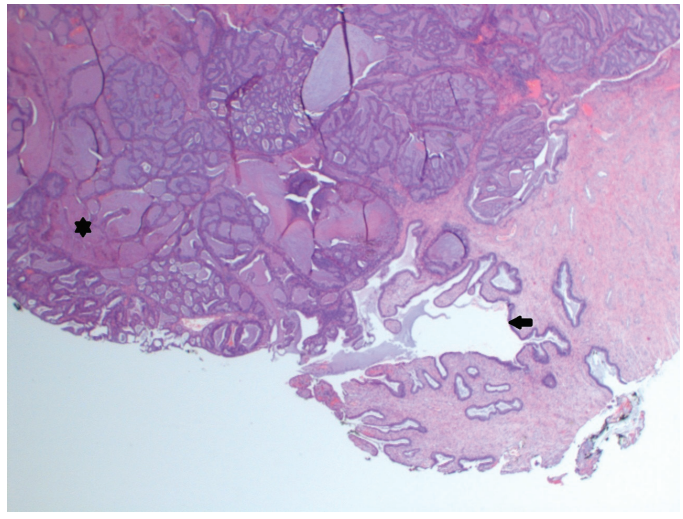

Figure 3. Black arrow in the figure show endocervical epithelium and asterisk show adenocarcinoma part of the tissue (HE X 25)

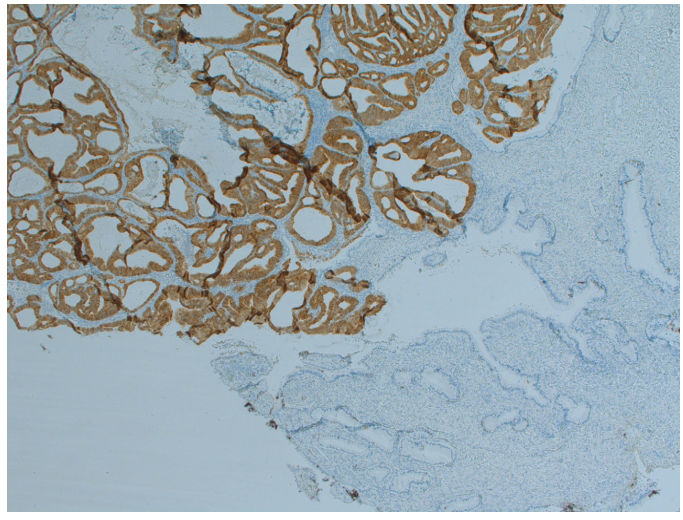

Figure 4. Carcinoma cells are immunopositive with P16 (p16 X 50)

consented to surgery and underwent a hysterectomy, bilateral salpingectomy, and pelvic lymph node dissection two months after delivery. In addition, ovarian transposition was performed, and the ovaries were removed from the pelvis. The patient was monitored in the clinic for two days postoperatively and was discharged in stable condition and fully recovered. The histopathological result was reported as normal at the surgical margins.

DISCUSSION

The most common histological subtypes of cervical cancer are squamous cell carcinoma and adenocarcinoma, seen in approximately 70% and 25% of all patients, respectively.[5] In this case, the histological type of cervical cancer was reported as adenocarcinoma. Symptoms may include abnormal, foul-smelling vaginal discharge (which may be watery, purulent or mucous), prolonged or irregular vaginal bleeding, and pelvic pain. As these symptoms may also be seen in other conditions during pregnancy, diagnosis can be difficult.[6] In this case, there was a complaint of vaginal bleeding. Histopathological examination was performed for a definitive diagnosis. Guidelines for cervical cancer during pregnancy recommend colposcopic biopsy without cervical curettage. The risk of HGSIL progressing to invasive cancer during pregnancy is thought to be less than 2%.[4] Diagnostic procedures during pregnancy should comply with standard oncological principles, such as colposcopic examination, preferably MRI, assessment of lymph node involvement, and FIGO staging.[3,6] However, unlike non-pregnant patients, imaging methods involving ionising radiation, such as CT or PET/CT, are contraindicated due to their teratogenic potential. Furthermore, gadolinium-based contrast agents used in MRI are often avoided due to association with poor pregnancy outcome, such as stillbirth.[7] The staging of cervical cancer is based on the size of the tumor, vaginal or parametrial involvement, spread to neighbouring organs such as the bladder or rectum, and distant metastases. For patients diagnosed during pregnancy, the gestational age (determined by ultrasound) and the patient's decision to continue the pregnancy must also be taken into account. In IA2 to IB1 stage cervical cancer up to 2 cm, pelvic lymphadenectomy and surgical staging are an important part of treatment planning. Laparoscopic staging provides low surgical morbidity while also allowing for accurate assessment of lymph node involvement.[8] If lymph node involvement is not detected, it is recommended to postpone cervical conization or simple trachelectomy until fetal maturity is achieved. As an alternative treatment, radical trachelectomy may lead to fetal death and significant blood loss, while simple trachelectomy (cervical amputation) is controversial.[9] In a study conducted by Vercellino et al.,[10] standard laparoscopic pelvic lymphadenectomy was performed on 32 cases of cervical cancer in the late first trimester and second trimester, and no complications or problems were encountered during surgery. The total number of lymph nodes removed during surgery was comparable to that in non-pregnant women. This study demonstrated that when performed by skilled practitioners, this method is safe and effective before the 22nd week of pregnancy.[10] However, MRI allows for cervical amputation/simple trachelectomy within limits where the disease has not spread, and can also be used to assess the suitability of the technique and for cervical cancer follow-up. As cervical adenocarcinoma can spread outside the pelvis and has a poor prognosis, aggressive treatment is recommended in these cases.[11] In this case, a speculum examination was performed, and a conization was carried out due to suspected cancer, but an endocervical curettage was not performed due to pregnancy. MRI was used as the imaging method. Moreover, the patient refused surgical intervention during pregnancy.

Studies have found that women diagnosed with cervical cancer during pregnancy have similar oncological prognoses to non-pregnant women.[12,13] However, no difference was found in terms of gestational age and preterm birth rates among the children of women diagnosed with invasive cervical cancer.[14] Furthermore, the effect of pregnancy on the progression of cervical cancer remains controversial. Increased levels of progesterone, oestrogen, and human chorionic gonadotropin during pregnancy, along with local immunosuppression, may indirectly affect the progression of cervical cancer during pregnancy by triggering reactivation of human papillomavirus. Furthermore, increased uterine blood flow and dilation of the cervix during childbirth may increase the likelihood of cancer cell spread and trigger the progression of cervical cancer.[12] However, most cases of cervical cancer detected during pregnancy are stage I, which may increase the likelihood of continuing the pregnancy and achieving a full recovery.[4] In this case, the cervical length was measured to be over 35 mm following cold conization. A cesarean section was performed at 38 weeks of gestation due to breech presentation during labor and endocervical adenocarcinoma. No additional treatment was given to the patient who underwent surgery for early-stage cervical cancer because the risk was low. However, cervical adenocarcinoma may regress, remain stable, or progress during treatment. For these reasons, personalized treatment is strongly recommended for pregnant women with cervical cancer, and the treatment decision may be made jointly by obstetricians, gynecologists, oncologists, paediatricians, and psychologists in consultation with the patient.[15] According to data from the International Network of Infertility and Pregnancy, the prognosis is no worse than for the non-pregnant population.[16] As cervical cancer is rare during pregnancy, further research or randomized studies are required.

CONCLUSION

Cervical cancer is the most common gynecological malignancy detected during pregnancy. Every pregnant woman should be assessed with a gynecological speculum examination. Treatment methods depend on various factors, including the stage of the disease, lymph node involvement, histological subtype, the patient's desire for pregnancy, gestational age, and the duration of pregnancy at the time of admission. Treatment management can be adapted according to the patient's desire for fertility during the reproductive period.

Ethics

Informed Consent: Written informed consent was signed by the patient for this case report.

Footnotes

Authorship Contributions

Surgical and Medical Practices: A.B., F.A., Ç.Ç., P.K., Concept: A.B., Data Collection or Processing: A.B., P.K., Analysis or Interpretation: F.A., Ç.Ç., P.K., Literature Search: F.A., Ç.Ç., Writing: A.B., P.K.

Conflict of Interest: No conflict of interest was declared by the authors.

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REFERENCES

1. Kurniadi A, Setiawan D, Kireina J, et al. Clinical and management dilemmas concerning early-stage cervical cancer in pregnancy - a case report. Int J Womens Health. 2023;15:1213-1218.
2. Apgar BS, Zoschnick LB. Triage of the abnormal Papanicolaou smear in pregnancy. Prim Care. 1998;25(2):483-503.
3. Amant F, Berveiller P, Boere IA, et al. Gynecologic cancers in pregnancy: guidelines based on a third international consensus meeting. Ann Oncol. 2019;30(10):1601-1612.
4. Mruzek H, Kacperczyk-Bartnik J, Dańska-Bidzińska A, Ciebiera M, Grabowska-Derlatka L, Derlatka P. Early-stage and locally advanced cervical cancer during pregnancy: clinical presentation, diagnosis and treatment. Medicina (Kaunas). 2024;60(10):1700.
5. C Cohen PA, Jhingran A, Oaknin A, Denny L. Cervical cancer. Lancet. 2019;393(10167):169-182.
6. Beharee N, Shi Z, Wu D, Wang J. Diagnosis and treatment of cervical cancer in pregnant women. Cancer Med. 2019;8(12):5425-5430.
7. Dąbrowska A, Perdyan A, Sobocki BK, Rutkowski J. Management of cervical cancer during pregnancy – a systematic review. Nowotwory. Journal of Oncology. 2024;74(1):27-33.
8. Rubach E. Cancer in pregnant women. Oncol Clin Pract. 2018;14(2):62-78.
9. Van Calsteren K, Hanssens M, Moerman P, et al. Successful conservative treatment of endocervical adenocarcinoma stage Ib1 diagnosed early in pregnancy. Acta Obstet Gynecol Scand. 2008;87(2):250-253.
10. Vercellino GF, Koehler C, Erdemoglu E, et al. Laparoscopic pelvic lymphadenectomy in 32 pregnant patients with cervical cancer: rationale, description of the technique, and outcome. Int J Gynecol Cancer. 2014;24(2):364-371.
11. Park JY, Kim DY, Kim JH, Kim YM, Kim YT, Nam JH. Outcomes after radical hysterectomy in patients with early-stage adenocarcinoma of uterine cervix. Br J Cancer. 2010;102(12):1692-1698.
12. He Z, Xie C, Qi X, Hu Z, He Y. The effect of preserving pregnancy in cervical cancer diagnosed during pregnancy: a retrospective study. BMC Womens Health. 2022;22(1):314.
13. Cintra GF, Derchain SFM, Bicalho DS, Filho ALDS, Primo WQSP. Cervical cancer in pregnancy. Rev Bras Ginecol Obstet. 2023;45(5):293-296.
14. Zemlickis D, Lishner M, Degendorfer P, Panzarella T, Sutcliffe SB, Koren G. Maternal and fetal outcome after invasive cervical cancer in pregnancy. J Clin Oncol. 1991;9(11):1956-1961.
15. Han SN, Verheecke M, Vandenbroucke T, Gziri MM, Van Calsteren K, Amant F. Management of gynecological cancers during pregnancy. Curr Oncol Rep. 2014;16(12):415.
16. Maggen C, Wolters VERA, Cardonick E, et al. Pregnancy and cancer: the INCIP project. Curr Oncol Rep. 2020;22(2):17.

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