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Turkish Journal of Obstetrics and Gynecology (formerly called Türk Jinekoloji ve Obstetrik Derneği Dergisi) is the official peer-reviewed journal of the Turkish Society of Obstetrics and Gynecology and is published quarterly on March, June, September and December.

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appropriately investigated and resolved. The statement about the authors' contributions should be placed in the cover letter. All persons who contributed to the work, but not sufficiently to be authors, must be acknowledged.

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PRISMA for preferred reporting items for systematic reviews and meta-analyses (Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 2009; 6(7): e1000097.) (http://www.prisma-statement.org/),

STARD checklist for the reporting of studies of diagnostic accuracy (Bossuyt PM, Reitsma JB, Bruns DE, Gatsonis CA, Glasziou PP, Irwig LM, et al, for the STARD Group. Towards complete and accurate reporting of studies of diagnostic accuracy: the STARD initiative. Ann Intern Med 2003;138:40-4.) (http://www.stard-statement.org/),

STROBE statement-checklist of items that should be included in reports of observational studies (http://www.strobe-statement.org/),

MOOSE guidelines for meta-analysis and systemic reviews of observational studies (Stroup DF, Berlin JA, Morton SC, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting Meta-analysis of observational Studies in Epidemiology (MOOSE) group. JAMA 2000; 283: 2008-12).

CARE guidelines are designed to increase the accuracy, transparency, and usefulness of case reports. (Gagnier JJ, Kienle G, Altman DG, Moher D, Sox H, Riley D; the CARE Group. The CARE Guidelines: Consensus-based Clinical Case Reporting Guideline Development.) (http://www.care-statement.org/)

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- A short title of no more than 50 characters, including spaces, for use as a running foot.

- All author name(s), institutional, corporate, or commercial affiliations, and up to two major degree(s).

- Corresponding author's name, address, telephone (including the mobile phone number), fax numbers and e-mail address (the corresponding author will be responsible for all correspondence and other matters relating to the manuscript).

### Precis

The precis is a one-sentence synopsis of no more than 30 words that describes the basic findings of the article. Precis sample can be seen below:

'Using a 45 point questionnaire, we have evaluated the trend of Robotic surgery training in the gynecologic surgery fellowship programs across the nation'.

### Abstract

All manuscripts should be accompanied by an abstract. All information in the abstract should be consistent with the information in the text, tables, or figures. Avoid use of commercial names in the abstract. Original research reports should have a structured abstract of no more than 250 words, using the following headings:

· Objective: Main question, objective, or hypothesis (single phrase starting with, for example, "To evaluate..." or "To estimate." [never start with "To determine."]).

· Materials and Methods: Study design, participants, outcome measures, and in the case of a negative study, statistical power.

· Results: Measurements expressed in absolute numbers and percentages, and when appropriate indicate relative risks or odds ratios with confidence intervals and level of statistical significance; any results contained in the abstract should also be presented in the body of the manuscript, tables, or figures.

· Conclusion: Directly supported by data, along with clinical implications.

Authors from Turkey or Turkish speaking countries are expected to submit a Turkish abstract including subheadings such as "Amaç, Gereç ve Yöntemler, Bulgular, Sonuç". The abstract of Authors whose native language is not Turkish will be provided free of charge translation services into Turkish language.

A structured abstract is not required with review articles and case reports.

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Below the abstract provide 3 to 5 keywords. Abbreviations should not be used as keywords. Keywords should be picked from the Medical Subject Headings (MeSH) list (www.nlm.nih.gov/mesh/MBrowser.html).

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**Table 1.** Manuscript length at a glance

| Article type | Abstract Length | Manuscript Word Count* | Maximum Number of Authors | Maximum Number of References$^{\Phi}$ |
|---|---|---|---|---|
| Original Research | 250 words | 5,500 words (~22 pages)$^{\Psi}$ | NA | 30 |
| Case report | 150 words | 2,000 words (~8 pages) | 4 | 8 |
| Systematic review | 300 words | 6,250 words (~25 pages) | 4 | 60 |
| Current commentary | 250 words | 3,000 words (~12 pages) | 4 | 12 |
| Procedure and Instruments | 200 words | 2,000 words (~8 pages) | 4 | 10 |
| Letters | NA | 350 words | 4 | 5 |

*Manuscript length includes all pages in a manuscript (ie, title page, abstract, text, references, tables, boxes, figure legends, and appendixes). $^{\Phi}$Suggested limit. $^{\Psi}$The Introduction should not exceed 250 words. ~approximately; NA, not applicable.

Original researches should have the following sections;

### Introduction

State concisely the purpose and rationale for the study and cite only the most pertinent references as background. Avoid a detailed literature review in this section.

### Materials and Methods

Describe the research methodology (the patients, experimental animals, material and controls, the methods and procedures utilized, and the statistical method(s) employed) in sufficient detail so that others could duplicate the work. Identify methods of statistical analysis and when appropriate, state the basis (including alpha and beta error estimates) for their selection. Cite any statistical software programs used in the text. Express p values to no more than two decimal places. Indicate your study's power to detect statistical difference.

Address "IRB" issues and participants informed consent as stated above, the complete name of the IRB should be provided in the manuscript. State the generic names of the drugs with the name and country of the manufactures.

### Results

Present the detailed findings supported with statistical methods. Figures and tables should supplement, not duplicate the text; presentation of data in either one or the other will suffice. Authors should report

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outcome data as both absolute and relative effects since information presented this way is much more useful for clinicians. Actual numbers and percentages should be given in addition to odds ratios or relative risk. When appropriate, number needed to treat for benefits (NNTb) or harm (NNTh) should be supplied. Emphasize only your important observations; do not compare your observations with those of others. Such comparisons and comments are reserved for the discussion section.

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Begin with a description of what your study found in relation to the purpose or objectives as stated in the Introduction. State the importance and significance of your findings to clinicians and actual patient care but do not repeat the details given in the Results section. Limit your opinions to those strictly indicated by the facts in your report. Compare your finding with previous studies with explanations in cases where they differ, although a complete review of the literature is not necessary.

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Provide information on the limitations of the study. No new data are to be presented in this section. A final summary is not necessary, as this information should be provided in the abstract and the first paragraph of the Discussion. Although topics that require future research can be mentioned, it is unnecessary to state, "Further research is needed."

### Conclusion

The conclusion of the study should be highlighted. The study's new and important findings should be highlighted and interpreted.

### Conflict of Interest

Authors must indicate whether or not they have a financial relationship with the organization that sponsored the research.

The main text of case reports should be structured with the following subheadings:

Introduction, Case Report, Discussion and References.

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References are numbered (Arabic numerals) consecutively in the order in which they appear in the text (note that references should not appear in the abstract) and listed double-spaced at the end of the manuscript. The preferred method for identifying citations in the text is using within parentheses. Use the form of the "Uniform Requirements for Manuscripts" (http://www.icmje.org/about-icmje/faqs/icmje-recommendations/). If number of authors exceeds seven, list first 6 authors followed by et al.

Use references found published in peer-reviewed publications that are generally accessible. Unpublished data, personal communications, statistical programs, papers presented at meetings and symposia, abstracts, letters, and manuscripts submitted for publication cannot be listed in the references. Papers accepted by peer-reviewed publications but not yet published ("in press") are not acceptable as references.

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Tables should be included in the main document after the reference list. Color figures or gray-scale images must be at minimum 300 DPI resolutions. Figures should be submitted in "*.tiff", "*.jpg" or "*.pdf" format and should not be embedded in the main document. Tables and figures consecutively in the order they are referred to within the main text. Each table must have a title indicating the purpose or content of the table. Do not use internal horizontal and vertical rules. Place explanatory matter in footnotes, not in the heading. Explain all abbreviations used in each table in footnotes. Each figure must have an accompanying descriptive legend defining abbreviations or symbols found in the figure. If photographs of people are used, the subjects must be unidentifiable and the subjects must have provided written permission to use the photograph. There is no charge for color illustrations.

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Revisions will be sent to the corresponding author. Revisions must be returned as quickly as possible in order not to delay publication. Deadline for the return of revisions is 30 days. The editorial board retains the right to decline manuscripts from review if authors' response delays beyond 30 days. All reviewers' comments should be addressed a revision note containing the author's responses to the reviewers' comments should be submitted with the revised manuscript. An annotated copy of the main document should be submitted with revisions. The Editors have the right to withdraw or retract the paper from the scientific literature in case of proven allegations of misconduct.

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## Clinical Investigations

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## LETTER FROM THE PRESIDENT

Dear Colleagues,

During these hard times of Coronavirus Pandemic, it was not possible to conduct our yearly National Congress of Obstetrics and Gynecology. When things were starting to get better, third wave of the pandemic put life to a stop. Thus we continued meeting through online lectures and web seminars. Even though it was not ideal, we did everything we could do to teach and share knowledge.

We need to stand strong and positive as the pandemic will hopefully lessen its burden on the community. We hope that as vaccination rates go up, infection rates will go down. We are eagerly waiting for better days. As the saying goes, the night is darkest before dawn and thing look the worst before getting better. If all goes well the corona pandemic will be a bad memory in our minds soon enough.

We want to make a difference in the scientific world as the Turkish Journal of Obstetrics and Gynecology. We are looking forward to your valuable submissions to publish in our journal and so we can together explore medicine further.

Sincerely,

**Ateş Karateke, Prof. MD**
**President of TJOD**

TURKISH JOURNAL OF OBSTETRICS AND GYNECOLOGY

## EDITORIAL

Dear Colleagues,

This year Masterclass Courses on fresh cadavers will be held on 8-12th of September 2021. The courses will be organized by special interest groups of our journal such as Endoscopy, Perinatology, Urogynecology, Cosmetic Genital Surgery, Gynecological Oncology and Reproductive Health. The courses are endorsed by Turkish Society of Obstetrics and Gynecology, Urogynecology Society, Gynecological Endoscopy Society. This years' hot topic is breast dissection and ultrasonography of female breast on fresh cadavers for gynecologists. During the courses online Gynecology lectures will be recorded and provided to our members free of charge.

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*Clinical Investigation / Araştırma*

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Turk J Obstet Gynecol 2021;18:79-84

# A novel low uterine segment sandwich technique (Caliskan's technique) for the management of post-cesarean hemorrhage due to placenta previa accreta

## *Plasenta previa accreta nedeniyle sezaryen sonrası kanama yönetiminde yeni alt uterin segment sandviç tekniği (Çalışkan tekniği)*

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### Abstract

**Objective:** Placenta previa (PP) and placenta accreta spectrum (PAS) disorders are major causes of postpartum hemorrhage (PPH). There is a variety of surgical management options with inexplicit reported success rates. Uterine sandwich is a combination of uterine compression sutures and intrauterine balloon placement to achieve hemostasis. The aim of this study was to present our experience of seven women managed with a novel "lower uterine sandwich" technique to control post-cesarean hemorrhage due to PP accreta.

**Materials and Methods:** Seven pregnant women diagnosed as having PP totalis accreta underwent a post-cesarean procedure combining bilateral ligation of the uterine artery, utero-ovarian artery, and internal iliac artery, Pereira compression sutures implemented on the uterine isthmus, Foley catheter placement into the lower uterine segment, and transvaginal cervical cerclage application, namely "Caliskan's uterine sandwich technique".

**Results:** All women included in this study had placental invasion abnormalities of varying degrees. Postoperative diffusion magnetic resonance imaging assessment revealed a completely normal and preserved uterine blood supply. All women menstruated regularly in their postoperative follow-up period and two women conceived again and delivered uneventfully. None of the patients experienced morbid complications nor required hysterectomy.

**Conclusion:** This novel procedure appears to be a plausible fertility and organ-preserving option in cases of intractable PPH, particularly in lower uterine segment bleeding. This uterine sandwich technique may allow physicians to manage massive hemorrhage due to PAS conservatively by preserving the uterus and its functions without major complications.

**Keywords:** Placenta previa, postpartum hemorrhage, uterine sandwich technique, uterine compression suture

### Öz

**Amaç:** Plasenta previa (PP) ve plasenta akreta spektrum (PAS) bozuklukları postpartum kanamanın (PPK) başlıca nedenleridir. Açıkça bildirilmemiş başarı oranları ile çeşitli cerrahi tedavi seçenekleri vardır. Uterin sandviç, hemostazı sağlamak için uterin kompresyon sütürleri ve uterus içi balon yerleştirilmesinin bir kombinasyonudur. Bu çalışmanın amacı, PP akretaya bağlı sezaryen sonrası kanamayı kontrol etmek için yeni bir "alt uterin sandviç" tekniği ile tedavi edilen yedi kadına ilişkin deneyimimizi sunmaktır.

**Gereç ve Yöntemler:** PP totalis akreta tanısı konulan ve uterin arter, utero-ovaryan arter ve internal iliak arterin bilateral ligasyonu ile sezaryen sonrası işlem uygulanan yedi gebe kadın, uterin istmusa Pereira kompresyon sütürleri, Foley kateterinin alt uterin segmente yerleştirilmesi ve transvajinal servikal serklaj uygulaması, "Çalışkan'ın Uterin Sandviç Tekniği", yapıldı.

**Bulgular:** Bu çalışmaya dahil edilen tüm kadınlarda farklı derecelerde plasental invazyon anormallikleri vardı. Postoperatif difüzyon manyetik rezonans incelemesi, tamamen normal ve korunmuş uterus kan akımını ortaya çıkardı. Tüm kadınlar postoperatif takiplerinde düzenli olarak adet gördüler ve 2 kadın tekrar gebe kaldı ve sorunsuz doğum yaptı. Hastaların hiçbiri morbid komplikasyon yaşamadı ve histerektomi gerektirmedi.

**PRECIS:** A novel low uterıne sandwich technique (Caliskan's technique) for placenta previa.

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**Sonuç:** Bu yeni prosedür, inatçı PPK olgularında, özellikle alt uterin segment kanamalarında makul bir doğurganlık ve organ koruma seçeneği gibi görünmektedir. Bu uterin sandviç tekniği, kliniğin uterusu ve fonksiyonlarını büyük bir komplikasyon olmaksızın koruyarak PAS'ye bağlı masif kanamaları konservatif olarak yönetmesine izin verebilir.
**Anahtar Kelimeler:** Plasenta previa, postpartum kanama, uterin sandviç tekniği, uterin kompresyon sutürü

## Introduction

Postpartum hemorrhage (PPH) is a catastrophic complication of human birth, associated with blood transfusion, hysterectomy, maternal intensive care unit admission, septicemia, thrombophlebitis, and even an increased risk for maternal death[1-3]. PPH may emerge after vaginal delivery or cesaraen section, either as an early or a late complication of a number of obstetric conditions, including uterine atony, placental retention, abnormalities of placentation and placenta previa (PP). PP occurs in approximately 5 in every 1000 pregnancies and the incidence has severely increased through the last decades, possibly due to the increase in the rate of cesarean section deliveries[4-6]. On the other hand, PP is frequently complicated by invasion of placental villi beyond the decidua basalis causing placenta accreta or increta, referred to as placenta accreta spectrum (PAS) disorders[7]. These clinical situation suggests an association between endometrial damage and uterine scarring and subsequent previa[8]. Consequently, PP is associated with numerous adverse maternal outcomes, including massive hemorrhage, adjacent organ damage, and hysterectomy with loss of reproduction[4,5].

The management of PPH due to PP or PAS consists of two therapeutic approaches; conservative and interventional approaches, and the latter should follow the former immediately in the event of failure. Conservative treatment of PPH due to PP consists of the administration of uterotonic drugs, uterine compression, and/or intrauterine balloon tamponade. When these initial therapeutic modalities fail, uterine compression sutures, uterine artery or internal iliac artery ligation, or radiologic embolization of the artery may be performed before hysterectomy is considered to control bleeding and to avoid maternal death[3,9,10]. However, hysterectomy results in the loss of reproduction function and arterial embolization techniques require high medical costs and sophisticated facilities. Thus, other minimally invasive procedures are required to treat PPH and preserve the uterus.

There is a variety of uterine compression sutures defined in the literature, including B-Lynch, Hayman and Cho sutures; however, all these suture techniques have some drawbacks[11,12]. The reported success rates of balloon tamponade methods are highly variable, possibly due to the heterogeneous causes of PPH and comorbidities accompanying the entity, thus these rates are not specific to PP[13,14]. Therefore, there are techniques combining uterus compression sutures and balloon tamponade, namely "uterine sandwich", in the literature, with the aim of defining a more successful and minimally invasive modality in controlling PPH[15-17]. The "sandwich" techniques combine the beneficial effects of "outer" compression sutures and "inner" pressure implicated by the intrauterine balloon placement. However, data on the literature of these techniques are quite scarce and there is no consensus on how and in whom uterine sandwich techniques should be used, as well as which uterine suture or balloon type should be employed.

The aim of this study was to present our experience on seven women who were managed conservatively with a novel "low uterine sandwich" technique to control post-cesarean hemorrhage due to PP accreta.

## Materials and Methods

This retrospective descriptive clinical study involved seven pregnant women who were diagnosed as having PP totalis using two-dimensional ultrasonography and color Doppler evaluation (Voluson E8 probe) between January 2013 and December 2017 at Bahcesehir University School of Medicine, İstanbul, Turkey. The study was performed in accordance with the ethical standards for human research established by the Declaration of Helsinki and Good Clinical Practice guidelines and approved by the local Ethics Committee of Bahcesehir University School of Medicine. All patients provided written informed for the application of this technique.

During the study period, 171 women with the risk of or onset of postpartum bleeding underwent surgery by the Emergency Obstetric Team led by Eray Caliskan. Among these, 38 women were diagnosed as having PP and 25 had PP accreta spectrum.

In addition to two peripheral vascular accesses made before the procedure, a central venous access was ensured in all women in the perioperative period. The skin incision was made through a Pfannenstiel incision. The fascia was cut transversely in the midline followed by a finger dissection to separate the rectus muscles and then opening the peritoneum. The myometrium was incised transversely at the lower segment (Munro-Kerr) in the midline, then opened and extended laterally with finger dissection despite anteriorly localized PP in six cases. The baby was delivered with external fundal pressure. The placenta was removed manually. After the removal of the placenta, 20 units of oxytocin (Synpitan Fort ampoule®, Deva, Turkey) in 500 cc Ringer's lactate, at the rate of 125 mL/h, was rapidly infused, in addition to intramuscular administration of 0.2 mg methylergonovine maleate (Metiler ampoule®, Adeka, Turkey).

The procedures were performed in the following order:

1. Uterine arteries, utero-ovarian arteries and internal iliac arteries were ligated bilaterally using 1-0 polyglycolic acid suture (Vicryl®; Ethicon, Sommerville, NJ, USA) on a 70-mm circular needle (Figure 1).
2. An 18-French Foley catheter was introduced from the uterine incision, with its caudal end being placed in the vagina through

the cervix, to be placed within the lower uterine segment and its balloon was inflated by 50-100 cc with warm saline solution.
3. The Foley catheter balloon was stabilized to the lower uterine segment at the isthmic level using circular Pereira sutures[18] passing from the medial aspects of bilateral uterine arteries (Figure 2).

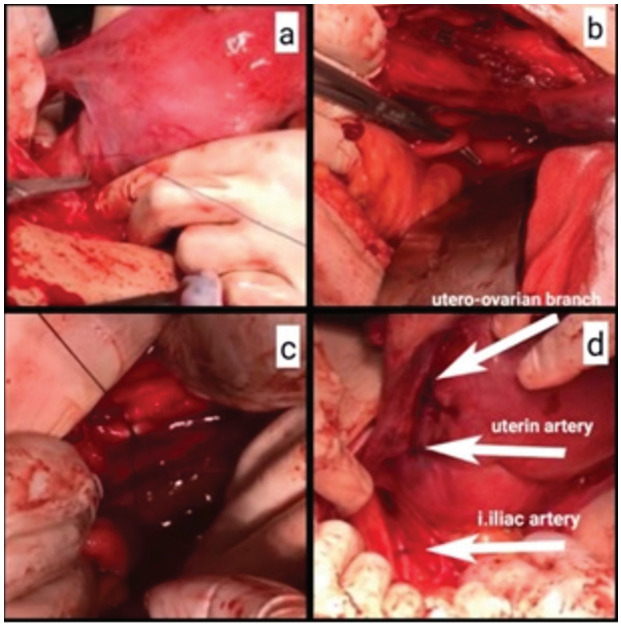


**Figure 1.** Systematic devascularization (a) Uterine artery ligation; (b), (c) Internal iliac artery ligation; (d) Uterine artery,utero-ovarian branches,internal iliac artery ligation

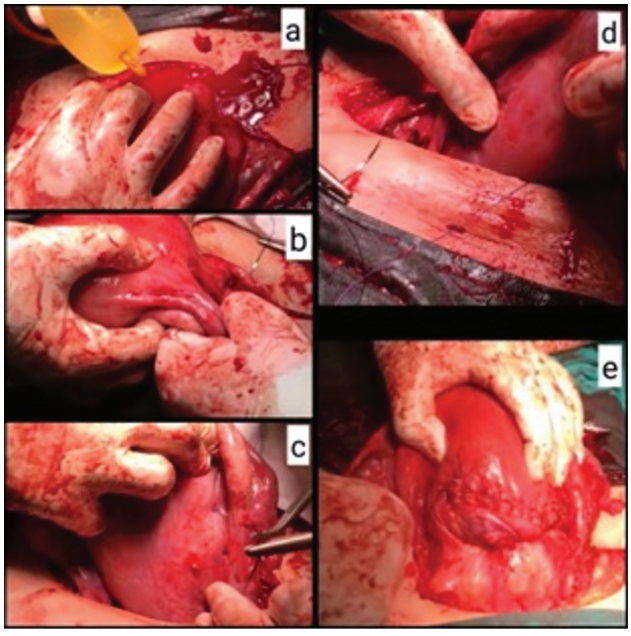


**Figure 2.** Balloon insertion into the lower uterine segment and the sandwich suture. (a) Foley catheter balloon; (b), (c), (d) Sandwich suture passing circularly from the medial aspects of bilateral uterine arteries; (e) The final view of the packaging suture

4. Cervical cerclage was applied transvaginally using 1-0 polyglycolic acid suture to keep the balloon in the uterine cavity and to prevent it from slipping downwards.
5. After the Hemovac drainage system was placed in the Douglas, the myometrial incision was closed with a double-layer suture with polyglycolic acid (Vicryl-Ethicon) 1-0 continuous locking suture.
The intraoperative surgical procedure and respective application of the procedure are illustrated with a stepwise explanation in figure 3 and figure 4.

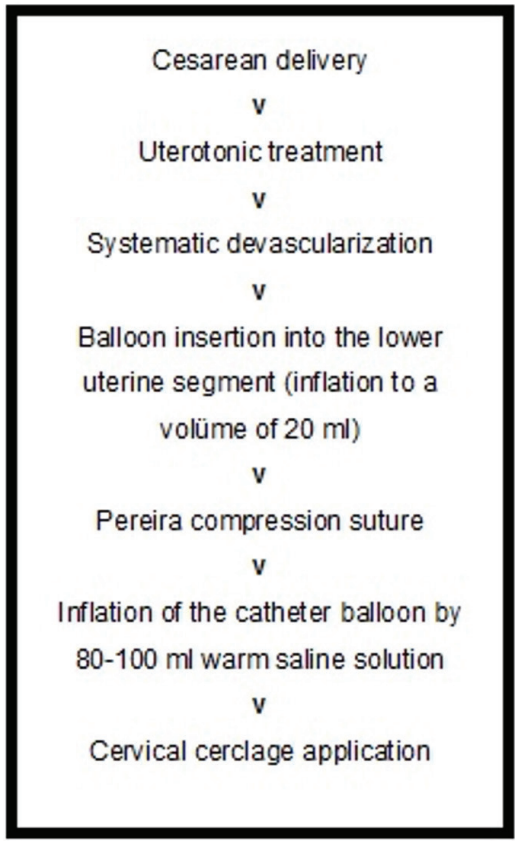


**Figure 3.** Intraoperative surgical procedure - flow chart

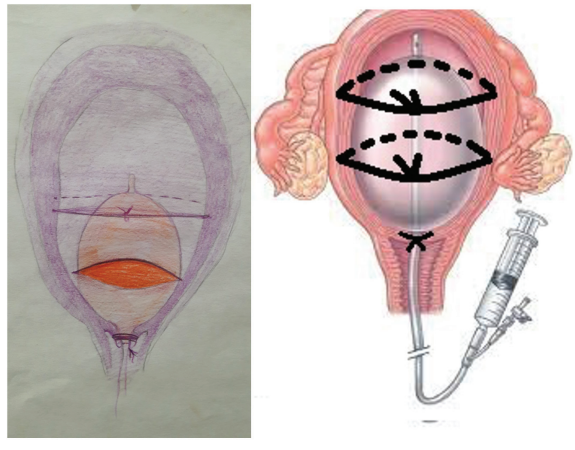

**Figure 4.** The illustration of surgical procedure

Estimated blood loss was calculated with sponge counts and aspirated blood in the intraoperative period, and erythrocyte suspension and fresh frozen plasma were prepared. Erythrocyte suspension and fresh frozen plasma were administered intravenously according to the intraoperatively measured blood loss estimate.

Uterine perfusion was assessed using diffusion magnetic resonance imaging (MRI) (Siemens Magnetom Aera 1.5 Tesla, Berlin, Germany) (Contrast solution; Optimark) on the postoperative first day (Figure 5).

In hemodynamically stable patients, the Foley balloon in the uterine cavity was gradually lowered and pulled.

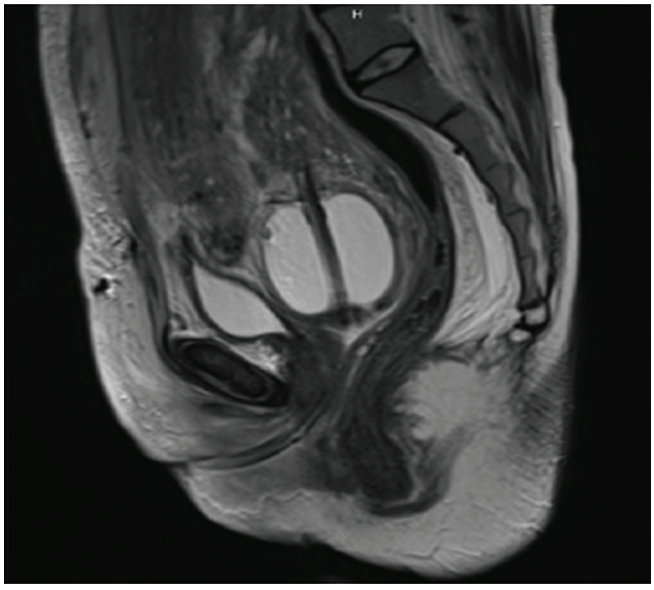

**Figure 5.** MRI view of the Foley catheter balloon in the lower uterine segment on the first postoperative day

*MRI: Magnetic resonance imaging*

## Results

All included women who had been diagnosed as having PP, had placental invasion abnormalities proven via pathologic examination, namely PAS of varying degrees. Seventeen (44%) of the 38 patients with PP and 12 with PP accreta spectrum underwent hysterectomy because they had at least two living children and did not desire further fertility. The remaining 13 patients with PP accreta spectrum were managed conservatively, six cases with posterior PP totalis benefit from uterine and bilateral hypogastric artery ligations. The seven patients featured in this report had continuing uterine bleeding despite uterine and hypogastric artery ligation. This lower segment uterine sandwich technique was performed to those with persistent uterine bleeding of PP percreta.

The remaining five patients had emergency cesarean delivery due to intensive vaginal bleeding.

The median (minimum-maximum) patient calendar age and gestational age at the time of delivery was 32 (range, 26-38) years and 35.5 (range, 33-38) weeks, respectively. Two women underwent Pomeroy's bilateral tubal ligation simultaneously. A mean of 6 (range, 4-11) U blood product transfusion was required in the intra- and post-operative period. The mean hospitalization period was 3.7 (range, 3-6) days and three women necessitated intensive care unit admission. None of the patients required a hysterectomy.

All included women reported regular menstruation at the end of a postoperative 1-year period. No patients experienced a morbid postoperative complication such as uterine necrosis or septicemia during the postoperative follow-up period. One patient in the second postoperative year and another woman in the third postoperative year conceived spontaneously, and both delivered uneventfully. One woman was lost to follow-up due to immigration. Characteristics, intra- and postoperative results,

**Table 1.** Patient characteristics and intra- and postoperative results

| | Patient 1 | Patient 2 | Patient 3 | Patient 4 | Patient 5 | Patient 6 | Patient 7 |
|---|---|---|---|---|---|---|---|
| Age (yrs) | 31 | 37 | 33 | 26 | 28 | 36 | 38 |
| Parity | 2 | 3 | 2 | 1 | 3 | 2 | 1 |
| Previous cesarean delivery | Y | Y | Y | Y | Y (2) | Y | Y (4) |
| Emergency cs | Y | Y | Y | No | No | Y | Y |
| Gestasyonal age (wks) | 36 | 34 | 36 | 38 | 37 | 33 | 35 |
| Hospitalization period (d) | 3 | 3 | 4 | 4 | 6 | 3 | 3 |
| Maternal ICU admission | - | - | 1 | 1 | 3 | - | - |
| Blood transfusion | 6 | 5 | 7 | 5 | 11 | 6 | 4 |
| Complication | - | - | - | - | Bladder injury | - | - |
| Intraop. diagnosis | P. percreta | P. percreta | P. percreta | P. percreta | P. percreta | P. percreta | P. increta |
| Follow-up | RM | RM, BTL | RM | RM | RM | RM | RM, BTL |

Spontaneous pregnancy after 2 yrs Spontaneous pregnancy after 3 yrs Lost-to follow up, ICU: Intensive care unit, RM: Regular menstruation, BTL: Bilateral tubal ligation, Y: Yes

and follow-up results of all included women are presented in Table 1.

## Discussion

The present study is the first to report the successful use of a novel low uterine sandwich technique, Caliskan's technique, which combines the systematic uterus devascularization, Foley's catheter balloon tamponade placement in the lower uterine segment, uterus compression suture, and cervical cerclage. Our data suggest that this novel technique achieved hemostasis with a high success rate in women with intractable PPH due to PP and PAS without compromising uterine blood flow and with no hysterectomy requirement.

Uterine sandwich techniques are surgical management methods that combine intrauterine balloon insertion and uterine compression sutures, aiming to control life-threatening obstetric hemorrhage[15,19]. A variety of uterine suturing methods have been defined in these uterine sandwich techniques, including B-Lynch et al.[20], Hayman et al. [11], or Cho et al. [21]; nevertheless, all have pros and cons. Yoong et al.[17] reported a series of 11 women presenting with uterine atony and PP, who were successfully managed with a uterine sandwich, employing Hayman sutures in nine and B-Lynch sutures in two women. However, both B-Lynch and Hayman sutures had some drawbacks; the longitudinal suture threads tend to slide off laterally or medially or the uterine body tends to fold anteriorly[12,22]. Matsubara et al.[23] reported a novel suture technique, namely the Matsubara-Yano suture, which was used concomitantly with an intrauterine balloon in 5 cases of PP. They claimed that this novel suturing method overcame the drawbacks of the former sutures because it transfixed the uterine fundus with longitudinal sutures and included transverse sutures laterally to prevent the longitudinal sutures from sliding off. Although similar, Caliskan's technique differs from the Matsubara-Yano uterine sandwich in that our technique employs systematic devascularization and stabilizes the Foley's catheter balloon to the lower uterine segment in a pressurized manner uing the Pereira suture from the top and by the cervical cerclage suture from below. This measure helps to achieve hemostasis in two ways; (i) it stabilizes the Foley's catheter balloon within the lower uterine segment where the PP and PAS bleeding occurs and does not allow it to slip downwards to the vagina, (ii) it increases intramyometrial pressure within the lower segment more efficiently, further helping to reduce the hemorrhage by collapsing the intramyometrial vessel openings. Uterine compression sutures have been reported to be related to some complications, including uterine necrosis and uterine synechiae[24,25]. Cho sutures are reported to be associated with these complications more frequently. It has been extrapolated that these complications might be associated with "compression tightness" and "uterine penetration"[26]. Lodhi et al.[27] reported uterine necrosis following application of B-Lynch compression suture and intrauterine balloon tamponade. By contrast, Yoong et al.[17] expressed that women undergoing a uterine sandwich procedure experienced lower rates of uterine necrosis as compared with those who received compression sutures only, possibly due to allowing the pressure exposed on the uterine wall to spread on a wider surface area[23,28]. They also suggested checking for signs of "uterine blanching" as a subjective measure of the balloon achieving its tamponade effect. In our clinical series, we assessed uterine blood supply using diffusion MRI on the first postoperative day, which revealed no findings of abnormal vascularization and diffuse or local loss of endomyometrial blood supply.

The Pereira suture was first described in a case series of seven women with PPH and consists of numerous transverse and longitudinal continuous sutures, in which a thread is placed in a circular fashion around the uterus[18]. This technique has the merit that it lacks uterine cavity penetration, thus is associated with a lower incidence of postoperative infection. Also, Pereira suture does not slide off laterally or medially, which is one of the main drawbacks of B-Lynch and Hayman sutures. Moreover, we experienced that the Pereira suture has been effective in achieving hemostasis via providing a higher pressure by compressing myometrial fibers in the uterine lower segment and, in turn, reducing its volume.

Systematic pelvic devascularization is an effective surgical method to control persistent PPH due to PP or PAS in women wishing to preserve their uterus and includes ligation of the uterine, utero-ovarian, and internal iliac arteries. Bilateral ligation of internal iliac arteries was reported to decrease the pulse pressure in the distal artery by as much as 85%, whereas blood flow is reduced by at most 50%[29]. Thus, we incorporated this surgical procedure, which we consider to accelerate the plug formation within the site of bleeding, into our technique.

### Study Limitations

Simultaneous use of intrauterine balloon catheter with B-Lynch suture has been defined by several groups to manage women with PPH due to uterine atony[15,16]. In all these cases, hemorrhage was due to atonic uterine myometrium; however, in all the PPH cases presented here, the etiologic factor was PP in addition to PAS. Given the lower uterine origin of PP hemorrhage, we stabilized the catheter balloon within the lower segment of the uterus. Similarly, Matsubara et al.[26] claimed that uterine compression sutures achieved better hemostasis in upper segment hemorrhage, but intrauterine balloon placement could be more appropriate in bleeding from the lower segment. Moreover, they stated that balloon placement in the lower segment might induce a uterine body contraction, possibly via neuronal reflex, which, in turn, achieves hemostasis.

## Conclusion

The novel Caliskan's uterine sandwich method appears to be a feasible and minimally invasive procedure in intractable PPH due to PP and/or PAS, particularly in women who wish to preserve their future fertility, without major morbidity,

hysterectomy necessity, and maternal mortality. However, the efficacy and safety of the technique must be tested and confirmed in large-scale clinical trials or case series.

### Ethics

**Ethics Committee Approval:** The study was performed in accordance with the ethical standards for human research established by the Declaration of Helsinki and Good Clinical Practice guidelines and approved by the local Ethics Committee of Bahcesehir University School of Medicine.
**Informed Consent:** All patients provided written informed for the application of this technique.
**Peer-review:** Externally peer-reviewed.

### Authorship Contributions

Surgical and Medical Practices: E.Ç., B.A., Concept: B.A., Design: E.Ç., Data Collection or Processing: Y.C., Analysis or Interpretation: C.K., Literature Search: C.K., Writing: E.Ç., Y.C.
**Conflict of Interest:** The authors report no conflict of interest.
**Financial Disclosure:** Authors have no financial interests about the research

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# Outcomes of cesarean scar pregnancy treatment: Do we have options?

## *Sezaryen skar gebelik tedavisi: Seçeneklerimiz neler?*

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### Abstract

**Objective:** To investigate the success and complications of medical and surgical modalities used in the treatment of cesarean scar pregnancies.
**Materials and Methods:** Medical and surgical approaches that have been used to treat cesarean scar pregnancies were evaluated retrospectively, Local, systemic, and combined methotrexate treatments were grouped as the medical approach, and dilatation and evacuation, hysteroscopic resection, laparoscopic and laparotomic approaches were grouped as the surgical approach. Fifty-three patients were diagnosed as having cesarean scar pregnancy during the study period, 48 of whom were included in the final analysis. Eighteen patients were treated with medical interventions and 30 patients were treated surgically.
**Results:** The success rate of surgical modalities was 96.6% and the medical treatment success was 33% (p<0.001). The complication rate was higher with medical approaches compared with surgical methods (66% vs 3.3%, respectively; p<0.001).
**Conclusion:** Surgical intervention seems safer and more successful than medical treatment.
**Keywords:** Ectopic pregnancy, cesarean scar pregnancy, cesarean scar ectopic pregnancy

### Öz

**Amaç:** Sezaryen skar gebeliklerin tedavisinde yararlanılan medikal ve cerrahi yöntemlerin etkinlik ve komplikasyonlarının incelenmesi amaçlanmıştır.
**Gereç ve Yöntemler:** Sezaryen skar gebelik tanısı alan toplam 53 hastanın verisi retrospektif olarak incelenmiştir. Lokal, sistemik ve combine metotreksat medikal yaklaşım olarak sınıflandırılırken; dilatasyon evakuasyon, histereskopik rezeksiyon, laparoskopik ve laparotomik rezeksiyon cerrahi yaklaşım olarak sınıflandırılmıştır. Elli üç hastanın 48'inin verisi final analizde yer almıştır. On sekiz hasta medikal, otuz hasta ise cerrahi yaklaşım grubunda bulunmaktadır.
**Bulgular:** Cerrahi yaklaşım ile tedavi edilen hastalarda tedavi başarısı %96,6 iken; medikal yöntemlerin kullanıldığı hastalarda tedavi başarısı %33 olarak bulunmuştur (p<0,001). Komplikasyon oranları ise medikal ve cerrahi grupta sırası ile %66 ve %33 olarak belirlenmiştir (p<0,001).
**Sonuç:** Sezaryen skar gebeliklerin tedavisinde cerrahi yöntemler medikal yaklaşımlara göre daha başarılı ve güvenlidir.
**Anahtar Kelimeler:** Ektopik gebelik, sezaryen skar gebelik, sezaryen skar ektopik gebelik

## Introduction

The cesarean delivery rate has increased worldwide and complications related to cesarean sections have also increased correspondingly. In this context, cesarean scar pregnancy (CSP) is seen as one of the rare complications, which is described as the embedding of the conceptus into the myometrium under cesarean scar tissue. CSP is classified as a subtype of ectopic pregnancy; some authors object to this because most of the placental tissue is within the endometrial cavity[1]. Flystra[2] noted that there were about 19 cases at the beginning of this century and scar pregnancy was the rarest type of ectopic pregnancy[3]. Recently, the incidence of CSP has begun to increase with the increment of cesarean delivery rates and the prevailing use of high-resolution transvaginal ultrasonography (USG). Contemporary studies report the incidence rate as 1/1800-2000, accounting for 6% of all ectopic pregnancies[1,4-6]. Early diagnosis and prompt treatment have paramount importance because there are high risks of severe hemorrhage, uterine rupture, and placental adhesion abnormalities[6].

**PRECIS:** Surgical treatments are safe and effective in treatment of cesarean scar pregnancies. Although medical approaches are less invasive; need for second-line therapy is higher.

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Vial et al.[7] categorized CSPs regarding their growth pattern and connection to the uterine cavity and serosa. Type 1 scar pregnancies grow toward the cervico-isthmic area, whereas type 2 pregnancies tend to grow toward the bladder serosa. Type 2 scar pregnancies seem to be accompanied by uterine rupture more often at early gestational weeks and severe hemorrhage, whereas type 1 scar pregnancies have greater potential for continuation, but with the risk of severe placental adhesion abnormalities and postpartum hemorrhage, hysterectomy, and maternal morbidity and mortality[7].

Risk factors of CSP are a high number of previous cesarean deliveries, uterine surgeries, cesarean delivery before labor onset, and pregnancy with artificial reproductive techniques[3,8]. The limited number of cases in the literature gave rise to insufficient data to constitute a standard treatment protocol[6]. The aim of this study was to investigate CSPs diagnosed and treated in a tertiary referral center, especially regarding treatment modalities.

## Materials and Methods

Patients who were diagnosed as having CSP between December 2012 and July 2019 were included in this retrospective cross-sectional observational study. The hospital record database was searched for all types of ectopic pregnancies and records were further examined for surgeries of CSPs.

Demographic features, medical histories, beta-human chorionic gonadotropin (beta-hCG) levels, route and time of prior deliveries, the indication of prior cesarean deliveries, treatment modalities, complications, and subsequent obstetric outcomes were obtained from the patient record database. A telephone-based search was also performed.

The following USG criteria were used for the diagnosis of CSP: (1) Absence of gestational sac, both in the uterine and cervical canal; (2) Presence of gestational sac in the anterior isthmic area and embedded in the hysterotomy scar; (3) Presence of fetal pole, whether the yolk sac and fetal cardiac activity are present or absent; (4) A present thin myometrial layer or no myometrial lining between the bladder and uterus; and (5) Discontinuity of the anterior uterine wall in the sagittal view. A diagnosis of CSP was made when all these criteria were observed.

Choice of treatment modality was made primarily depending on the patients' clinical features, USG findings, and desire for future fertility. Medical treatment modalities included local, systemic, and combined methotrexate administration. These modalities were preserved for patients who did not have heavy bleeding and were hemodynamically stable. Clinical features, which included contraindications for methotrexate such as active liver disease, were questioned, especially before methotrexate administration, and an effective contraception method was recommended after treatment because of the possible fetotoxicity of the drug. Surgical approaches were performed in the event of heavy vaginal bleeding that required prompt medical attention and in patients who failed to respond to medical treatment.

All available treatment options were explained in detail to all patients, except in emergency cases for which a surgical attempt was required. Patients were informed about the possible adverse effects of the medication, risk of heavy bleeding during follow-up, need for emergency hysterectomy, failure rates of treatments, and the risk of placental adherence abnormalities in the event of continuation of pregnancy in light of the literature. After this briefing, the treatment modality was determined with the consensus of the physician and the patient. Informed consent forms were signed by all patients.

The cytotoxic effect of methotrexate on trophoblastic cells is the common mechanism of action for systemic, local, and combined methotrexate therapy, thus they are grouped as the medical approach. These modalities also do not require a major invasive procedure. Dilatation curettage, and hysteroscopic, laparoscopic, and laparotomic resections are grouped as surgical approaches because they all necessitate surgically invasive procedures and require mechanical removal of the ectopic mass.

## Intervention

**Systemic methotrexate:** A single-dose regimen with a 50 mg/m$^2$ intramuscular injection. Four and 7 days after the injection, beta-hCG levels, complete blood count, and liver function tests were measured. A beta-hCG decrement less than 15% between days 4 and 7 was regarded as treatment failure.

**Local methotrexate:** The required dose was calculated as 50 mg/m$^2$. While the patient was in the lithotomy position, after disinfection of the vagina with 10% povidone-iodine, a double-lumen oocyte pick-up needle was inserted vaginally and the gestational sac was disrupted, and the content was aspirated as much as possible. Half of the calculated dose was injected into the sac and the remaining dose was injected into the periphery of the gestational sac. During all these processes, transabdominal USG imaging (Logiq Alpha 200 Ultrasound, General Electric Medical Systems) was used for guidance. Local methotrexate at a dose of 50 mg/m$^2$ was administered. In the event of a beta-hCG level decrement less than 25% 7 days after the injection, a systemic rescue dose (50 mg/m$^2$) of methotrexate was added. The requirement for rescue systemic methotrexate was also recorded as a treatment failure.

**Combined methotrexate:** Local and systemic administration of 50 mg/m$^2$. Local administration and systemic injections were given at the same time. Beta-hCG levels were measured weekly. Outpatient follow-up was preferred for medically treated patients as long as they were clinically stable. Patients were informed and warned to present to the emergency department in the event of symptoms such as severe abdominal pain, hypotensive attacks, and massive vaginal bleeding. Weekly transvaginal USG was also performed to follow the resorption of the ectopic mass. Beta-hCG levels, renal and liver function tests were performed to check for the possible adverse effects of methotrexate every week during the follow-up.

**USG-guided dilatation-evacuation (D&E):** This procedure was conducted in an operating room with the patient under sedation. Number 5 and 6 Carmen aspiration cannulas were used to evacuate the gestational content. Transabdominal USG guidance was used to visualize the uterus.

**Hysteroscopic resection:** A hysteroscopic resectoscope was used to remove gestational content, and bipolar cautery was used to control the bleeding areas.

**Laparoscopic resection:** The CSP area was cut using harmonic bipolar cautery and removed and the myometrial defect was sutured using non-absorbable interrupted sutures.

**Laparotomic resection:** A Pfannenstiel incision was made to reach the abdominal cavity. Gestational content and cesarean scar tissue were resected, and myometrial defects were repaired using interrupted absorbable sutures.

**Expectant management:** Patients with positive fetal cardiac activity who desired to continue the pregnancy opted for expectant management. The high risk of placental adherence abnormalities, severe life-threatening bleeding, and the need for emergency hysterectomy was fully explained. Close follow-up in a tertiary referral center with the facility for high-risk pregnancies and a neonatal intensive care unit (NICU) was offered.

The study was approved by the Institutional Ethics Committee (date: 15/10/2019; project no.: KA19/331).

### Statistical Analysis

Statistical analysis was performed using the SPSS statistical package (Version 17.0, SPSS Inc., Chicago, IL, USA). Categorical measurements are reported as number and percentage, and continuous measurements are summarized as mean values and standard deviations. Comparisons between groups were performed using Student's t-test for normally distributed data, and the Mann-Whitney U test was used for data that were not normally distributed. The categorical variables between the groups were analyzed using the chi-square test or Fisher's exact test. Values of $p<0.05$ were considered statistically significant.

## Results

Seven hundred sixty-nine patients were diagnosed as having ectopic pregnancies between December 2012 and July 2019, 53 of whom had CSPs; the incidence rate among all ectopic pregnancies was 6.8%. Two of the 53 patients declined treatment and left the center, and three patients desired to continue the pregnancy despite all the explained risks. As a result, the treatment outcomes of 48 out of 53 patients were available for the final analysis (Figure 1).

The mean age of the study group was 33.7 (range, 23-43 years). The mean numbers of gestations and previous cesarean deliveries were 3.5 and 1.6, respectively. The general clinical features of the study group are summarized in Table 1.

The mean gestational week at the time of diagnosis was 6.3 weeks, the mean gestational sac diameter was 15 (range, 6-50) mm, and the mean beta-hCG level at the time of diagnosis was 48.106 mIU/mL. All diagnoses were made using transvaginal USG imaging. The features of CSP are shown in Table 2.

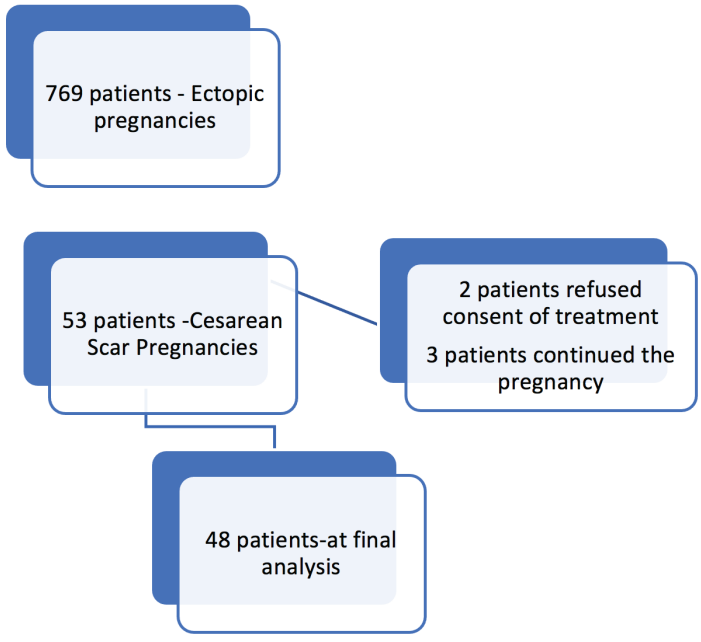


**Figure 1.** Flow diagram of the study

There were five, nine, and four patients in the systemic methotrexate, local methotrexate, and combined approach groups, respectively. Hysteroscopic resection was performed in eight patients, 19 patients underwent USG-guided D&E, and laparotomic and laparoscopic resection of CSP was performed for one and two patients, respectively. These treatment modalities were for the surgical approach group.

The age and number of gestations and previous cesarean deliveries were similar between the medical and surgical approach groups ($p=0.11$, $p=0.25$, $p=0.14$, respectively). The success rate of the medical treatment group and the surgical group was 33.3% and 96.6%, respectively, the difference was found to be statistically significant ($p<0.001$) (Table 3). The complication rates for the medical and surgical approaches were 66.6% and 3.3%, respectively. The complication rate of medical treatment was significantly higher than for surgical methods ($p<0.001$). The treatment outcome of each treatment modality is shown in Table 4 and 5. The most frequent complication of the entire study group was treatment failure and the need for second-line treatment.

The mean interval to a negative beta-hCG was determined as 28 days. The decrement of beta-hCG levels is shown in figure 2. Although the mean interval to a negative beta-hCG in the surgically managed group was shorter by 10 days (mean 18 days), beta-hCG levels were not monitored postoperatively in most patients in the surgical group due to the complete removal of CSP material.

**Table 1.** Clinical characteristics of the patients

| | Mean | Number of patients | % |
|---|---|---|---|
| Age at diagnosis (years) | 33.7 (23-43) | 52 n/a: 1 | |
| Gravida | 3.5 (2-8) | 52 n/a: 1 | |
| Parity | 1.6 (1-3) | 52 n/a: 1 | |
| Gestational week at last delivery (weeks) | 37.9 (30-41) | 47 n/a: 6 | |
| Number of previous C/S deliveries | 1<br>2<br>3 | 23<br>25<br>4<br>52<br>n/a: 1 | 43.4%<br>47.2%<br>7.5% |
| Indications of last C/S delivery | Previous C/S<br>Obstructed delivery<br>Maternal request<br>Fetal distress<br>Presentation anomalies<br>Multiple pregnancies<br>Cephalopelvic Disproportion<br>Placenta previa | 26<br>2<br>9<br>7<br>1<br>1<br>1<br>1<br>n/a: 5 | 49.1%<br>3.8%<br>17%<br>13.2%<br>1.9%<br>1.9%<br>1.9%<br>1.9% |
| History of additional uterine surgery | None<br>D&C<br>H/S polyp resection<br>D&C+Surgical H/S | 25<br>24<br>2<br>1<br>n/a: 1 | 47.2%<br>45.3%<br>3.8%<br>1.9% |
| Ectopic pregnancy history | None<br>Tubal<br>Cesarean scar | 50<br>1<br>1<br>n/a: 1 | 94.3%<br>1.9%<br>1.9% |
| Time after last delivery | 5.6 (range, 1-13) years | | |

n/a: Not available, C/S: Cesarean section, H/S: Hystreroscopy, D&C: Dilatation and curettage

Three patients preferred to continue their pregnancies after being informed about the potential risks. During the follow-up of these three patients, placental adherence abnormalities were detected. One patient presented to the emergency department at the 32nd gestational week with symptoms of lower abdominal pain and preterm birth was diagnosed. Bilateral hypogastric artery ligation was performed due to severe intrapartum hemorrhage, but this procedure failed and hysterectomy was performed. Bladder injuries occurred in several areas and were repaired primarily; four units of red blood cell transfusion were needed. The newborn was followed in the NICU for 10 days and was given phototherapy for hyperbilirubinemia. The second patient was admitted to the emergency department with

**Table 2.** Characteristics of cesarean scar pregnancies

| | | Number of patients | % |
|---|---|---|---|
| Pregnancy type | Spontaneous<br>ART | 47<br>2<br>n/a: 4 | 88.7%<br>3.8% |
| Gestational week at the time of diagnosis | Mean: 6.3 (range, 5-10) | | |
| Number of fetuses | Singleton<br>Twin | 51<br>1<br>n/a: 1 | 96.2% |
| Fetal cardiac activity at the time of diagnosis | (+)<br>(-) | 14<br>35<br>n/a: 4 | 26.4%<br>66% |
| Imaging modality used for diagnosis | TVUSG | 53 | 100% |
| Symptoms | Asymptomatic<br>Vaginal Bleeding<br>Irregular bleeding<br>Abdominal Pain | 33<br>13<br>1<br>3<br>n/a: 3 | 62.3%<br>24.5%<br>1.9%<br>5.7% |

**Table 3.** Comparison of success and complication rates of medical versus surgical treatment modalities

| | Medical treatment | Surgical Treatment | p |
|---|---|---|---|
| Complication rate | n=12 (66%)* | n=1 (3.3%)† | <0.001 |
| Success of treatment | n=6 (33.3%) | n=29 (96.6%) | <0.001 |

*In the medical treatment group, only six patients had no complications. There were 18 patients in total in the medically treated group,
†: In the surgically treated group, only one patient had a complication, 29 patients did not. There were 30 patients in total in the surgically managed group

symptoms of vaginal bleeding. After the bleeding worsened at the 35th gestational week, an emergency cesarean section was performed. Intrapartum heavy bleeding led to a hysterectomy. The newborn of this patient had respiratory insufficiency and died in the NICU. The last patient's delivery occurred in another center. A telephone interview revealed that the patient had severe intrapartum bleeding and was managed by hysterectomy and a massive transfusion was needed.

Forty-five of the 53 patients' follow-up data were obtained. In total, 20 pregnancies were detected subsequently, 19 of which were spontaneous, and none were *in vitro* fertilization pregnancies. Two patients had another CSP (10% of subsequent pregnancies). Fifteen patients gave birth, and five aborted. One patient had cervical insufficiency in her subsequent pregnancy and one had preterm premature rupture of membranes.

## Discussion

One of the main results of our study was that the surgical approach was found to be more effective in the treatment of

**Table 4.** Complication rate and types according to treatment modality

| | Complication (+) | Complication (-) | Types of complication |
|---|---|---|---|
| Systemic methotrexate | 2 (40%) | 3 (60%) | Persistance of scar pregnancy (n=2) |
| Local methotrexate and GS aspiration | 7 (77%) | 2 (22%) | Massive bleeding (n=2) Intrauterine infection (n=1) Persistance of scar pregnancy (n=4) |
| Combined methotrexate* | 3 (75%) | 1 (25%) | Massive bleeding (n=1) Persistance of scar pregnancy (n=1) Persistance of ectopic mass (n=1) |
| Hysteroscopic resection | 0 | 8 (100%) | |
| D&E | 1 (5.3) | 18 (94.7) | Persistance of ectopic mass (n=1) |
| Laparoscopic resection | 0 | 1 (100%) | |
| Laparotomic resection | 0 | 2 (100%) | |
| Total | 13 | 35 | |

D&E: Dilatation-evacuation

**Table 5.** The success rate of treatment modalities

| | Success rate of treatments | Number of patients |
|---|---|---|
| **Systemic methotrexate** | **n=3 (60%)** | **n=5** |
| Local methotrexate and GS aspiration | n=2 (22.2%) | n=9 |
| Combined methotrexated | n=1 (25%) | n=4 |
| Hysteroscopic resection | n=8 (100%) | n=8 |
| D&E | n=18 (94.7%) | n=19 |
| Laparoscopic resection | n=1 (100%) | n=1 |
| Laparotomic resection | n=2 (100%) | n=2 |
| Total | | 48 |

D&E: Dilatation-evacuation

CSP with lower complication rates compared with the medical approach. Also, we observed that the risks of placental adhesion abnormalities and severe postpartum hemorrhage were quite high with the continuation of viable CSPs.

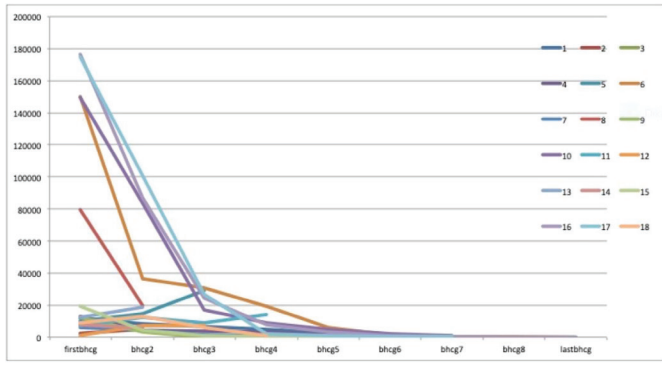


**Figure 2.** Decrement of beta-hCG levels in the medically treated group

Although there were limited cases until the early 2000s, the incidence rate of scar pregnancies has risen and now accounts for almost 6% of all ectopic pregnancies[9]. In this study, we also found the rate of scar pregnancies among all ectopic pregnancies as 6.8%. There are more than 30 approaches described in the literature, and their efficacy has been investigated, mostly in case series. In one series, Timor-Trisch et al.[1] found local methotrexate to be an effective and safe treatment choice. Some studies propose local methotrexate as a first-line treatment[10,11]. In another study comprising 24 non-tubal ectopic pregnancies, it was concluded that the conservative approach should be preferred first[12]. Although the time to negative beta-hCG is longer, systemic methotrexate treatment was found to be effective in a 26-patient case series, and it could protect patients against more invasive surgical procedures[13].

The need for second-line treatment was found at rates of 8.3%, 25%, and 33%, for combined methotrexate, systemic methotrexate, and expectant approaches, respectively, in the case series of Grechukhina et al.[14]. A study from the United Kingdom reported the success rates of medical and surgical treatments as 46% and 96%, respectivel[15].

There is no standardized treatment protocol for CSP because it is a relatively rare clinical condition and studies have contradictory outcomes. A systematic review including 52 studies concluded that local, systemic, and combined methotrexate treatments should not be used as first-line treatment because of high failure and complication rates[16]. In the present study, the success and complication rates were 33.3% and 66.6% for the medical approach and 96.6% and 3.3% for surgical approaches, respectively. The results of our study favor surgical approaches as the first-line treatment, supporting the results of the systematic review of Birch et al.[16].

Kim et al.[17] reported that the risk of massive hemorrhage and emergency hysterectomy was higher in patients managed with dilation and curettage (D&C), even if it was performed under USG guidance. The complication rate of D&C was found to be about 20% in a systematic review, and the authors recommended not to use D&C as the first-line treatment because of the high complication rates[16]. Contrary to the literature, in our study,

we found that D&E was successful as a first-line approach for 94% of patients (18 out of 19 patients); only one patient needed second-line treatment because of a persistent mass in the scar area even though the beta-hCG level was negative, and this patient was successfully managed with operative hysteroscopy. The main reason for our lower complication rates might be the avoidance of sharp curettage in most cases and evacuation with suction cannula as described under the "material and method topic".

Potential parameters to predict the efficacy of various management strategies were investigated by some authors. Less invasive medical approaches were found to be appropriate for patients with low beta-hCG levels, type 1 CSP, and small gestational sac diameter at the time of diagnosis[18]. Surgical treatment modalities were recommended as the first-line approach in patients with large gestational sac diameters and increased trophoblastic charge[19]. In a prospective observational study of Sun et al.[20], a risk stratification model was established that took the number of previous cesarean deliveries, residual myometrial thickness, gestational sac diameter, fetal cardiac activity, and Doppler USG findings into account. Evacuation was recommended for the low-risk group, uterine artery embolization for the intermediate-risk group, and laparoscopic resection was recommended for patients at high-risk.

Age, gravidity, parity, and previous cesarean deliveries were similar between the medically and surgically managed patients in this study. The mean beta-hCG levels at the time of diagnosis were 12.423 mIU/mL and 14.799 mIU/mL for medically and surgically treated patients, respectively (p=0.8). A comparison regarding gestational sac diameter could not be made because diameter information was not available in most patients' records. Persistent mass at the scar area was the only complication in the surgically managed group. Our preferential surgical approach was D&E without sharp curettage in 19/30 patients and hysteroscopy in 8/30 cases. No patients needed an emergency hysterectomy in the surgery group. The low complication and failure rates are advantages when we take the young age and fertility desire of these patients into account. Although most of the complications were treatment failure and the need for a second-line approach, three patients had severe, life-threatening hemorrhage in the medically managed group. Massive transfusion was needed for two of these patients. The absence of life-threatening complications in surgically managed patients suggests that these modalities are safe. However, this must be evaluated with caution because these procedures were performed by experienced surgeons in a tertiary setting. It should not be forgotten that there may be a need for emergency hysterectomy in both medically and surgically managed patients. Another advantage of surgical procedures was the shorter mean interval for a negative beta-hCG level, which was 18 and 28 days for the medical and surgical groups, respectively.

Although most authors recommend the termination of viable CSPs, some patients may choose to continue their pregnancy. CSP and placenta accreta share the same histopathologic characteristics[21]. Cali et al.[22] reported a rate of 75% for placental adhesion abnormalities in their expectantly managed group and stated that two-thirds of the patients had placenta percreta in their meta-analysis. Three patients who chose to continue their pregnancies in this case series also had placenta percreta, and all of them needed postpartum hysterectomy against intractable life-threatening hemorrhage. The risk of placental adhesion abnormalities and the risk of severe hemorrhage should be highlighted for patients who have positive fetal cardiac activity and desire continuation of pregnancy.

There are limited data on future fertility after CSPs in the literature. In one study, four out of 10 pregnancies that occurred after CSP treatment were also scar pregnancies (Grechukhina et al.[14], 2018) Although most patients can conceive spontaneously after a scar pregnancy, the risks of recurrence and placental adhesion abnormalities increase[23]. In our patient group, 20 pregnancies occurred after scar pregnancies, five (25%) of which resulted in spontaneous abortions and two (10%) were recurrent CSPs.

### Study Limitations

The main limitation of this study arises from its retrospective nature. Objective discrimination of CSP type was not available. Not every treatment approach described in the literature was performed in this case series. For example, no patients were managed with uterine artery embolization; therefore, no comment or comparison could be made regarding these modalities. On the other hand, this study was conducted in a tertiary center that was representative of its region, and the size of the patient group was satisfactory when given the rarity of this clinical entity.

## Conclusion

The results of this study support surgical approaches due to their success and safety. Besides having fewer failures and lower complication rates, the shorter interval to negative beta-hCG is another advantage of surgical treatment. However, the results should be interpreted cautiously because this study is also a retrospective case series of a tertiary referral center. Randomized prospective studies are needed for an objective categorization of the relationship of conceptus and the endometrial cavity to better determine the most appropriate treatment. Risk stratification studies may be useful in this context. No comment could be made in this study regarding the prediction of appropriate individualized treatment choices; surgical treatment seems more effective than medical modalities. The decision for continuation of pregnancy in the event of positive fetal cardiac activity is extremely risky; placental adhesion abnormalities are almost always detected in such cases and severe postpartum hemorrhage and hysterectomy risks should be highlighted for patients.

### Ethics

**Ethics Committee Approval:** The study was approved by the Institutional Ethics Committee (date: 15/10/2019; project no.: KA19/331).
**Informed Consent:** Informed consent forms were signed by all patients.
**Peer-review:** Externally peer-reviewed.

### Authorship Contributions

Concept: S.Y.Ş., T.Ç., Design: S.Y.Ş., Data Collection or Processing: D.A.Y., Ş.Y.B., T.Ç., E.B.K., Analysis or Interpretation: E.Ş., D.A.Y., Ş.Y.B., Literature Search: T.Ç., E.B.K., Writing: S.Y.Ş., E.Ş., E.B.K.
**Conflict of Interest:** The authors report no conflict of interest.
**Financial Disclosure:** Authors have no financial interests about the research.

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# Delivery method of the placenta in cesarean deliveries and the effect of uterine incision repair area on morbidity: A randomized controlled study

## *Sezaryen operasyonunda plasentanın doğurtulma yöntemi ve uterin kesi onarım alanının morbiditeye etkisi: Randomize kontrollü bir çalışma*

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### Abstract

**Objective:** We evaluated the effects of spontaneous or manual delivery of the placenta and repair of uterine incision inside or outside the abdomen on intraoperative blood loss, postoperative infection morbidity, and postoperative hospitalization time.

**Materials and Methods:** We conducted a prospective randomized controlled study with 150 patients among 160 patients who were indicated to undergo emergency cesarean procedures in our tertiary hospital. We divided the patient population into four groups. These four groups were formed by comparing the way the placenta was delivered manually and by spontaneous traction with the repair of the uterus inside and outside the abdomen. Blood loss was determined using quantitative and gravimetric methods. A numeric rating scale was used, which is a one-dimensional method used for uterine sensitivity distribution and pain measurement.

**Results:** The amount of bleeding was 339 mL in group 1, 237 mL in group 2, 470 mL in group 3, and 490 mL in group 4, which were significantly different ($p<0.001$). The mean surgical time was 30.8±5.5 minutes in group 1, 30.7±4.4 minutes in group 2, 38.5±6.9 minutes in group 3, and 43.9 minutes in group 4 ($p<0.001$). When the distribution of uterine tenderness among the groups was examined in the fundus examinations performed on the postpartum 1st day of the patients, we found a significant difference ($p<0.001$). When all groups were compared, there was a significant difference between group 1 and group 4 in terms of hospital stay ($p<0.004$). Among the contributing factors were endometritis, maternal body weight ($p<0.053$), advanced gestational week ($p<0.004$), prolonged surgical time ($p<0.009$), and the presence of meconium.

**Conclusion:** Manual removal of the placenta resulted in higher blood loss, increased uterine tenderness, and longer hospitalization compared with the spontaneous separation method. The uterine incision repair site did not affect morbidity.

**Keywords:** Cesarean section, postpartum hemorrhage, blood loss, endometritis

### Öz

**Amaç:** Sezaryen operasyonu esnasında, plasentanın spontan veya manuel yolla doğurtulmasının ve uterin insizyonun batın içinde veya dışında onarımının, intraoperatif kan kaybı, postoperatif enfeksiyon morbiditesi ve postoperatif hastanede kalış süresi üzerindeki etkilerini değerlendirdik.

**Gereç ve Yöntemler:** Üçüncü basamak hastanemizin kadın hastalıkları ve doğum kliniğinde acil sezaryen operasyonu endikasyonu alan 160 hasta arasından çalışmaya uygun 150 hasta ile prospektif randomize kontrollü çalışma gerçekleştirdik. Hasta popülasyonunu dört gruba ayırdık. Bu dört grup, plasentanın elle ve spontan traksiyon yöntemiyle çıkarılma şekli ile uterus insizyonunun batın içi ve batın dışında onarılması metodlarının karşılaştırılması yoluyla oluşturuldu. Kan kaybı, kantitatif ve gravimetrik yöntemler kullanılarak belirlendi. Uterin hassasiyet dağılımı ve ağrı ölçümü için kullanılan tek boyutlu bir yöntem olan sayısal derecelendirme ölçeği kullanılmıştır.

**Bulgular:** Kanama miktarı grup 1'de 339 mililitre, grup 2'de 237 mililitre, grup 3'te 470 mililitre ve grup 4'te 490 mililitreydi ve farklı bulundu ($p<0,001$). Ortalama ameliyat süresi grup 1'de 30,8±5,5 dakika, grup 2'de 30,7±4,4 dakika, grup 3'te 38,5±6,9 dakika, grup 4'te 43,9 dakika idi ($p<0,001$). Hastaların postpartum 1. gününde yapılan fundus muayenelerinde uterus hassasiyetinin gruplar arası dağılımı incelediğimizde anlamlı fark bulduk ($p<0,001$). Tüm

**PRECIS:** Postoperative morbidity after cesarean operation.

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gruplar birbirleri ile karşılaştırıldığında, grup 1 ile grup 4 arasında hastanede kalış süresi açısından anlamlı fark mevcuttu (p<0,004). Endometrit oluşumuna katkıda bulunan faktörler arasında maternal vücut ağırlığı (p<0,053), ileri gebelik haftası (p<0,004), uzamış ameliyat süresi (p<0,009) ve mekonyum varlığı belirleyicilerdi.

**Sonuç:** Sezaryen operasyonu esnasında, plasentanın manuel olarak çıkarılmasının, spontan doğurtulma yöntemine göre kıyaslandığında daha fazla kan kaybına, artmış uterin hassasiyete ve daha uzun süre hastanede kalınmasına neden olmuştur. Uterin kesi onarım bölgesinin morbidite üzerinde etkisi olmadığı belirlendi.

**Anahtar Kelimeler:** Sezaryen, doğum sonu kanama, kan kaybı, endometrit

## Introduction

The World Health Organization (WHO) reports that since 1985, the cesarean rate that will reduce maternal and infant mortality is between 10 and 15%. According to the systematic review by WHO, it shows that the number of maternal, newborn, and infant deaths in a society decrease when the cesarean rates reach 10-15%. The increase in cesarean delivery rates above this level does not correlate with a decrease in mortality rates. When performed for medical reasons, cesarean section reduces maternal and perinatal mortality and morbidity. However, there is no evidence showing the benefits of cesarean delivery for mothers and babies when cesarean delivery is not required. In recent years, governments and physicians have been reporting an increasing number of cesarean deliveries and the potential negative consequences of cesarean delivery on maternal and child health[1].

In Turkey, there is an upward trend, although the rate of cesarean section varies according to the year when we look at the past thirty years. We know that the cesarean rate, which was 5% in 1988, was over 45% in 2010. The Turkish Gynecology and Obstetrics Association and the Ministry of Health aimed to reduce this rate with a joint project started in 2011. However, in 2013, the cesarean rate in our country increased by 35%[2]. In 2017, according to the Organization for Economic Cooperation and Development report, Turkey's cesarean rate increased to 53.1%[3]. Although the relevant institutions and associations of the Ministry of Health have followed a policy of reducing the cesarean rates and took various steps, the desired success has not yet been achieved. Therefore, it has become more valuable to develop surgical techniques to reduce and prevent cesarean-related morbidity.

Cesarean delivery is a surgical procedure that we perform today, and we see an increase in cesarean delivery rates every year. Given that we cannot reduce our cesarean rate as a delivery method in order not to take risks in terms of medicolegal concerns and maternal and fetal health, we should at least develop ways to reduce the morbidity that may occur for this procedure. The aim of our study, which we created with this hypothesis, was to investigate the effects of spontaneous or manual delivery of the placenta and repair of uterine incision inside or outside the abdomen on intraoperative blood loss, postoperative infection morbidity, and postoperative hospitalization time.

## Materials and Methods

We conducted this prospective randomized study at Adana City Training and Research Hospital Gynecology and Obstetrics Clinic between September 2020 and December 2020. In our hospital, an average of 1100 births per month are performed, and it is an intensive clinic with the characteristics of a tertiary center with 12,000 births per year. We conducted our study together with fourth-year senior assistant physicians under the supervision of the responsible specialist physician and the responsible specialist physician. We obtained approval from the ethics committee of our hospital for the study (Adana City Training and Research Hospital Clinical Research Ethics Committee, 26.08.2020/1047). We received written informed consent form from all volunteers for the study. Our study was conducted in accordance with the Helsinki Declaration Principles.

The study population comprised patients with indications for cesarean delivery who were found to be in active labor. Just before we transported the patient to the operating room, we randomized patients using a computer-generated random number table with the groups determined in closed opaque envelopes. After opening the envelope, the surgeon performed the cesarean section according to the specified group. Group 1, the placenta was separated spontaneously by traction, and we repaired the uterine incision in the abdomen; group 2, the placenta was detached spontaneously by traction, and we repaired the uterine incision outside the abdomen; group 3, the placenta was removed manually, and we repaired the uterine incision in the abdomen; and group 4, the placenta was removed manually, and we repaired the uterine incision outside the abdomen.

The study population comprised women with a defined obstetric emergency indication for cesarean delivery. Patients with placental adhesion anomaly, placental detachment, those who received intrapartum antibiotic treatment for any reason, patients with chorioamnionitis, iron deficiency anemia, polyhydramnios, coagulation disorders, uterine atony, uterine leiomyomas, severe heart disease, systemic disease, and those who did not want to be included in the analysis were excluded. We divided cesarean indications into eight major groups. The reason for this was that there were frequently multifactorial factors affecting the mother and fetus in the cesarean indications of the patients. Head-pelvis incompatibility, acute fetal distress, and advanced gestational age indications in the same patient are examples of this situation. In such cases, we

aimed to emphasize that the result was significant according to the primary indication that led the patient to cesarean section. Otherwise, a different indication group would have had to be created for each patient and this would distract us from the result.

We performed all surgeries under regional spinal anesthesia. We recorded the surgical time as the time from beginning the skin incision to the end of the last suture. During the procedure, we administered 2 grams of cefazolin sodium to all patients as perioperative prophylaxis after the umbilical cord was clamped. After the birth of the fetus, we added 20 international units of oxytocin to intravenous fluids as a uterotonic agent. The hemogram values of the subjects were calculated preoperatively and at the 48$^{th}$ hour after surgery. We examined the difference between the two values.

Blood loss was determined using a quantitative method. We created a dry weight list for cesarean delivery materials that could be wetted with blood to measure blood loss. To determine the actual amount of blood lost, we subtracted the fluid volume from the fluid volume before dispensing the placenta after delivering the placenta. It is important to remember that most of the fluid collected after the birth of the placenta is blood. To determine the cumulative blood volume, we added the wet abdominal compresses and the volume of fluid collected in the aspirator chamber to the measured blood volume by weighing the wetted substances. The number of abdominal compresses and square pads (sponges) used for each operation was noted to determine blood loss. It was determined as 1 gram weight =1 milliliter of blood loss volume. The equation used to calculate the blood loss of a substance immersed in blood was as follows: Wet matter gram weight - Dry matter gram weight = Milliliter blood in matter. Identifying blood loss will never be accurate. However, we know that some measurements are more accurate than relying on visual estimates alone[4].

The length of hospital stay (LOS) started at the time of the cesarean section and was reported as the following days. The picture of endometritis was characterized body temperature exceeding 38 °C twice with an interval of 6 hours, sensitivity of the uterus on bimanual examination and malodorous discharge. We managed subjects with suspected endometritis with triple antibiotics including ampicillin 2 g/i.v. every 6 hours, gentamicin 80 mg, 1.5 mg/kg/i.v. every 8 hours, and clindamycin 600 mg/i.v. every 8 hours. Endometrial cultures were not accepted because they brought in uncertain results related to contaminated specimens attained transcervically. After cesarean delivery, the skin incision was checked and wound site infection was checked during dressing on the second day of discharge and the tenth day at the follow-up examination.

A numerical rating scale (NRS) was used, which is a one-dimensional method used for uterine sensitivity distribution and pain measurement, according to the groups. On this scale, there are increasing numbers from 0 to 10 spaced on a line. We asked the patients to mark the number on the scale determining the severity of pain. In the numbering form 0-10, 0 was determined as no pain, and 10 as the worst pain imaginable[5]. We performed this test on the first postoperative day during routine patient examination and, observed the sensitivity of the uterus while massaging the fundus of the uterus to check whether the uterus was contracting. Then, we marked the uterine sensitivity and pain degrees of the patients and the physicians who conducted the study on this scale.

### Statistical Analysis

One-Way analysis of varinace, the Kruskal-Wallis and chi-square test, Tukey's honestly significant difference (HSD) test, t-test, Levene's test, the Mann-Whitney U test, Fisher's Exact test, and Spearman's correlation coefficients were used in the statistical analysis of the data. We took the level of significance as $p<0.05$. Data analysis was performed using the SPSS 20.0 statistics package.

## Results

For this study, we identified 160 patients who received cesarean indications according to research criteria. We excluded 10 of these patients because they refused to take part in the study. We excluded nine of the remaining 150 patients because they did not meet the research criteria. Thirty-four patients were in group 1, 36 were in group 2, 30 comprised group 3, and 41 patients made up group 4 (Figure 1).

When we compared the maternal data between groups, we found no significant difference regarding age distribution, parity number, maternal weight, week of gestation time from membrane rupture to cesarean, preoperative hemoglobin (Hb), and preoperative hematocrit values (Table 1).

When the surgical times were compared in Table 2, we found significant differences between the groups ($p<0.001$). According to these results, group 4 differed from all other groups and group 3 from groups 1 and 2 according to Tukey's HSD test.

When the amount of bleeding was compared using Tukey's HSD test, we found that the bleeding in group 3 differed from that in group 2, and in group 4 from that in groups 1 and 2. The number of abdominal compresses used differed between the study groups, but there was no difference between the sponges used. For these values in Tukey's HSD test, we saw that groups 2 and 4 differed from group 1.

When the distribution of birth weights was examined between the groups, we saw that groups 2 and 4 differed from group 1 in Tukey's HSD test. When the distribution of uterine sensitivity was compared between the groups according to the NRS as determined in fundus examinations performed on the first postpartum day, we found a significant difference ($p<0.001$). We observed that groups 2 and 3 had a moderate sensitivity rate of 27% and 18%, whereas group 1 had 76.5% lower uterine sensitivity, and group 4 had a severe sensitivity rate of 29%.

We detected seven (20.6%) patients with endometritis in group 1, 10 (27.8%) group 2, seven (23.3%) in group 3, and 15 (36.5%) patients in group 4 (Table 2).

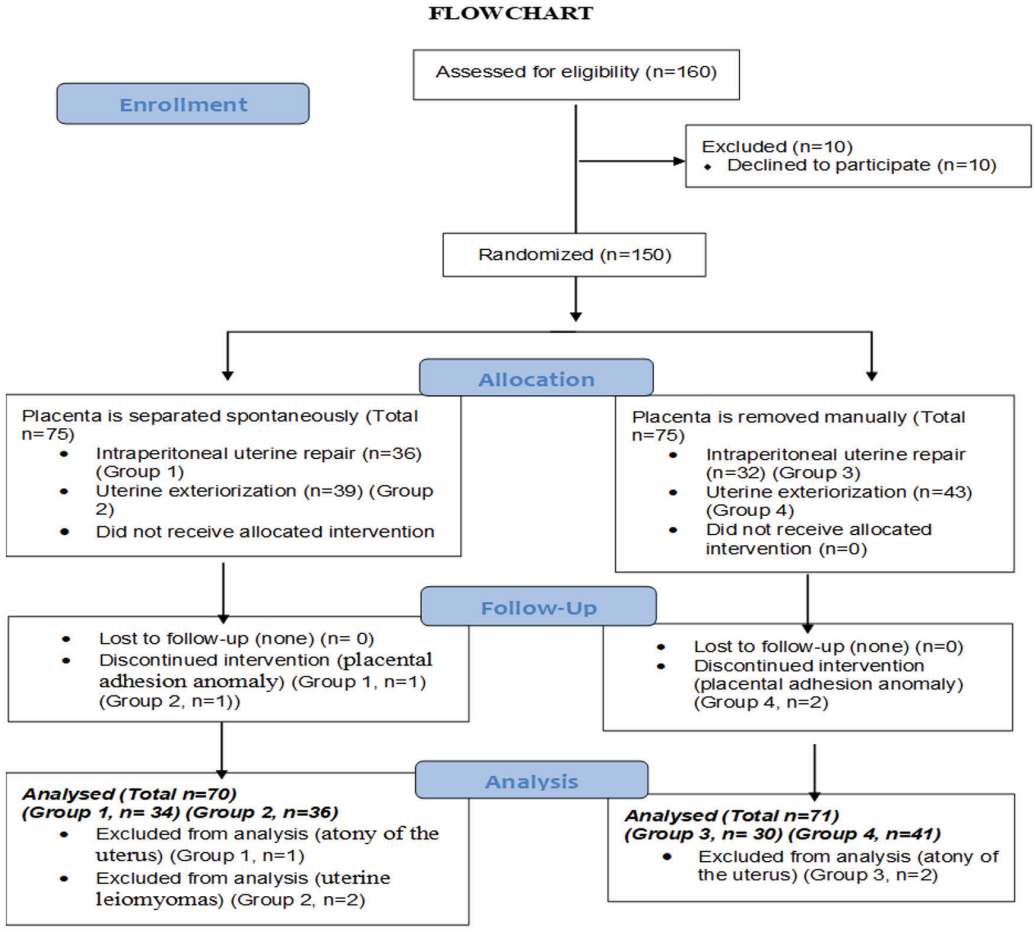



**Figure 1.** Flowchart

**Table 1.** Distribution of maternal data between the groups

| Intergroup comparisons maternal data | | | | | | |
|---|---|---|---|---|---|---|
| | Group 1 | Group 2 | Group 3 | Group 4 | F ratio | p-value |
| Mother age-year | 27.2±5.6 | 27.6±4.8 | 27.7±5.2 | 27.7±5.0 | 0.0722 (ANOVA Test) | 0.9748 (ANOVA) |
| Number of births (n) | | | | | 2.2598 (KW-chi-square test) | 0.5203 (KW-chi-square test) |
| 0 | 13 | 12 | 14 | 17 | | |
| 1 | 14 | 13 | 11 | 12 | | |
| 2 | 6 | 6 | 4 | 6 | | |
| 3 | 1 | 2 | | 3 | | |
| 4 | | 2 | | 2 | | |
| 5 | | | 1 | 1 | | |
| 7 | | 1 | | | | |
| Weight of mother (kg) | 72.7±10.l | 74.2±8.4 | 74.3±13.1 | 76.7±12.9 | 0.7879 (ANOVA) test | 0.5026 (ANOVA) test |
| Gestational week | 38.6±1.9 | 39.6±1.2 | 39.2±1.5 | 39.2±1.4 | 2.2453 (ANOVA) test | 0.0858 (ANOVA) test |
| Rupture of membrans/ hour | 13.0±15.6 | 6.8±6.1 | 11.3±18.4 | 5.0±6.l | 1.2220 (ANOVA) | 0.3130 (ANOVA) |
| Preoperative -Hb (g/dL) | 11.2±1.4 | 11.6±1.5 | 11.5±1.1 | 11.2±1.3 | 0.6903 (ANOVA) | 0.5594 (ANOVA) |
| Preoperative -Htc (%) | 33.9±4.0 | 35.2±4.1 | 34.2±3.4 | 33.7±3.6 | 1.1250 (ANOVA) | 0.3413 (ANOVA) |

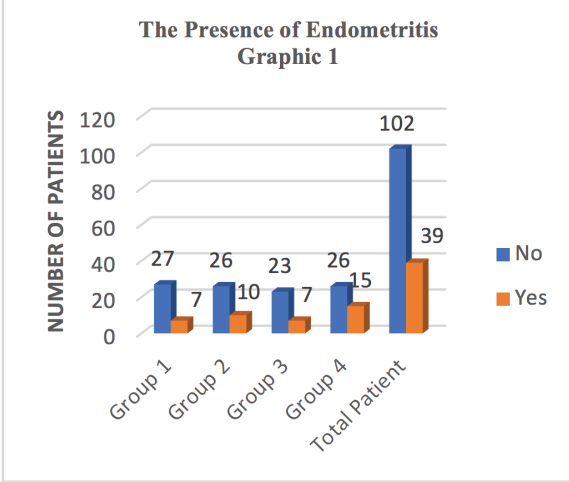
Hb: Hemoglobin

**Table 2.** Intrapartum-Postpartum criteria and statistical value

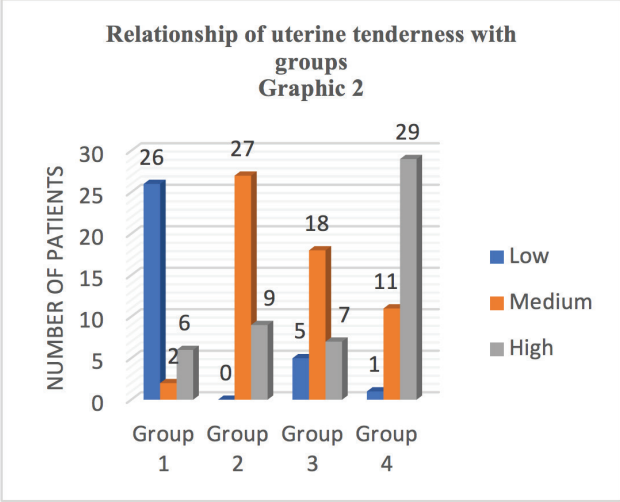
| | Group 1 | Group 2 | Group 3 | Group 4 | F ratio (ANOVA) | p-value (ANOVA) |
|---|---|---|---|---|---|---|
| Operation time/minute | 30.8±5.5 | 30.7±4.4 | 38.5±6.9 | 43.9±8.1 | 36.4927 | <0.001 |
| Blood loss/mL | 339.7±27.3 | 237.5±94.3 | 470.0±29.4 | 490.2±343.3 | 8.5808 | <0.001 |
| Number of sponges | 16.8±4.7 | 14.8±5.2 | 17.9±7.0 | 18.1±6.1 | 2.462 | 0.065 |
| Number of abdominal drapes | 2.2±0.8 | 3.2±0.8 | 2.9±1.1 | 3.2±1.3 | 6.5227 | <0.001 |
| Birth weight/g. | 3049.4±562.6 | 3473.6±535.9 | 3218.3±686.7 | 3432.4±542.9 | 4.1086 | 0.008 |
| Endometritis | | | | | | |
| No | 27 | 26 | 23 | 26 | | |
| Yes | 7 | 10 | 7 | 15 | | |
| Uterine Sensitivity | | | | | 50.3321 (KW-$\chi^2$) | <0.001 (KW-$\chi^2$) |
| Low | 26 | | 5 | 1 | | |
| Medium | 2 | 27 | 18 | 11 | | |
| High | 6 | 9 | 7 | 29 | | |
| Mechonium Presence | | | | | 2.5466 ($\chi^2$) | 0.467 ($\chi^2$) |
| Yes | 26 | 31 | 21 | 32 | | |
| No | 8 | 5 | 9 | 9 | | |
| Postoperative Hb (g/dL) | 10.6+1.6 | 11.0±1.4 | 10.4±1.3 | 10.3±1.7 | 1.5389 | 0.207 |
| Postoperative Htc (%) | 32.2±4.5 | 33.3±4.1 | 31.2±4.0 | 30.3±4.3 | 3.3459 | 0.021 |
| Hospitalitation/Day | | | | | 12.5905 (KW-$\chi^2$) | 0.006 (KW-$\chi^2$) |
| 2 | 14 | 2 | | | | |
| 3 | 12 | 23 | 22 | 25 | | |
| 4 | 1 | 5 | | 6 | | |
| 5 | 6 | 5 | 7 | 7 | | |
| 6 | 1 | 1 | | 2 | | |
| 7 | | | 1 | 1 | | |

In the postoperative period, there was a significant difference in hematocrit (Htc, %) values in group 2 compared with group 4 (p<0.021). Among the methods performed, we saw the most bleeding in the postoperative period in group 4. Endometritis and the factors affecting it are presented in Table 2 and Table 3 (Graphic 1, 2).

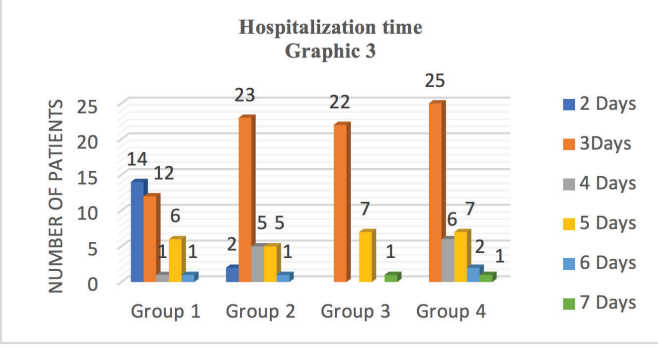
We also compared these parameters with maternal characteristics and intrapartum features. One parameter that affected the amount of blood loss that accumulated in the aspirator was maternal weight another was surgical time. Only surgical time caused a significant increase in the number of sponges used. The first parameter affecting the number of abdominal compresses used in the surgery was maternal weight, followed by surgical time and birth weight. Another feature of the number of compresses used was that it increased uterine sensitivity (Graphic 3).




**Graphic 1.** The presence of endometritis




**Graphic 2.** Relationship of uterine tenderness with groups



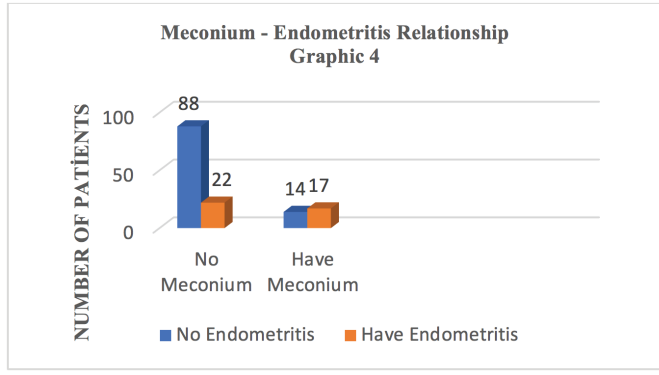

**Graphic 3.** Hospitalization time

There was one patient with wound infection in group 1, 2 and 3, we observed wound infection in three patients in group 4. When all groups were compared, LOS was different between groups 1 and 4 (p<0.004) (Graphic 4).

We observed a significant decrease in Hb and Htc values in the postoperative period compared with before the operation, and a significant increase in white blood cell values. We tested these values as the expected normal result of the procedure. However, another striking finding was that although there was a non-significant decrease in platelet values in group 1, 2, and 3 when compared using the paired t-test, there was a significant decrease in group 4 (Table 3).

We compared the effects of maternal criteria and intrapartum features on endometritis using the two-tail t-test (Table 4). We determined that the increase in maternal body weight was effective in creating endometritis (p<0.053) and we encountered more endometritis in advanced weeks of gestation (p<0.004). Prolonged surgical time was another factor that contributed to creating endometritis (p<0.009).

As seen in Table 5, we found no significant difference between parity and endometritis. However, a significant relationship was found between the existence of meconium and endometritis (p<0.001) (Table 6).




**Graphic 4.** Meconium-endometritis relationship

**Table 3.** Comparison of preoperative and postoperative values of complete blood count with intergroup paired t-test

| | Group 1 | Group 2 | Group 3 | Group 4 |
|---|---|---|---|---|
| **Preop. Hb (g/dL)** | 11.25 | 11.66 | 11.51 | 11.28 |
| **Postop. Hb (g/dL)** | 10.66 | 11.05 | 10.46 | 10.31 |
| **t-test (p-value)** | 0.001 | 0.001 | 0.001 | 0.001 |
| **Preop. Htc. (%)** | 33.99 | 35.28 | 34.28 | 33.76 |
| **Postop. Htc. (%)** | 32.23 | 33.38 | 31.28 | 30.39 |
| **t-test (p-value)** | 0.001 | <0.001 | <0.001 | <0.001 |
| **Preop. Wbc mm³** | 12282.35 | 10663.89 | 11190.00 | 11773.17 |
| **Postop. Wbc mm³** | 15314.71 | 14086.11 | 13623.33 | 14031.71 |
| **t-test (p-value)** | <0.001 | <0.001 | 0.001 | 0,0001 |
| **Preop. Plt. mm³** | 227,000.00 | 236,111.11 | 208,600.00 | 220,146.34 |
| **Postop. Plt. mm³** | 226,147.06 | 234,388.89 | 198633.33 | 204439.02 |
| **t-test (p-value)** | 0.886 | 0.816 | 0.142 | 0.008 |

Hb: Hemoglobin, Preop: Preoperative, Postop: Postoperative, Wbc: White blood cell, Plt: Platelet

Among the cesarean indication groups, pregnant mothers with preeclampsia and severe preeclampsia made up 2.9% of group 1. Twenty-two pregnant women with head-pelvis incompatibility made up 16.2% of group 2. Patients who became pregnant after

**Table 4.** The relationship between maternal-intrapartum characteristics and the presence of endometritis

| | No endometritis | Have endometritis | 2-Tail sig (t-test) (p-value) |
|---|---|---|---|
| Maternal age/year | 27,676514,818 | 27,384615,985 | 0.786 |
| Maternal body weight/kg. | 73,2941±9,989 | 78,0769±13,756 | 0.053 |
| Gestational week | 38,980411,641 | 39,769211,327 | 0.004 |
| Time from membrane rupture to operation/hour | 7,3676114231 | 9,3548110,956 | 0.621 |
| Surgical duration/minute | 35,009817,997 | 9,615419,427 | 0.009 |
| Blood accumulated in the aspirator/mL | 365,68631234,941 | 435,9741321,172 | 0.219 |
| Abdominal Sponge Pads/pcs | 16,323515,430 | 18,615416,885 | 0.040 |
| Abdominal Drapes/pcs | 2,911811,100 | 3,076911,244 | 0.470 |
| Baby birth weight/gram | 3313,5294±585,958 | 3282,8205±636,590 | 0.794 |

**Table 5.** Parity-endometritis relationship

| Parity/endometritis ratio | | | |
|---|---|---|---|
| | No Endometritis | Have Endometritis | 2-Tailed P Mann-Whitney U-test. p-value |
| **Number of Parity** | | | 0.801 |
| 0 | 37 | 19 | |
| 1 | 43 | 7 | |
| 2 | 14 | 8 | |
| 3 | 2 | 19 | |
| 4 | 4 | 0 | |
| 5 | 1 | 1 | |
| 7 | 1 | 0 | |

**Table 6.** Meconium-endometritis relationship

| Meconium-endometritis relationship | | | |
|---|---|---|---|
| | No Endometritis | Endometritis | Chi-square test p-value |
| | | | 0.00013 |
| No meconium | 88 | 22 | |
| Meconium | 14 | 17 | |

**Table 7.** The effect of maternal and intrapartum characteristics on endometritis collectively

| | Chi-square test f-value | Chi-square test p-value |
|---|---|---|
| Patient weight/kg | 0.007 | 0.828 |
| Time from membrane rupture to operation/hour | 0.048 | 0.162 |
| **Operation time/minute** | 0.013 | 0.833 |
| Gestational week | 0.653 | 0.031 |
| Abdominal sponges/pcs | 0.110 | 0.204 |
| Meconium presence | 0.574 | 0.181 |
| Operation type (group) | | 0.759 |

receiving primary infertility treatment and those whose age was over 35 years made up group 3. Forty-seven women who had a previous cesarean delivery made up group 4 with a rate of 47%. Forty women with acute fetal distress made up group 5 with a rate of 40%. Four women who underwent cesarean due to multiple pregnancies made up group 6 with 4%. Eleven women with primigravid breech presentation and other presentation anomalies made up group 7 with 11%. Two women with intrauterine growth restriction made up group 8 with 2%.

We tested the endometritis picture within these groups. Among the cesarean groups, we observed endometritis in 18 (47.4%) of the women who underwent cesearean with the diagnosis of AFD. The other two most common indications for endometritis were head-pelvis incompatibility in nine (23.7%) women and presentation anomalies in four women (10.5%). Maternal and intrapartum features affecting endometritis are shown in Tables 4, 6, and 7.

As seen in Table 7, only the gestational week was found associated with endometritis (p<0.031). However, as seen in Table 4, the results were more significant when the time from membrane rupture, which had no direct effect on the procedure, was excluded group (Table 8). As seen in Table 9, when membrane rupture was excluded, surgical duration (p<0.041), gestational week (p<0.057), and meconium (p<0.001) were effective on endometritis.

When the cesarean groups were added to the parameters in Table 8, we found that they affected the creation of endometritis (Table 9). In our study, we determined that prolonged surgical duration and the presence of meconium in amniotic fluid contributed to the formation of endometritis.

Although none of the maternal and intrapartum features affected the postoperative Hb concentration, only surgical duration affected the postoperative Hct percentage. Accordingly, we determined that the increase in surgical duration made a significant difference in all parameters except Hb concentration, which is affected by the amount of bleeding (Table 10).

## Discussion

In our study, the method of delivering the placenta during cesarean section clinically and statistically affected operative blood loss, surgical duration, endometritis formation, and LOS. Although we found an increase in all these parameters in the groups in which the placenta was removed manually, we saw that the uterine repair site had no direct clinical effect on patients undergoing cesarean section.

There are varied forms of cesarean surgery, so the selected procedures can cause particular morbidity related to this procedure. The technique of separating the placenta is an essential process that could contribute to acceleration or maybe a reduction in cesarean morbidity[6]. The form of placental removal during cesarean birth is even a controversial issue because previous research has reported uncertain and heterogeneous results[7]. In our research, while investigating the specifications that influenced bleeding, we examined the average blood volume in the aspirator chamber, the number of abdominal sponges and compresses used in the procedure, preoperative and postoperative complete blood count values, and surgical groups.

There are many approaches to establishing the quantity of blood loss during cesarean section[8]. The American College of Obstetricians and Gynecologists authorizes the meaningful recommendations and concerns. They claimed that quantitative procedures of testing obstetric blood loss were more precise than visual estimates in measuring obstetric blood loss. Studies that analyzed visual assessments for quantitative appraisal found that visual estimates were more likely to underestimate the correct blood loss when amounts were serious and overestimate when amounts were low. Although quantitative assessment is more accurate than visual assessment for measuring obstetric blood loss, the efficacy of quantitative blood loss assessment has not been shown in scientific studies[9]. During this investigation, we accepted gravimetric and volumetric approaches to analyze intraoperative blood loss[10]. We believe this method is practical in terms of applicability and accurate enough to measure intraoperative blood loss.

In line with the information in the literature, we saw that the amount of bleeding increased when we manually removed the placenta from the uterus[7,11]. While there was no difference

**Table 8.** Presence of endometritis (rupture of membranes were excluded)

| | Chi-square test f-value | Chi-square test p-value |
|---|---|---|
| Maternal weight/kg | 0,0135 | 0.475 |
| Surical duration/minute | 0,0760 | 0.041 |
| Gestational week | 0,3091 | 0.057 |
| Abdominal sponges/pcs | 0,0501 | 0.208 |
| Meconium presence | 0,8238 | 0.001 |
| Operation type (group) | | 0.417 |

**Table 9.** Parameters affecting endometritis when cesarean indication groups were included in the study

| | Chi-square test f-value | Chi-square test p-value |
|---|---|---|
| Maternal weight/kg | 0.0194 | 0.368 |
| Operation time/minute | 0.0970 | 0.032 |
| Gestational week | 0.1946 | 0.274 |
| Abdominal sponges/pcs | 0.0768 | 0.105 |
| Meconium presence | 0.6666 | 0.022 |
| Operation type (group) | | 0.351 |
| Cesarean indication group | | 0.198 |

**Table 10.** Statistical evaluation of the parameters affecting bleeding

| | Blood accumulated in the aspirator/mL $\chi^2$ | Abdominal Sponge Pads/pcs $\chi^2$ | Abdominal Compress/pcs $\chi^2$ | Postop. Hb (g/dL) $\chi^2$ | Postop. Htc (%) $\chi^2$ |
|---|---|---|---|---|---|
| Maternal age/year | 0.271 | 0.205 | 0.138 | 0.881 | 0.528 |
| Parity number parity | 0.263 | 0.898 | 0.108 | 0.448 | 0.527 |
| Gestational week | 0.817 | 0.135 | 0.507 | 0.900 | 0.992 |
| Maternal weight/kg | 0.018 | 0.556 | 0.002 | 0.581 | 0.913 |
| Operation time/minute | 0.0001 | 0.029 | 0.013 | 0.088 | 0.003 |
| Baby birth weight/g | 0.317 | 0.564 | 0.008 | 0.931 | 0.859 |
| Uterine tenderness | 0.108 | 0.252 | 0.007 | 0.454 | 0.095 |

Hb: Hemoglobin, Preop: Preoperative, Postop: Postoperative, Wbc: White blood cell, Plt: Platelet

in the number of sponges used, the number of abdominal compresses used in group 4 and group 2 differed from group 1 (p<0.001). Although it was a clinical finding, we expected this for group 4, in which we removed the placenta manually, but we did not expect this for group 2, where we separated the placenta spontaneously. In both groups, the repair of the uterine incision outside the abdomen was remarkable in terms of the importance of the uterine repair site in bleeding[12-15].

In the study conducted by Baksu et al.[16], the authors found that the decrease in Hb values in the postoperative period in the groups in which the placenta was separated by itself was statistically different from the groups in which the placenta was separated manually (p<0.05)[16]. In our study, we found no statistical difference in the decrease in Hb values. However, when the decrease in Hct values was compared in the groups in which the placenta was removed manually, the difference was statistically significant (p<0.001). There was also no significant difference between the decrease in postoperative Hct values in the extra-abdominal and intra-abdominal groups after repair of the uterine incision line (p=0.83).

McCurdy et al.[17] found that the estimated blood loss was higher in the manual removal group compared with the group that spontaneously removed the placenta during cesarean delivery. However, they reported that the decrease in Hb values was higher at the postoperative 48$^{th}$ hour in the group in which the placenta was removed manually, contrary to our study[17].

Wilkinson and Enkin.[18] stated in their research that uterine incision repair performed outside the abdomen had no significant effect on blood loss. However, they expressed that manual removal of the placenta was correlated with a considerable increase in maternal blood loss[19,20]. In their 2004 study, Dehbashi et al. and Morales et al.[20,21] found that the groups in which the placenta was removed manually had over 1000 mL of blood loss.

Some investigators reported that the method of placental management after delivery of the fetus might still be an efficient part of the etiology of post-cesarean endometritis[22]. When prophylactic antibiotics are not administered, the incidence of endometritis after cesarean section is 20-40%[23]. In contrast with placebo or no treatment, the benefit of prophylactic antibiotics in women undergoing cesarean section reduced the percentage of wound infection, endometritis, and serious infectious complications by 60% to 70%[24]. Researchers confirmed that manual removal of the placenta was associated with an increased incidence of post-cesarean endometritis compared with spontaneous removal of the placenta[19,20]. By contrast, Gün et al.[25] showed that manual removal of the placenta was not associated with postpartum blood loss and infection development compared with the spontaneous separation method.

We determined that the prolongation of surgical duration caused a significant increase, creating endometritis and more blood loss during the procedure (p<0.009). Ramadani[26] stated that surgical duration was significantly shorter in the group in which the placenta was removed manually (40.0±3.0 minutes) compared with the group in which the placenta was separated spontaneously (45.0±4.0 minutes). Ramadani[26] investigated the relationship between blood loss during cesarean and the method of placental separation and described similar results. The authors declared that the blood loss correlated with spontaneous separation and manual removal of the placenta was (702±250 milliliters) and (710±243 milliliters)[26]. Darj and Nordstrom[27] also stated this in their studies. Tran et al.[28] found that the risk of postoperative infection increased 2.4 times in every procedure where cesarean delivery lasted more than an hour. Although it is stated in the literature that endometritis is more common in nulliparas women, we observed no significant difference in our study[29].

### Study Limitations

One limitation of our investigation was the variations in the capability of the surgical team to perform the cesarean section. Although all obstetricians who adhered to the method were at the same academic and scientific status, it was difficult to control the skill and promptness. It was not possible to conduct the research with a single obstetrician performing all these operations to reduce skill diversity among operators. There is no unique standard technique for testing blood loss but we used methods to measure the defined variables in our research. Another limitation of this study is to investigate surgical blood loss in a healthy patient population without known additional risk factors. Patients with excessive blood loss for additional risk factors in the studied population were not included in the study and therefore we did not use different quantitative measurement techniques for this condition. Finally, it is not possible to avoid any other fetal body fluid such as amniotic fluid or fetal urine. If we include these fluids in blood loss, the results may be erroneous.

## Conclusion

Manual removal of the placenta leads to a clinically and statistically high rate of operative blood loss, surgical duration, increased uterine sensitivity, and LOS. We observed the least blood loss when the placenta was delivered spontaneously and we repaired the uterine incision outside the abdomen. Other factors that affect bleeding are the mother's weight, the baby's birth weight, and surgical duration. We associate the prolongation of surgical duration with increased febrile morbidity and the amount of bleeding.

We found that the method in which the placenta was separated spontaneously and the uterine incision was repaired outside the abdomen resulted in the shortest surgical duration and the least blood loss.

Cesarean delivery is a major predisposing clinical factor in terms of the frequency and severity of pelvic infection. Among the cesarean delivery indications, cephalopelvic disproportion

and fetal distress create the most endometritis. Other factors that affect the formation of endometritis include gestational week, surgical duration, the presence of meconium in amniotic fluid, and the mother's weight. Parity number, the time from membrane rupture to cesarean delivery, and surgical groups did not affect endometritis statistically. Delivering the placenta with a manual method and repairing the uterine incision outside the abdomen caused the most clinical postoperative endometritis. The uterine repair site has no significant statistical effect on postoperative endometritis, surgical duration, and operative blood loss.

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**Ethics**

**Ethics Committee Approval:** We obtained approval from the ethics committee of our hospital for the study (Adana City Training and Research Hospital Clinical Research Ethics Committee, 26.08.2020/1047).
**Informed Consent:** We received written informed consent form from all volunteers for the study.
**Peer-review:** Externally and internally peer-reviewed.

**Authorship Contributions**

Surgical and Medical Practices: S.K., Concept: S.K., Design: S.K., Data Collection or Processing: S.K., Analysis or Interpretation: A.P.K., Literature Search: A.P.K., Writing: S.K.
**Conflict of Interest:** The authors report no conflict of interest.
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# Should isolated aberrant right subclavian artery be ignored in the antenatal period? A management dilemma

## *Antenatal dönemde izole aberran sağ subklavyen arter gözardı edilmeli mi? Bir yönetim ikilemi*

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### Abstract

**Objective:** To investigate the frequency and types of chromosomal abnormalities in fetuses with the aberrant right subclavian artery (ARSA) and to evaluate its association with other ultrasonographic findings.

**Materials and Methods:** In all, 11,666 fetal anatomic surveys were performed between March 2014 and March 2020. The cases diagnosed as ARSA were examined. Accompanying ultrasound findings and chromosomal abnormalities were collected.

**Results:** ARSA was detected in 140 fetuses (1.2%). The ARSA appeared isolated in 47.1% (66/140) of cases and the remaining 52.9% (74/140) of cases were associated with cardiac or extracardiac malformations and soft markers. Chromosomal abnormalities were detected in 17.8% (25/140) of all cases. Trisomy 21 was the most common chromosomal anomaly with a prevalence of 11.4% (16/140). The corresponding rate was 3% (2/66) and 18.9% (14/74) for isolated and non-isolated ARSA, respectively. DiGeorge syndrome was detected in 3% (n=2) and Turner syndrome was in 3% (n=2) of the isolated group. ARSA was not an isolated finding in any of the 4 fetuses with trisomy 18.

**Conclusion:** Isolated ARSA may be the only antenatal predictor of trisomy 21 or other chromosomal anomalies, including DiGeorge or Turner syndrome. Hence, visualization of the right subclavian artery should be a part of the fetal anatomic survey and genetic analysis should be recommended even in the absence of associated findings.

**Keywords:** Aberrant right subclavian artery, DiGeorge syndrome, Down syndrome, Turner syndrome, prenatal diagnosis

### Öz

**Amaç:** Aberran sağ subklavyen arteri (ASSA) olan fetüslerde kromozomal anomalilerin sıklığını ve tiplerini belirlemek ve diğer sonografik bulgularla ilişkisini değerlendirmektir.

**Gereç ve Yöntemler:** Mart 2014 ile Mart 2020 tarihleri arasında toplam 11,666 fetal anatomik inceleme yapıldı. ASSA tanısı konulan olgular incelendi. Eşlik edilen ultrason bulguları ve kromozom anormallikleri toplandı.

**Bulgular:** Yüz kırk fetüste (%1,2) ASSA tespit edildi. ASSA, olguların %47,1'inde (66/140) izole olarak göründü ve olguların geri kalan %52,9'u (74/140) kardiyak anomaliler, ekstrakardiyak malformasyonlar veya minör belirteçler ile ilişkili bulundu. Tüm olguların %17,8'inde (25/140) kromozom anormallikleri tespit edildi. Trizomi 21, %11,4 (16/140) prevalansı ile en sık görülen kromozomal anomaliydi. İzole ve izole olmayan ASSA için karşılık gelen oranlar sırasıyla %3 (2/66) ve %18,9 (14/74) idi. İzole grupta %3 (n=2) DiGeorge sendromu ve %3 (n=2) Turner sedromu da saptandı. ASSA, trizomi 18'i olan 4 olgunun hiçbirinde izole bir bulgu değildi.

**Sonuç:** İzole ASSA, trizomi 21'in veya DiGeorge veya Turner sendromu dahil diğer kromozomal anomalilerin tek antenatal prediktörü olabilir. Bu nedenle, sağ subklavyen arterin görselleştirilmesi fetal anatomik incelemenin bir parçası olmalı ve ilişkili bulguların yokluğunda bile genetik analiz önerilmelidir.

**Anahtar Kelimeler:** Aberran sağ subklavyen arter, DiGeorge sendromu, Down sendromu, Turner sendromu, prenatal tanı

**PRECIS:** Aberrant right subclavian artery (ARSA) may be the only antenatal ultrasound finding of trisomy 21, DiGeorge and Turner syndromes in the second or third trimester.

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## Introduction

Aberrant right subclavian artery (ARSA) is the most common congenital abnormality of the aortic arch with a frequency of 1-1.5% in an apparently healthy population[1-3]. In normal anatomy, the right subclavian artery originates from the brachiocephalic trunk, one of the three main branches of the aortic arch. In contrast, ARSA is an anatomic variation in which the right subclavian artery originates from the aortic arch directly as an additional artery, usually distal to the left subclavian artery. It must course from the left side to right of the midline, usually behind the trachea and esophagus[4]. Typically, ARSA is a benign finding and usually asymptomatic. However, ARSA occasionally causes dysphagia or dyspnea in the pediatric population[5,6].

In recent years, ARSA has been associated with chromosomal abnormalities and has gained notoriety. The first report demonstrating the ARSA and relationship with Down syndrome was published in 2005[7], and thereafter a few other studies emphasized the importance of this benign variant, even if isolated and showing the presence of trisomy 21 in isolated cases[4,5,8,9]. Most trials revealed that additional cardiac or extracardiac abnormalities accompanied ARSA in fetuses with trisomy 21[10,11]. Moreover, ARSA has been reported with other less common genetic disorders such as 22q11.2 deletion or Turner syndrome[12,13].

This study aimed to determine the frequency and types of chromosomal anomalies among fetuses with ARSA and to evaluate the additional sonographic abnormal findings associated with ARSA in a large study group.

## Materials and Methods

This study was approved by our institutional review board. A waiver of informed consent was obtained owing to the study's retrospective nature. We performed a retrospective review of fetuses antenatally diagnosed as having ARSA between March 2014 and March 2020 in the perinatology unit of our hospital, which is a reference center in our city.

Fetuses with ARSA were identified from hospital databases and hospital charts. Both low and high-risk patients in the second and third trimesters were included in the study. We collected data by focusing on antenatal screening tests, fetal anatomy ultrasound scans, fetal echocardiograms, and reports of genetic analysis, and reviewed all neonatal and pediatric records. Examinations were performed using high-resolution equipment (Voluson E6 expert, GE Healthcare, Milwaukee, WI, USA) by perinatologists who were experts in fetal anatomic surveys and echocardiography. Color Doppler ultrasonography was used for visualizing the right subclavian artery as previously described by Chaoui et al.[7] (Figure 1). ARSA was detected as an additional vessel arising from the junction of the aortic arch and ductus arteriosus, and passing behind the trachea to the opposite side. In all patients with a diagnosis of ARSA, detailed fetal anatomical scanning and echocardiography were performed to look for additional abnormal ultrasound findings. The cases of ARSA were divided into two groups as isolated if ARSA was the only antenatal sonographic finding in the 2nd or 3rd trimester, and non-isolated, those with concomitant sonographic findings including cardiac or extracardiac abnormalities and soft markers. Nuchal fold thickness, aplasia or hypoplasia of nasal bone, echogenic intracardiac focus, hyperechogenic bowel, mild pyelectasis, and short femur or humerus (<5th percentile) were accepted as soft markers. Extracardiac abnormalities referred to all abnormal sonographic findings including fetal growth restriction, except for cardiac anomalies. Fetal biometric measurements were made according to Hadlock nomograms and estimated fetal weight (EFW) was calculated with the Hadlock formula. Those with abdominal circumference (AC)/EFW <3rd percentile or absent-reverse end-diastolic flow in the umbilical artery or AC/EFW <10th percentile combined with a pulsatility index >95th percentile in either the umbilical or uterine artery were considered to have an intrauterine growth restriction[14].

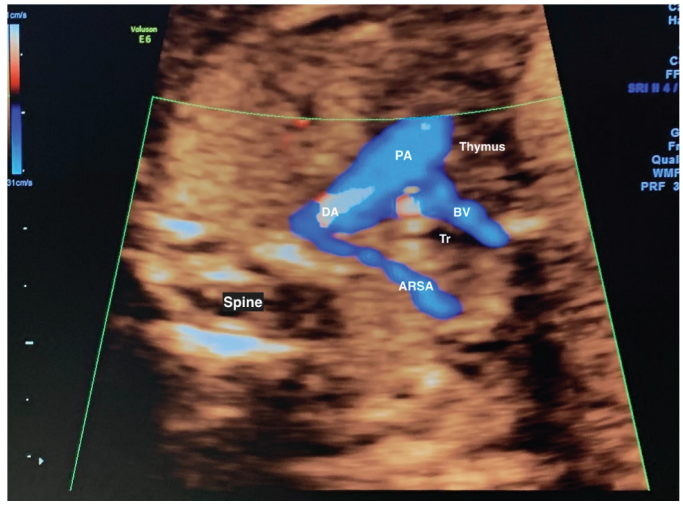


**Figure 1.** Transabdominal color Doppler axial image shows an aberrant right subclavian artery. ARSA arising directly from the junction of the aortic arch and ductus arteriosus and passing behind the trachea to the opposite side

*ARSA: Aberrant right subclavian artery, DA: Ductus arteriosus, PA: Pulmonary artery, BV: Brachiocephalic vein, Tr: Trachea*

Prenatal invasive diagnostic tests for karyotype analysis including fluorescence *in situ* hybridization (FISH) analysis were proposed in each case of ARSA. Blood samples were taken in the postnatal period for genetic analysis from infants whose parents did not accept the antenatal invasive test. The presence of ARSA in all cases was confirmed through postnatal echocardiography or computed tomography. Cases without prenatal or postnatal genetic diagnostic tests and postnatal confirmation were excluded from the study.

### Statistical Analysis

We used the IBM SPSS 21.0 for Windows (SPSS Inc., Chicago, IL, USA) statistical package for the statistical evaluation of our

research data. The measured variables are presented as mean ± standard deviation and categorical variables are presented as numbers and percentages (%). The Kolmogorov-Smirnov test was used to determine whether the numerical data matched normal distribution. The Student's t-test and Mann-Whitney U test were used to compare the groups. A p-value <0.05 was considered to be statistically significant.

## Results

The anatomic screening data of a total of 11,666 fetuses were assessed and ARSA was identified in 140 fetuses over the study period. The antenatal prevalence of ARSA in our study was 1.2%. ARSA was diagnosed in the second trimester in 92/140 (65.7%) patients and the third trimester in 48/140 (34.3%) patients. At the time of diagnosis, the mean gestational age was 22.3±4.5 weeks, and the mean maternal age was 31.2±5.5 years. ARSA appeared isolated in 47.1% (66/140) of cases and it was found to be associated with a cardiac or extracardiac abnormal finding and/or a soft marker in the remaining 52.9% (74/140). Cardiac anomalies, extracardiac malformations, and soft markers were detected in 21.6% (16/74), 51.3% (38/74), and 40.5% (30/74) of cases, respectively. Some of the fetuses had more than one type of abnormal finding (e.g. cardiac and/or extracardiac anomalies and soft markers in the same fetus).

Antenatal screening tests were performed in 97/140 (69.2%) patients, including 57 first-trimester screening, 18 triple tests, and 22 quadruple tests. In 24 of these patients, cell-free fetal DNA screening was also performed.

Prenatal invasive diagnostic tests and karyotype analysis using FISH were performed in 88/140 cases. Sampling was performed by amniocentesis in 65/88 cases, cordocentesis in 13/88, and chorionic villus biopsy in the remaining 10/88 cases. Postnatal genetic examinations were performed in the remaining 52/140 cases. Chromosomal abnormalities were detected in 17.8% (25/140) of all cases. The corresponding rate was 9% (6/66) and 25.6% (19/74) for isolated and non-isolated ARSA, respectively. Trisomy 21 was the most common chromosomal anomaly with a prevalence of 11.4% (16/140). The corresponding rate was 3% (2/66) and 18.9% (14/74) for isolated and non-isolated ARSA, respectively. The other chromosomal anomalies were trisomy 18, 22q11.2 deletion (DiGeorge syndrome), and Turner syndrome. The distribution of chromosomal abnormalities in fetuses with ARSA is shown in Table 1.

The list of sonographic findings observed in fetuses with non-isolated ARSA is shown in Table 2. The most common cardiac anomaly associated with ARSA was a ventricular septal defect (n=6, 4.2%), and the most common extracardiac finding and soft marker was fetal growth restriction (n=8, 5.7%) and echogenic cardiac focus (n=12, 8.5%), respectively.

Details of cases with a chromosomal abnormality are presented in Table 3.

**Table 1.** Distribution of chromosomal abnormalities in fetuses with ARSA by gestational age and maternal age

| | Isolated (n=66) | Non-isolated (n=74) | Total (n=140) |
|---|---|---|---|
| Mean GA at diagnosis, weeks (SD) | 21.6±4.2 | 23.4±2.8 | 22.3±4.5 |
| Mean maternal age, years (SD) | 32.3±5.3 | 31.4±5.1 | 31.2±5.5 |
| Maternal age ≥35 | 21(31.8) | 20 (27) | 41(29.2) |
| Trisomy 21 * | 2 (3) | 14 (18.9) | 16 (11.4) |
| DiGeorge syndrome | 2 (3) | 1 (1.3) | 3 (2.1) |
| Turner syndrome | 2 (3) | None | 2 (1.4) |
| Trisomy 18 | None | 4 (5.4) | 4 (2.8) |
| All anomalies ** | 6 (9) | 19 (25.6) | 25 (17.8) |

*p=0.024, ** p=0.003, p>0.05 for all other parameters. Percentage values are shown in parentheses, Student's t-test, Mann-Whitney U test, ARSA: Aberrant right subclavian artery

## Discussion

Previous studies revealed the prevalence rate of ARSA ranging between 0.4% and 2% among the general population[3,10,15]. Our study is one of the largest on ARSA in the literature and we identified 140 cases of ARSA with a prevalence rate of 1.2%.

During the last decade, many studies in the literature investigated isolated or non-isolated ARSA with additional abnormalities and its relationship with chromosomal anomalies[5]. Esmer et al.[5] first reported 14 trisomy-21 cases between 18 and 33 weeks of gestation and ARSA was detected in 5/14 (35.7%). In one of these cases, ARSA was the only abnormal ultrasound finding. Gul et al.[9] also reported 17 cases of ARSA and only one case was diagnosed with trisomy 21. ARSA was the only ultrasound finding in this fetus. Similarly, Borenstein et al.[3] published a case series of 8 fetuses with Down syndrome with ARSA, and in one of them, the ARSA was isolated. Zalel et al.[16] reported three cases of ARSA in eight fetuses with Down syndrome, but none of these cases was isolated. In another large study, Svirsky et al.[17] found a high prevalence of trisomy 21 in fetuses with ARSA, but none in the isolated group.

In our study, we demonstrated 16 cases of trisomy-21 in fetuses with ARSA and two were in the isolated group. Paladini et al.[18] reported a case series of 27 fetuses with ARSA and Down syndrome and ARSA was an isolated sonographic finding in eight (29.6%). In this study, the authors suggested that in addition to nasal bone aplasia/hypoplasia and nuchal fold thickness, ARSA should be one of the most important ultrasound markers of Down syndrome in the 2nd trimester.

In 2006, Chaoui et al.[19] reported the prevalence of ARSA in fetuses with major chromosomal abnormalities as 34% (16/47). Ratios were found as 28.5% (4/14), 55.5% (5/9), and 50% (2/4) in trisomy 21, trisomy 18, and trisomy 13, respectively. Also, ARSA was detected at a rate of 43% (3/7) in Turner syndrome and 14% (1/7) in DiGeorge syndrome. ARSA was not the only ultrasound finding in any of these cases.

**Table 2.** Sonographic findings of fetuses with non-isolated ARSA in second or third trimester ( some of the fetuses had more than one abnormal finding)

| Cardiac anomalies | n (%) | Extracardiac findings | n (%) | Soft markers | n (%) |
|---|---|---|---|---|---|
| Ventricular septal defect | 6 (4.2) | Fetal growth restriction | 8 (5.7) | Echogenic Intracardiac focus | 12(8.5) |
| Coarctation of aorta | 3 (2.1) | Ventriculomegaly | 7 (5) | Mild pyelectasis | 8 (5.7) |
| PLSVC | 3 (2.1) | Single umbilical artery | 5 (3.5) | Hyperechoic bowel | 7 (5) |
| AVSD | 2 (1.4) | Corpus callosum agenesis | 3 (2.1) | | |
| Tetralogy of fallot | 2 (1.4) | Omphalocele | 2 (1.4) | Nasal bone hypo/aplasia | 6 (4.2) |
| DORV | 2 (1.4) | Club foot | 2 (1.4) | Short femur/ humerus | 6 (4.2) |
| Interrupted aortic arch | 1 (0.7) | Micrognathia | 2 (1.4) | Thick nuchal fold | 1 (0.7) |
| Aortic stenosis | 1 (0.7) | PRUV | 2 (1.4) | | |
| | | Cleft lip palate | 2 (1.4) | | |
| | | Hand deformities | 2 (1.4) | | |
| | | Polyhydroamnios | 2 (1.4) | | |
| | | Holoprosencephaly | 1 (0.7) | | |
| | | Dandy-Walker malformation | 1 (0.7) | | |
| | | Thymic hypoplasia | 1 (0.7) | | |
| | | Hyperechogenic kidney | 1 (0.7) | | |
| | | Cystic hygroma | 1 (0.7) | | |
| | | | 1 (0.7) | | |

PLSVC: Persistent left superior vena cava, AVSD: Atrioventricular septal defect, DORV: Double outlet right ventricule, PRUV: Persistent right umblical vein, ARSA: Aberrant right subclavian artery

**Table 3.** Details of ARSA cases with a chromosomal abnormality

| Case | Maternal Age | Gestational Age | Antenal screening | Cardiac finding | Extracardiac finding | Soft marker | Karyotype |
|---|---|---|---|---|---|---|---|
| 1 | 35 | 22+2 | NP | Subaortic VSD | DWM, single umblical arter, FGR | None | Trisomy 21 |
| 2 | 28 | 23+4 | Positive (FTS), cffDNA | AVSD | None | Nasal bone hyoplasia | Trisomy 21 |
| 3 | 33 | 21+5 | Positive (QT) | None | Omphalocele, | None | Trisomy 21 |
| 4 | 27 | 22+0 | NP | None | Bilateral clubfoot | Mild pyelectasis | Trisomy 21 |
| 5 | 36 | 32+1 | NP | Coarctation of aorta PLSVC | None | Short femur | Trisomy 21 |
| 6 | 25 | 21+2 | Negative (TT) | İnlet VSD | None | EIF | Trisomy 21 |
| 7 | 32 | 23+3 | Positive (FTS) | None | Ventriculomegaly, PRUV | Nasal bone hypoplasia | Trisomy 21 |
| 8 | 38 | 19+2 | Positive (FTS), cffDNA | Tetralogy of fallot | None | Thick nuchal fold | Trisomy 21 |
| 9 | 36 | 24+1 | NP | None | Ventriculomegaly | EIF | Trisomy 21 |
| 10 | 30 | 15+5 | Positive (FTS) | None | Cystic hygroma | None | Trisomy 21 |
| 11 | 40 | 18+3 | Negative (TT) | İnlet VSD | None | None | Trisomy 21 |
| 12 | 27 | 22+4 | Negative (FTS) | None | FGR | EIF | Trisomy 21 |
| 13 | 41 | 21+1 | Negative (QT) | None | None | EIF, HEB | Trisomy 21 |
| 14 | 28 | 20+3 | Positive (cffDNA) | None | None | Mild pyelectasis | Trisomy 21 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 15 | **35** | **21+2** | **NP** | **None** | **None** | **None** | **Trisomy 21** |
| 16 | **29** | **23+4** | **Negative(TT)** | **None** | **None** | **None** | **Trisomy 21** |
| 17 | 36 | 22+4 | Negative (QT) | DORV | Thymic hypoplasia | None | 22q11.2 del |
| **18** | **27** | **24+0** | **Negative (FTS,TT)** | **None** | **None** | **None** | **22q11.2 del** |
| **19** | **38** | **20+5** | **NP** | **None** | **None** | **None** | **22q11.2 del** |
| **20** | **26** | **22+1** | **Negative (QT)** | **None** | **None** | **None** | **45,X0** |
| **21** | **29** | **23+0** | **Positive(FTS)** | **None** | **None** | **None** | **45,X0** |
| 22 | 24 | 22+4 | NP | None | ACC, ventriculomegaly, hand/foot deformities | Nasal bone hyoplasia | Trisomy 18 |
| 23 | 30 | 19+5 | Positive (FTS) | None | Micrognathia, hand/foot deformities | HEB | Trisomy 18 |
| 24 | 33 | 20+1 | NP | AVSD | FGR, single umblical artery, | None | Trisomy 18 |
| 25 | 31 | 18+5 | Positive (FTS) | DORV | Polihidramnios, FGR | HEB | Trisomy 18 |

NP: Not performed, DORV: Double outlet right ventricule, VSD: Ventricular septal defect, AVSD: Atrioventricular septal defect, PLSVC: Persistent left superior vena cava, EIF: Echogenic intracardiac focus, DWM: Dandy Walker malformation, FGR: Fetal growth restriction, HEB: Hyperechoic bowel, ACC: Agenesis of corpus callosum, FTS: First trimester screening, TT: Triple test, QT: Quadruple test, cffDNA: Cell free fetal DNA, ARSA: Aberrant right subclavian artery

Although the relationship between ARSA and Down syndrome has been demonstrated, there are conflicting data in the literature regarding the association of isolated ARSA and trisomy 21 or other chromosomal abnormalities to recommend karyotyping[20]. Rembouskos et al.[21] detected DiGeorge syndrome in a case of ARSA with only increased NT as an additional finding and emphasized the addition of FISH analysis for microdeletion syndromes to fetal karyotyping, even if ARSA was the only ultrasound finding on the second or third trimester.

We detected three cases with 22q11 deletion and in two of them, ARSA was the only ultrasound finding in the second-trimester fetal anatomic survey and one case with DORV and thymic hypoplasia.

Aortic arch abnormalities can be observed in Turner syndrome. However, there are limited data in the literature about the relationship between Turner syndrome and ARSA. In a study with 99 patients with Turner syndrome, ARSA was reported in 8% of cases[22].

ARSA was the only ultrasound finding in the second-trimester fetal anatomic screening in two fetuses in which we found Turner syndrome. Antenatal screening tests were not performed in one of the cases, but the other had increased nuchal translucency at the first-trimester screening.

## Conclusion

ARSA may be the only ultrasound finding in trisomy 21 and also in DiGeorge and Turner syndrome in the second or third trimester. Hence, imaging the right subclavian artery should be part of the fetal anatomical survey and standard karyotyping and FISH analysis should be recommended, even in isolated ARSA, especially in patients who do not have antenatal screening tests.

### Ethics

**Ethics Committee Approval:** This study was approved by our institutional review board (approved number: KAEK/2019.03.46).

**Informed Consent:** A waiver of informed consent was obtained owing to the study's retrospective nature.

**Peer-review:** Externally peer-reviewed.

### Authorship Contributions

Surgical and Medical Practices: M.B., S.S.Ç., S.S., A.Ç.E., Concept: M.B., S.S.Ç., S.C.O., S.S., A.Ç.E., Design: M.B., S.S.Ç., S.C.O., S.S., A.Ç.E., Data Collection or Processing: M.B., S.S.Ç., S.S., A.Ç.E., Analysis or Interpretation: M.B., S.S.Ç., S.C.O., Literature Search: M.B., S.S.Ç., S.C.O., Writing: M.B., S.S.Ç., S.C.O., Critical Review: M.B., S.S.Ç., S.C.O.

**Conflict of Interest:** The authors report no conflict of interest.

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# Antenatal follow-up, anesthesia management and perinatal outcomes in pregnancy with renal transplant

## *Renal transplantlı gebelerin antenatal takibi, anestezi yönetimi ve perinatal sonuçları*

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### Abstract

**Objective:** Due to the recent increase in the successful pregnancies after renal transplant, the number of renal transplant recipients having vaginal or cesarean delivery possibly associated with high maternal, fetal and/or neonatal risk requiring team approach increased. We aimed to evaluate antenatal follow-up, perinatal outcomes, and anesthesia management in pregnancies with renal transplantation and to compare them with the current literature.

**Materials and Methods:** After ethics committee approval, renal transplant recipients who gave birth in our hospital between January 2010 and December 2019 were documented in this retrospective study. Demographic characteristics, comorbidities, antenatal follow-up, anesthesia management, and maternal, fetal, and neonatal outcomes were presented.

**Results:** A total of 20 pregnant women who underwent renal transplant were identified. The mean age of the parturients was 31±5 years. The median interval from transplantation to conception was 8.15±4.8 years. Antenatal mean serum creatinine level and proteinuria were 1.48±1.39 mg/dL and 1.397±1.316 mg/dL, respectively. No allograft rejection was recorded. Comorbidities including hypertension (n=12), preeclampsia (n=6), and preterm delivery (n=10) were noted. The median gestational age was 35±3 weeks and the median newborn weight was 2.520±832 gram. There was one abortion, two pregnancy terminations, and 17 deliveries (3 vaginal and 14 cesareans). Cesarean sections (11/14; 78.6%) were mostly performed under spinal block and general anesthesia was performed in three (21.4%) women. Epidural analgesia for vaginal delivery was recorded in one parturient.

**Conclusion:** Despite the presence of preterm delivery and comorbidities, antenatal/peripartum follow-up and analgesia/anesthesia management of renal transplant recipients revealed good perinatal outcomes.

**Keywords:** Anesthesia, spinal, general, surgery, cesarean/labor and delivery, renal transplantation

### Öz

**Amaç:** Son zamanlarda böbrek nakli sonrası başarılı gebeliklerin artması nedeniyle, yüksek maternal, fetal ve/veya neonatal risk ile ilişkili olarak ekip yaklaşımı gerektiren vajinal veya sezaryen doğum olan böbrek transplant alıcıları artmıştır. Renal transplantasyonlu gebeliklerde antenatal takibi, perinatal sonuçları ve anestezi yönetimini güncel literatürle karşılaştırmak için değerlendirmeyi amaçladık.

**Gereç ve Yöntemler:** Etik kurul onayından sonra, Ocak 2010 - Aralık 2019 tarihleri arasında hastanemizde doğum yapan böbrek nakli alıcıları bu retrospektif çalışmada belgelendi. Demografik özellikler, komorbiditeler, antenatal takip, anestezi yönetimi ve maternal, fetal ve neonatal sonuçlar sunuldu.

**Bulgular:** Böbrek nakli yapılan toplam 20 gebe belirlendi. Doğum yapanların ortalama yaşı 31±5 yıldı. Transplantasyondan gebe kalmaya kadar geçen medyan aralık 8,15±4,8 yıldı. Antenatal ortalama serum kreatinin düzeyi ve proteinüri sırasıyla 1,48±1,39 mg/dL ve 1,397±1,316 mg/dL idi. Allogreft reddi izlenmedi. Hipertansiyon (n=12), preeklampsi (n=6) ve erken doğum (n=10) gibi komorbiditeler izlendi. Ortanca gebelik yaşı 35±3 hafta ve ortanca yenidoğan ağırlığı 2,520±832 gramdı. Bir dilatasyon küretaj, 2 gebelik terminasyonu ve 17 doğum (3 vajinal ve 14 sezaryen) vardı. Sezaryenlerin çoğu (11/14; %78,6) spinal anestezi altında yapıldı ve üç (%21,4) gebeye genel anestezi uygulandı. Doğum eylemi ve vajinal doğum için epidural analjezi 1

**PRECIS:** In our study, we evaluated antenatal follow-up, perinatal outcomes and anesthesia management in pregnancies with renal transplantation by comparing them with the current literature.

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gebede uygulandı.
**Sonuç:** Preterm doğum ve komorbiditelerin varlığına rağmen, renal transplant alıcılarının antenatal/peripartum takibi ve analjezi/anestezi yönetimi iyi perinatal sonuçlar ortaya koydu.
**Anahtar Kelimeler:** Anestezi, spinal, genel, cerrahi, sezaryen ve doğum, renal transplantasyon

## Introduction

After the first successful pregnancy in a renal transplant recipient in 1958[1], a recent meta-analysis including 4,706 pregnancies among 3,570 renal transplant recipients reported a live birth rate of 73.5%[2]. Pregnancy after renal transplantation carries maternal (e.g. allograft rejection, infection, hypertension or preeclampsia), fetal (spontaneous abortion, premature delivery, fetal growth restriction, and intrauterine fetal death) and neonatal (recurrence risk of the underlying maternal kidney disease that might occur in offspring) high risk[3-6]. Additionally, the type of anesthesia and/or analgesia and its management may be challenging in these pregnant women due to either preoperative hypovolemia or spinal anesthesia-induced hypotension along with the changed renal physiology during pregnancy, and rarely, the presence of immunosuppressive therapy, which may increase infection risk[7]. As the number of renal transplantations and parturients with renal transplant have increased, there is an anticipated high risk in perinatal outcomes because this particular group of patients is under immunosuppression treatment and has several comorbidities. Therefore, we aimed to revisit the risks and characteristics of these recipients by documenting our experience to provide updated national information for comparison with international data.

## Materials and Methods

After obtaining approval from the ethics committee (decision number: 503, dated: 20.07.2020), the database of our institution was searched between January 1st, 2010, and December 31st, 2019, for renal transplants and pregnancy. We specifically identified post-renal transplant, pregnant patients. Data including maternal age, the time elapsed from renal transplant to delivery, reason for transplantation, maternal comorbidities, gestational age, gravity and parity, and immunosuppressant medication were documented. Antenatal follow-up of renal functions in terms of serum creatinine (SCr) levels and estimated glomerular filtration rate (eGFR) were recorded from the records to elucidate the incidence of allograft rejection. Antenatal or peripartum anesthesia data were the mode of delivery, analgesia or anesthesia provided, anesthesia monitoring used, and complications related to obstetrics or anesthesia. Obstetric outcomes in terms of maternal, fetal and neonatal were noted from the records. Maternal outcomes included the rate of maternal mortality, cesarean section (CS), preeclampsia and/or proteinuria (total urine protein >0.3 g/day during pregnancy), hypertension, gestational diabetes mellitus, and anemia (hemoglobin <10.5 g/dL and <11 g/dL in the 2nd and 3rd trimester, respectively). All patients' blood pressures were under control with an antihypertensive agent. Fetal outcomes consisted of spontaneous abortion, stillbirth, preterm birth, intrauterine growth retardation, perinatal death, newborn weight, and Apgar scores (at 1 and 5 minutes).

### Statistical Analysis

Statistical analysis was conducted using the SPSS version 21.0 package. After performing descriptive statistics, data were presented as number (n), rate (%), mean and standard deviation or median where appropriate. Neonatal data according to maternal eGFR groups were compared using the t-test. The number of patients with three different eGFR intervals was compared using the chi-square test. A p-value <0.05 was considered statistically significant.

## Results

The demographic characteristics of parturients (as renal transplant recipients), those who underwent normal spontaneous vaginal deliveries (NSVD) or CS, are presented in Table 1. The mean maternal age was 31±5 years, the rate of nulliparity was 45%, and two patients became pregnant via in vitro fertilization. Renal transplant recipients (two of whom had two deliveries) included three NSVD, 14 cesarean deliveries, two pregnancy terminations, and one abortion. The mean interval from transplantation to conception was 8.15±4.83 years. The causes of end-stage renal failure requiring transplant and immunosuppressive regimen of the patients are presented (Table 1).

### Antenatal Follow-up

Antenatal follow-up of renal outcomes is presented in Table 2. The mean SCr level in the 1st trimester was 1.48±1.39 mg/dL and the mean 1st-trimester eGFR was 78.1±8.3 mL/min/1.73 $m^2$. After delivery, the mean SCr level and eGFR were 1.42±0.22 mg/dL and 64.7±8 mL/min/1.73 $m^2$, respectively. These parameters were not different between the 1st trimester and after delivery.

Then, 1st-trimester eGFR was assigned as <60, 60-89 and ≥90 mL/min/1.73 $m^2$. The number of patients with each eGFR is presented in Table 2. The mean 24-h urine protein was 1,397±1,316 g/day; 60% of them had >0.3 g/day proteinuria. No allograft rejection records were observed in any of the recipients, either before or after pregnancy.

### Perinatal Outcome

The obstetric outcomes, maternal comorbidities before pregnancy and peripartum morbidity and mode of delivery,

**Table 1. Demographics and clinical characteristics of the parturients (mean ± SD, range, n or %)**

| | |
|---|---|
| Maternal age (years) | 31±5 (19-42) |
| Gestational age (week) | 35±3 (28.6-40) |
| Gravity | 2.4±1.9 (1-7) |
| Parity | 0.6±0.9 (0-3) |
| Nulliparity | 9 (45%) |
| IVF | 2 (10%) |
| Interval between transplantation to delivery (years) | 8.15±4.83 (2-19) |
| **Reason for renal transplantation** | |
| Glomerulonephritis | 4 (20%) |
| Hypertension | 4 (20%) |
| Reflux nephropathy | 3 (15%) |
| Unspecified end-stage renal diseases | 5 (25%) |
| Wilms tumor | 1 (5%) |
| Amyloidosis | 1 (5%) |
| DM | 1 (5%) |
| Recurrent UTI | 1 (5%) |
| **Immunosuppressive medication** | |
| Tacrolimus | 90% |
| Prednisone | 75% |
| Azathioprine | 75% |
| Tacrolimus/azathioprine/prednisolone | 12 (60%) |
| Tacrolimus/azathioprine | 3 (15%) |
| Other combination | 5 (25%) |

DM: Diabetes mellitus, UTI: Urinary tract infection, IVF: *In vitro* fertilization, SD: Standard deviation

indications for CS, and type of anesthesia are shown in Table 3. There were 17 singleton live births, 14 of which were CS and three were NSVD. Eleven parturients received single-shot spinal anesthesia using 10 mg of hyperbaric bupivacaine with opioids (fentanyl 10 µg and morphine 100 µg). Three patients received general anesthesia. General anesthesia induction was provided using intravenous (IV) 5 mg/kg of thiopental and 1 mg/kg succinylcholine followed by 1 MAC of sevoflurane in 50% oxygen-air mixture until delivery of the newborn, and then by adding 0.2 µg/kg/h of IV remifentanil infusion. One of the NSVDs received epidural analgesia using 0.125% bupivacaine with 2 µg/mL fentanyl.

Peripartum fluid administration was 78% saline and 21% Ringer's lactate. The mean perioperative arterial pressure (MAP) ranged between 77±12 to 105±14 mm Hg. Records revealed that spinal anesthesia-induced hypotension was treated with ephedrine or noradrenaline. Post-dural puncture headache was reported in four out of 14 patients who underwent CS.

**Table 2.** Renal function tests and outcomes (mean ± SD, range, n or %)

| | |
|---|---|
| Before delivery-1st trimester (n=20) | |
| Creatinine (mg/dL) | 1.48±1.39 (0.6-5.89) |
| eGFR (mL/min/1.73 m$^2$) | 78.1±8.3 (8.3-136.8) |
| <60 | 6 (30%) |
| 60-89 | 5 (25%) |
| >90 | 9 (45%) |
| **After delivery (n=17)** | |
| Creatinine (mg/dL) | 1.42±0.22 (0.6-3.91) |
| eGFR (mL/min/1.73 m$^2$) | 64.7±8 (13. 4-119.3) |
| <60 | 8 (47%) |
| 60-89 | 4 (23%) |
| >90 | 5 (30%) |
| 24 h urine protein | 1.397±1.316 (138-4.511) |
| >0.3 g/day | 12 (60%) |
| **Allograft rejection during or after pregnancy (n=20)** | |
| Yes | 0 |
| No | 20 |

eGFR: Estimated glomerular filtration rate, SD: Standard deviation

### Neonatal Outcome

The median duration of gestation was 35±3 weeks (abortion and terminations were not included). There were 10 (58%) preterm deliveries. Preterm birth indications were ablatio placenta (n=2), spontaneous preterm birth (n=3), premature rupture of the membranes (n=2), and severe preeclampsia (n=3). The median birth weight was 2,520±832 grams (10 females and 7 males), with five newborns (29%) having low birth weight and two newborns (11%) having very low birth weight. Two newborns (11%) had Apgar scores <7 at 1 minute and 1 newborn (5%) had an Apgar score <7 at 5 minutes. The mean umbilical artery pH was 7.37±0.05.

We assigned our patients into three groups according to their eGFR as <60, 60-90, >90 mL/min/1.73 m$^2$ (Table 4). Then, we compared their perinatal results including gestational week at delivery, birth weight, umbilical artery pH, and Apgar scores. In group eGFR >90 mL/min/1.73 m$^2$, we observed higher birth weight, gestational week at delivery, and 1st minute Apgar score, but there were no significant differences between the groups (p=0.580, p=0.788, and p=0.715 respectively). The neonatal intensive care unit admission rate was 41.2%; the indications were tachypnea (57.1%) and low Apgar score (28.6%).

## Discussion

We have reported antenatal follow-up, and anesthesia and/or analgesia management and perinatal outcomes in parturients with renal transplantation who underwent CS or NSVD.

**Table 3.** Renal recipient data, type of delivery and anesthesia (mean ± SD, range, n or %)

| | |
|---|---|
| **Comorbidity before pregnancy (n=20)** | |
| Hypertension | 4 (20%) |
| Type 2 DM | 1 (5%) |
| **Maternal data (n=17)** | |
| Preeclampsia | 6 (35%) |
| Gestational DM | 2 (11%) |
| Anemia | 12 (70%) |
| •No treatment (n) | 3 |
| •IV Iron (FCM) replacement (n) | 2 |
| •Blood product (ES) Use (n) | 7 |
| **Mode of delivery (n)** | |
| CS | 14 (82.4%) |
| NSVD | 3 (17.6%) |
| **Indication for CS** | |
| Previous CS | 7 (50%) |
| Maternal medical indication | 3 (21.4%) |
| Presentation abnormality | 2 (14.3%) |
| Placental abruption | 2 (14.3%) |
| **Anesthesia type for CS (n=14)** | |
| Spinal (n=11) | 11 (78.6%) |
| General (n=3) | 3 (21.4%) |
| Epidural Analgesia for NSVD (n) | 1 |

DM: Diabetes mellitus, IV: Intravenous, FMC: Ferric carboxymaltose, ES: Erythrocyte suspension, CS: Cesarean section, NSVD: Normal spontaneous vaginal delivery, SD: Standard deviation

**Table 4. Neonatal data according to maternal eGFR (mL/min/1.73 m$^2$) (mean ± SD)**

| | eGFR <60 | eGFR 60-89 | eGFR≥90 | p |
|---|---|---|---|---|
| Gestation at | 34.2±3.7 | 34.68±4.1 | 36.67±1.8 | 0.788 |
| **Delivery (week)** | | | | |
| UA pH | 7.3±0.1 | 7.4±0 | 7.3±0 | 0.702 |
| Birth weight | 2.296±812 | 1.650±1421 | 2.506±476 | 0.580 |
| Apgar at 1 min | 7.5±3 | 6.5±3.5 | 8.2±0.8 | 0.715 |
| Apgar at 5 min | 9±2 | 8±1.4 | 9±1 | 0.723 |

UA: Umbilical artery, SD: Standard deviation, Abortion and termination were not included in the average delivery week of gestation

Perinatologists and anesthesiologists need to deal with those patients more frequently because the number of pregnant women who previously underwent renal transplantation has increased[2]. According to the report of the American Transplantation Association, pregnancy should occur at least a year after renal transplantation[8] though highest maternal complications and the least favorable birth outcomes were observed in the <2-year interval between renal transplantation and pregnancy[2]. In the present study, we audited an average interval of 8 years (from 2 to 19 years) between renal transplantation and pregnancy, which is very much acceptable and reliable. Pregnancies after transplantation are considered as high risk because of the higher incidence of pregnancy complications such as miscarriage, preeclampsia, gestational diabetes, need for CS, and premature birth compared with otherwise healthy pregnant women[5,6]. Gill et al.[5] found a rate of 32.7% of preterm birth among 453 pregnant women who had undergone renal transplantation. Bramham et al.[6] observed preeclampsia at a rate of 30% but no increased risk of gestational diabetes. The CS rate was 82% among 105 pregnant women with renal transplantation. Similarly, in our study, we documented gestational diabetes, preeclampsia and miscarriage, in addition to rates of CS and preterm delivery of 82.4% and 58%, respectively.

National authors have shown that maternal and fetal outcomes of renal transplant recipients were mostly dependent on transplanted kidney function determined by eGFR in the 1$^{st}$ trimester of pregnancy[9]. In our study, eGFR >90 mL/min/1.73 m$^2$ were recorded in 9 out of 20 patients in the 1$^{st}$ trimester, whereas it was in 5 out of 17 parturients after delivery.

Immunosuppressive medication including tacrolimus, azathioprine, and low-dose corticosteroids are well tolerated in pregnancy without significant risk in renal transplant recipients[10,11], but mycophenolate mofetil, sirolimus, and mammalian target of rapamycin inhibitors are contraindicated in pregnancy[12]. Sixty percent of our patients were using a combination of tacrolimus, azathioprine, and prednisolone, and none of the chemotherapeutics that are contraindicated was documented and used in our audit. Immunosuppressive medication can manifest serious adverse effects or complications, steroids and tacrolimus may cause commonly leukopenia and rarely epidural abscess[13]. Currently, no such serious adverse effects or complications have been documented. Regarding the use of neuraxial analgesia and/or anesthesia techniques in renal transplant recipients, obeying a strict aseptic technique is a must as stated[13]. Although there is no particular recommendation for prophylactic antibiotic use, it is routinely administered before the skin incision in our obstetric anesthesia practice.

In a retrospective analysis of a multicenter cohort study, 83 renal transplant recipients had vaginal and cesarean delivery with a mean gestation of 36±0.5 (range, 25-40) weeks. Then, 44 out of 83 (53%) parturients underwent CS; 33 out of 44 (75%) of these parturients received neuraxial anesthesia and 11 out of 44 (25%) underwent general anesthesia. The choice of neuraxial techniques includes single-shot spinal (56.8%), epidural (13.6%), and CSE anesthesia (4.6%)[7]. In our single-

center retrospective analysis including 17 deliveries (17.6% and 82.4% were NSVD and CS, respectively) at 35±3 weeks of gestation, neuraxial anesthesia was the most commonly chosen technique for CS (11 out of 14; 78.6%); the remainder (21.4%) received general anesthesia. In contrast to the multicenter study including three major tertiary hospitals in Israel[7], our CS rate was very much higher (82.4% vs 53%) due to the comorbidities and previous CS indication that required CS. Additionally, single-shot spinal anesthesia was the only technique we chose, accounting for 78.6%, and higher than the 56.8% rate reported by Ioscovich et al.[7].

According to national data related to pregnancy and renal transplantation, eight pregnancies in eight renal transplant recipients were reported between 1975 to 2003 (≈28-year period) and pregnancy had no negative impact on renal function after a 2-year follow-up[14]. The mean gestation time in the seven planned pregnancies was 35.5±3.0 (range 31.2 to 38) weeks[14].

Herein, 17 pregnant renal transplant recipients delivered successfully with both predelivery and postdelivery good graft function during a 10-year period. Similarly, the present mean gestation time for all these parturients was 35±3 (range 28.6-40) weeks, which was comparable to previous studies[7,14]. We documented that single-shot spinal anesthesia was provided with hyperbaric bupivacaine plus opioids. The average intraoperative fluid administration in our study was 1.2-1.3 L of saline and/or lactated Ringer's solution. In this population, adequate volume replacement has been recommended as a prerequisite to maintain placental perfusion and to avoid critical renal hypoperfusion[7]. Spinal anesthesia-induced hypotension is a known common complication, and we needed to treat only four patients (the rest were mostly hypertensive) with vasopressors to maintain maternal renal and placental perfusion. We provided a strict aseptic technique during neuraxial anesthesia practice to avoid spinal/epidural abscess or any other infectious complications because these patients are also at high risk because of their ongoing immunosuppressive therapy. In the current retrospective analysis, despite the presence of preterm delivery and comorbidities, antenatal and peripartum follow-up and analgesia/anesthesia management of parturients as renal transplant recipients were uneventful and revealed good perinatal outcomes, consistent with both international and national analyses.

### Study Limitations

Our study has some limitations. First, it has a retrospective design and the second is that it is conducted in a single institution. Studies involving many centers and evaluating more patients will improve our knowledge about kidney transplant patients.

## Conclusion

When we evaluated all these obstetric and neonatal data in our study, we observed that renal transplant patients have been found to have higher obstetric complications like preterm delivery than the normal population. However antenatal/peripartum follow-up and analgesia/anesthesia management of renal transplant recipients revealed good perinatal outcomes.

### Ethics

**Ethics Committee Approval:** The local ethics committee approved the study (decision number: 503, dated: 20.07.2020).
**Informed Consent:** Retrospective study.
**Peer-review:** Externally and internally peer-reviewed.

### Authorship Contributions

Concept: D.B.G., M.B., E.T., Design: D.B.G., M.B., E.T., Data Collection or Processing: S.K., B.B., Analysis or Interpretation: D.K., G.İ., Literature Search: D.B.G., G.İ., Writing: E.T., D.B.G., G.İ., B.B.

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# Evaluation of psychological resilience and anxiety levels of patients with hyperemesis gravidarum diagnosis and comparison with healthy pregnant women

## *Hiperemezis gravidarum tanılı hastaların psikolojik dayanıklılık ve anksiyete düzeylerinin değerlendirilmesi ve sağlıklı gebe kadınlarla karşılaştırılması*

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### Abstract

**Objective:** To compare the psychological resilience and anxiety levels of patients diagnosed with hyperemesis gravidarum (HG) and healthy pregnant women.

**Materials and Methods:** A sociodemographic data form and the Resilience scale for Adults (RSA) and the State-Trait Anxiety Inventory (STAI) were administered. The sociodemographic data form was completed by the physician, and the RSA and STAI were completed by the participant. The sample of the study consisted of 60 pregnant women with HG and hospitalized and 97 healthy voluntary pregnant women with similar characteristics to the research group without any pregnancy complications. Data were evaluated using descriptive statistical analyses, the independent samples t-test, the Mann-Whitney U test and Pearson's correlation analysis.

**Results:** The age range was 18-42 years for HG group and 20-43 years for control group. The average age of the HG group was 28.17±5.96 years and that of the control group was 29.45±5.83 years. There was no statistically significant difference between the groups in terms of pregnancy week. Regarding the prevalence of state and trait anxiety between the groups, it was found that 66.7% of the HG group had a high level of trait anxiety and 51.7% had a high level of state anxiety. It was found that 61.9% of the control group had a high level of trait anxiety and 38.1% had a high level of state anxiety. There was no difference between the healthy pregnant group and the HG group in terms of anxiety (p=0.125). It was found that there was a significant difference between the groups in terms of only sub-dimensions of RSA, which were perception of self (U=2385.00, p=0.044) and perception of future (U=2350.50, p=0.030). The perception of self and perception of future scores of the healthy control group were higher.

**Conclusion:** There was no difference between the healthy pregnant group and the HG group in terms of anxiety. It was observed that the HG group had a lower perception of self and future. Apart from the usual increase in anxiety levels during pregnancy, HG accompanied by stubborn nausea and vomiting does not create an extra psychological burden, either as a cause or a result.

**Keywords:** Hyperemesis gravidarum, pregnancy, resilience, anxiety

**PRECIS:** Using the Resilience scale for Adults and State-Trait Anxiety inventory, we compared normal pregnant women with hyperemesis gravidarum in terms of psychological resilience and anxiety.

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**Öz**

**Amaç:** Çalışmanın amacı hiperemezis gravidarum (HG) tanısı alan hastaların psikolojik dayanıklılıkları ve kaygı düzeylerinin sağlıklı gebeler ile karşılaştırılmasıdır.

**Gereç ve Yöntemler:** Sosyodemografik veri formu, Yetişkinler İçin Psikolojik Dayanıklılık ölçeği (YİPDÖ) ve Durumluk Sürekli Kaygı ölçeği (DSKÖ) uygulanmıştır. Sosyodemografik Veri Formu klinisyen tarafından, YİPDÖ ve DSKÖ ise katılımcı tarafından doldurulmuştur. Çalışmanın örneklemini, HG tanısı alan ve hastaneye yatırılmış 60 gebe ve herhangi bir gebelik komplikasyonu olmayan, araştırma grubu ile benzer özellikte 97 sağlıklı gönüllü gebe oluşturmaktadır. Veriler betimsel istatistiksel analizler, Bağımsız Örneklemler t-testi, Mann-Whitney U ve Pearson korelasyon analizi ile değerlendirilmiştir.

**Bulgular:** Yaş aralığı HG grubu için 18-42, kontrol grubu için 20-43'tür. HG grubunun yaş ortalaması 28,17±5,96, kontrol grubunun 29,45±5,83'tür. Gebelik haftası yönünden gruplar arasında istatistiksel olarak anlamlı fark görülmemiştir. DSKÖ'nün her iki grup arasındaki yaygınlığına bakıldığında, HG'li grubun %66,7'sinün yüksek sürekli kaygıya düzeyine, %51,7'sinin yüksek durumluk kaygı düzeyine sahip oldukları bulunmuştur. Kontrol grubunun %61,9'unun yüksek sürekli kaygıya düzeyine, %38,1'inin yüksek durumluk kaygı düzeyine sahip oldukları bulunmuştur. YİPDÖ alt boyutlarından sadece kendilik algısı ve gelecek algısı açısından gruplar arasında anlamlı farklılık bulunmuştur. Sağlıklı kontrol grubunun kendilik algısı ve gelecek algısı puanları daha yüksektir.

**Sonuç:** Sağlıklı gebe grubuyla HG grubu arasında kaygı düzeyi açısından fark görülmemektedir. HG grubunun kendilik ve gelecek algısının daha düşük olduğu görülmüştür. Gebelikte olağan kaygı düzeyi artışı haricinde, inatçı bulantı kusmaların eşlik ettiği HG durumu hem sebep olarak hem de sonuç olarak fazladan bir psikolojik yük oluşturmamaktadır.

**Anahtar Kelimeler:** Hiperemezis gravidarum, gebelik, psikolojik dayanıklılık, kaygı

## Introduction

Nausea and vomiting is a condition that affects the physical and psychological condition, and quality of life of pregnant women during pregnancy[1-3]. These symptoms become severe and deteriorate in 2% of pregnant women, and they are hospitalized because of hyperemesis gravidarum (HG)[1,4-6]. HG is characterized by stubborn nausea and vomiting that may cause malnutrition requiring hospitalization and can result in dehydration ketonuria, electrolyte and metabolic disorders, and weight loss[7,8]. Various studies were conducted on the etiology of HG and it is now accepted that it is a psychosomatic disease caused by the interaction of biologic, psychological, and sociocultural factors[8,9]. HG is an uncontrollable, stressful, and distressing condition, and makes it difficult to be satisfied with treatment and care; therefore, women can be hospitalized several times during pregnancy[10].

The fact that when vomiting and nausea will stop and how to manage this is unknown causes women to experience frustration, despair, weakness, and anxiety. Anxiety can exacerbate symptoms such as nausea and vomiting, and increased nausea and vomiting also increases anxiety levels. HG disrupts the life routine of pregnant women, making them unable to do daily work, and causing a sense of inadequacy[11]. On the other hand, pregnant women nurture concerns about both their own health and the health of their baby. The process may also cause that the thoughts of pregnant women about the future to change in a negative direction. With stubborn nausea and vomiting, which has already changed the body physiology significantly with the pregnancy process, when pregnant women have not fully adapted, the emotions and perceptions of pregnant women can change completely into fear, anxiety, and helplessness. In this respect, determining the challenging psychological factors emerging during the treatment of hospitalized patients with HG and developing support systems for them will have positive effects on the treatment process.

Psychological resilience (PR) is a general concept, and includes factors shown to be protective against psychological disorders, and is generally defined as "the power to recover oneself", "the ability to overcome disasters", or "the ability to adapt positively"[12]. PR allows the individual to make use of social resources (family, friends), social adequacy (being extrovert, communication skills, flexibility in inter-personal relations, ability to establish close relations), personal resources (self-reliability, hope, realistic orientation towards life) simultaneously[13].

PR was originally considered to be a personality trait, and some people were hypothesized to be inherently "resilient"; however, it was later considered to be "learnable" and "improvable" over time. For this reason, its implementation in treatment as an intervention strategy has come to the fore. Today, PD is considered in a multifaceted manner, allowing individuals to deal with challenging life events accurately, bringing together structural variables such as temperament and personality, as well as original abilities such as problem-solving[14].

Anxiety and depression are commonly reported among pregnant women worldwide because the transition to motherhood is challenging, involving significant changes both physically and psychologically[15]. During this critical period, women are susceptible to the negative effect of life events that could result in prenatal anxiety or depression[16]. The etiology of HG remains unclear and may be multi-factorial with biologic, psychological, and socioeconomic antecedents[17]. Historically, a pregnant woman's vomiting was thought to represent various psychological conflicts. However, it is also plausible that psychological symptoms are a result of the stress and the physical burden of HG, rather than a cause[17]. Women with prior psychiatric or medical conditions are more likely to develop HG when pregnant[18]. The prevalence of major depression, generalized anxiety disorder, avoidant personality disorder, and obsessive-compulsive personality disorder is higher in women with HG[19]. In addition, for pregnant women, recent research found that resilience could affect sleep quality and mediate the relationship between maternal stress and sleep quality in pregnant women[20]. However, studies assessing resilience specifically in pregnant women and its impact on

prenatal anxiety and depression are still lacking. Nonetheless, it was noted that no studies have evaluated the relationship between PR and the anxiety levels of individuals, and compared pregnant women with HG with healthy pregnant women. The purpose of the present study was to compare the PR and anxiety levels of patients with HG and healthy pregnant women.

## Materials and Methods

### Participants

This study was conducted between March 2019 and August 2019 in the Early Pregnancy Department. After the required approvals for the study were obtained from the institution (decision number: 90057706-799, date: 19.02.2019), the study was commenced. The sample of the study consisted of 157 participants, which included 60 voluntary patients who were admitted with HG in the first three months of pregnancy, and 97 healthy voluntary pregnant women with similar characteristics as the HG group, with no pregnancy complications. Informed consent of the participants was obtained. The inclusion criteria were having conceived willingly, ketone positivity in urine, and being hospitalized with a diagnosis of HG. The exclusion criteria were a diagnosis of psychiatric disease or receiving psychiatric treatment in the last year, alcohol or substance use disorder, presence of co-morbidities, presence of plural pregnancy, and having miscarriage history. The control group consisted of pregnant women who were admitted to the clinic for routine follow-up purposes.

Medical characteristics such as gestational week, parity, alcohol and smoking status, comorbid diseases, and surgical history were noted. In addition, the sociodemographic characteristics of the participants such as age, living quarters, economic status, and educational status were also recorded. The gestational weeks of the pregnant women were calculated according to their last menstrual periods. Educational status was classified as illiterate, primary school, high school, university, and doctorate. The economic situation was determined to be low, moderate, good, and very good with the answers given by the participant with the limits not determined by us, reflecting the participant's living standards and their own perception of their current economic situation. Family structure was classified as those living with their spouse, those living with their spouse and children, those living with extended families, and those living alone. Additional diseases of the participants were also questioned. Eight pregnant women in the HG group had additional diseases, as did 13 pregnant women in the control group. In the HG group, there was hypothyroidism (n=2), asthma (n=3), migraine (n=2), and gastritis (n=1), and in the healthy pregnant group, there was hypothyroidism (n=4), migraine (n=4), asthma (n=1), irritable bowel syndrome (n=2), vertigo (n=1), and Behçet's disease (n=1) noted in the medical history.

### Data Collection Tools

#### The Resilience Scale for Adults

The Resilience scale for Adults (RSA) was developed by Friborg et al.[13] When it was first developed, it had four sub-dimensions, personal power, structural style, social competence, and family agreement; however, the personal power sub-dimension was divided into two as perception of self and perception of future[21]. Thus, the scale consists of five sub-dimensions. The Turkish validity and reliability study was conducted by Basim and Cetin[22]. The scale consists of 33 items and is answered in a 5-point Likert scale. The Cronbach alpha reliability coefficient for the sub-dimensions varies between 0.66-0.81[22].

#### State-Trait Anxiety Inventory

The scale was developed by Spielberg et al.[23]. State-Trait Anxiety inventory (STAI) consists of 40 items, 20 of which measure trait anxiety and 20 items measure state anxiety. The state anxiety subscale measures anxiety at the time when the scale is applied. The trait anxiety subscale measures the general anxiety trend. The scale is answered on a 4-point Likert-style scale, and high total scores show that the level of anxiety is increased. The total score obtained from the subscales varies between 20 and 80. The mean score in applications varies between 36 and 41. A score of 36 and below indicates mild anxiety, 37-41 moderate anxiety, and 42 and above indicate high anxiety levels. The Turkish validity and reliability study of the scale was conducted by Oner and LeCompte[24] Pearson's coefficient was calculated between 0.26 and 0.68 for the state anxiety scale and 0.71 to 0.86 for Trait Anxiety scale in the test re-test reliability study.

### Procedure

Volunteering participants gave informed consent for the study. Each completed a Sociodemographic data form, the RSA, which consisted of 33 questions, and the STAI, which had two components consisting of 20 questions. The sociodemographic data form was filled out by the physicians and the RSA and STAI were completed by the participants.

### Statistical Analysis

Whether the distribution of the continuous numerical variables was normal was examined using the Kolmogorov-Smirnov test. The Levene test was used to check whether the assumption of homogeneity was met by the variances. Descriptive statistics are expressed as mean, standard deviation (SD) (±) or median (minimum-maximum) for continuous numeric variables, and categorical variables are expressed as participant count and percentage (%). As a result of Goodness of Fit tests, whether parametric test statistical assumptions were met and the significance of the difference in terms of the continuous numerical variables was evaluated with Independent Samples t-test (Student's t-test). The significance of the difference in terms of continuous numerical variables in which parametric test statistic assumptions were not met was examined with

the Mann-Whitney U test when the number of independent groups was 2. Whether the continuous numerical variables had statistically significant correlations was examined using Pearson's correlation test. Categorical data were evaluated using Pearson's chi-square test. The data were analyzed using IBM SPSS Statistics 23 (IBM Corporation, Armonk, NY, USA) package program. P-values <0.05 were considered statistically significant.

## Results

The HG group and the healthy control group were compared in terms of demographic and clinical characteristics and the results are presented in Table 1. The mean age of the HG group was 28.17 (SD ±5.96) years, and that of the healthy control group was 29.45 (SD ±5.83) years; no statistically significant differences were detected between the groups in terms of age (p=0.185). Statistically significant differences were detected between the groups in terms of education durations (p=0.007). The education period of the HG group (12 years) was more than that of the control group (10 years). Statistically significant differences were detected between the groups in terms of educational status (p=0.043), 41.5% were university graduates in the HG group, and 46% of the control group were primary school graduates.

No statistically significant differences were detected between the groups in terms of the number of pregnancies (gravida) (p=0.060). Statistically significant differences were detected between the groups in terms of the number of pregnancies (parity) that resulted in childbirth. The reason for the difference was that parity was higher in the control group (p=0.030). No statistically significant differences were detected between the groups in terms of gestational weeks (p=0.880). No statistically significant differences were detected between the groups in terms of the presence of additional disease (p=0.990), surgical history (p=0.900), family history of hyperemesis (p=0.148), economic status (p=0.050), working status (p=0.062), and the house lived (p=0.608).

Statistically significant differences were detected between the groups in terms of whether the residential area was a city center or district (p=0.001); the distribution in this respect was similar in the control group. Three-quarters (76.7%) of the HG group reported that they lived in the city center. Statistically significant differences were detected between the groups in terms of the distribution of the family structure (p=0.016). Approximately 60% of the control group stated that they lived with their spouse and children; 50% of the hyperemesis group lived with their spouse, and 34.5% lived with their spouses and children.

No statistically significant differences were detected between the groups in terms of alcohol use (p=0.260). Statistically significant differences were detected between the groups in terms of smoking (p=0.007). There were no smokers in the HG group; however, 11.3% of the control group said that they smoked.

**Table 1.** Demographic data of the study and control group

| | HG group (n=60) | | Healthy control group (n=97) | | p |
|---|---|---|---|---|---|
| | n | % | n | % | |
| **Age** | | | | | |
| 18-30 | 44 | 73.3 | 57 | 58.7 | 0.185[a] |
| 31-43 | 16 | 26.7 | 41 | 42.3 | |
| Mean | 28.17 | | 29.45 | | |
| SD | 5.96 | | 5.83 | | |
| **Education duration (years)** | | | | | |
| Median/min-max | 12 (0-18) | | 12 (5-18) | | 0.007[b] |
| **Educational status** | | | | | |
| Illiterate | 1 | 1.5 | 0 | 0 | 0.043[c] |
| Primary school | 16 | 27 | 44 | 46 | |
| High school | 16 | 27 | 29 | 31 | |
| University | 23 | 41.5 | 21 | 22 | |
| Post-graduate/ doctorate | 2 | 3 | 1 | 1 | |
| **Economic status** | | | | | |
| Low | 3 | 5 | 6 | 6.2 | 0.050[c] |
| Moderate | 25 | 41.7 | 61 | 62.9 | |
| Good | 30 | 50 | 28 | 28.9 | |
| Very good | 2 | 3.3 | 2 | 2.1 | |
| **Working status** | | | | | |
| Working | 24 | 40 | 25 | 25.8 | 0.062[c] |
| Not working | 36 | 60 | 72 | 74.2 | |
| **Residence** | | | | | |
| City center | 46 | 76.7 | 49 | 50.5 | 0.001[c] |
| Rural area | 14 | 23.3 | 48 | 49.5 | |
| **Family structure** | | | | | |
| Living with spouse | 29 | 50 | 26 | 28.3 | 0.016[c] |
| Living with spouse and children | 20 | 34.5 | 55 | 59.8 | |
| Extended family | 9 | 15.5 | 10 | 10.9 | |
| Alone | 0 | 0 | 1 | 1.1 | |
| **Gravida** | | | | | |
| Median/min-max | 1 (1-6) | | 2 (1-5) | | 0.060[b] |
| Parity | | | | | |
| Median/min-max | 0 (0-3) | | 1 (0-4) | | 0.030[b] |
| Gestational week | | | | | |
| Median/min-max | 8 (5-39) | | 9 (5-42) | | 0.880[b] |
| **Additional disease** | | | | | |
| Yes | 8 | 13.3 | 13 | 13.4 | 0.990[c] |
| No | 52 | 86.7 | 84 | 86.6 | |
| **Surgical history** | | | | | |
| Yes | 18 | 31.6 | 26 | 30.6 | 0.900[c] |
| No | 39 | 68.4 | 59 | 69.4 | |
| **HG family history** | | | | | |
| Yes | 9 | 15 | 23 | 24.7 | 0.148[c] |
| No | 51 | 85 | 70 | 75.3 | |
| **Alcohol** | | | | | |
| Yes | 0 | 0 | 3 | 2.1 | 0.260[c] |
| No | 60 | 100 | 95 | 97.9 | |
| **Smoking** | | | | | |
| Yes | 0 | 0 | 11 | 11.3 | 0.007[c] |
| No | 60 | 100 | 86 | 88.7 | |

[a]: Independent samples t-test, [b]: Mann-Whitney U test, [c]: Chi-square test, SD: Standard deviation, min-max: Minimum-Maximum, HG: Hyperemesis gravidarum

When the prevalence of state and trait anxiety was evaluated between the groups, it was found that 66.7% of the HG group had a higher trait anxiety level (TAS>41), and 51.7% had a high trait anxiety level (SAS>41). It was also found that 61.9% of the control group had a high trait anxiety level (TAS>41), and 38.1% had a high state anxiety level (SAS>41).

According to the results of the Mann-Whitney U test, significant differences were detected between the HG group and the healthy controls in terms of the RSA perception of self (U=2385.00, p=0.044) and Perception of Future (U=2350.50, p=0.030) sub-dimensions. It was found that the perception of self and perception of future scores of the healthy control group were higher. No significant differences were detected between the groups in terms of RSA total scores and other sub-dimensions (Table 2). No statistically significant differences were detected between the groups in terms of the STAI total scores (t=1.54, p=0.125), and the STAI sub-dimensions, which were state anxiety (t=1.76, p=0.080) and trait anxiety (t=0.85, p=0.398) (Table 3).

The correlation coefficients among the variables of the groups are given in Table 4. A positive and significant relation was detected between education durations and perception of self (r=0.43, p=0.001) and perception of future (r=0.40, p=0.002) scores, and between state anxiety, age, and STAI total score (r=0.38, p=0.003) in the HG group (r=0.43, p=0.001). A significantly positive relation was detected between gestational week and structural style (r=0.27, p=0.039), and a significantly negative relation was detected between state anxiety (r=-0.31, p=0.017) and STAI total scores (r=-0.26, p=0.010) in the HG group. The relations between RSA total scores, sub-dimensions of perception of self, perception of future, structural style, social competence, and family agreement and trait anxiety and STAI in the HG group were negative and significant. The relations between RSA total scores, perception of self, perception of future, state anxiety, trait anxiety, and STAI total scores were also negative and significant in the healthy control group. A negative and significant relation was also detected between social competence, trait anxiety, and STAI total scores.

**Table 2. Mann-Whitney U test results of total RSA Sub-dimension scores of the hyperemesis and healthy control group**

| | Hyperemesis group (n=60) | | Healthy control group (n=97) | | | |
|---|---|---|---|---|---|---|
| | Rank (median) | Sum (min-max) | Rank (median) | Sum (min-max) | U | p |
| Perception of self | 70.25<br>22.5 | 4215.00<br>6-30 | 85.16<br>26 | 8346.00<br>8-30 | 2385.00 | 0.044* |
| Perception of future | 69.68<br>16 | 4180.50<br>6-20 | 85.52<br>16 | 8380.50<br>4-20 | 2350.50 | 0.030* |
| Structural style | 72.77<br>16 | 4366.00<br>4-20 | 83.62<br>16 | 8195.00<br>4-20 | 2536.00 | 0.139 |
| Social competence | 76.28<br>23 | 4576.50<br>10-30 | 81.47<br>26 | 7984.50<br>10-30 | 2746.50 | 0.483 |
| Family agreement | 75.28<br>26 | 4517.00<br>14-30 | 82.08<br>26 | 8044.00<br>12-30 | 2684.00 | 0.348 |
| Social resources | 70.58<br>31 | 4235.00<br>19-35 | 84.96<br>31 | 8326.00<br>15-35 | 2405.00 | 0.051 |
| RSA total | 71.52<br>134.5 | 4291.00<br>19-35 | 84.39<br>141 | 8270.00<br>76-165 | 2461.00 | 0.086 |

RSA: The resilience scale for adults, min-max: Minimum-maximum, *p<0.05

**Table 3. T-test results of total and sub-dimensions of state-trait anxiety inventory of the hyperemesis and healthy control group**

| | Hyperemesis group (n=60) | | Healthy control group (n=97) | | t | p |
|---|---|---|---|---|---|---|
| | Mean | SD | Mean | SD | | |
| State anxiety | 42.05 | 9.73 | 39.13 | 10.29 | 1.76 | .080 |
| Trait anxiety | 44.93 | 7.61 | 43.84 | 7.92 | 0.85 | .398 |
| STAI total | 86.58 | 191.96 | 82.97 | 16.31 | 1.54 | .125 |

STAI: State-trait anxiety inventory, SD: Standard deviation

**Table 4. Pearson correlation coefficients among the variables**

| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1. Age | **1** | 0.2 | 0.51** | 0.52** | -0.11 | 0.09 | -0.06 | 0.11 | -0.04 | -0.03 | 0.03 | 0.03 | 0.02 | -0.08 | -0.02 |
| 2. Education duration | **0.17** | **1** | -0.21* | -0.20 | -0.01 | 0.16 | 0.09 | 0.12 | 0.12 | -0.001 | 0.05 | 0.15 | -0.11 | -0.20* | -0.17 |
| 3. Gravida | **0.33*** | **0.22** | **1** | 0.84** | -0.05 | 0.03 | -0.05 | -0.11 | -0.07 | -0.10 | 0.17 | -0.07 | 0.04 | -0.08 | -0.01 |
| 4. Parity | **0.28*** | **0.17** | **0.82**** | **1** | 0.001 | 0.04 | -0.05 | -0.10 | -0.08 | 0.02 | 0.11 | -0.03 | 0.08 | -0.10 | 0.007 |
| 5. Gestational week | **-0.21** | **-0.19** | **-0.14** | **-0.21** | **1** | 0.08 | 0.19 | 0.08 | 0.10 | -0.009 | -0.09 | 0.15 | -0.09 | -0.05 | -0.08 |
| 6. Perception of self | **-0.15** | **0.43**** | **0.17** | **0.04** | **0.11** | **1** | 0.63** | 0.18 | 0.38** | 0.38** | 0.13 | 0.81** | -0.20* | -0.42** | -0.33** |
| 7. Perception of future | **-0.13** | **0.40**** | **0.01** | **0.02** | **0.04** | **0.66**** | **1** | 0.08 | 0.19 | 0.33** | -0.03 | 0.69** | -0.33** | -0.41** | -0.41** |
| 8. Structural style | **-0.14** | **0.12** | **-0.12** | **-0.16** | **0.27*** | **0.50**** | **0.50**** | **1** | 0.22* | 0.07 | 0.06 | 0.28** | -0.12 | -0.21* | -0.18 |
| 9. Social competence | **-0.03** | **0.20** | **-0.12** | **-0.10** | **0.07** | **0.38*** | **0.25** | **0.05** | **1** | 0.25* | -0.06 | 0.62** | -0.13 | -0.27** | -0.21* |
| 10. Family agreement | **-0.24** | **0.12** | **-0.08** | **-0.14** | **0.11** | **0.67**** | **0.58**** | **0.46**** | **0.36**** | **1** | 0.07 | 0.60** | -0.15 | -0.17 | -0.18 |
| 11. Social resources | **-0.01** | **0.15** | **0.03** | **0.07** | **-0.05** | **0.23** | **0.22** | **0.18** | **0.23** | **0.19** | **1** | 0.07 | -0.14 | -0.11 | -0.14 |
| 12. RSA total | **-0.20** | **0.34**** | **-0.02** | **-0.08** | **0.15** | **0.84**** | **0.77**** | **0.60**** | **0.60**** | **0.82**** | **0.30*** | **1** | -0.29** | -0.44** | -0.40** |
| 13. State anxiety | **0.42**** | **0.18** | **0.18** | **0.25** | **-0.31*** | **-0.23** | **0.08** | **-0.17** | **-0.18** | **-0.09** | **0.23** | **-0.16** | **1** | 0.60** | 0.92** |
| 14. Trait anxiety | **0.22** | **-0.17** | **-0.03** | **0.14** | **-0.26** | **-0.60**** | **-0.46**** | **-0.31*** | **-0.27*** | **-0.43**** | **-0.17** | **-0.58**** | **0.48**** | **1** | 0.86** |
| 15. STAI total | **0.38**** | **0.03** | **0.10** | **0.23** | **-0.33**** | **-0.45**** | **-0.18** | **-0.27*** | **-0.26*** | **-0.27*** | **0.06** | **-0.40**** | **0.89**** | **0.82**** | **1** |

RSA: The resilience scale for adults, STAI: State-trait anxiety inventory
*p<0.05, **p<0.01. Bold numbers show Pearson's r coefficients obtained for the hyperemesis group, and normal numbers show Pearson's r coefficients obtained for the healthy control group

## Discussion

In the present study, 60 women who were diagnosed as having HG in the first 3 months of their pregnancies, and 97 healthy pregnant women who had similar characteristics as the HG group were compared in terms of PR and anxiety levels. No significant differences were detected between the groups in terms of anxiety levels. PR was measured using RSA, and a significant difference was detected between the groups in terms of Perception of Self and perception of future, which are the sub-dimensions. The HG group had lower perception of self and perception of future scores than the healthy control group. We found that as age increased, state anxiety scores also increased, and state anxiety scores decreased as the gestational week progressed in the HG group. Negative and significant correlations were detected between the PR scores and anxiety scores of both groups.

The HG and control groups were compared according to some sociodemographic variables. We found that age, gravida, gestational week, economic status, and working status did not differ significantly between the groups. These findings are consistent with the results of similar studies in the literature[19,25-27]. In the present study, a significant difference was found between the HG and the control group in terms of educational status. The percentage of university graduates in the HG group was higher than in the control group. However, previous results regarding education status are conflicting: according to some comparative studies, there was no difference between HG and control groups in terms of educational status[19,25-27], but one study reported that the HG group had a lower education level than the healthy group[28]. Likewise, results regarding parity in women with HG are controversial. Our findings showed significantly lower parity in the HG group than in the control group. In line with our findings, some studies reported a nulliparity risk factor for HG, and also primiparous women needed hospital care more because of HG[29,30]. By contrast, some studies found no difference in parity between HG and healthy groups[27,28]. When comparing family structure, we found a difference between the HG and control groups. A higher percentage of the HG group lived with their

spouses, whereas a higher percentage of the control group lived with their spouses and children. This finding is parallel to the parity result. In other words, the higher parity in the control group was compatible with living with a spouse and children in terms of family structure.

In the present study, no significant differences were detected between the groups in terms of state and trait anxiety and STAI total scores. An important part of the literature reported that levels of depression and anxiety increased in women with HG[31-33]. Previous studies comparing women with HG and healthy controls reported that the HG group had higher anxiety scores[19,25-27]. Although it is expected that stubborn nausea and vomiting decrease the quality of life significantly and impair the perception of health of the person, the present study found no significant differences in terms of anxiety levels. Women with HG had higher anxiety, depression, and stress levels when they were newly admitted to hospital and their anxiety, depression; and stress levels decreased with time[34]. In the present study, the fact that the women with HG were hospitalized may have reduced their anxiety levels. However, anxiety and depression may increase in pregnancy, and pregnancy is a risk factor for depression and anxiety[35-37]. Besides, different scales were used to measure the anxiety levels of pregnant women with HG in previous studies (e.g. Beck Anxiety inventory, SCL-90, SCID-II), which may account for the disparity between our findings and those in the literature.

In the literature, no studies were detected dealing with PR in pregnant women with HG. Studies were focused on the relations of PR in pregnant women with other psychological factors and did not include any control groups[20,38,39]. We found that the RSA subscales, perception of self, and perception of future scores of the HG group were significantly lower in the HG group than in the control group. According to Friborg et al.[21], self-perception and future perception, which represent personal strength, are associated with emotional resilience, which is among personality traits. Also, future perception is considered to be associated with the responsibility of the personality. The lower perceptions of the HG group detected in the present study regarding themselves and the future compared with the control group may show that they faced difficulties emotionally with a sense of responsibility for their future.

PR is a protective factor for the mother's psychological health[39], and points at internal and interpersonal protective resources, which may facilitate the adaptation and tolerance to stress[21]. A negative relation was reported in previous studies between prenatal stress, depression, and anxiety levels of pregnant women and their PR scores[20,38-40]. These results are consistent with the negative correlation finding between PR and anxiety scores in both groups in our study. Our findings indicate that as depression, anxiety, and stress levels increase during pregnancy, PR scores decrease. However, it is interesting that perception of self, perception of future, and other RSA sub-dimensions were negatively correlated with trait anxiety and total anxiety scores, not state anxiety scores in the HG group. On the other hand, PR scores were associated with both state and trait anxiety scores in the healthy group. This means that trait anxiety, known as a personal characteristic, is associated with PR in the HG group. We also found that anxiety levels decreased as the gestational week of the HG group increased. In other words, it means that there is a decrease in anxiety in pregnant women with HG towards the end of the first trimester.

Studies show that strong PR is associated with psychological well-being[41,42]. PR is effective in dealing with physical pain, reducing negative attitudes towards pain, and strengthening psychological well-being and positive emotions[43,44]. Coping with HG characterized by persistent nausea and vomiting and increasing the PR resources of women diagnosed with HG will improve their psychological well-being. PR may increase resistance to the negative effect of prenatal stress on anxiety and depression[41]. PR in pregnant women with HG is recommended to be investigated together with other variables that may be related in future studies (e.g. coping with stress, self-esteem, self-sufficiency). However, PR can be considered as a factor that needs to be dealt with in intervention programs aimed at improving psychological health in pregnant women.

### Study Limitations

The small sample size of the study caused a limitation in terms of the generalization of the findings. Our study is the first to compare pregnant women with HG and healthy pregnant women in terms of PR. It was found that the HG group was significantly different from healthy pregnant women in terms of perception of self and perception of future. No significant differences were detected between the groups in terms of anxiety levels. The cross-sectional design of the study was another limitation. More significant associations may be obtained in future studies in which HG and control groups are followed up in terms of anxiety and PR in the third trimester. Also, planning future studies with a longitudinal design with pregnant women with HG will provide a better understanding and explain the psychosocial dimension of HG.

## Conclusion

It is predictable that when a complication such as HG is added during pregnancy it can increase the anxiety and fear of the person during a period that is believed to increase the probability of anxiety and depression. As our study showed that self-perception and future perception were lower in the HG group, these patients should be evaluated multidisciplinary by an obstetrician, psychologist, and social worker. For this reason, healthcare professionals must be aware of the fact that extra psychological support may be needed during the treatment and follow-up of the patient. Psychological support should be provided to increase PR owing to the future anxiety and decreased self-perception of the patient. Psychologically supportive treatment during follow-up may significantly reduce

the severity of the disease. We also think that the relatives of the patient can have a positive effect. The support of the relatives in reducing the patient's anxiety and increasing the perception of value will contribute to the recovery process.

### Ethics

**Ethics Committee Approval:** The required approvals for the study were obtained from the University of Health Sciences Turkey, Ankara Etlik Zübeyde Hanım Women's Health Training and Research Hospital (decision number: 90057706-799, date: 19.02.2019).

**Informed Consent:** Informed consent of the participants was obtained.

**Peer-review:** Externally peer-reviewed.

### Authorship Contributions

Concept: A.C.K., Design: A.C.K., S.E., Data Collection or Processing: B.S.Ö., Analysis or Interpretation: B.S.Ö., A.B., S.E., Literature Search: G.A., I.B.Ç., Writing: B.E., M.V.

**Conflict of Interest:** The authors report no conflict of interest.

**Financial Disclosure:** Authors have no financial interests about the research.

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# DLK1 and Nesfatin-1 levels and the relationship with metabolic parameters in polycystic ovary syndrome: Prospective, controlled study

## *Polikistik over sendromunda DLK1 ve Nesfatin-1 düzeyleri ve metabolik parametrelerle ilişkisi: Prospektif kontrollü çalışma*

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### Abstract

**Objective:** Delta-like 1 (DLK1) is known to inhibit adipocyte differentiation and nesfatin-1 is a neuropeptide that plays a role in the regulation of nutrition and metabolism. We aimed to assess both the levels of DLK1 and nesfatin-1 in polycystic ovary syndrome (PCOS) and determine the association of DLK1 and nesfatin-1 with metabolic parameters.

**Materials and Methods:** Forty-four patients with PCOS and 40 healthy women as the control group were included in this study. Venous blood samples of the participants were collected, and hormonal, metabolic parameters, DLK1 and nesfatin-1 blood levels were determined. Anthropometric parameters were also determined. For a double comparison, the Mann-Whitney U test was used for non-parametric numerical data, and Student's t-test was used for parametric numerical data. Bivariate correlations were investigated using Spearman's correlation analysis. The diagnostic performance of the parameters was evaluated using receiver operating characteristic curve analysis.

**Results:** The findings showed that DLK1 and nesfatin-1 levels were lower among the PCOS group, and the differences in these values were found to be statistically significant. A significant negative correlation was found between DLK1 levels and body mass index (BMI), waist/hip ratio, visceral adiposity index (VAI), fasting serum insulin (FSI), homeostasis model of assessment-insulin resistance (HOMA-IR) and triglyceride levels. A significant negative correlation was found between nesfatin-1 levels and BMI, VAI, FSI, HOMA-IR and triglyceride.

**Conclusion:** The findings showed that DLK1 and nesfatin-1 levels were lower in PCOS. Based on this study, DLK1 may be culpable for metabolic disorders in PCOS and can be a novel marker for PCOS in the future.

**Keywords:** Polycystic ovary syndrome, delta-like 1, nesfatin-1, visceral adiposity index, insulin resistance

### Öz

**Amaç:** Delta benzeri 1'in (DLK1) adiposit farklılaşmasını inhibe ettiği bilinmektedir ve Nesfatin-1 beslenme ve metabolizmanın düzenlenmesinde rol oynayan bir nöropeptiddir. Polikistik over sendromunda (PCOS) hem DLK1 hem de Nesfatin-1 düzeylerini değerlendirmeyi ve DLK1 ve Nesfatin-1'in metabolik parametrelerle ilişkisini belirlemeyi amaçladık.

**Gereç ve Yöntemler:** Kırk dört PCOS tanısı alan kadın ve kontrol grubu olarak da 40 sağlıklı kadın çalışmaya dahil edildi. Katılımcıların venöz kan örnekleri alınarak hormonal, metabolik parametreler, DLK1 ve Nesfatin-1 kan düzeyleri belirlendi. Antropometrik parametreler de belirlendi. İkili karşılaştırma için parametrik olmayan sayısal veriler için Mann-Whitney U testi, parametrik sayısal veriler için Student t-testi kullanıldı. İki değişkenli korelasyonlar, Spearman'nin korelasyon analizi ile araştırıldı. Parametrelerin tanısal performansı alıcı işletim karakteristiği eğri analizi ile değerlendirildi.

**Bulgular:** Bulgular, DLK1 ve Nesfatin-1 düzeylerinin PCOS grubunda daha düşük olduğunu ve bu değerlerdeki farklılıkların istatistiksel olarak anlamlı olduğunu gösterdi. DLK1 seviyeleri ile vücut kitle indeksi (VKİ), bel kalça oranı (BKO), viseral adipozite indeksi (VAİ), açlık serum insülini (FSI), HOMA-IR ve trigliserit seviyeleri arasında anlamlı negatif korelasyon bulundu.

**PRECIS:** DLK1 and Nesfatin-1 protein levels are lower in women with PCOS.

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**Sonuç:** Bulgularımız, DLK1 ve Nesfatin-1 düzeylerinin PCOS'da daha düşük olduğunu gösterdi. Bu çalışmaya dayanarak, DLK1 PCOS'daki metabolik bozukluklardan sorumlu olabilir ve gelecekte PCOS için yeni bir belirteç olabilir.
**Anahtar Kelimeler:** Polikistik over sendromu, delta benzeri 1, Nesfatin-1, viseral adipoz indeksi, insülin direnci

## Introduction

Polycystic ovary syndrome (PCOS) is an endocrinopathy prevalent among women of reproductive age, characterized by oligomenorrhea, amenorrhoea, hirsutism, and polycystic ovaries. Its prevalence ranges from 6% to 20%, depending on the diagnostic criteria[1]. Environmental and genetic issues are associated with the etiology of PCOS by combining with obesity, ovarian dysfunction, and hormonal factors[2]. Risk of type 2 diabetes mellitus (T2DM), hypertension, dyslipidemia, cerebrovascular disease, central obesity, and cardiovascular morbidity related to metabolic dysfunction increases in PCOS. In addition to these, insulin resistance (IR) is also a remarkable factor for the pathophysiology of PCOS, which exacerbates underlying metabolic abnormalities[3].

Delta-like 1 (DLK1) is also called preadipocyte factor 1 or fetal antigen protein and is a transmembrane protein very similar to the Notch/Delta/Serrate family[4,5]. It is expressed by a gene present in the long arm of chromosome 14 (14q32.2). It has been revealed to be associated with the Temple syndrome, clinical findings of which include prenatal and postnatal growth failure, central precocious puberty, truncal obesity, hypotonia, as well as small hands and feet[6]. The primary function of DLK1 is known to inhibit adipocyte differentiation. DLK1 is highly expressed in preadipocytes, whereas it disappears during adipogenesis and is not detected in adipocytes. Thus, it is also considered a marker for preadipocyte[7]. Adipose tissue development is impacted by genetic background, hormonal balance, diet, and physical activity. An increase in the number of fat cells due to the differentiation of preadipocytes into adipocytes leads to obesity[7]. Moreover, ***in vitro*** studies have revealed that DLK1 improves insulin synthesis and secretion[8]. Gomes et al.[5] detected PCOS in 20% of women who had precocious puberty with the DLK1 mutation. Upon this finding, they reported that women diagnosed as having both precocious puberty and PCOS should be examined related to DLK1 mutations. However, levels of DLK1 in PCOS have never been probed before, despite there being common clinical and metabolic characteristics that can be detected in PCOS and with the DLK1mutation.

Nesfatin-1 is a nucleobindin-2 induced neuropeptide that plays a role in the regulation of nutrition and metabolism. It was primarily identified in the central nervous system and then expressed in gastro-endocrine cells, adipocytes, and pancreatic beta cells[9]. Nesfatin-1 has been shown to increase glucose-induced insulin secretion in pancreatic β cells by increasing $Ca^{2+}$ flow through L-type channels in mice[10]. Furthermore, nesfatin-1 also has an anorexigenic effect by lessening the number of meals and extending the interval between meals[11]. Due to these metabolic properties, levels of nesfatin-1 were assessed in PCOS, which frequently co-exists with obesity and IR, and it was determined to be lower in some studies[11-13], whereas it was determined to be higher in others[9,14,15].

In our study, we aimed to assess both the levels of DLK1, which have never been evaluated related to PCOS previously, as well as the serum levels of nesfatin-1 in PCOS, which has contradictory results in previous studies regarding its levels in PCOS, both of which are closely associated with obesity and IR.

## Materials and Methods

This case-control study was performed between January 2020 and August 2020 in the Department of Obstetrics and Gynecology, Faculty of Medicine, at Yozgat Bozok University after obtaining ethical approval from the ethics committee (protocol number: 2017-KAEK-189_2019.09.11_04). The principles of the Declaration of Helsinki (Fortaleza, Brazil, 2013) were adhered to throughout this study and written informed consent was obtained from all participants. A power analysis was conducted using the G*Power version 3.1.7 software based on the findings of comparable studies[12]. An effect size of 0.81 was used with a power set at 0.95 and alpha at 0.05. We specified the explanations of the abbreviations as soon as they were first written, determining that an n=40 sample size was required in each group.

### Study Population

Forty-four patients with PCOS aged between 18 and 39 years who were admitted to the gynecology outpatient clinic and met the 2003 Rotterdam criteria were included in this study, and 40 healthy women who did not meet the PCOS diagnostic criteria and had regular menstrual cycles (26-30 days) were included as the control group. The diagnosis of PCOS was reached based on the Rotterdam criteria[3], those who met two of the three specified criteria were diagnosed as having PCOS: oligo and/or anovulation (>35 days or <8 spontaneous menstruation/year), biochemical and/or clinical (Ferriman-Gallwey score >8) hyperandrogenism, and polycystic ovary on ultrasound (each 12 or more follicles of 2 to 9 mm in diameter and/or ovarian volume >10 mL in each ovary). Morphologic features of the ovaries in all participants were examined through transabdominal and/or transvaginal ultrasonography (GE Voluson E8; GE Healthcare, Chicago, IL, USA).

The participants did not receive any medications (ovulation induction agents, glucocorticoids, antiandrogens, oral contraceptives, insulin sensitizers, or anti-obesity drugs) for at least the last 6 months that could influence the biochemical profile and metabolic variables. Pregnant women, smokers, women in early menopause, women who were breastfeeding, and those diagnosed as having Cushing syndrome, hypertension,

adrenal hyperplasia, hyperprolactinemia, diabetes mellitus, thyroid dysfunction, and androgen-secreting tumors were excluded from the study.

Height and weight measurements of all women were recorded, and body mass index (BMI) was calculated as weight/height$^2$ (kg/m$^2$). Waist circumference (cm) was determined by measuring the circumference of the midpoint of the junction of the 10$^{th}$ rib and spina iliaca anterior superior. Hip circumference (cm) was measured as the circumference of the greater trochanter line. The waist/hip ratio (WHR) was calculated. All measurements were performed by the same person.

### Laboratory Measurements

Venous blood samples were collected between 8:00 and 9:00 AM after overnight fasting. All analyses were performed on the same day, except nesfatin-1 and DLK1. Blood samples for nesfatin-1 and DLK1 were centrifuged for 10 min at 3.000 rpm, after which the supernatant was quickly removed and kept frozen at -80 °C until the assays were performed by a specialist who was blind to patient status. Nesfatin-1 was measured in blood samples using a Human nesfatin-1 enzyme-linked immunosorbent assay (ELISA) kit (Bioassay Technology Laboratory, Cat.No E3063Hu, Shanghai, China), with a measurement interval of 0.3-90 ng/mL. DLK1 was measured in blood samples using a Human DLK1 ELISA kit (Bioassay Technology Laboratory, Cat. No E5959Hu, Shanghai, China), with a measurement interval of 20-6000 ng/L. Fasting glucose, total cholesterol, high-density lipoprotein cholesterol (HDL-C), and triglyceride (TG) levels were analyzed on a Roche COBAS 6000 c501 (Roche Diagnostics) autoanalyzer. Low-density lipoprotein cholesterol was calculated using the Friedewald formula when the TG level was less than 400 mg/dL[16].

### Hormonal Assay

Blood samples were collected on the 2$^{nd}$ or 3$^{rd}$ days of the menstrual cycle. Serum insulin, luteinizing hormone (LH), follicle-stimulating hormone, estradiol, dehydroepiandrosterone, thyroid-stimulating hormone, and prolactin levels were measured using an electrochemiluminescence immunoassay on a Roche COBAS 6000 e601 (Roche Diagnostics, Mannheim, Germany) autoanalyzer.

The concentrations of serum nesfatin-1 and DLK1 were measured using commercially available ELISA kits (Bioassay technology laboratory, Shanghai, China), according to the manufacturer's instructions.

IR was determined using the homeostatic model assessment IR index (HOMA-IR): fasting plasma glucose (mg/dL) × fasting serum insulin (FSI) (mU/mL)/405[17]. Visceral adiposity index (VAI) is a sensitive marker of visceral obesity, which uses both anthropometric and metabolic parameters. VAI was calculated using the following formula: [Waist circumference/(36.58 + (1.88XBMI)] x (Triglyceride/0.81) x (1.52/HDL-C)[18].

### Statistical Analysis

In this study, data were analyzed using the SPSS 20 software (IBM Corp. released 2011, IBM SPSS Statistics for Windows, version 20.0, Armonk, NY: IBM Corp.). Data are presented as mean ± standard deviation. Continuous variables were examined using analytical methods (Kolmogorov-Smirnov/Shapiro-Wilk's test) to investigate whether they were normally distributed. For a double comparison, the Mann-Whitney U test was used for non-parametric numerical data, and Student's t-test was used for parametric numerical data. Bivariate correlations were investigated using Spearman's correlation analysis. The diagnostic performance of the parameters was evaluated using receiver operating characteristic (ROC) curve analysis. The results were considered to be statistically significant at $p<0.05$.

## Results

The demographic characteristics and biochemical values of the PCOS and control groups are shown in Table 1. As shown in Table 1, when the PCOS group was compared with the control group, it was determined that DLK1 and nesfatin-1 levels were lower among the PCOS group, and the differences in these values were found to be statistically significant ($p<0.001$ and $p<0.001$, respectively).

The correlation analysis of the parameters, which were assessed for the patients with PCOS using DLK1 and nesfatin-1, is presented in Table 2. A significant negative correlation was found between DLK1 levels and BMI/WHR/VAI (r=-0.368, p=0.014; r=-0.409, p=0.006; and r=-0.359, p=0.017; respectively). Also, a significant negative correlation was determined between DLK-1 levels and FSI/HOMA-IR/TG levels (r=-0.302, p=0.047; r=-0.336, p=0.026; and r=-0.332, p=0.028; respectively). A significant negative correlation was found between nesfatin-1 levels and BMI/VAI values (r=-0.307, p=0.042; and r=-0.339, p=0.024; respectively). Moreover, a significant negative correlation was also determined between nesfatin-1 levels and levels of FSI/HOMA-IR/TG (r=-0.369, p=0.014; r=-0.355, p=0.018; and r=-0.423, p=0.004, respectively)

The optimal ROC cut-off value of DLK1 for PCOS was calculated as 2018.8 ng/L with a sensitivity of 70% and a specificity of 68.1% [area under the curve (AUC): 0.801]. The optimal ROC cut-off value of nesfatin-1 for PCOS was calculated as 18.6 ng/mL with a sensitivity of 72.5% and a specificity of 72.7% (AUC: 0.805) (Figure 1, Table 3).

## Discussion

We found in our study that the serum levels of DLK1, known as an inhibitor of adipocyte differentiation, and nesfatin-1, an anorexigenic neuropeptide, were decreased among women with PCOS. We also determined a significant negative correlation between both nesfatin-1 and DLK1 levels and BMI, VAI, and HOMA-IR in PCOS.

It was found in previous studies that, in mice, which DLK1-null[19] and overexpressed DLK1[20,21], IR developed,

**Table 1. Demographic characteristics and biochemical values of the PCOS and control groups**

| | Patients with PCOS (n=44) | Control (n=40) | p-value |
|---|---|---|---|
| Age (years) | 26.41±5.036 | 28.23±5.09 | 0.102* |
| BMI (kg/m$^2$) | 24.07±2.97 | 24.7±3.7 | 0.341** |
| Waist/hip ratio | 0.82±0.06 | 0.75±0.05 | **<0.001*** |
| FBG (mg/dL) | 84.69± 8.23 | 84.6±7.77 | 0.999** |
| FSI (µU/mL) | 13.5±6.9 | 8.7±4.04 | **<0.001**** |
| HDL (mg/dL) | 52.65±12.6 | 53.7±12.3 | 0.734* |
| LDL (mg/dL) | 88.5± 30.8 | 93.04±34.5 | 0.531** |
| Total cholesterol (mg/dL) | 158.7±32.1 | 162.9±38.07 | 0.513* |
| Triglyceride (mg/dL) | 88.7±40.6 | 82.71±32.4 | 0.594* |
| FSH (mIU/mL) | 5.79±1.19 | 6.4±1.44 | **0.016*** |
| LH (mIU/mL) | 8.9±4.17 | 5.2±1.6 | **<0.001*** |
| Prolactin (ng/mL) | 17.1±7.1 | 12.4±5.08 | **0.002*** |
| Total testosterone (ng/mL) | 0.31±0.17 | 0.17±0.08 | **<0.001**** |
| DHEA (µg/dL) | 264.3±118.4 | 213.6±76.4 | **0.015*** |
| TSH (mIU/mL) | 2.05±1.08 | 2.18±0.9 | 0.387* |
| Estradiol (pg/mL) | 38.04±20.4 | 36.2±14.3 | 0.632* |
| HOMA-IR | 2.8±1.5 | 1.8±0.91 | **0.001*** |
| VAI | 3.7±2.7 | 2.8±1.5 | 0.144* |
| Serum DLK-1 (ng/L) | 1419.7±1053 | 2955.7±1389 | **<0.001*** |
| Serum nesfatin-1 (ng/mL) | 17.08±13.8 | 36.8±20.7 | **<0.001*** |

Values are given as mean ± standard deviation. *Mann-Whitney U test, **Independent simple t-test, BMI: Body mass index, FBG: Fasting blood glucose, FSI: Fasting serum insulin, HDL: High-density lipoprotein, LDL: Low-density lipoprotein, FSH: Follicle-stimulating hormone, LH: Luteinizing hormone, DHEA: Dehydroepiandrosterone, TSH: Thyroid-stimulating hormone HOMA-IR: Homeostasis model of assessment-insulin resistance, VAI: Visceral adiposity index, PCOS: Polycystic ovary syndrome

accompanied by weight abnormalities. This finding suggests that favorable development of adipose tissue and function is critical for maintaining glucose/insulin homeostasis. Lee et al.[22] administered DLK1 to mice for 4 weeks and revealed that DLK1 manifested its metabolic effects by activating AMPK, increasing fatty acid oxidation in the liver, and inhibiting gluconeogenesis. Ultimately, they determined a decrease in IR and fasting blood glucose in DLK1-administered mice. IR also plays a remarkable role in the pathophysiology of PCOS and IR has been reported in 50-80% of women with PCOS, and a correlation between insulin levels and PCOS severity has been demonstrated[17]. Similarly, we determined a significant negative correlation between DLK1 and HOMA-IR among the PCOS group in our study.

**Table 2. Spearman correlation coefficients (r) between nesfatin-1, DLK1 and measured parameters in patients with PCOS**

| Variable | DLK1 | | Nesfatin-1 | |
|---|---|---|---|---|
| | r-value | p-value | r-value | p-value |
| BMI | -0.368 | **0.014** | -0.307 | **0.042** |
| WHR | -0.409 | **0.006** | -0.229 | 0.136 |
| FBG | -0.218 | 0.155 | 0.078 | 0.613 |
| FSI | -0.302 | **0.047** | -0.369 | **0.014** |
| HOMAIR | -0.336 | **0.026** | -0.355 | **0.018** |
| VAI | -0.359 | **0.017** | -0.339 | **0.024** |
| HDL | 0.168 | 0.275 | 0.122 | 0.432 |
| LDL | -0.078 | 0.615 | 0.082 | 0.599 |
| Total cholesterol | -0.094 | 0.543 | 0.034 | 0.825 |
| Triglyceride | -0.332 | **0.028** | -0.423 | **0.004** |
| FSH | -0.092 | 0.551 | -0.026 | 0.867 |
| LH | -0.062 | 0.688 | 0.148 | 0.336 |
| Total testosterone | -0.085 | 0.584 | 0.065 | 0.676 |

BMI: Body mass index, WHR: Waist-to-hip ratio, FBG: Fasting blood glucose, FSI: Fasting serum insulin, HOMA-IR: Homeostasis model of assessment-insulin resistance, VAI: Visceral adiposity index, HDL: High-density lipoprotein, LDL: Low-density lipoprotein, FSH: Follicle-stimulating hormone, LH: Luteinizing hormone, PCOS: Polycystic ovary syndrome

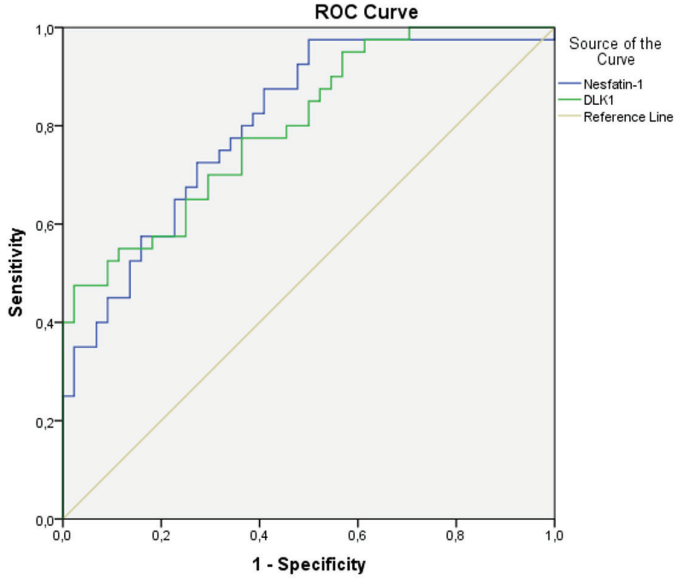


**Figure 1.** ROC analysis of DLK1 and Nesfatin-1 for patients with PCOS

*ROC: Receiver operating characteristic, DLK1: Delta-like 1, PCOS: Polycystic ovary syndrome*

In one study, the weight of large fat stores (inguinal, retroperitoneal, and gonadal) was significantly higher in DLK1-null mice compared with the control group. Furthermore,

**Table 3. ROC analysis of DLK1 and Nesfatin-1 for patients with PCOS**

| | Cut-off level | AUC | Sensitivity (%) | Spesifity (%) | p-value |
|---|---|---|---|---|---|
| DLK-1 (ng/L) | 2018.8 | 0.801 | 70 | 68.18 | <0.001 |
| Nesfatin-1 (ng/mL) | 18.6 | 0.805 | 72.50 | 72.73 | <0.001 |

ROC: Receiver operating characteristic, DLK1: Delta-like 1, PCOS: Polycystic ovary syndrome, AUC: Area under the curve

free fatty acids, cholesterol, and circulating levels of TGs, which are often associated with obesity, also increased in these mice[7]. Similarly, Dauber et al.[23] demonstrated an increase in the percentage of body fat, which was shown by electrical impedance analysis that visceral abdominal fat was predominant in some women with a DLK1 deletion. On the other hand, mice overexpressing DLK-1 had resistance to high-fat diet-induced obesity, which was accompanied by a remarkable reduction in adipose tissue mass[21]. These studies corroborate the fact that DLK1 deficiency increases adipogenesis and DLK1 is a negative regulator of adipogenesis. In addition to menstrual irregularity and hyperandrogenism in women with PCOS, another common clinical problem is obesity, and the risk of metabolic syndrome is increased fourfold. Fifty percent of women with PCOS are overweight or obese, and central obesity is common among them as well. Fat accumulation in the central abdominal region has been observed even among women with normal weight PCOS[24-26]. VAI is recommended for clinical practice because it is useful in the evaluation of IR and cardiometabolic risk[27]. In line with this, we assessed the VAI of all women and determined a higher VAI and WHR among the PCOS group in our study. Also, we found a negative correlation between serum levels of DLK1 and VAI and BMI in the PCOS group, in line with the literature.

Although the above-mentioned studies support our results, some studies suggest otherwise. For instance, Jensen et al.[28] revealed that there was a positive correlation between DLK1 levels and both body fat and HOMA-IR. These contradictory findings suggest that the accurate dosage and timing of DLK1 might be crucial for its metabolic impact on adipose tissue. This concept is also endorsed by a study suggesting that the tightly regulated dosage control of DLK1 is significant for its regulatory function in neurogenesis[29]. These varying results could be attributed to differences in populations of the studies and/or the use of different DLK1 test kits.

Given the anorexigenic effect of nesfatin-1, as well as its increasing effect on insulin secretion, it is not surprising that we determined lower nesfatin-1 levels among patients with PCOS in our study. In previous studies, it has been shown that nesfatin-1 is lower in women with both T2DM and gestational diabetes mellitus (GDM) than in healthy individuals. T2DM and GDM show similar properties to PCOS due to weight and IR[30,31]. It has been shown that intravenous administration of nesfatin-1 to mice increases the effect of insulin and decreases glucose concentrations[32]. However, contrary to our study, nesfatin-1 was found to be higher in PCOS in some studies[9,14], and Ademoglu et al.[9] showed that this result could arise from nesfatin-1 resistance, which is characterized by impaired receptor and post-receptor signaling in target tissues. Moreover, a positive correlation has been revealed in some studies, whereas some studies demonstrated a negative correlation between nesfatin-1 levels and BMI and HOMA-IR, consistent with our study[12,14]. We consider that these differences stem from the heterogeneity of the study groups. Kim et al.[33] demonstrated that nesfatin-1 was expressed in the hypothalamus and ovaries of mice and argued that nesfatin-1 might have a regulatory role on the hypothalamo-pituitary-ovarian (HPO) axis. In another study, it was shown that nesfatin-1 injections reduced LH and gonadotropin-releasing hormone expression in the hypothalamus[34]. Therefore, it can be thought that nesfatin-1 could prevent the development of PCOS by both reducing BMI with its appetite-inhibiting effect and by its regulatory role on the HPO. In the light of this information, it is an expected result that we found that nesfatin-1 was less in women with PCOS in our study.

### Study Limitations

Our study had some limitations. The first limitation was that free testosterone and sex hormone-binding globulin values were not examined. The second limitation was that we did not classify the PCOS group according to phenotypes. Thus, we need more data from patients with PCOS, such as AES/Rotterdam criteria and women with different phenotypes to document whether DLK1 and nesfatin-1 are associated with PCOS, not merely fat metabolism. On the other hand, the fact that we evaluated the DLK1 level for the first time in PCOS is the main strength of our study.

## Conclusion

We found that both DLK1 and nesfatin-1 levels were lower in PCOS. Moreover, we determined that both proteins were negatively correlated with BMI, VAI, and HOMA-IR in PCOS. Based on this study, it is considered that DLK1 may be culpable for metabolic disorders in PCOS and could be a novel marker for PCOS in the future. However, more detailed ***in vivo*** and ***in vitro*** studies are needed to clarify the effects of both molecules on weight gain and ovarian function.

### Ethics

**Ethics Committee Approval:** This case-control study was performed between January 2020 and August 2020 in the Department of Obstetrics and Gynecology, Faculty of Medicine, at Yozgat Bozok University after obtaining ethical approval from the ethics committee (protocol number: 2017-KAEK-189_2019.09.11_04).

**Informed Consent:** Written informed consent was obtained from all participants.
**Peer-review:** Externally peer-reviewed.

### Authorship Contributions

Surgical and Medical Practices: M.D.Ç., A.C., Concept: M.D.Ç., A.C., Design: M.D.Ç., A.C., Data Collection or Processing: S.E.Y., Analysis or Interpretation: S.E.Y., Literature Search: D.A.K., E.B., E.S.Y., Writing: M.D.Ç.

**Conflict of Interest:** The authors report no conflict of interest.
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# Clinical and ethical perspectives of medical professionals towards female genital cosmetic procedures

## *Tıp uzmanlarının genital kozmetik müdahalelere klinik ve etik açıdan bakış açıları*

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### Abstract

**Objective:** To evaluate the attitudes of medical students and professionals towards female genital cosmetic procedures (FGCPs) in terms of medical justification, applicability in practical life, ethical concerns, patient autonomy, and the clinical/social/psychological benefits-harms of these procedures.

**Materials and Methods:** A semi-structured questionnaire providing information about the attitudes of medical students and specialists (n=623) towards FGCPs including G-spot amplification, clitoral hood reduction, vaginoplasty, labia majora augmentation/reduction, labia minora augmentation/reduction, hymenoplasty, laser procedures, vulvar/perianal bleaching, and liposculpture, was completed by a target population and evaluated statistically.

**Results:** Participants stated that FGCPs could be performed only upon patient request and there could rarely be a medical indication for their performance ($p<0.05$). Nearly half (44.5%) of the participants regarded hymenoplasty as controversial in terms of ethical issues, and 44.6% of participants do so for G-spot amplification. Over half (54.5%) of the participants agreed on the positive effect of FGCPs on improving the quality of life, 55.4% on improving self-esteem, and 54.1% on improving sexual functions of women. About half (49.3%) of respondents thought that the advertising and encouragement of FGCPs should be forbidden and 47% were indecisive about whether FGCPs constituted genital mutilation.

**Conclusion:** The majority of the participants declared that FGCPs could be performed only upon patient request and improve self-esteem, quality of life, and sexual functions. The most controversial procedures in terms of ethics were hymenoplasty and G-spot amplification. Detailed guidelines for the protection of both patients and physicians are needed because the recommendations on FGCPs are insufficient to define the boundaries of medical justification, genital mutilation, advertising, and ethical concerns.

**Keywords:** Cosmetic surgery, ethics, G-spot, hymenoplasty, vaginoplasty

### Öz

**Amaç:** Tıp öğrencilerinin ve profesyonellerin kadın genital kozmetik prosedürlerine (KGKP) tıbbi gerekçelendirme, pratik hayatta uygulanabilirliği, etik kaygılar, hasta otonomisi ve prosedürlerin klinik/sosyal/psikolojik yararları-zararları açısından bakış açılarını değerlendirmek.

**Gereç ve Yöntemler:** Tıp öğrencileri ve uzmanların (n=623) G-noktası augmentasyonu, klitoral hudoplasti, vajinoplasti, labia majora büyütme/küçültme, labia minora büyütme/küçültme, himenoplasti, lazer prosedürleri, vulvar/perianal beyazlatma ve liposculpturing dahil olmak üzere KGKP'lere yönelik tutumları hakkında bilgi veren bir anket hedef popülasyona uygulanmış ve istatistiksel olarak değerlendirilmiştir.

**Bulgular:** Katılımcılar, KGKP'lerin yalnızca hasta talebi üzerine gerçekleştirilebileceğini ve nadiren prosedürün tıbbi bir endikasyonu olabileceğini belirtti ($p<0,05$). Katılımcıların %44,5'i himenoplastiyi etik açıdan tartışmalı bulurken, katılımcıların %44,6'sı aynı yorumu G-noktası amplifikasyonu için yapmaktadır. Katılımcıların %54,5'i, KGKP'lerin yaşam kalitesini iyileştirme, %55,4'ü benlik saygısı geliştirme ve %54,1'i kadınların cinsel işlevlerini iyileştirme üzerindeki pozitif etkisi konusunda hemfikirdir. Ankete katılanların %49,3'ü, KGKP'ler ile ilgili reklam stratejilerinin ve teşviklerinin yasaklanması gerektiğini düşünürken, %47'si KGKP'lerin genital mutilasyon olarak görülmesi konusunda kararsızdı.

**PRECIS:** By using a self-administered questionnaire, we evaluated the clinical, ethical, and sociocultural perspectives of medical professionals and students towards female genital cosmetic procedures.

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**Sonuç:** Katılımcıların büyük çoğunluğu, KGKP'lerin sadece hastanın isteği üzerine yapılabileceğini ve benlik saygısını, yaşam kalitesini ve cinsel fonksiyonları iyileştirdiğini belirtmiştir. Etik açıdan en tartışmalı prosedürlerin, kızlık zarı dikimi ve G-noktası amplifikasyonu olduğu bildirildi. KGKP'ye yönelik kılavuzlar tıbbi gerekçelendirme, genital mutilasyon, reklam ve etik kaygıların sınırlarını tanımlamak için yetersiz olduğundan; hem hastaların hem de doktorların korunması için ayrıntılı kılavuzlara ihtiyaç vardır.
**Anahtar Kelimeler:** Kozmetik cerrahi, etik, G-noktası, himenoplasti, labioplasti, vajinoplasti

## Introduction

The term "female genital cosmetic procedures" (FGCPs) encompasses numerous interventions, including surgeries (G-spot amplification, labia majora augmentation, labia majora reduction, labia minora augmentation, labia majora reduction, clitoral hood reduction, vaginoplasty, and hymenoplasty) and non-surgical procedures (vulvar/perianal bleaching/whitening, liposculpture, laser for vaginal tightening, and laser for genitourinary syndrome of menopause). Although there is increasing popularity, patient demand and performance rate, ethical and safety concerns have been raised about the performance of FGCPs. The perception of "genital beautification" augmented by the Internet and media forces, caused women to fail in the decision of whether her vulvar image was normal[1,2]. Bioethical analysis of cosmetic surgery revives several controversial issues regarding the principles of ethical medical care[3]. The ethical concept of beneficence and non-maleficence has been forcing authorities to question the ethics of undergoing surgical risk to improve the physical appearance. In addition to medical objections, many critics are concerned about the social and cultural aspects of cosmetic surgery[3,4]. The results of a survey could be useful in determining clinical strategies regarding FGCPs in terms of health policies.

The goals of this survey were to analyze the attitudes of medical professionals and students towards FGCPs in terms of medical justification, applicability in practical life, ethical concerns, patient autonomy, and the clinical/social/psychological benefits-harms of these procedures.

## Materials and Methods

This cross-sectional study was performed via a web-based, semi-structured questionnaire. Forms were collected between December 15th, 2019, and March 30th, 2020. The study was approved by the Institutional Review Board (E1/180/2019). The respondents were informed and consent for participation was obtained before administering the questionnaire.

The survey form was planned after a comprehensive review of the literature including medical indications, ethical issues, and controversial issues regarding esthetic gynecologic procedures[5,6].

The survey consisted of questions for 12 FGCPs (G-spot amplification, clitoral hood reduction, labia majora augmentation, labia majora reduction, labia minora augmentation, labia majora reduction, laser vaginal tightening, laser for genitourinary syndrome of menopause, vaginoplasty, vulvar/perianal bleaching, liposculpture and hymenoplasty) including:

1. First section: The demographics of the participants [age, sex, differentiation (students, specialists), speciality].
2. Second section: Participants' opinion about the existence of "G-spot" and ethical issues regarding hymenoplasty - 3 questions, 3-point Likert scale including answers: "agree", "indecisive", and "disagree".
3. Third section: The participants were questioned about whether the procedure was medically justifiable, and could be performed with only patient demand - 2 questions for 12 FGCPs separately, 3-point Likert for asking medical justification including answers "never/rarely/often" or 2-point Likert scale for others including answers "yes/no".
4. Fourth section: Participants were asked whether the procedures were "ethical", "unethical" or "debatable" in terms of medical ethics. Participants answered question separately for each of 12 FGCPs.
5. Fifth section: Participants opinions were asked about given speculative comments regarding patient selection criteria, age limit and potential benefits/harms - 13 questions were evaluated using 3-point Likert with answers: "agree", "indecisive", and "disagree".

The link of the questionnaire was sent to the target population via email (collected from the databases of medical societies), and also posted in specific social network groups for physicians/medical students. The data of the respondents were collected automatically through a web-based system (https://docs.google.com/forms, CA, USA). Statistical power analysis was performed before applying to the ethics committee, which showed that a sample of 387 would be enough to achieve a confidence level of 95% and a confidence interval of 5% according to the estimated size of the population of physicians and medical students in our country.

### Statistical Analysis

The statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS) software, version 20.0 (IBM Corp., Armonk, NY, USA). The chi-square test was used for the analysis of variables, and $p<0.05$ was considered statistically significant.

## Results

### Characteristics of Participants

The number of participants who received the survey was 623. One hundred twenty of the respondents were medical students/residents (81% were residents). Specialists were classified into four groups as follows: obstetrics and gynecology (n=183, 37%), general practitioners (n=101, 20%), other surgical

(n=117, 23%), and other non-surgical (n=102, 20%). Two hundred sixty-five (42.5%) of the participants were male and 358 (57.5%) were female. Assistants (speciality trainees) were also included in the specialists' group. All participants were working in public hospitals, and 243 (39%) were lecturers in universities. Two hundred twenty-nine (36.7%) respondents were aged ≤30 years, 186 (29.8%) were aged between 31 and 40 years, 160 (25.6%) were aged 41-50 years, and 49 participants were aged ≥51 years. Eighty-eight (14.1%) respondents planned to undergo plastic surgery and 36 (5.8%) had undergone at least one plastic surgery.

### Results of Survey

Almost half (49.3%) of the participants found reasonable that a woman's need for hymenoplasty originated from social oppression (Figure 1). Differentiation (student/specialist) and sex was not an identifier on this statement. Most (63.2%) of participants agreed that women who are in demand should have hymenoplasty (Figure 1). One-third (33.9%) of the participants stated that performing hymenoplasty had no indications ever and this opinion was more common among specialists (Table 1). The opinion of the participants about hymenoplasty was evaluated as ethical, unethical or debatable in terms of ethics and the ratios were 40.3%, 15.2%, and 44.5%, respectively. The statement that hymenoplasty was controversial in terms of medical ethics was higher among females compared with males ($p<0.05$). Details of data regarding ethical perceptions are given in Figure 2 and Table 2. One-quarter (24.1%) of the participants considered that the G-spot existed (Figure 1); 26.4% of the females and 22.3% of the males agreed on

**Table 1.** Opinions of specialists on the medical justification of female genital cosmetic procedures

| | Never % (n/N) | | | | Rarely% (n/N) | | | | Often % (n/N) | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | ObGyn | GP | Other surgical | Other non-surgical | ObGyn | General practioner | Other surgical | Other non-surgical | ObGyn | General practioner | Other surgical | Other non-surgical | p |
| G-spot amplification | 39.3% 72/183 | 34.7% 35/101 | 25.6% 30/117 | 25.5% 26/102 | 43.2% 79/183 | 57.4% 58/101 | 64.1% 75/117 | 66.7% 68/102 | 17.5% 32/183 | 7.9% 8/101 | 10.3% 12/117 | 7.8% 8/102 | **<0.01*** |
| Clitoral hood reduction | 22.4% 41/183 | 30.7% 31/101 | 17.9% 21/117 | 29.4% 30/102 | 57.9% 106/183 | 60.4% 61/101 | 70.1% 82/117 | 60.8% 62/102 | 19.7% 36/183 | 8.9% 9/101 | 12% 14/117 | 9.8% 10/102 | **0.02*** |
| Hymenoplasty | 38.8% 71/183 | 34.7% 35/101 | 36.8% 43/117 | 36.3% 37/102 | 41% 75/183 | 57.4% 58/101 | 50.4% 59/117 | 53.9 55/102 | 20.2% 37/183 | 7.9% 8/101 | 12.8% 15/117 | 9.8% 10/102 | **0.03*** |
| Labia majora augmentation | 25.1% 46/183 | 28.7% 29/101 | 26.5% 31/117 | 24.5% 25/102 | 55.2% 101/183 | 62.4% 63/101 | 59.8% 70/117 | 67.6% 69/102 | 19.7% 36/183 | 8.9% 9/101 | 13.7% 16/117 | 7.8% 8/102 | 0.08 |
| Labia majora reduction | 18% 33/183 | 26.7% 27/101 | 18.8% 22/117 | 26.5% 27/102 | 59.6% 109/183 | 65.3% 66/101 | 66.7% 78/117 | 65.7% 67/102 | 22.4% 41/183 | 7.9% 8/101 | 14.5% 17/117 | 7.8% 8/102 | 0.01 |
| Labia minora augmentation | 33.3% 61/183 | 28.7% 29/101 | 23.9% 28/117 | 26.5% 27/102 | 46.4% 85/183 | 63.4% 64/101 | 58.1% 68/117 | 65.7% 67/102 | 20.2% 37/183 | 7.9% 8/101 | 17.9% 21/117 | 7.8% 8/102 | **<0.01*** |
| Labia minora reduction | 14.2% 26/183 | 24.8% 25/101 | 24.8% 29/117 | 28.4 29/102 | 57.9% 106/183 | 68.3% 69/101 | 61.5% 72/117 | 63.7% 65/102 | 27.9% 51/183 | 6.9% 7/101 | 13.7% 16/117 | 7.8% 8/102 | **<0.01*** |
| Vaginoplasty | 3.8% 7/18 | 19.8% 20/101 | 8.5% 10/117 | 23.5% 24/102 | 55.2% 101/183 | 69.3% 70/101 | 66.7% 78/117 | 66.7% 68/102 | 41% 75/183 | 10.9% 11/101 | 24.8% 29/117 | 9.8% 10/102 | **<0.01*** |
| Laser vaginal tightening | 18.6% 34/183 | 25.7% 26/101 | 21.4% 25/117 | 24.5% 25/102 | 56.8% 104/183 | 63.4% 64/101 | 60.7% 71/117 | 67.6% 69/102 | 24.6% 45/183 | 10.9% 11/101 | 17.9% 21/117 | 7.8% 8/102 | **0.01*** |
| Laser for GSM[a] | 15.3 28/183 | 22.8 23/101 | 17.9% 21/117 | 23.5% 24/102 | 57.9% 106/183 | 66.3% 67/101 | 62.4% 73/117 | 66.7% 68/102 | 26.8% 49/183 | 10.9% 11/101 | 19.7% 23/117 | 9.8% 10/102 | **0.01*** |
| Vulvar/ perianal bleaching | 32.2% 59/183 | 31.7% 32/101 | 25.6% 30/117 | 29.4% 30/102 | 46.4% 85/183 | 60.4% 61/101 | 59% 69/117 | 62.7% 64/102 | 21.3% 39/183 | 7.9% 8/101 | 15.4% 18/117 | 7.8% 8/102 | **0.01*** |
| Liposculpture | 32.8% 60/183 | 28.7% 29/101 | 34.2 40/117 | 25.5% 26/102 | 49.2% 90/183 | 64.4% 65/101 | 53.8% 63/117 | 66.7% 68/102 | 18% 33/183 | 6.9% 7/101 | 12% 14/117 | 7.8% 8/102 | **0.02*** |

[a]GSM: Genitourinary syndrome of menopause, *statistically significant

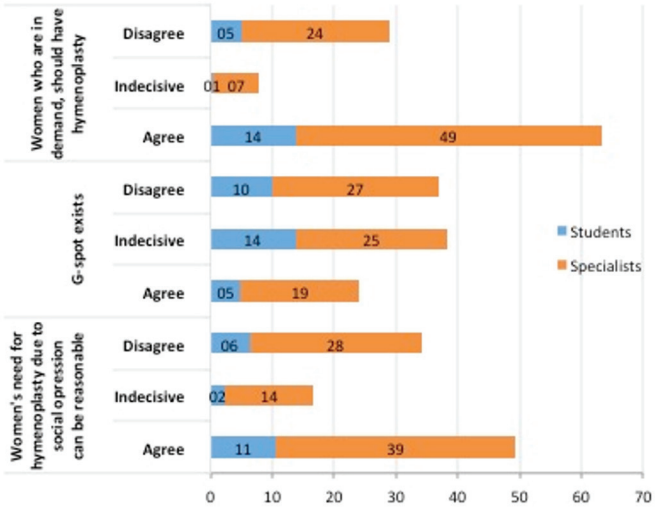


**Figure 1.** Expression of participants' thoughts about the existence of "G-spot" and ethical issues regarding hymenoplasty as percentages

the existence of the G-spot. In the entire cohort, 184 (29.5%) participants stated that there was no medical indication to perform G-spot amplification. Details about specialities are given in Table 1. Just over half (53%) of the entire cohort considered that G-spot amplification could be performed only upon patient request. The sex of the participants did not affect the attitude regarding G-spot procedures. Indecision about the ethical issues in G-spot amplification was higher among females (p<0.05). Details of data regarding ethical perceptions are given in Table 2 and Figure 2.

In the entire cohort, participants stated that all FGCPs could "rarely" be performed with a medical indication. The rate of answers that there was never a medical reason to perform the procedures was significantly higher for specialists compared with students, except for vaginoplasty (p<0.05). Surgeons (gynecologists and other surgical specialities) were more likely to think that labia majora reduction, labia minora augmentation, and vaginal laser procedures could be performed often with a medical indication (Table 1). The sex of the participants did not affect the opinion on medical indications of other cosmetic gynecologic procedures, except being a male was associated with the consideration of labia minora augmentation could often be performed with a medical indication (13.1% vs 19.6; p<0.05).

For all cosmetic gynecologic procedures, most of the participants considered that it could be appropriate to perform surgery only upon patient request (53% for G-spot amplification, 74% for clitoral hood reduction, 67% for hymenoplasty, 77% for labia major augmentation, 79% for labia majora reduction, 76% for labia minora augmentation, 78% for labia majora reduction, 81% for vaginoplasty, 78% for laser procedures, 78% for bleaching and 76% for liposculpture). Agreement on this statement was significantly low in specialist groups compared with the students. Typically, the ratio of the agreement on patient autonomy was significantly lower in the non-surgical specialist and general practitioner groups (p<0.05). In questioning procedures in terms of ethical principles, the most frequent answer was "ethical" (Table 2). Sex did not affect the ethical view of the participants, except for vulvar bleaching; being male was related to thinking that vulvar bleaching was unethical (6.8% vs 1.7%; p<0.05). Details of data on ethical perceptions are given in Table 2 and Figure 2. The majority (80.1%) of the participants stated that FGCPs should not be performed on girls aged under 18 years. More than half (56.3%) of the respondents agreed that FGCPs should be treated similarly to the surgeries at any anatomic site. Disagreement on this topic was most common among gynecologists and statistically significant, followed by the non-surgical specialities, general practitioners, and other surgical specialities, and the ratios were 50.5%, 27.1%, 13.1%, and 9.3%, respectively. The ratio of the participants who thought that the patient should be evaluated by a psychiatrist before undergoing surgery was 44.8%. The disagreement rate on psychiatric evaluation was significantly higher among gynecologists (58.3% of gynecologists, 8.6% of general practitioners, 13.7% of other surgeons, 19.4% of physicians in the non-surgical group; p<0.05).

One fifth (20.7%) of the participants stated that the procedures should not be performed in public hospitals and 49.3% thought that advertising and encouragement of FGCPs should be forbidden. Just under half (47%) were indecisive about the evaluation of FGCPs as genital mutilation. Indecision was more common among specialists. About one-fifth (19.1%) of physicians stated that FGCPs should be considered as genital mutilation and the rate of this statement was highest among gynecologists compared with other specialities (49.5% of gynecologists, 8.1% of general practitioners, 26.3% of other surgeons, 16.2% of physicianss in the non-surgical group; p<0.05).

Just over half (54.5%) of the participants agreed on the FGCPs effect on improving the quality of life, 55.4% on improving self-esteem, and 54.1% on improving sexual functions of women. While 25.4% of the study group considered that FGCPs were a temporary trend, 32.6% thought the opposite (Table 3).

The participants were indecisive about whether these procedures would improve dyspareunia and urinary incontinence, yet the disagreement rate was highest among gynecologists (dyspareunia; 65.5% of gynecologists, 17.1% of general practitioners, 5.3% of other surgeons, 11.8% of physicians in the non-surgical group; p<0.05) (urinary incontinence; 66% of gynecologists, 14.4% of general practitioners, 10.3% of other surgeons, 9.3 of physicians in the non-surgical group; p<0.05).

## Discussion

The current survey showed that the majority of the participants considered that FGCPs were appropriate to perform only upon patient request (p<0.05). Procedures considered to be the most controversial in terms of ethics were hymenoplasty and G- spot

**Table 2.** Perceptions of specialists about ethical perspectives of female genital cosmetic procedures

| | Ethical % (n/N) | | | | Debatable in terms of medical ethics % (n/N) | | | | Unethical % (n/N) | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | ObGyn | General practioner | Other surgical | Other non-surgical | ObGyn | General practioner | Other surgical | Other non-surgical | ObGyn | General practioner | Other surgical | Other non-surgical | p |
| **G-spot amplification** | 42.1% 77/183 | 30.7% 31/101 | 65.8% 77/117 | 34.3% 35/102 | 45.4% 83/183 | 60.4% 61/101 | 26.5% 31/117 | 61.8% 63/102 | 12.6% 23/183 | 8.9% 9/101 | 7.7% 9/117 | 3.9% 4/102 | **<0.01*** |
| **Clitoral hood reduction** | 69.4% 127/183 | 33.7% 34/101 | 74.4% 87/117 | 38.2% 39/102 | 28.4% 52/183 | 56.4% 57/101 | 15.4% 18/117 | 59.8% 61/102 | 2.2% 4/183 | 9.9% 10/101 | 10.3% 12/117 | 2% 2/102 | **<0.01*** |
| **Hymenoplasty** | 47% 86/183 | 24.8% 25/101 | 44.4% 52/117 | 32.4% 33/102 | 36.1% 66/183 | 62.4% 63/101 | 38.5% 45/117 | 48% 49/102 | 16.9% 31/183 | 12.9% 13/101 | 17.1% 20/117 | 19.6% 20/102 | **<0.01*** |
| **Labia majora augmentation** | 72.1% 132/183 | 41.6% 42/101 | 75.2% 88/117 | 51% 52/102 | 27.3% 50/183 | 50.5% 51/101 | 18.8% 22/117 | 49% 50/102 | 0.5% 1/183 | 7.9% 8/101 | 6% 7/117 | 0% 0/102 | **<0.01*** |
| **Labia majora reduction** | 71% 130/183 | 43.6% 44/101 | 76.1% 89/117 | 40.2% 41/102 | 27.9% 51/183 | 51.5% 52/101 | 19.7% 23/117 | 57.8% 59/102 | 1.1% 2/183 | 5% 5/101 | 4.3% 5/117 | 2% 2/102 | **<0.01*** |
| **Labia minora augmentation** | 71.6% 131/183 | 43.6% 44/101 | 70.9% 83/117 | 48% 49/102 | 26.8% 49/183 | 50.5% 51/101 | 23.1% 27/117 | 52% 53/102 | 1.6% 3/183 | 5.9% 6/101 | 6% 7/117 | 0% 0/102 | **<0.01*** |
| **Labia minora reduction** | 72.1% 132/183 | 43.6% 44/101 | 72.6% 85/117 | 46.1% 47/102 | 27.3% 50/183 | 50.5% 51/101 | 20.5% 24/117 | 52% 53/102 | 0.5% 1/183 | 5.9% 6/101 | 6.8% 8/117 | 2% 2/102 | **<0.01*** |
| **Vaginoplasty** | 74.9% 137/183 | 49.5% 50/101 | 79.5% 93/117 | 53.9% 55/102 | 24% 44/183 | 46.5% 47/101 | 16.2% 19/117 | 46.1% 47/102 | 1.1% 2/183 | 4% 4/101 | 4.3% 5/117 | 0% 0/102 | **<0.01*** |
| **Laser vaginal tightening** | 73.2% 134/183 | 42.6% 43/101 | 75.2% 88/117 | 39.2% 40/102 | 26.2% 48/183 | 50.5% 51/101 | 18.8% 22/117 | 58.8% 60/102 | 0.5% 1/183 | 6.9% 7/101 | 6% 7/117 | 2% 2/102 | **<0.01*** |
| **Laser for GSM[a]** | 75.4% 138/183 | 43.6% 44/101 | 75.2% 88/117 | 51% 52/102 | 24% 44/183 | 51.5% 52/101 | 17.1% 20/117 | 47.1% 48/102 | 0.5% 1/183 | 5% 5/101 | 7.7% 9/117 | 2% 2/102 | **<0.01*** |
| **Vulvar/ perianal bleaching** | 69.4% 127/183) | 38.6% 39/101 | 71.8% 84/117 | 49% 50/102 | 27.3% 50/183 | 56.4% 57/101 | 20.5% 24/117 | 48% 49/102 | 3.3% 6/183 | 5% 5/101 | 7.7% 9/117 | 2.9% 3/102 | **<0.01*** |
| **Liposculpture** | 71.6% 131/183 | 41.6% 42/101 | 69.2% 81/117 | 47.1% 48/102 | 27.9% 51/183 | 52.5% 53/101 | 25.6% 30/117 | 46.1% 47/102 | 0.5% 1/183 | 5.9% 6/101 | 5.1% 6/117 | 6.9% 7/102 | **<0.01*** |

[a]GSM: Genitourinary syndrome of menopause, *statistically significant

amplification. The majority of the participants agreed on the effect of FGCPs on improving the quality of life, improving self-esteem, and sexual functions of women. Near half of the respondents thought that the advertising and encouragement of FGCPs should be forbidden and were indecisive about whether FGCPs were genital mutilation.

In 2013, the Royal College of Obstetricians and Gynaecologists published an ethical opinion paper and pointed out that "the presentation of female genital cosmetic surgery (FGCS) as an unproblematic lifestyle choice is undesirable because it misleads women as to the need for and the efficacy of such surgical techniques" and stated that FGCS should not be undertaken unless it was medically indicated[7]. In July 2018, the United States Food and Drug Administration issued a warning against the use of energy-based devices outside of standardized research protocols for cosmetic vaginal procedures or vaginal "rejuvenation," citing their potential complications, including vaginal burns/scarring, dyspareunia, and chronic pain[8]. In January 2020, the American College of Obstetricians and Gynecologists (ACOG) offered the term FGCS only for procedures "not medically indicated" and defined FGCS as "surgical alteration of the vulvovaginal anatomy intended for cosmesis in women who have no apparent structural or functional abnormality". The ACOG also recommended informing women about the lack of high-quality data supporting the effectiveness of genital cosmetic surgical procedures and their potential complications[9].

For most FGCPs including hymenoplasty, G-spot augmentation, and clitoral hood reduction, the majority of the participants stated that there was rarely medical justification to perform the

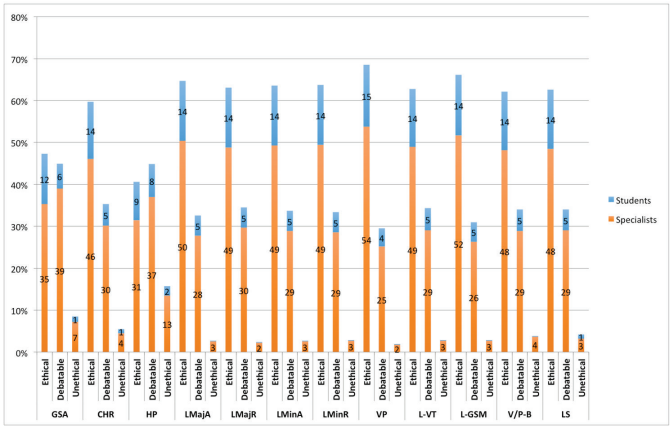


**Figure 2.** Perceptions of participants in terms of medical ethics

*GSA: G-spot amplification, CHR: Clitoral hood reduction, HP: Hymenoplasty, LMajA: Labia majora augmentation, LMajR: Labia majora reduction, LMinA: Labia minora augmentation; LMinR: Labia minora reduction, VP: Vaginoplasty, L-VT: Laser vaginal tightening, L-GSM: Laser for genitourinary syndrome, V/P-B: Vulvar/perinal bleaching, LS: Liposculpturing*

procedures despite recommendations of specialty committees. Although there is a lack of data to support the medical justification, especially for hymenoplasty, it is debatable if it can be performed because of religious reasons, after sexual abuse or preventing "honor" killings. According to the current survey, nearly half of the participants (49.3%) found reasonable of a woman's need for hymenoplasty originated from social oppression. It can be lifesaving for a woman in Muslim societies, and it can be demanded to revive a sexual life by another woman living in another society[10]. On the other hand, authorities have concerns about violating women's rights and perpetuating human rights abuses[6]. The indication for G-spot procedures is also controversial because anatomic, radiologic, and biochemical studies regarding the G-spot have failed to provide evidence of its existence[11]. In the current survey, 52.7% of the participants considered that the G-spot existed but 52.8% found the procedure debatable/unethical. The procedure that participants found most ethically controversial was hymenoplasty, with 59.7% of the participants stating that hymenoplasty was debatable or unethical.

The participants considered that FGCPs could be performed, only upon patient request without medical indications. Although autonomy is the most important principle of medical ethics, patient requests could be ignored if the procedure is against "non-maleficence"[9]. Patients who use autonomy should have sufficient knowledge about the procedure including scientific data about outcomes, complications, and comparisons of results with non-intervention[12].

"The International Society for the Study of Vulvovaginal Disease" (ISSVD) stated that genital surgeons should determine whether the patient is competent to make medical decisions as a first step and recommended psychological counseling to all women who were considering FGCPs to give them a chance to express undisclosed thoughts and feelings[4,13,14]. Body dysmorphic disorder (BDD) is another entity that should be considered during preoperative evaluation[15]. The prevalence of BDD was determined as 53.6% in patients demanding esthetic surgery and 61.1% in patients demanding genital cosmetic surgeries. In our cohort, although nearly half (44.8%) of the respondents supported psychological counseling before surgery, disagreement with this statement was highest among gynecologists.

The demand for FGCPs has been increasing in adults and teenagers[8]. Reaching adequate mental maturity is important for the patient to make rational decisions and also genital maturity should be provided to examine "normality" objectively. The Royal Australian College of General Practitioners, the ACOG, and the ISSVD recommend that FGCS should not be performed on girls aged younger than 18 years[4,16-18]. In the current survey, 81% of the participants also supported not performing FCGPs on girls aged under 18 years, irrespective of consent.

Just over half (54.5%) of the participants agreed on the effect of FGCPs on improving the quality of life, 55.4% on improving self-esteem, and 54.1% on improving sexual functions of women. While 25.4% of the study group considered that FGCPs were only a temporary trend, 32.6% thought the opposite. Some authors suggested that labiaplasty and vaginal tightening could improve sexual function and quality of life, whereas others failed to demonstrate improvement[19-22]. In January 2020, the ACOG stated in their revised bulletin regarding FGCPs that surgical alteration of the labia that was not necessary to the health of patients aged younger than 18 years was a violation of federal criminal law in the United States[9,23]. The World Health Organization defined female genital mutilation as "all procedures involving partial or total removal of the external female genitalia or other injuries to the female genital organs for non-medical reasons" and this statement also raises concern about whether genital cosmetic surgeries constitute genital mutilation[24]. Compatible with this discussion, nearly half of the participants (47%) were indecisive and 19.1% considered FGCPs as genital mutilation. In surgical specialties, the rate of disagreeing with the idea that genital cosmetic surgeries are genital mutilation was higher, while the opposite was raised in non-surgical specialties.

In many business areas, especially thanks to the fact that social media is also in our lives and the number of active users is increasing rapidly, professionals are free to advertise their work. However, advertising is not clear-cut in medical practice because of moral, ethical and deontologic concerns. Almost half of the participants (47%) did not find advertising suitable in terms of FGPCs. However, when the specialists' responses were examined independently, the group with the highest proportion of participants who thought that advertising could be used by cosmetic surgeons, was gynecologists.

**Table 3.** Participants opinions about speculative comments regarding female genital cosmetic procedures

| | Agree % (n/N) | | Indecisive % (n/N) | | Disagree % (n/N) | | |
|---|---|---|---|---|---|---|---|
| FGCPs | Student | Specialist | Student | Specialist | Student | Specialist | p |
| **Should not be performed under age 18 years** | 75.8% 91/120 | 81.1% 408/503 | 15.8% 19/120 | 13.5% 68/503 | 8.3% 10/120 | 5.4% 27/503 | 0.34 |
| **Should be considered as any other surgery** | 61.7% 74/120 | 55.1% 277/503 | 26.7% 32/120 | 23.7% 119/503 | 11.7% 14/120 | 21.3% 107/503 | 0.06 |
| **Performed after psychiatric consultation** | 40% 48/120 | 45.9% 231/503 | 32.5% 39/120 | 26.4% 133/503 | 27.5% 33/120 | 27.6% 139/503 | 0.36 |
| **Can be peformed in public hospitals** | 57.5% 69/120 | 53.5% 269/503 | 33.3% 40/120 | 23.1% 116/503 | 9.2% 11/120 | 23.5% 118/503 | **<0.01*** |
| **Should not be advertised** | 45.8% 55/120 | 50.1% 252/503 | 30.8% 37/120 | 24.7% 124/503 | 23.3% 28/120 | 25.2% 127/503 | **0.38** |
| **Should be considered as genital mutilation** | 16.7% 20/120 | 19.7% 99/503 | 59.2% 71/120 | 44.1% 222/503 | 24.2% 29/120 | 36.2% 182/503 | **0.01*** |
| **Improve self-esteem** | 66.7% 80/120 | 52.7% 265/503 | 25.8% 31/120 | 28.8% 145/503 | 7.5% 9/120 | 18.5% 93/503 | **<0.01*** |
| **Improve sexual function** | 64.2% 77/120 | 51.7% 260/503 | 30.8% 37/120 | 34.4% 173/503 | 5% 6/120 | 13.9% 70/503 | **0.01*** |
| **Improve quality of life** | 61.7% 74/120 | 52.9% 266/503 | 34.2% 41/120 | 34.6% 174/503 | 4.2% 5/120 | 12.5% 63/503 | **0.02*** |
| **Decrease dyspareunia** | 37.5% 45/120 | 34.4% 173/503 | 58.3% 70/120 | 50.5% 254/503 | 4.2% 5/120 | 15.1% 76/503 | **0.01*** |
| **Decrease urinary incontinence** | 43.3% 52/120 | 35.4% 178/503 | 48.3% 58/120 | 45.3% 228/503 | 8.3% 10/120 | 19.3% 97/503 | **0.01*** |
| **Have no benefit** | 7.5% 9/120 | 8.5% 43/503 | 23.3% 28/120 | 32.2% 162/503 | 69.2% 83/120 | 59.2% 298/503 | 0.12 |
| **Only a temporary trend** | 29.2% 35/120 | 24.5% 123/503 | 38.3% 46/120 | 42.9% 216/503 | 32.5% 39/120 | 32.6% 164/503 | 0.51 |

### Study Limitations

The weak point of this survey is that all of the physicians who answered the questionnaire were working in public hospitals. Although the opinions of physicians working in the private sector may affect the results, the perceptions/attitudes of physicians working in public hospitals may be more objective because they have no conflicts of interests.

## Conclusion

The majority of participants declared that FGCPs could be performed only upon patient request and improved self-esteem, quality of life, and sexual functions. The most controversial procedures in terms of ethics were hymenoplasty and G-spot amplification. As the recommendations on the FGCPs are insufficient to define the boundaries of medical justification, genital mutilation, advertising, and ethical concerns, detailed guidelines for the protection of both patients and physicians are needed.

### Ethics

**Ethics Committee Approval:** The study was approved by the Institutional Review Board (E1/180/2019).

**Informed Consent:** The respondents were informed and consent for participation was obtained before administering the questionnaire.

**Peer-review:** Externally and internally peer-reviewed.

### Authorship Contributions

Concept: G.F.Y., G.K., E.E.T., Design: G.F.Y., G.K., E.İ.S., Data Collection or Processing: G.F.Y., G.K., E.İ.S., İ.B.B., Analysis or Interpretation: H.L.K., Literature Search: H.L.K., Writing: G.F.Y., G.K., A.F.Y.

**Conflict of Interest:** The authors report no conflict of interest.

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*Review / Derleme*

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# A meta-analysis of the association of the ACE I/D and PAI-1 4G/5G polymorphisms with recurrent pregnancy loss in Iranian women: Are the investigations adequate?

## *İranlı kadınlarda tekrarlayan gebelik kaybı ile ACE I/D ve PAI-1 4G/5G polimorfizmlerinin ilişkisine yönelik bir meta-analiz: Araştırmalar yeterli mi?*

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**Abstract**

The associations of ACE I/D and PAI-1 4G/5G polymorphisms with recurrent pregnancy loss (RPL) in Iranian women have yielded controversial results. Thus, we conducted a meta-analysis to obtain more certain results. A comprehensive literature search was performed in the PubMed, Web of Sciences, Scopus, MedRxiv, SID, and CNKI databases up to January 1st, 2021, using the appropriate terms. All case-control studies were included. Odds ratios (ORs) and 95% confidence intervals (CIs) were used to estimate the strength of associations. A total of 14 studies including eight studies with 783 patients and 761 healthy subjects on ACE I/D and six studies with 1.155 patients and 699 healthy subjects on PAI-1 4G/5G were included. Combined data revealed that ACE I/D polymorphism was significantly associated with RPL risk in Iranian women under three models i.e., allele [OR=0.744, 95% CI: (0.640-0.864); p≤0.001], dominant [OR=0.774, 95% CI: (0.601-0.996); p=0.047], and recessive [OR=0.767, 95% CI: (0.611-0.963); p=0.022]. Moreover, the pooled data showed a significant association between the PAI-1 4G/5G polymorphism and RPL risk under all five models i.e., allele [OR=2.352, 95% CI: (1.623-3.408); p≤0.001], heterozygote [OR=8.364, 95% CI: (4.744-14.756); p≤0.001), homozygote [OR=2.192, 95% CI: (1.093-4.394); p=0.027), dominant [OR=2.354, 95% CI: (1.309-4.235); p=0.004], and recessive [OR=5.208, 95% CI: (3.005-9.025); p≤0.001]. Stratification analysis revealed that these polymorphisms were associated with RPL risk by the number of miscarriages. Our pooled data indicated that ACE I/D and PAI-1 4G/5G polymorphisms were significantly associated with an increased risk of RPL in Iranian women. These significant findings showed that the investigation might be adequate for ACE I/D and PAI-1 4G/5G polymorphisms in the Iranian population.

**Keywords:** Pregnancy loss, miscarriage, thrombophilia, plasminogen activator inhibitor-1, angiotensin-I-converting enzyme, polymorphism

**Öz**

İranlı kadınlarda ACE I/D ve PAI-1 4G/5G polimorfizmlerinin tekrarlayan gebelik kaybı (TGK) ile ilişkisi tartışmalı sonuçlar vermiştir. Bu yüzden, daha güvenilir sonuçlar almak için bir meta-analiz gerçekleştirdik. PubMed, Web of Sciences, Scopus, MedRxiv, SID ve CNKI veritabanlarında uygun terimler kullanılarak 01 Ocak 2021 tarihine kadar kapsamlı bir literatür taraması gerçekleştirildi. Tüm olgu kontrol çalışmaları dahil edildi. İlişkilerin gücünü tahmin etmek için olasılık oranları (OO'lar) ve %95 güven aralıkları (GA) kullanıldı. Meta-analize ACE I/D ile ilgili 783 hasta ve 761 sağlıklı denek içeren 8 çalışma ve PAI-1 4G/5G ile ilgili 1.155 hasta ve 699 sağlıklı denek içeren 6 çalışma dahil olmak üzere toplam 14 çalışma dahil edildi. Birleşik veriler, ACE I/D polimorfizminin; allel (OO=0,744, %95 GA: 0,640-0,864, p≤0,001), dominant (OO=0,774, %95 GA: 0,601-0,996, p=0,047) ve resesif (OO=0,767, %95 GA: 0,611-0,963, p=0,022) olmak üzere üç model altında İranlı kadınlarda TGK riski ile önemli ölçüde ilişkili olduğunu ortaya koymuştur. Ayrıca,

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havuzlanmış veriler, PAI-1 4G/5G polimorfizmi ile TGK riski arasında, beş modelin tümünde, yani allel (OO=2,352, %95 GA: 1,623-3,408, p≤0,001), heterozigot (OO=8,364, %95 GA: 4,744-14,756, p≤0,001), homozigot (OO=2,192, %95 GA: 1,093-4,394, p=0,027), dominant (OO=2,354, %95 GA: 1,309-4,235, p=0,004) ve resesif (OO=5,208, %95 GA: 3,005-9,025, p≤0,001) modellerinde anlamlı ilişkinin varlığını göstermiştir. Tabakalaşma analizi, bu polimorfizmlerin düşük sayısına göre TGK riski ile ilişkili olduğunu ortaya çıkarmıştır. Birleştirilmiş verilerimiz, ACE I/D ve PAI-1 4G/5G polimorfizmlerinin, İranlı kadınlarda artmış TGK riski ile önemli ölçüde ilişkili olduğunu gösterdi. Bu önemli bulgular bizi, İran popülasyonunda ACE I/D ve PAI-1 4G/5G polimorfizmleri açısından araştırmanın yeterli olabileceği kararına götürdü.
**Anahtar Kelimeler:** Gebelik kaybı, düşük, trombofili, plazminojen aktivatör inhibitörü-1, anjiyotensin-I-dönüştürücü enzim, polimorfizm

## Introduction

Recurrent pregnancy loss (RPL) is one of the main public health issues with a rate of 5% among women of reproductive age[1,2]. RPL is defined as the loss of three or more successive pregnancies before viability and includes all pregnancy losses from the time of conception until 24 weeks of gestation[3-5]. The most commonly cited causes of miscarriage are structural chromosome abnormalities of one of the partners, uterine abnormalities, elevated random levels of homocysteine, and antiphospholipid syndrome[6,7]. Thrombophilia is described as a susceptibility to arterial or venous thrombotic complications due to hemostatic system defects, which may be acquired, like the antiphospholipid syndrome, or inherited[8,9]. Adverse pregnancy outcomes, such as pregnancy failure (i.e. sporadic and RPL, late fetal loss), pre-eclampsia, and HELLP syndrome, are associated with thrombotic mechanisms and thrombophilia[10]. Thrombotic disorders are detectable in 40-50% of RPL cases[11]. It has been presumed that the etiology of RPL is associated with factors involved in fibrinolysis and coagulation[3,12]. In the past two decades, several investigators suggested that thrombophilia had an impact on susceptibility to RPL[13-15]. Thus, genotyping of genetic variants at thrombophilic genes is useful to describe the etiology of RPL, and improvement our knowledge about the nature of this disease[16].

Currently, there are a limited number of genetic variants as independent risk factors for venous thromboembolism in women with RPL[17]. There is growing evidence of a causal relationship of genetic variations at plasminogen activator inhibitor-1 (PAI-1) and angiotensin-converting enzyme (ACE) genes with RPL in different populations[3,18]. PAI-1, a 52 kDa glycoprotein belonging to the serine proteinase inhibitor superfamily, is the principal inhibitor of tissue and urinary plasminogen activators[3,19,20]. PAI-1 is involved in various physiologic functions and associated with many diseases[21-23]. The most commonly studied functional variant in the PAI-1 gene is the 4G/5G polymorphism, which is characterized by a single guanosine nucleotide insertion/deletion variation at -675 bp to the transcription start site of the *PAI-1* gene[24,25]. Moreover, ACE or kininase II, is a dipeptidyl carboxypeptidase that plays an important role in regulating blood pressure and electrolyte balance[26,27]. The most widely studied polymorphism of ACE is an insertion/deletion (I/D), which is characterized by insertion or deletion of a 287-non-coding base pair Alu repeat sequence[28,29].

RPL is one of the main reproductive health issues in Iran[30,31]. However, there is no consensus regarding the frequency of RPL in Iranian women. In the past decade, several molecular studies have evaluated the association of ACE I/D and PAI-1 4G/5G polymorphisms with RPL risk in Iran[3,18]. Nevertheless, their results were inconsistent and inconclusive. Moreover, the findings provided limited evidence due to relatively small sample sizes and might have been underpowered to estimate the risk. Thus, meta-analysis is a standardized approach to combine the results of different studies on ACE I/D and PAI-1 4G/5G polymorphisms to provide more reliable conclusions. Therefore, we conducted this meta-analysis to obtain a more precise estimation on the association of ACE I/D and PAI-1 4G/5G polymorphisms with RPL risk in Iranian women from all eligible case-control studies published in English and Farsi.

## Materials and Methods

### Search Strategy

We performed a comprehensive search on the United States National Library of Medicine's PubMed, Scopus, EMBASE, Web of Knowledge, MedRxiv, Cochrane Library, Google Scholar, Scientific Information Database, WanFang, VIP, Chinese Biomedical Database, Scientific Electronic Library Online and China National Knowledge Infrastructure database to find all relevant publications on the association of ACE I/D and PAI-1 4G/5G polymorphisms with RPL in Iranian women up till January 1st, 2021. The following keywords and terms were used for the search: ("Pregnancy Loss" OR "RPL" OR "Recurrent Pregnancy Loss" OR "Recurrent Miscarriage" OR "recurrent spontaneous abortion" OR "Idiopathic/Unexplained Recurrent Pregnancy Loss") AND ("Angiotensin-Converting Enzyme" OR "ACE" OR "SERPINE1") AND ("Insertion/Deletion Polymorphism" OR "ACE I/D" OR "rs4646994") AND ("Plasminogen Activator Inhibitor-1" OR "PAI-1") AND ("4G/5G" OR "rs1799889") AND ("Gene" OR "Genotype" OR "Allele" OR "Polymorphism" OR "Single nucleotide polymorphisms" OR "SNP" OR "Variation" OR "Mutation"). Articles were limited to the English and Farsi languages. Additionally, the reference lists of each eligible study, previous meta-analyses, and review articles were manually checked to find more relevant publications.

### Inclusion and Exclusion Criteria

The criteria employed to retrieve publications for this meta-analysis were as follows: (1) studies with case-control or cohort design; (2) studies conducted among Iranian populations; (3)

studies that evaluated the association of ACE I/D and PAI-1 4G/5G polymorphisms with RPL; (4) studies that provided sufficient data on the genotype frequencies of the polymorphisms to calculate the pooled odds ratio (OR) with corresponding 95% confidence interval (CI). The exclusion criteria were as follows: (1) studies not relevant to RPL; (2) case-only studies or no controls; (3) linkage studies and family-based studies (twins and sibling); (4) duplicate studies and incomplete data; (5) abstracts, posters, presentations, letters, case reports, case series, comments, conference editorials, reviews and previous meta-analyses; and (6) unpublished data and studies without extractable data.

### Data Extraction

Data were carefully extracted from all eligible studies independently by two authors according to the criteria listed above. Then, to minimize bias and to improve the reliability of the data, the authors checked all potentially relevant studies independently and reached a consensus or a third author was consulted to make a final decision. The following data were collected from each study: name of the first author, year of publication, genotyping method, numbers of patients with RPL and healthy controls, genotypes and alleles frequencies in patients and controls for ACE I/D and PAI-1 4G/5G polymorphisms, minor allele frequency, and p-values for Hardy-Weinberg equilibrium (HWE) tests in control subjects. If a study included more than one case-control group, each studied group was considered as an independent dataset. For studies with overlapping data or samples by the same author, the larger sample size or the study that was published more recently was included in the meta-analysis.

### Statistical Analysis

The strength of the association between ACE I/D and PAI-1 4G/5G polymorphisms and RPL risk in Iranian women was calculated using odds ratios (ORs) with 95% confidence intervals (CIs). The significance of the pooled OR was determined using the Z-test, in which a p-value <0.05 was considered significant. The pooled ORs for ACE I/D and PAI-1 4G/5G polymorphisms were estimated under all five genetic comparison models, i.e., allele (A vs B), homozygote (AA vs BB), heterozygote (BA vs BB), dominant (AA+BA vs BB), and recessive (AA vs BA+BB). A Cochrane-based Q statistical test was used to test between-studies heterogeneity, in which p-values <0.1 indicated the absence of indicated heterogeneity. Moreover, we used the inconsistency index ($I^2$) (range of 0 to 100%) to quantify the proportion of the total variation due to heterogeneity, in which the heterogeneity was considered low, moderate, and high based on $I^2$ values of 25%, 50%, and 75%, respectively. If heterogeneity was observed among the studies, the random-effects model (the DerSimonian and Laird method) was used to estimate the pooled OR. Otherwise, a fixed-effects model (the Mantel-Haenszel method) was adopted. For each study, the HWE in healthy subjects was estimated using the chi-square goodness-of-fit test and p<0.05 was considered statistically significant. Sensitivity analysis was performed by sequential omission of individual studies to assess the stability of pooled data in this meta-analysis. Moreover, sensitivity analysis was performed by excluding studies that deviated from the HWE. Both Begg's funnel plot and Egger's weighted regression tests were used to assess publication bias. If publication bias existed, the Duval and Tweedie non-parametric "trim and fill" method was applied to adjust results. All statistical analyses were performed using the Comprehensive Meta-analysis (CMA) software version 2.0 (Biostat, USA). Two-sided probability (p) values of <0.05 were considered statistically significant.

## Results

### Study Selection and Characteristics

A flow chart detailing the inclusion/exclusion process is shown in Figure 1. The primary online database queries and manual reference searches generated 337 potentially relevant studies that reported the association of ACE I/D and PAI-1 4G/5G polymorphisms with susceptibility to RPL. After the removal of duplicate articles, the search retrieved 218 items. Based on the title, abstract screening, or both, 129 articles were excluded according to the eligibility criteria. Subsequently, 75 publications were excluded because they were reviews, previous meta-analyses, and evaluated the association of RPL with other polymorphism of ACE and PAI-1 genes. Finally, a total of 14 studies involving eight studies with 783 patients and 761 controls on the ACE I/D polymorphism[6,18,29,32-35] and six studies with 1155 patients and 699 controls on the PAI-1 4G/5G polymorphism[18,31,34,36-38] were included in this meta-analysis. One study in the present meta-analysis did not state the source of controls. Two genotyping methods were used, including ARMS-PCR and PCR-RFLP. The genotype distributions among the controls in the two studies were not consistent with the HWE on the ACE I/D polymorphism (Table 1).

### Quantitative Data Synthesis

### ACE I/D Polymorphism

The pooled results on the association of ACE I/D polymorphism with RPL risk in Iranian women are presented in Table 2. When all eligible studies were pooled together, a significant association between ACE I/D polymorphism and increased risk of RPL in Iranian women was found only under three models i.e., allele [D vs I: OR=0.744, 95% CI: (0.640-0.864); p≤0.001, Figure 2A], dominant [DD+DI vs II: OR=0.774, 95% CI: (0.601-0.996); p=0.047, Figure 2B], and recessive [DD vs DI+II: OR=0.767, 95% CI: (0.611-0.963); p=0.022, Figure 2C]. When stratified by the number of recurrent miscarriages (RM), a significant association between the ACE I/D polymorphism and increased risk of RPL was detected in the group of studies with ≥2 RMs under the allele genetic model [D vs I: OR=0.666, 95% CI: (0.539-0.822); p≤0.001], but not in studies with ≥3 RM.

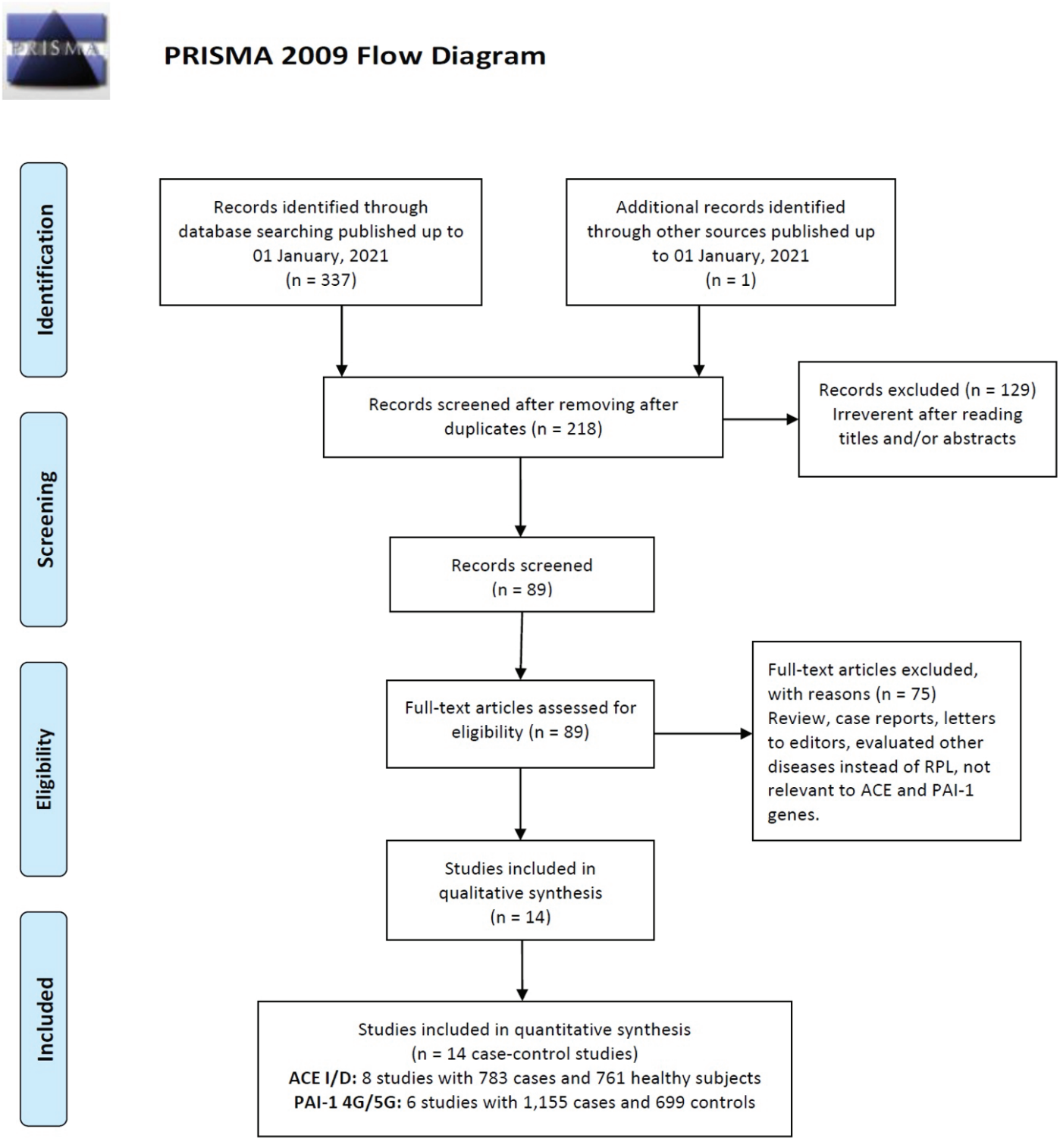


**Figure 1.** Flow diagram of selection of studies included in the meta-analysis

Moreover, a significant association was found between ACE I/D and RPL in ARMS-PCR group studies under two genetic models i.e., allele [D vs I: OR=0.799, 95% CI: (0.659-0.967); p=0.022] and recessive [DD vs DI+II: OR=0.734, 95% CI: (0.544-0.989); p=0.042], and PCR-RFLP group studies under the allele model [D vs I: OR=0.667, 95% CI: (0.524-0.850); p=0.001).

### PAI-1 4G/5G Polymorphism

Table 3 summarizes the main results of the meta-analysis for the PAI-1 4G/5G polymorphism and RPL in Iranian women. Overall pooled data showed that there was a significant association between the PAI-1 4G/5G polymorphism with

**Table 1.** Main characteristics of studies included in this meta-analysis

| First author | Genotyping technique | RM NO. | Case/ Control | Cases | | | | | Controls | | | | | MAFs | HWE |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Genotype | | | Allele | | Genotype | | | Allele | | | |
| ACE I/D | | | | II | ID | DD | I | D | II | ID | DD | I | D | | |
| Soltanghoraee et al.[32] | PCR-RFLP | ≥2 | 129/94 | 29 | 62 | 38 | 112 | 128 | 22 | 47 | 25 | 108 | 116 | 0.484 | 0.992 |
| Bagheri et al.[33] | ARMS-PCR | ≥3 | 50/63 | 7 | 26 | 17 | 40 | 60 | 12 | 27 | 24 | 51 | 75 | 0.404 | 0.380 |
| Aarabi et al.[34] | PCR-RFLP | ≥3 | 63/94 | 14 | 30 | 19 | 54 | 62 | 22 | 47 | 25 | 91 | 97 | 0.484 | 0.992 |
| Poursadegh Zonouzi et al.[35] | ARMS-PCR | ≥2 | 89/50 | 35 | 31 | 23 | 101 | 77 | 15 | 28 | 7 | 58 | 42 | 0.580 | 0.135 |
| Shahkarami et al.[18] | PCR-RFLP | ≥2 | 100/100 | 6 | 60 | 34 | 74 | 128 | 0 | 48 | 52 | 48 | 152 | 0.240 | 0.001 |
| Fazelnia et al.[29] | ARMS-PCR | ≥2 | 100/100 | 31 | 40 | 29 | 102 | 98 | 23 | 33 | 44 | 79 | 121 | 0.395 | 0.001 |
| Heidari et al.[6] | ARMS-PCR | ≥3 | 202/210 | 49 | 102 | 51 | 200 | 204 | 41 | 99 | 70 | 181 | 239 | 0.431 | 0.573 |
| Maziri et al.[2] | ARMS-PCR | ≥2 | 50/50 | 36 | 13 | 1 | 85 | 15 | 26 | 22 | 2 | 74 | 26 | 0.260 | 0.310 |
| PAI-1 4G/5G | | | | **5G5G** | **5G4G** | **4G4G** | **5G** | **4G** | **5G5G** | **5G4G** | **4G4G** | **5G** | **4G** | | |
| Arabi et al.[34] | PCR-RFLP | ≥3 | 54/99 | 21 | 23 | 10 | 65 | 43 | 31 | 66 | 2 | 128 | 70 | ≤0.001 | 0.354 |
| Jeddi-Tehran et al.[36] | PCR-RFLP | ≥2 | 100/100 | 60 | 31 | 9 | 151 | 49 | 72 | 27 | 1 | 171 | 29 | 0.373 | 0.145 |
| Idali et al.[37] | PCR-RFLP | ≥3 | 106/100 | 35 | 53 | 18 | 123 | 89 | 72 | 27 | 1 | 171 | 29 | 0.373 | 0.145 |
| Khosravi et al.[38] | PCR-RFLP | ≥2 | 595/100 | 128 | 208 | 85 | 464 | 375 | 72 | 27 | 1 | 171 | 29 | 0.373 | 0.145 |
| Shahkarami et al.[18] | PCR-RFLP | ≥2 | 100/100 | 33 | 50 | 17 | 116 | 84 | 45 | 50 | 5 | 140 | 60 | 0.300 | 0.056 |
| Bigdeli et al.[31] | PCR-RFLP | ≥3 | 200/200 | 70 | 112 | 18 | 252 | 148 | 150 | 43 | 7 | 343 | 57 | 0.089 | 0.143 |

PCR: Polymerase chain reaction, RFLP: Restriction fragment length polymorphism, RM: Recurrent miscarriage, MAF: Minor allele frequency, HWE: Hardy-Weinberg equilibrium

RPL risk under all five genetic models i.e., allele [4G4G vs 5G5G: OR=2.352, 95% CI: (1.623-3.408); p≤0.001, Figure 3A], heterozygote [4G4G4 vs 5G5G5: OR=8.364, 95% CI: (4.744-14.756); p≤0.001, Figure 3B], homozygote [4G5G vs 5G5G: OR=2.192, 95% CI: (1.093-4.394); p=0.027, Figure 3C], dominant [4G4G4+4G5G vs 5G5G5: OR=2.354, 95% CI: (1.309-4.235); p=0.004, Figure 3D], and recessive [4G4G4 vs 4G5G+5G5G5: OR=5.208, 95% CI: (3.005-9.025); p≤0.001, Figure 3E]. When stratified by RM, a significant association between PAI-1 4G/5G polymorphism and increased risk of RPL was detected in the group of studies with ≥2 RMs under four genetic models i.e., allele [4G4G vs 5G5G: OR=2.083, 95% CI: (1.617-2.682); p≤0.001], homozygote [4G5G vs 5G5G: OR=8.390, 95% CI: (3.509-20.061); p≤0.001], dominant [4G4G4+4G5G vs 5G5G5: OR=2.003, 95% CI: (1.472-2.727); p≤0.001], and recessive [4G4G4 vs 4G5G+5G5G5: OR=5.871, 95% CI: (2.528-13.631); p≤0.001], and ≥3 under three genetic models i.e., allele [4G4G vs 5G5G: OR=2.653, 95% CI: (1.299-5.418); p=0.007], homozygote [4G5G vs 5G5G: OR=8.345, 95% CI: (3.955-17.606); p≤0.001], and recessive [4G4G4 vs 4G5G+5G5G5: OR=4.764, 95% CI: (2.305-9.845); p≤0.001].

### Heterogeneity Test and Sensitivity Analysis

There was no between-study heterogeneity found in all five genetic models and thus the fixed-effect model was applied to calculate their combined OR. Moreover, we conducted a sensitivity analysis to investigate whether the absence of each study would alter the pooled ORs and stability of our results. However, we observed no significant change in the association level of ACE I/D and PAI-1 4G/5G polymorphisms with RPL risk in the Iranian population by excluding any of the studies. This suggests that that the current meta-analysis results were relatively robust and stable.

### Publication Bias

The publication bias of the studies was assessed using a funnel plot and Egger's test (Table 2 and Figure 4A-B). The funnel plot did not indicate any evidence of funnel plot asymmetry for the ACE I/D polymorphism. Moreover, the results of Egger's test revealed no significant publication bias for the ACE I/D polymorphism. However, Begg's funnel plot and Egger's tests showed publication bias for the PAI-1 4G/5G polymorphism under two genetic models i.e., heterozygote (4G4G4 vs

**Table 2.** Summary risk estimates for association of ACE I/D polymorphism with RPL in Iranian women

| Subgroup | Genetic model | Type of model | Heterogeneity | | Odds ratio (OR) | | | | Publication bias | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | $I^2$ (%) | $P_H$ | OR | 95% CI | $Z_{OR}$ | $P_{OR}$ | $P_{Beggs}$ | $P_{Eggers}$ |
| Overall | D vs I | Fixed | 6.65 | 0.379 | 0.744 | 0.640-0.864 | -3.863 | ≤0.001 | 0.386 | 0.857 |
| | DI vs II | Fixed | 0.00 | 0.472 | 0.872 | 0.657-1.157 | -0.952 | 0.341 | 0.710 | 0.778 |
| | DD vs II | Random | 52.55 | 0.039 | 0.941 | 0.595-1.487 | -0.260 | 0.795 | 0.901 | 0.947 |
| | DD+DI vs II | Fixed | 13.69 | 0.323 | 0.774 | 0.601-0.996 | -1.988 | 0.047 | 0.710 | 0.368 |
| | DD vs DI+II | Fixed | 45.76 | 0.074 | 0.767 | 0.611-0.963 | -2.285 | 0.022 | 0.265 | 0.458 |
| RM NO. | | | | | | | | | | |
| ≥2 | D vs I | Fixed | 27.81 | 0.245 | 0.666 | 0.539-0.822 | -3.790 | ≤0.001 | 0.734 | 0.211 |
| | DI vs II | Fixed | 28.12 | 0.243 | 0.753 | 0.499-1.136 | -1.1351 | 0.177 | 0.089 | 0.209 |
| | DD vs II | Fixed | 59.04 | 0.062 | 0.781 | 0.494-1.233 | -1.061 | 0.289 | 0.734 | 0.520 |
| | DD+DI vs II | Fixed | 22.68 | 0.275 | 0.754 | 0.516-1.101 | -1.461 | 0.144 | 0.734 | 0.154 |
| | DD vs DI+II | Random | 72.38 | 0.012 | 0.827 | 0.446-1.535 | -0.601 | 0.548 | 0.089 | 0.237 |
| ≥3 | D vs I | Fixed | 0.00 | 0.613 | 0.838 | 0.676-1.039 | -1.611 | 0.107 | 0.296 | 0.055 |
| | DI vs II | Fixed | 0.00 | 0.560 | 0.975 | 0.657-1.448 | -0.124 | 0.901 | 0.296 | 0.231 |
| | DD vs II | Fixed | 10.49 | 0.327 | 0.790 | 0.513-1.217 | -1.070 | 0.285 | 1.000 | 0.186 |
| | DD+DI vs II | Fixed | 0.00 | 0.461 | 0.896 | 0.618-1.300 | -0.576 | 0.565 | 0.296 | ≤0.001 |
| | DD vs DI+II | Fixed | 0.00 | 0.399 | 0.796 | 0.572-1.108 | -1.354 | 0.176 | 1.000 | 0.414 |
| Genotyping methods | | | | | | | | | | |
| ARMS-PCR | D vs I | Fixed | 13.73 | 0.324 | 0.799 | 0.659-0.967 | -2.298 | 0.022 | 0.734 | 0.441 |
| | DI vs II | Fixed | 15.59 | 0.314 | 0.831 | 0.590-1.172 | -1.054 | 0.292 | 0.734 | 0.781 |
| | DD vs II | Fixed | 22.51 | 0.276 | 0.693 | 0.474-1.011 | -1.903 | 0.057 | 0.734 | 0.179 |
| | DD+DI vs II | Fixed | 0.00 | 0.605 | 0.761 | 0.554-1.047 | -1.680 | 0.093 | 0.734 | 0.414 |
| | DD vs DI+II | Fixed | 55.14 | 0.083 | 0.734 | 0.544-0.989 | -2.030 | 0.042 | 0.308 | 0.288 |
| PCR-RFLP | D vs I | Fixed | 23.37 | 0.271 | 0.667 | 0.524-0.850 | -3.275 | 0.001 | 1.000 | 0.625 |
| | DI vs II | Fixed | 17.81 | 0.296 | 0.932 | 0.560-1.551 | -0.272 | 0.786 | 0.296 | 0.115 |
| | DD vs II | Fixed | 53.67 | 0.115 | 1.039 | 0.591-1.827 | 0.134 | 0.893 | 0.296 | 0.130 |
| | DD+DI vs II | Fixed | 37.97 | 0.199 | 0.985 | 0.609-1.590 | -0.064 | 0.949 | 0.296 | 0.120 |
| | DD vs DI+II | Fixed | 65.79 | 0.054 | 0.824 | 0.578-1.176 | -1.067 | 0.286 | 1.000 | 0.555 |

RM: Recurrent miscarriage, ARMS: Amplification-refractory mutation system, RFLP: Restriction fragment length polymorphism

5G5G5: $P_{Beggs}$=0.060 and $P_{Eggers}$=0.021) and recessive (4G4G4 vs 4G5G+5G5G5: $P_{Beggs}$=0.132 and $P_{Eggers}$=0.028). One probable explanation is that the results were underpowered and biased by limited sample sizes. Therefore, the Duval and Tweedie non-parametric "trim and fill" method was applied to adjust for publication bias on the PAI-1 4G/5G polymorphism under the heterozygote and recessive models. However, the results with and without "trim and fill" did not draw different results, indicating that the current meta-analysis results are statistically robust and reliable.

## Discussion

The etiology of RPL is complicated, and several risk factors are involved in the development of the disease. In addition to fetal and maternal factors, including chromosomal abnormalities, endocrine and metabolic aberrations, and autoimmune abnormalities, genetic single nucleotide polymorphisms at different loci, also play essential roles in RPL[6,12,39]. In this meta-analysis, we evaluated the association of the ACE I/D and PAI-1 4G/5G polymorphisms with RPL risk in Iranian women from all eligible case-control studies.

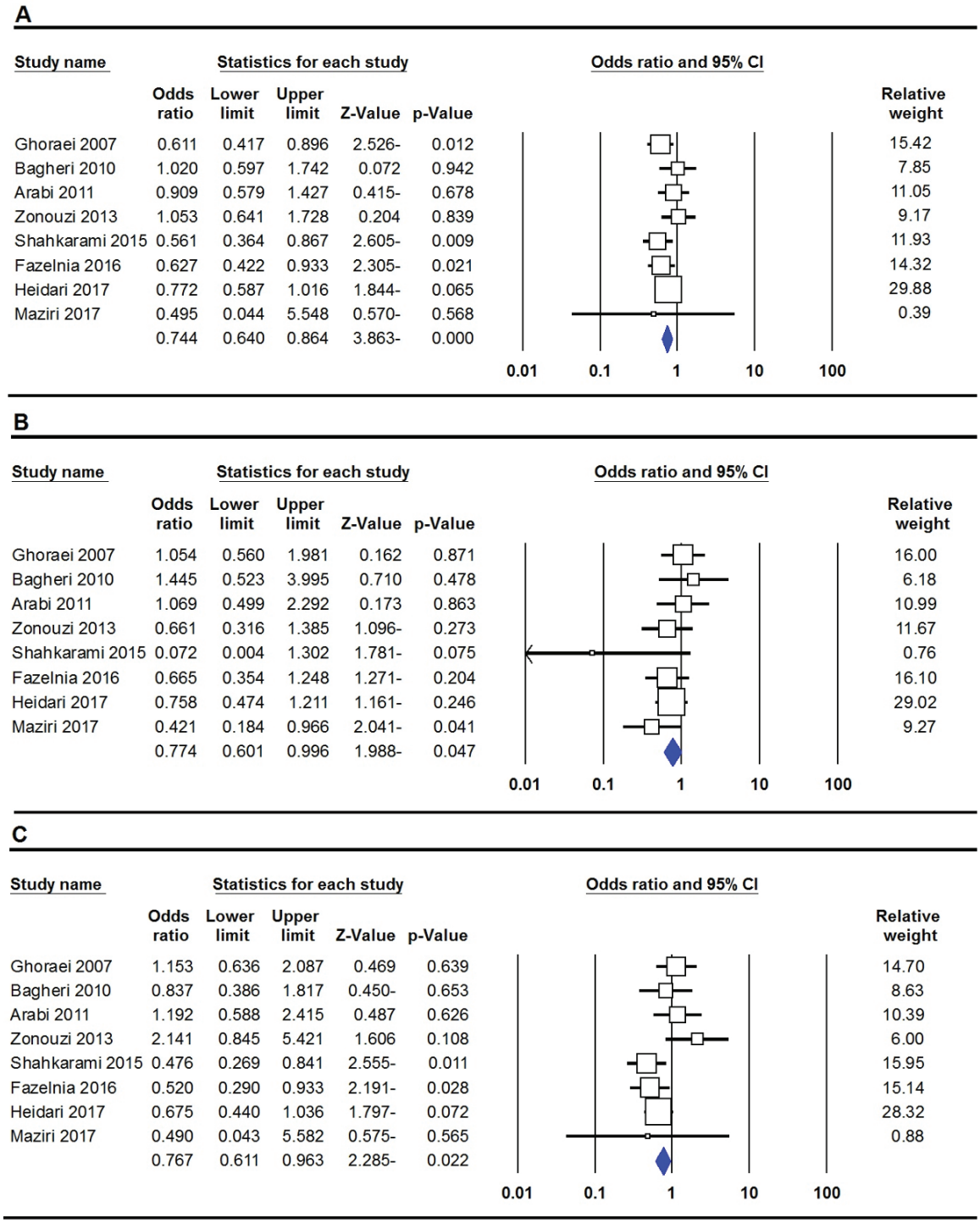


**Figure 2.** Forest plots for the association of ACE I/D polymorphism with risk of RPL risk in Iranian women. A: allele model; B: dominant model; and C: recessive model

The 4G/5G polymorphism is a major genetic variant determinant of plasma PAI-1 levels. The 4G allele has been reported to increase the risk for different diseases such as atherosclerosis and coronary artery disease[40]. On the other hand, the 5G allele may increase the risk of conditions such as abdominal aortic aneurysm. In this meta-analysis, our combined data based on six studies with 1,155 patients and 699 healthy subjects revealed that the PAI-1 4G/5G polymorphism was associated with an increased risk of RPL in Iranian women. In 2003, Wolf et al.[41] first reported an increased risk of RPL in Austrian women in association with the PAI-1 4G/5G polymorphism. However, later studies in different ethnicities yielded controversial results[18,34,42,43]. In 2018, Adler et al.[44] evaluated the associations of the -675 I/D and 4G/5G polymorphisms

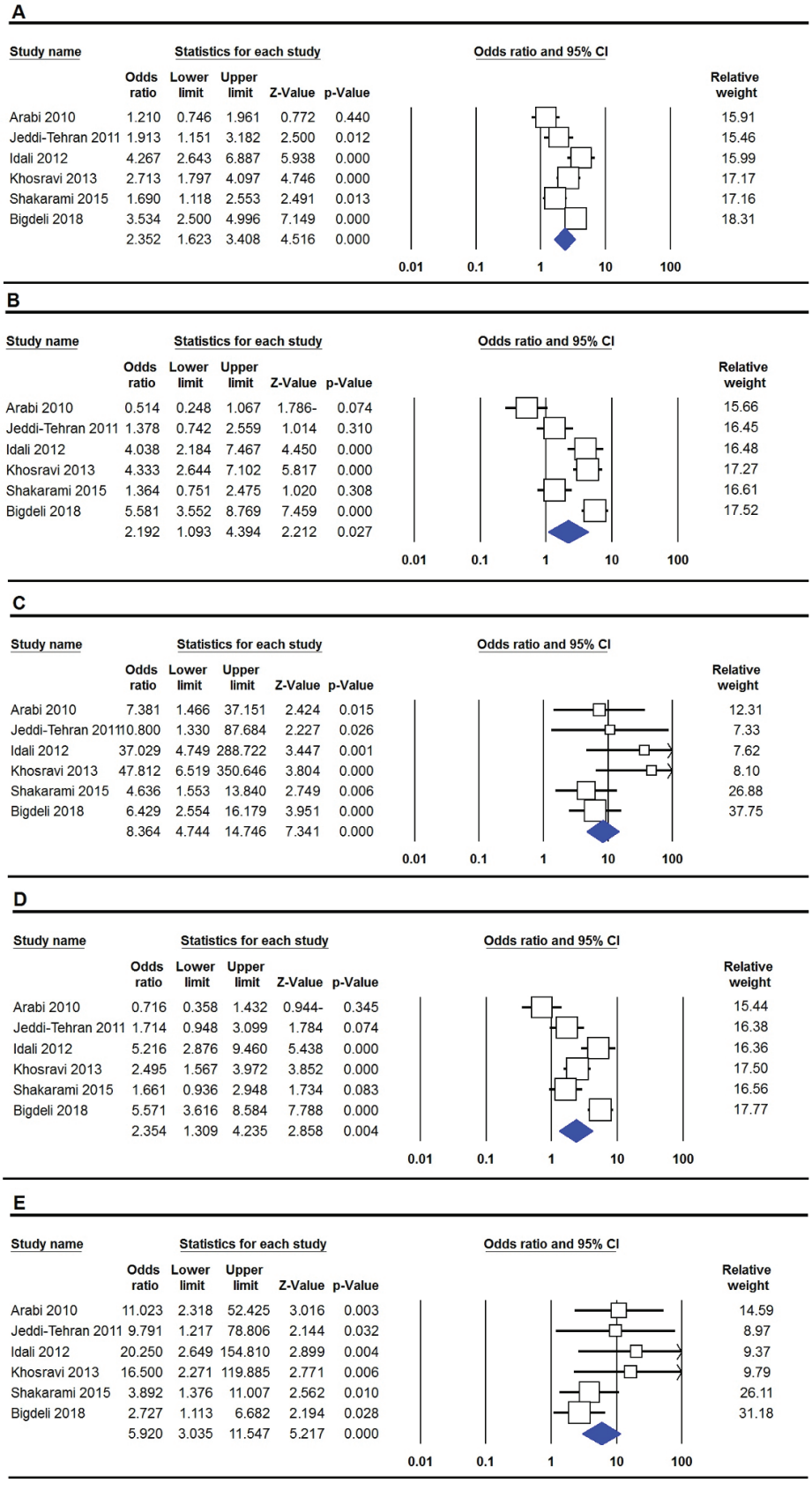


**Figure 3.** Forest plots for the association of PAI-1 4G/5G polymorphism with risk of RPL risk in Iranian women. A: allele model; B: heterozygote model; C: homozygote model; D: dominant model; and C: recessive model

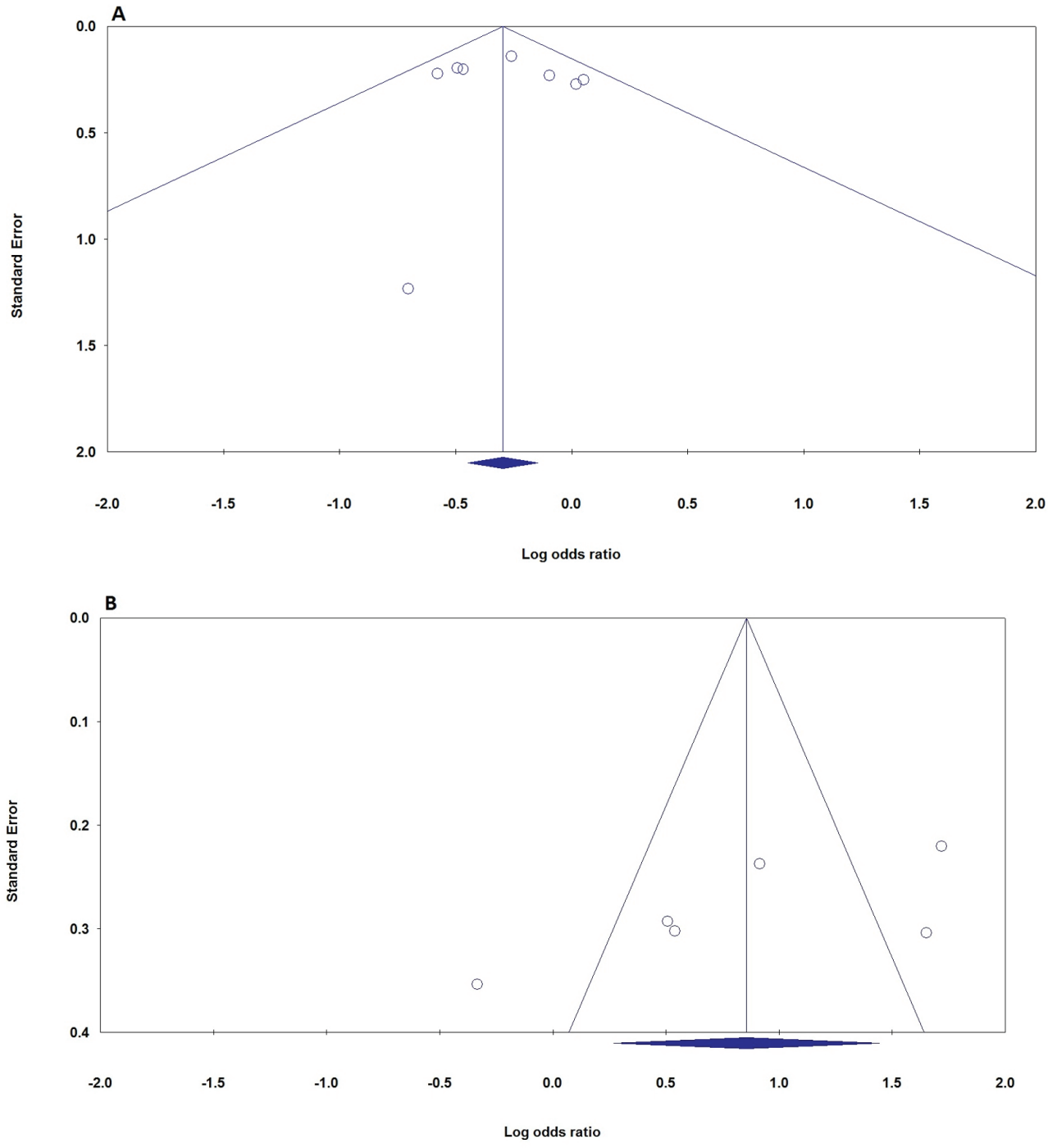


**Figure 4.** Begg's funnel plot of publication bias test for association of ACE I/D and PAI-1 4G/5G polymorphisms with risk of RPL risk in Iranian women. A: ACE (allele model); B: PAI-1 4G/5G (dominant model)

and PAI-1 with susceptibility to pregnancy loss in European and worldwide populations. Their pooled data revealed that there was no significant relationship between the 4G/5G polymorphism and pregnancy loss both in Europe or elsewhere in the world. However, Huang et al.[12], in a meta-analysis based on 31 studies with 5617 patients and 3.952 healthy subjects reported that that the PAI-1 4G/5G polymorphism might contribute to the susceptibility of RPL; their subgroup analysis by ethnicity indicated a significantly elevated risk of RPL in Asians, Caucasians, and Africans. In 2015, Liu et al.[45], in a meta-analysis of 22 studies with 4306 patients and 3076 controls, showed that the PAI-1 4G/5G polymorphism might be associated with RPL in the overall population [OR=1.89; 95% CI: (1.34-2.67); p<0.001]. In a subgroup analysis, they found that the PAI-1 4G/5G polymorphism was significantly associated with an increased risk of RPL in Caucasian

**Table 3. Summary risk estimates for association of PAI-1 4G/5G polymorphism with RPL in Iranian women**

| Subgroup | Genetic model | Type of model | Heterogeneity | | Odds ratio (OR) | | | | Publication bias | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | $I^2$ (%) | $P_H$ | OR | 95% CI | $Z_{OR}$ | $P_{OR}$ | $P_{Beggs}$ | $P_{Eggers}$ |
| Overall | 4G4G vs 5G5G | Random | 77.18 | 0.001 | 2.352 | 1.623-3.408 | 4.516 | ≤0.001 | 0.452 | 0.379 |
| | 4G5G vs 5G5G | Random | 88.76 | ≤0.001 | 2.192 | 1.093-4.394 | 2.212 | 0.027 | 0.060 | 0.021 |
| | 4G4G vs 5G5G | Fixed | 22.68 | 0.263 | 8.364 | 4.744-14.756 | 7.341 | ≤0.001 | 0.259 | 0.061 |
| | 4G4G+4G5G vs 5G5G | Random | 85.59 | ≤0.001 | 2.354 | 1.309-4.235 | 2.858 | 0.004 | 0.259 | 0.120 |
| | 4G4G vs 4G5G+5G5G | Random | 23.72 | 0.256 | 5.208 | 3.005-9.025 | 5.882 | ≤0.001 | 0.132 | 0.028 |
| RM no | | | | | | | | | | |
| ≥2 | 4G4G vs 5G5G | Fixed | 25.21 | 0.263 | 2.083 | 1.617-2.682 | 5.684 | ≤0.001 | 1.000 | 0.848 |
| | 4G5G vs 5G5G | Random | 83.16 | 0.003 | 2.046 | 0.920-4.551 | 1.756 | 0.079 | 1.000 | 0.102 |
| | 4G4G vs 5G5G | Fixed | 51.41 | 0.128 | 8.390 | 3.509-20.061 | 4.783 | ≤0.001 | 1.000 | 0.374 |
| | 4G4G+4G5G vs 5G5G | Fixed | 0.00 | 0.465 | 2.003 | 1.472-2.727 | 4.416 | ≤0.001 | 1.000 | 0.114 |
| | 4G4G vs 4G5G+5G5G | Fixed | 0.00 | 0.392 | 5.871 | 2.528-13.631 | 4.118 | ≤0.001 | 1.000 | 0.207 |
| ≥3 | 4G4G vs 5G5G | Random | 87.73 | ≤0.001 | 2.653 | 1.299-5.418 | 2.678 | 0.007 | 1.000 | 0.698 |
| | 4G5G vs 5G5G | Random | 93.44 | ≤0.001 | 2.318 | 0.613-8.774 | 1.238 | 0.216 | 0.296 | 0.329 |
| | 4G4G vs 5G5G | Fixed | 14.93 | 0.309 | 8.345 | 3.955-17.606 | 5.570 | ≤0.001 | 0.296 | 0.389 |
| | 4G4G+4G5G vs 5G5G | Random | 92.39 | ≤0.001 | 2.814 | 0.860-9.202 | 1.711 | 0.087 | 0.296 | 0.423 |
| | 4G4G vs 4G5G+5G5G | Random | 55.99 | 0.103 | 4.764 | 2.305-9.845 | 4.215 | ≤0.001 | 0.296 | 0.067 |

RM: Recurrent miscarriage

populations [OR=2.23; 95% CI: (1.44-3.46); p<0.001], but they reported that the PAI-1 4G/5G polymorphism was not significantly associated with RPL risk in Asian populations[45].

The current meta-analysis results showed that ACE I/D polymorphism was associated with increased risk of RPL in Iranian women under the allele genetic model [D vs I: OR=0.745, 95% CI: (0.641-0.866); p≤0.001]. Recently, Gumus[46] in a case-control study, showed that the ACE I/D polymorphism was associated with idiopathic recurrent pregnancy loss (IRPL), and women with DD or ID genotypes had a 72% higher risk of developing IRPL than women with the II genotype. In 2018, Aslebahar et al.[39], in a meta-analysis of 26 case-control studies with 3140 patients with RPL and 3.370 controls, showed that that ACE I/D polymorphism was associated with increased risk of RPL in the overall population. Similarly, Wang et al.[47], in a meta-analysis on 11 studies with a total of 3.357 individuals showed that the polymorphism was linked with an increased risk of recurrent miscarriage. By contrast, Pereza et al.[48], in a meta-analysis based on 1,192 patients and 736 healthy subjects, showed no association between the ACE I/D polymorphism and RPL. Moreover, they performed a case-control study on 149 women (with ≥3 spontaneous abortions) and 149 healthy subjects to evaluate the association among Croatian women. Similarly, they showed a negative association between the ACE I/D polymorphism and the risk of RPL[48]. In 2013, Su et al.[49], in a meta-analysis based on 11 studies, reported a significant association between the ACE I/D polymorphism and IRPL. However, they found no significant association between the ACE I/D polymorphism and IRPL in Caucasian and non-Caucasian patients[49].

To our knowledge, this is the first meta-analysis to prove a significant association of the ACE I/D and PAI-1 4G/5G polymorphisms with RPL risk in Iranian women. However, the results presented here should be interpreted with caution because of several potential limitations. First, only published studies were included in this meta-analysis and some unpublished studies may have been missed, which may have biased the observed associations of ACE I/D and PAI-1 4G/5G polymorphisms with RPL in Iranian women. Second, there was relatively high heterogeneity under some genetic models. Third, the number of studies and the sample sizes were relatively small for analysis, thereby having insufficient power to estimate the association of ACE I/D and PAI-1 4G/5G polymorphisms with RPL in Iranian women. Fourth, the pooled estimates were based on unadjusted data, which might have affected the accuracy of the results. This is a meta-analysis with insufficient individual data to stratify results by other risk factors such as maternal age, environmental pollution, smoking; therefore, the association in these factors could not be assessed. Finally, RPL is a multifactorial disease influenced by many compound factors, including single or combined genetic polymorphisms and environmental factors. However, the impact of gene-gene,

gene-environment interactions and also ACE I/D and PAI-1 4G/5G polymorphisms interactions were precluded owing to insufficient original data.

## Conclusion

Considering all the results, the pooled data indicated that ACE I/D and PAI-1 4G/5G polymorphisms were associated with an increased risk of RPL in Iranian women. Moreover, these polymorphisms were associated with RPL risk by the number of previous miscarriages. These significant findings suggest that investigation might be adequate for ACE I/D and PAI-1 4G/5G polymorphisms in association with RPL in Iranian women.

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### Ethics

**Peer-review:** Internally peer-reviewed.

### Authorship Contributions

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*Review / Derleme*

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# Systematic review of the safety and efficacy of tramadol during office hysteroscopy

## *Ofis histeroskopi sırasında tramadolün güvenlik ve etkinliğinin sistematik derlemesi*

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**Abstract**

Office hysteroscopy (OH) is a common procedure in gynecology. Pain is the most frequently reported problem in OH. In this study, we aimed to investigate the role of tramadol administration in relieving pain in women undergoing OH. We searched PubMed, the Cochrane Library, ClinicalTrials.gov, MEDLINE, Scopus, and Web of Science databases for relevant clinical trials based on our search terms. We included randomized controlled trials and included all published trials in all six searched databases from their inception until February 28th 2021.

We included pain as the primary outcome, and the incidence of adverse events of tramadol as secondary outcomes. We performed the analysis of continuous data using mean difference (MD) and dichotomous data using risk ratio (RR). We found that tramadol led to significantly less pain during the actual procedure [MD=-1.27, 95% confidence interval (CI): (-1.66, -0.88); p<0.001], immediately after the procedure [MD=-1.03, 95% CI: (-1.40, -0.67); p<0.001], and 30 minutes after the procedure [MD=-0.74, 95% CI: (-1.06, -0.41); p<0.001]. Regarding safety endpoints, no significant difference was noted for dizziness [RR=1.88, 95% CI: (0.79, 4.47); p=0.16] or vomiting [RR=1.80, 95% CI: (0.40, 8.18); p=0.45]. Based on the available data, we conclude that tramadol administration seems to be both effective and safe for patients undergoing office hysteroscopy.

**Keywords:** Office hysteroscopy, tramadol, office surgery, ERAS protocol, ERAS hysteroscopy

**Öz**

Ofis histeroskopi (OH) jinekolojide yaygın bir prosedürdür. OH için en sık bildirilen komplikasyon ağrıdır. Bu çalışmada, OH uygulanan kadınlarda ağrının giderilmesinde tramadol uygulamasının rolünü araştırmayı amaçladık. Arama terimlerimize dayalı olarak ilgili klinik çalışmalar için PubMed, Cochrane Library, ClinicalTrials.gov, MEDLINE, Scopus ve Web of Science veritabanlarında tarama yaptık. Derlemeye randomize kontrollü çalışmaları dahil ettik. Tarama yaptığımız 6 veri tabanındaki yayınlanmış tüm çalışmalar, başlangıçlarından 28 Şubat 2021'e kadar dahil edildi. Ağrıyı birincil sonlanım ve tramadolün advers olaylarının insidansını ikincil sonlanım olarak kabul ettik. Sürekli verilerin analizini ortalama farkı (MD) kullanarak; ikili verilerin analizini risk oranını (RO) kullanarak gerçekleştirdik. Tramadolün gerçek prosedür sırasında önemli ölçüde daha az ağrıya neden olduğunu bulduk [MD=-1,27 %95 güven aralığı (GA)=(-1,66, -0,88) p<0,001], işlemden hemen sonra [MD=-1,03 %95 GA=(-1,40, -0,67) p<0,001] ve prosedürden 30 dakika sonra [MD=-0,74 %95 GA=(-1,06, -0,41) p<0,001]. Güvenlik sonlanım noktaları ile ilgili olarak, baş dönmesi [RO=1,88 (%95 GA=0,79, 4,47) p=0,16] veya kusma [RO=1,80 %95 GA=(0,40, 8,18) p=0,45] açısından anlamlı bir fark kaydedilmedi. Mevcut verilere dayanarak, tramadol uygulamasının OH yapılan hastalar için hem etkili hem de güvenli olduğu sonucuna vardık.

**Anahtar Kelimeler:** Ofis histeroskopi, tramadol, ofis cerrahisi, ERAS protokolü, ERAS histeroskopi

## Introduction

Hysteroscopy is considered the gold standard investigation for the evaluation of uterine abnormalities[1-3]. One very useful variant of this is office hysteroscopy (OH), where minimally invasive tools are used alongside local anesthesia to perform hysteroscopy in the office setting. Like traditional hysteroscopy with general anesthesia, OH involves visualization of the cervical

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canal, uterine cavity, endometrium, and the origin of the fallopian tubes via a miniaturized endoscope that is introduced directly through the cervix without the need for dilation. A uterine distending medium, usually saline, is continuously pumped into the uterine cavity during the procedure to maintain distension[4]. The main two types of hysteroscopes include rigid and flexible. The rigid type consists of an optic channel (contprocaining a camera and optical prisms) and an outer sheath that allows entry and return of the fluid used in the examination. The second type is the flexible hysteroscope that consists of a system of optical fibers and a flexible sheath. Many authors have reported flexible hysteroscopes to be associated with less pain[5,6].

OH is indicated in diagnostic cases and can be therapeutic such as in resection of fibroma or polyp. The main indications for this investigation include menstrual cycle abnormalities such as menorrhagia or metrorrhagia, postmenopausal bleeding, suspected pathology of the uterine cavity (fibroid, polyp, or cancer of the uterine lining endometrium), uterine malformation, uterine synechia, as well as in the investigation of infertility, repeated abortions and to assist in the removal of an intrauterine device whose strings are not otherwise visible[7-9]. In addition to avoiding general anesthesia, another advantage of OH is the sparing of the patient of many expenses such as hospital stay and operating room fees[8,10]. Nevertheless, the pain associated with OH remains a troublesome barrier for women, and the ideal regimen or combination of local or systemic anesthesia is still being investigated[11].

The nature of pain experienced at the time of OH is not completely understood, but many authors attribute the majority of the pain to mechanical cervical dilation necessary to access the uterine cavity during the procedure, as well as the distending agent[12,13].

Several approaches have been suggested by different authors to control this pain. Some suggested regimens have included the oral administration of non-steroidal anti-inflammatory drugs (NSAIDs) at the time of hysteroscopy[2], and others have attempted local anesthesia to improve pain[14,15]. Tramadol (Ultram) is a synthetic codeine analogue, with central analgesic properties with effects similar to other opioids, such as morphine and codeine, acting on specific opioid receptors. Unlike traditional opioids such as morphine and oxycodone, tramadol's main mechanism of action is unknown, resulting in lower addictive potential and classification as schedule IV in the United States Drug Enforcement Agency (DEA) classification. As a result, tramadol is widely used in postoperative pain management in obstetrics and gynecology. Common adverse effects of tramadol include nausea, vomiting, headache, dizziness, gastric pain, anxiety, panic attacks and depression. Tramadol can be administered orally or parenterally before hysteroscopy. The oral route allows reducing the discomfort by avoiding injection, but some authors have reported it may have limited benefit compared with the parenteral route[16].

Since the last major meta-analysis of the use of tramadol in OH[17], our authors observed the publication of two major randomized controlled trials (RCTs) on this same topic[18,19]. As a result, in response to the new relative wealth of data, we aimed to systematically review all available data concerning the efficacy and safety of tramadol in relieving the pain of OH.

## Materials and Methods

We conducted this systematic review according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines[20], and performed all steps in strict accordance with the Cochrane handbook of systematic reviews of interventions[21].

### Literature Search Strategy

We conducted a detailed search using several electronic databases including ClinicalTrials.gov, MEDLINE, PubMed, SCOPUS, and the Cochrane Library. Our search protocol involved different combinations of these MeSH terms: (Tramadol OR Tramundin OR Biodalgic OR Jutadol OR Nobligan OR Prontofort OR Zytram OR Takadol OR Theradol OR Tiral OR Topalgic OR Tradol OR Tradonal OR Tralgiol OR "Trama AbZ" OR "Trama Dorsch" OR Biokanol OR Tramabeta OR Tramadin OR Tramadoc OR "Trama 1A Pharma" OR Trasedal OR Xymel OR Zamudol OR Zumalgic OR Zydol OR Tramadura OR Tramagetic OR Tramagit OR Tramake OR Tramal OR Tramex OR Adolonta OR Contramal OR Amadol OR Qdolo OR Ryzolt OR ConZip) AND (Hysteroscopy OR Hysteroscopies OR "Uterine Endoscopy" OR Uteroscopy OR Uteroscopies OR "Uterine Endoscopies" OR "Hysteroscopic Surgical Procedure" OR "Hysteroscopic Surgery" OR "Hysteroscopic Surgeries"). Studies were collected up to February 28th, 2021. We then manually reviewed all of the references of the originally located studies, as well as all of the references of the systematic reviews that have been previously published on this topic. These were all reviewed to search for any RCTs that could have been missed by our original search strategy.

### Eligibility Criteria and Study Selection

Two independent authors screened the titles and abstracts of the identified articles to assess relevance to this meta-analysis. In case of disagreement, the full text was retrieved and reviewed independently by a senior author for a final decision. We included every RCT that we could locate that included a comparison of tramadol and placebo for reducing pain associated with OH. We did not include any restriction as far as the age or race of the patients, the country of origin of the study, or the date that the study was published. We excluded the following four groups of studies: (1) studies not published in the English language, (2) studies that were based on conference posters, found in books, review articles, doctoral thesis, opinionated editorials, letters to the editor, non-randomized case series, and isolated case reports, (3) data that could not be considered to be reliably extracted, studies with overlapping sets of data, studies that

had only the abstract available, and (4) studies that had animal participants. Duplicates were removed and retrieved references were screened in two steps: the first step was to screen titles/abstracts for matching our inclusion criteria and the second step was to screen the full-text articles of eligible abstracts for eligibility for meta-analysis.

### Data Extraction

Two independent authors extracted the relevant data from the included studies. The initial selected data included the patient's body mass index, indication for hysteroscopy, age, gestational parity, and the total duration of the hysteroscopy in minutes. The primary outcome that we extracted was the score assessed using a visual analog scale (VAS) associated with the hysteroscopy. We extracted data to measure this pain scale during three separate periods. These included pain that occurred during the procedure, immediately following the procedure, and lastly, half an hour after the conclusion of the procedure). We also extracted a secondary outcome: tramadol adverse effects, which include dizziness and vomiting in a form of number and percentage.

### Quality of Included Studies and Risk of Bias Assessment

The risk of bias and quality of the eligible studies was assessed by two independent reviewers. We used the Cochrane Collaboration's tool for the assessment of the risk of bias [21]. Any discrepancies were solved through discussion and consensus between reviewers. The domains upon which the included articles were assessed were sequence generation (selection bias), allocation sequence concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective outcome reporting (reporting bias) and other potential sources of bias. The authors' judgment was categorized as "Low risk", "High risk" or "Unclear risk" of bias.

### Data Synthesis

In the statistical analysis, we used the Review Manager Software (RevMan version 5.3). Relative risk and 95% confidence intervals (CI) were used in our analysis. In dichotomous data, event and total were used to represent the data, and in continuous data, mean (M) and standard deviation (SD) were used. The missing SD was calculated from the standard error, 95% CI, or range according to Wan et al.[22]. To test for statistical heterogeneity between trials, chi-square and $I^2$ tests were employed; values of 0-40%, 30-60%, 50-90%, and 75-100% represented low, moderate, substantial, and considerable heterogeneity respectively. A p-value of ≥0.1 was set as the level of significant homogeneity.

## Results

### Results of Literature Search

Following our literature search and removal of duplications, there were 82 studies available for title and abstract screening. Seventeen studies were initially eligible for full-text screening. Only six studies (738 patients) fulfilled our eligibility criteria, and five were included in our meta-analysis figure 1 illustrates the PRISMA flow diagram)[18,19,23-25]. The sixth study was not included in our analysis because it reported the outcomes in the form of median only, so we could not convert the data into means and SD values for meaningful comparison with the other included studies[26]. All included studies were double-blinded RCTs. The summary of baseline characteristics of enrolled patients is presented in Table 1.

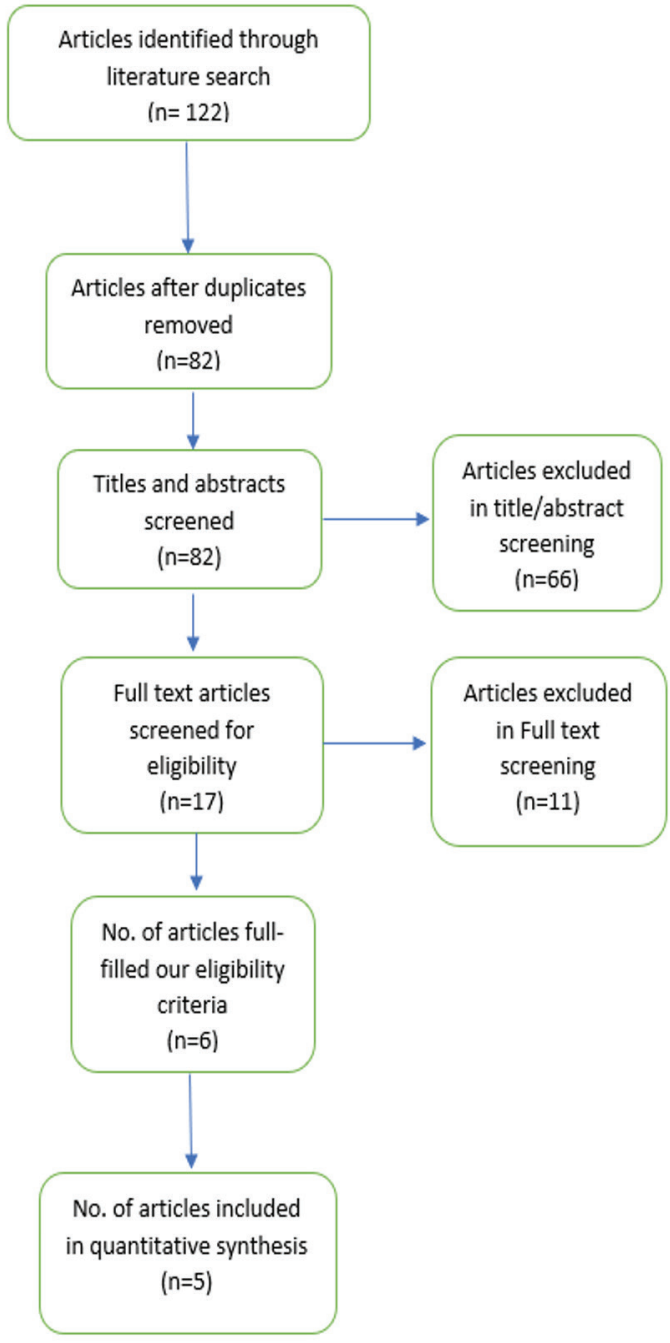


**Figure 1.** PRISMA flow diagram

**Table 1.** Baseline characteristics of included studies

| Author/year | Study groups | Age (Years) (mean ± SD) | Duration of procedure (min) n. (%) | No. of multiparous women n. (%) | BMI (mean ± SD) | Indication of hysteroscopy | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | Ab-normal uterine bleeding (AUB) n. (%) | Re-current mis-carriage n. (%) | Infertility n. (%) |
| Bharathi et al.[18] | Tramadol (50 mg orally) | 46.2±8.9 | 3.76±2.53 | 46 (92) | NA | 35 (70) | NA | NA |
| | Placebo | 45.4±8.4 | 3.75±2.35 | 47(94) | NA | 40 (80) | NA | NA |
| Floris et al.[23] | Tramadol (100 mg/2 mL I.V) | 47.2±2.8 | 1.63±0.16 | 25 (100) | NA | 10 (40) | NA | NA |
| | placebo | 44.3±2.5 | 1.64±0.18 | 25 (100) | NA | 8 (32) | NA | NA |
| Hassan et al.[24] | Tramadol (100 mg orally) | 29.25±6.39 | 1.92±0.98 | 25 (35.7) | 25.77±4.37 | 16 (22.9) | 10 (14.2) | 39 (55.8) |
| | Placebo | 30.8±6 | 2.02±0.83 | 34 (48.6) | 25.84±4.46 | 27 (38.6) | 4 (5.7) | 34 (48.6) |
| Hassan et al.[25] | Tramadol (50 mg orally) | 31.5±7.4 | 2.4±1.2 | NA | 29.1±2.9 | 17 (24) | 16 (23) | 30 (43) |
| | Placebo | 32.3±8.1 | 2.1±1.1 | NA | 28.8±2.8 | 14 (20) | 19 (27) | 32 (46) |
| Samy et al.[19] | Tramadol (50 mg orally) | 57.8±7.3 | 3.3±1.7 | NA | 27.9±3.4 | NA | NA | NA |
| | Placebo | 60.4±6.7 | 3.1±1.1 | NA | 29.1±3.4 | NA | NA | NA |
| Kadiroğulları et al.[26] | Tramadol (100 mg orally) | 45±1.4 | NA | NA | 27±2.8 | 15 (34) | NA | NA |
| | Placebo | 44.08±1.3 | NA | NA | 28.2±1.9 | 19 (43) | NA | NA |

NA: Not available, n: Number, SD: Standard deviation

### Results of Quality Assessment

According to the Cochrane risk of bias assessment tool[21], the overall risk of bias of the included studies was low. All included studies were at low risk of random sequence generation, blinding of participants and personnel, incomplete data, and selective reporting. However, three studies were unclear in the term of allocation concealment[23,25,26]. Also, three studies were unclear in the blinding of outcome assessment[19,23,25]. Figure 2 illustrates the results of risk of bias assessment for each domain in included studies.

## Results of Outcomes

### Pain Score

### Pain During The Procedure

All studies[18,19,23-25] reported pain score outcomes during the procedure using VAS scores. The analysis significantly favored the tramadol group over the placebo group [MD=-1.27, 95% CI: (-1.66, -0.88); p<0.001). Data were homogenous (p=0.66, $I^2$=0%). A forest plot of these data is shown in Figure 3.

### Pain Immediately After The Procedure

All studies[18,19,23-25] reported pain score outcomes after the procedure using VAS scores. The analysis significantly favored the tramadol group over the placebo group [MD=-1.03, 95% CI: (-1.40, -0.67); p<0.001]. Data were homogenous (p=0.999,

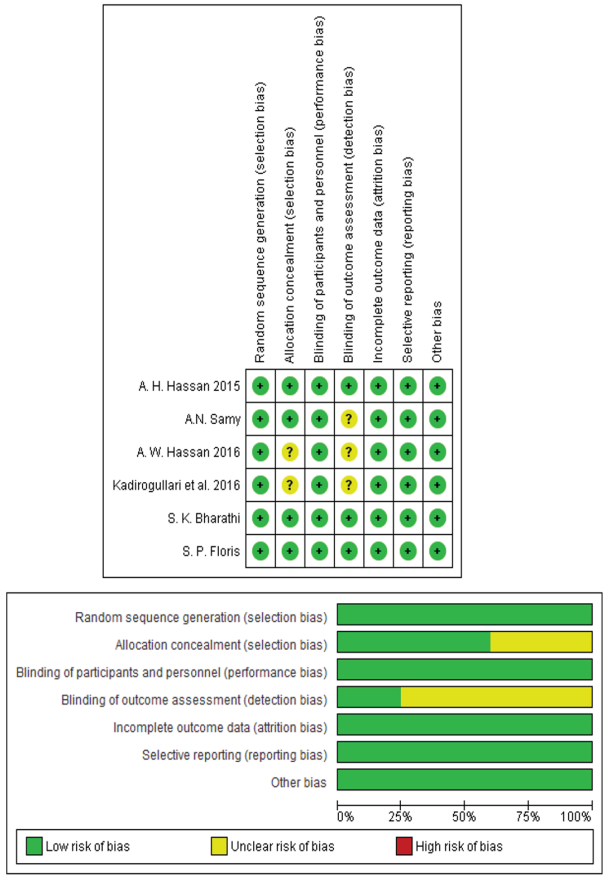


**Figure 2.** Risk of bias assessment

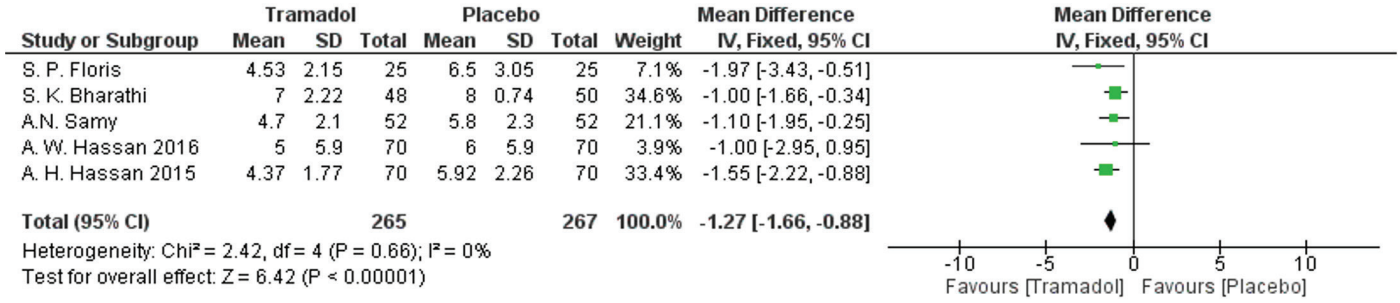


**Figure 3.** Forest plot of visual analog scale pain outcomes during the procedure

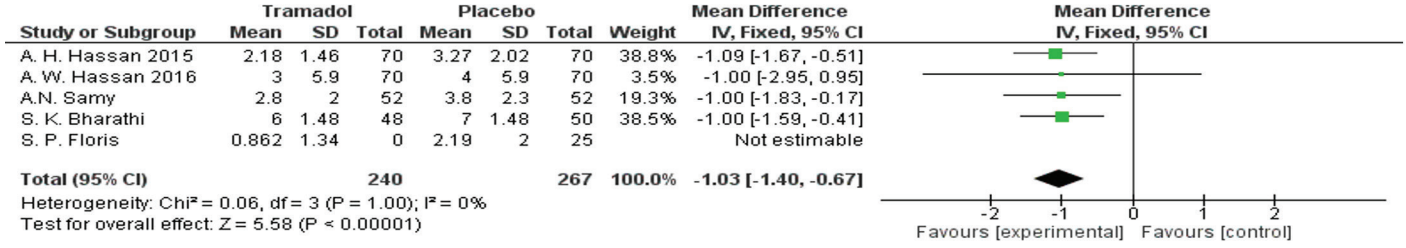


**Figure 4.** Forest plot of visual analog scale pain outcomes immediately after the procedure

$I^2$=0%). A forest plot of these data I presented in Figure 4.

### Pain Half an Hour After the Procedure

All studies[18,19,23-25] reported pain score outcomes 30 minutes after the procedure using VAS scores except Floris et al.[23]. The analysis significantly favored the tramadol group over the placebo group [MD=-0.74, 95% CI: (-1.06, -0.41); p<0.001]. Data were homogenous (p=0.19, $I^2$=36%). A forest plot of this data is shown in Figure 5.

### Time Until the Patient Was Pain-free

Hassan et al.[24] and Samy et al.[19] reported the elapsed time until the patient was pain-free. The analysis significantly favored the tramadol group over the placebo group [MD=-8.65, 95% CI: (-12.41, -4.89); p<0.001]. Data were homogenous (p=0.43, $I^2$=0%). A forest plot of these data is presented in Figure 6.

## Adverse Effects

### Dizziness

Samy et al.[19] and Bharathi et al.[18] reported dizziness outcomes. There was no significant difference between tramadol and placebo groups [RR=1.88, 95% CI: (0.79, 4.47); p=0.16]. Data were homogenous (p=0.81, $I^2$=0%). A forest plot of these data is shown in Figure 7.

### Vomiting

Samy et al.[19] and Floris et al.[23] reported vomiting outcomes. There was no significant difference between tramadol and placebo groups [RR=1.80, 95% CI: (0.40, 8.18); p=0.45]. Data were homogenous (p=0.71, $I^2$=0%). A forest plot of these data is presented in Figure 8.

## Discussion

Our analysis found that the use of tramadol before the hysteroscopy procedure could significantly reduce pain scores (VAS score) during and 30 minutes after the procedure. We also found that the time until the patient was completely pain-free was significantly shorter in the tramadol group when compared with the placebo. As for safety, our review analyzed two adverse effects, dizziness and vomiting, and we found that there was no significant difference between tramadol and placebo groups. A major impetus for this review was the review two years ago performed by Mattar et al.[17] in 2019 that first showed an improvement in pain scores with the use of tramadol during OH. This review also found that the use of tramadol resulted in no significant adverse effects. These results were similar to those of our analysis. This earlier analysis included only four studies[23-26]. Our study was able to include six studies, allowing a much larger sample size because more data have become available[18,19,23-25]. The previous analysis analyzed only patients of reproductive and perimenopausal age. Our analysis has additionally been able to assess patients in the post-menopausal period to ensure diverse data covering the entire range of patients undergoing hysteroscopy. Hence, we consider that this analysis may be seen as more comprehensive. In addition, this analysis assessed new outcomes (time to until the patient is pain-free) and a new adverse effect (dizziness).

A range of pharmacologic interventions, such as local anesthesia, oral and intravenous opioids, NSAIDs, misoprostol, lidocaine-prilocaine cream, dinoprostone, and buprenorphine) and non-pharmacologic interventions [including transcutaneous electrical nerve stimulation (TENS), bladder distension, music and warm saline] have been used to reduce the pain associated

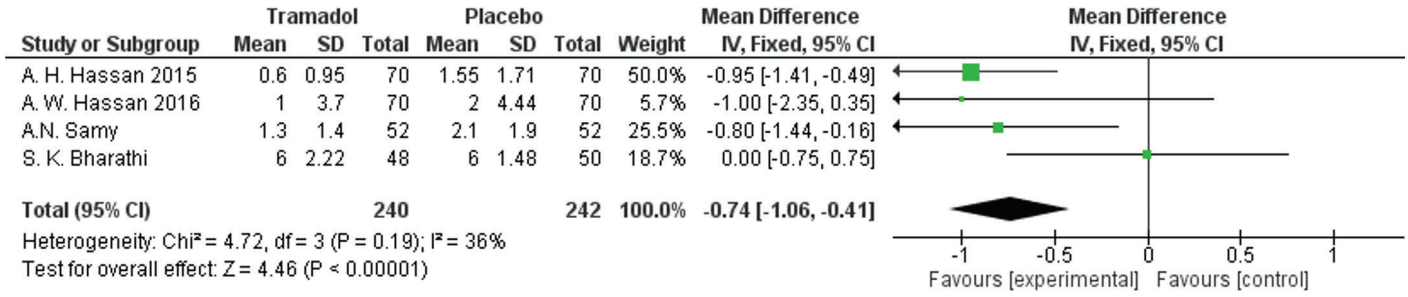


**Figure 5.** Forest plot of visual analog scale pain outcomes 30 minutes after the procedure

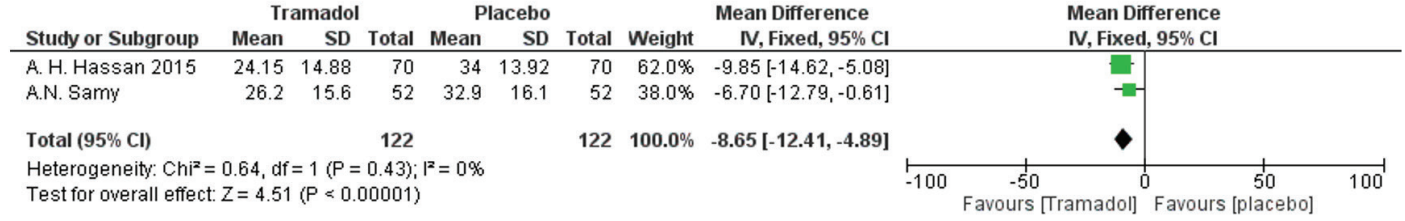


**Figure 6.** Forest plot of elapsed time until the patient is pain-free

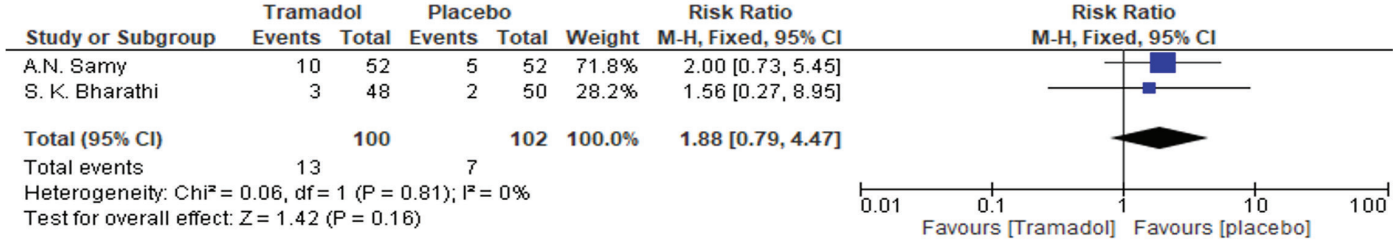


**Figure 7.** Forest plot of the incidence of patient-reported dizziness as an adverse effect

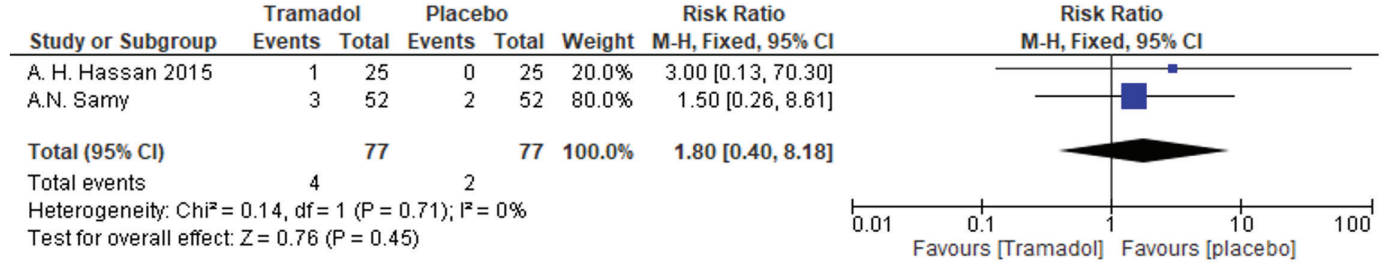


**Figure 8.** Forest plot of the incidence of vomiting as an adverse effect

with the hysteroscopy procedure. A recent review and meta-analysis evaluated these interventions to detect the highest-ranked intervention that could be applied. The review concluded that the combination of misoprostol and local anesthesia was the most effective pharmacologic intervention. As for non-pharmacologic interventions, TENS and bladder distension were effective but further investigations were recommended[27]. Another recent review compared the efficacy of different types and routes of administration of local anesthesia (topical, paracervical, intracervical, topical and transcervical, and intracornual), and found that any route of administration could be considered in pain management during OH. It also found that mepivacaine and bupivacaine were the only local anesthetics that seemed to significantly reduce the pain score after the procedure[28]. Nevertheless, Cooper et al.[29] concluded that local anesthesia via the intracervical route was the best in pain management during OH compared with different routes of local anesthesia administration.

A review by Ahmad et al.[30] assessed the efficacy of various analgesics used to reduce the pain associated with the hysteroscopy procedure. The authors found that neither opioids nor NSAIDs significantly reduced the pain score during the procedure and 30 min after the procedure.

As for lidocaine, De silva et al.[28] concluded that it could relieve the pain only during OH, but there was no significant reduction in the pain after the procedure. These findings were similar to an RCT by Samy et al.[19] who found the superiority of lidocaine to placebo in pain control during and 10 min after the procedure, but there was no significant difference 30 min after the procedure.

Mohammadi et al.[31] reported that rectal diclofenac was better than intrauterine lidocaine in pain control during OH; however, no significant difference in the pain score was found between the two groups. Similarly, El-Gamal found that oral diclofenac was more effective than lidocaine in pain management during OH[32]. However, Senturk and Guraslan[33] found that intrauterine lidocaine was superior to rectal indomethacin in pain relief while performing OH.

Prostaglandins are another medication proposed to reduce discomfort in hysteroscopic procedures[29]. They act by ripening the cervix to facilitate easy dilatation[34]. A review by Cooper et al.[29] assessed their efficacy in the pain relief associated with hysteroscopy compared with placebo in both premenopausal and postmenopausal women. It concluded that there was no evidence that the use of either misoprostol or mifepristone could reduce the pain associated with the procedure.

In a comparison with other analgesics, Samy et al.[19] found that there was no significant difference between tramadol and lidocaine in either the reduction of the pain scores or time until the patient was pain-free. Hassan et al.[24,25] found that there was no significant difference between tramadol and celecoxib in the reduction of the pain scores during and after OH, but found celecoxib had fewer adverse effects.

### Study Strengths and Limitations

The main strength of our analysis is the inclusion of double-blinded controlled trials with a low risk of bias. Also, the data of the included studies are homogenous. The main limitation is the low number of included studies.

Further RCTs are needed to establish the safety and efficacy of tramadol in postmenopausal women undergoing OH, although our initial data here are promising. The comparison of the different tramadol doses and different routes of administration would also give valuable insight into the most efficacious way to administer tramadol, and may maximize pain relief.

## Conclusion

This analysis has found that tramadol can be used effectively and safely in the management of pain in OH.

### Ethics

**Peer-review:** Externally peer-reviewed.

### Authorship Contributions

Surgical and Medical Practices: H.M., G.J.M., K.W., A.M., A.K., S.R., G.B., H.U., J.P., A.A., K.S., M.A.S., Concept: H.M., G.J.M., K.W., A.M., A.K., S.R., G.B., H.U., J.P., A.A., K.S., M.A.S., Design: H.M., G.J.M., K.W., A.M., A.K., S.R., G.B., H.U., J.P., A.A., K.S., M.A.S., Data Collection or Processing: H.M., G.J.M., K.W., A.M., A.K., S.R., G.B., H.U., J.P., A.A., K.S., M.A.S., Analysis or Interpretation: H.M., G.J.M., K.W., A.M., A.K., S.R., G.B., H.U., J.P., A.A., K.S., M.A.S., Literature Search: H.M., G.J.M., K.W., A.M., A.K., S.R., G.B., H.U., J.P., A.A., K.S., M.A.S., Writing: H.M., G.J.M., K.W., A.M., A.K., S.R., G.B., H.U., J.P., A.A., K.S., M.A.S.

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

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# Perinatal outcomes of high-dose vitamin D administration in the last trimester

## *Son trimesterde yüksek doz D vitamini uygulamasının perinatal sonuçları*

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**Abstract**

In recent years, interest in the evaluation of vitamin D levels and the possible outcomes of their deficiency during pregnancy has increased. However, there is no consensus on when to start vitamin D supplementation, its duration, dosage, and the optimum level during pregnancy. The toxicity of vitamin D is as important as its deficiency. From the history of a 5-day-old male baby who was investigated for hypercalcemia, it was learned that the mother took 300,000 IU vitamin D-five ampoules/oral at 30 weeks of gestation every other day. The infant was born prematurely, postpartum bradycardia required positive pressure ventilation, and his hypercalcemia lasted approximately 4 months despite treatment. Maternal excessive and inappropriate use of vitamin D can cause preterm labor and severe hypercalcemia, which is a life-threatening complication in the neonatal period. This case is presented to draw attention to the negative effects of maternal high-dose vitamin D during pregnancy.

**Keywords:** Hypercalcemia, 25 (OH) vitamin D, vitamin D intoxication, neonatal outcomes

**Öz**

Son yıllarda D vitamininin gebelikte değerlendirilmesi ve eksikliğinin olası sonuçlarına yönelik ilgi artmıştır. Ancak gebelikteki D vitamini desteğinin ne zaman başlanacağı, süresi, dozu ve olması gereken optimum düzeyi konusunda fikir birliği bulunmamaktadır. D vitamininin eksikliği kadar toksisitesi de önemlidir. Hiperkalsemi nedeni ile danışılan beş günlük erkek bebeğin öyküsünden annenin 30. gebelik haftasında, gün aşırı, 300.000 IU D vitamini-beş ampul/oral aldığını öğrenildi. Olgu, prematüre doğmuş, doğum sonrası bradikardi nedeni pozitif basınçlı ventilasyon gereksinimi olmuş ve hiperkalsemisi tedavilere rağmen yaklaşık dört ay sürmüştü. D vitaminin maternal aşırı ve uygunsuz dozda kullanımı; erken doğum eylemine ve yenidoğan döneminde hayatı tehdit edici bir komplikasyon olan ciddi hiperkalsemiye neden olabilmektedir. Gebelikte maternal yüksek doz D vitaminin olumsuz etkilerine dikkat çekmek amacı ile bu olgu sunulmuştur.

**Anahtar Kelimeler:** Hiperkalsemi, 25 (OH) vitamin D, vitamin D intoksikasyonu, yenidoğan sonuçları

## Introduction

Vitamin D maintains the normal plasma levels of calcium and phosphorus and is essential for growth. Maternal vitamin D deficiency during pregnancy is known to play a role in preeclampsia, gestational diabetes mellitus, postpartum depression, low birth weight, periodontal diseases, and affects the development of the skeletal system, respiratory system, and central nervous system of the fetus[1,2]. It has been reported that vitamin D deficiency is seen in 80% of women in the reproductive period in Turkey, severe vitamin D deficiency is found in 27% of pregnant women, and 64% of cord blood[3]. However, there is no consensus on when to start vitamin D supplementation during pregnancy, the duration, dosage, and optimum level of vitamin D[1]. In recent years, there has been increased interest in the assessment of vitamin D levels during pregnancy and the possible consequences of deficiency[2]. However, its toxicity is as important as vitamin D deficiency. In this article, a case of neonatal hypercalcemia due to vitamin D intoxication after maternal high dose vitamin D intake during pregnancy will be discussed.

## Case Presentation

Written informed consent was obtained from the parents of the patient. A 5-day-old male baby was referred to endocrine

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clinic due to hypercalcemia. It was learned that he was born by cesarean section due to bradycardia detected in a non-stress test, from a 33-year-old mother's first pregnancy, with 7/9 Apgar score, at 34 weeks with a birth weight of 2.140 grams. Positive pressure ventilation was applied to the baby for 15 minutes due to postpartum bradycardia. He was then admitted to the neonatal intensive care unit for prematurity and bradycardia. In intensive care follow-up, cord blood gas analysis revealed the following results: pH: 7.21, $HCO_3$: 14.3 meq/L, base deficit: -12.5, lactate: 9.3 mg/dL (N: 0-2). Intravenous 0.9% NaCl loading at a dose of 20 mL/kg was performed. The patient was hospitalized with a preliminary diagnosis of lactic acidosis-metabolic disease because the follow-up blood gas analysis revealed acidosis and hypoglycemia. There was no tachypnea, bradycardia, and hypoglycemia in the follow-up. There was no pathology in the amplitude-integrated electroencephalography, which was examined for the possibility of convulsions due to hypoxia. Patent foramen ovale and thin ductus were found in echocardiography, no pulmonary hypertension was detected, and the metabolic test results and eye examinations were normal.

On the postnatal fifth day, serum calcium level was 10.8 (N: 8.9-10.8) mg/dL, ionized calcium: 1.44 (N: 1-1.3) mg/dL, phosphorus: 3.5 (N: 4.5-9) mg/dL, alkaline phosphatase: 132 IU/mL, parathormone <2.5 (N: 11-67) pg/mL, and albumin was 2.9 g/dL. The follow-up calcium value increased to 12 mg/dL and ionized calcium value increased to 1.57 mg/dL. When a more detailed history was taken, it was learned that the mother took five ampoules from 300,000 IU vitamin D ampules orally every other day at her 30$^{th}$ gestational week with the advice of her obstetrician (1,500,000 IU/total dose). The maternal serum calcium level was 9.4 mg/dL, phosphorus: 3.2 mg/dL, parathormone: 26.1 pg/mL, 25 OH vitamin D: 143.4 ng/mL, and renal ultrasonography revealed nephrocalcinosis. In our case, hydration, thiazide diuretic, steroid and alendronate treatments were given respectively for hypercalcemia. Calcium and its related laboratory test results under treatment are presented in Table 1. In the follow-up of the patient, the 25 OH vitamin D levels gradually decreased; however, hypercalcemia persisted for 3.5 months and crystalloidosis was detected in the imaging of the kidneys, and elevated platelet and troponin levels were detected during follow-up.

## Discussion

Vitamin D deficiency in pregnant women is a global public health problem. It is known that maternal vitamin D deficiency during pregnancy has many negative consequences[1,2,4]. 1.25-OH vitamin D levels start to increase from the first weeks of pregnancy to maintain intrauterine calcium homeostasis. The increase in 1.25-OH vitamin D during pregnancy has been associated with increased intestinal calcium absorption. Maternal 25-OH vitamin D crosses the placenta and is the main source of vitamin D for the fetus. It has also been reported that there is an increase in vitamin D-binding protein levels during pregnancy and therefore a decrease in free vitamin D levels[4]. Although vitamin D supplementation is recommended to all pregnant women, there is no consensus on the optimum dose and duration[1].

The mother of our patient was given five ampoules of 300,000 units vitamin D during the last trimester. The vitamin D ampoules were thought to be 30,000 units by the gynecologist. When he was considering giving a total amount of 150,000 units of vitamin D, he had inadvertently administered a 10-fold dose. As a result, it was determined that the mother's vitamin D levels increased to intoxication levels with 142 ng/mL and developed nephrocalcinosis and preterm labor when our case was evaluated due to hypercalcemia. In addition, although our patient's vitamin D levels decreased, his hypercalcemia returned to normal after a long time despite treatment and his troponin levels and platelet counts were also high for an extended period. We present this case to emphasize that intrauterine vitamin D intoxication (maternal administration of vitamin D at 30 weeks of gestation, delivery at 34 weeks of gestation, intrauterine exposure of toxic vitamin D doses for 4 weeks) affect the set points of vitamin D in the fetus (e.g. 24,25 hydroxylase activity, which is responsible for vitamin D degradation and calcium receptor sensitivity). The changes in set points prolong the treatment process; caution should be taken with vitamin D supplementation during pregnancy.

Hashemipour et al.[5] divided pregnant women with vitamin D levels below 30 ng/mL at 24-26 weeks of gestation into two groups. The first group received 200 mg of calcium and 400 units/day of vitamin D and the second group was administered an additional 50,000 units of vitamin D weekly. They found that the mothers who received an additional 50,000 units/week vitamin D for 8 weeks after 24-26 weeks had more weight gain and that their infants had better growth compared with the group that did not take the additional dose[5]. In a study in which breastfeeding mothers used vitamin D for 3 months at a dose of 4.000 units/day or 60,000 units/month, no evidence of toxicity was reported in both mothers and infants receiving breast milk[6,7]. In our case, the mother used 5 ampoules of 300,000 IU vitamin D (total 1,500,000 IU) every other day in the last five weeks of gestation and gave birth to her baby with fetal distress due to preterm labor at 34 weeks of gestation. In the literature, there is a case report of a woman who took 300,000 units of vitamin D weekly (5 ampoules as prescribed in our case) in the last 40 days of pregnancy. Her baby's serum Ca levels were found to be 19.2 mg/dL at the age of nine days, and the mother and the baby's vitamin D levels were 430 and 480 ng/dL, respectively. It was emphasized that hypercalcemia improved with hydration, furosemide, and prednisolone treatments[8]. This is another case of neonatal vitamin D intoxication due to intrauterine vitamin D exposure to toxic levels in the literature. Term birth at normal weight was achieved because the exposure to toxic doses of vitamin D

**Table 1. Follow-up the laboratory findings and treatment of the case**

| Follow-up days | 5 | 17 | 21 | 30 | 38 | 64 | 73 | 105 |
|---|---|---|---|---|---|---|---|---|
| Calcium (mg/dL) (8.9-10.8) | 10.7 | 11.3 | 11.7 | 11.1 | 11 | 10.1 | 11.2 | 10.1 |
| Ionized calcium (mmol/L) (1-1.3) | 1.52 | | 1.57 | 1.56 | 1.44 | 1.4 | 1.49 | 1.28 |
| Phosphorus (mg/dL) (4.5-6.7) | 2.9 | 4.7 | 5.3 | 4.6 | 4 | 4.4 | 4.7 | 7.6 |
| Parathormone (pg/mL) (11-67) | | <2.5 | <2.5 | | <2.5 | 5.1 | <2.5 | 80 |
| 25 (OH) vitamin D (ng/mL) | | 85.3 | | | 40.2 | 25 | | |
| Urine Ca/ creatinine | | | 2.89 | | 2.0 | 1.18 | 2.7 | 0.004 |
| Platelet $x10^3$/L (150-400) | 498 | 567 | | | | | 515 | 590 |
| Troponin I (0-0.06) | 0.555 | 1.741 | 1.127 | | | | 0.303 | 0.11 |
| Renal USG | | N | | | Cryst-alloid | Cryst-alloid | | |
| Treatment | Iv hydration diuretic | 1 mg/kg/day prednisolone p.o. | 1 mg/kg/day prednisolone p.o. | 1 mg/kg/day prednisolone p.o. | 1 mg/kg/day prednisolone p.o. | 1 mg/kg/day prednisolone p.o. | 1 mg/day alendronate p.o. | Stop |

in this case report was in the last 40 days of pregnancy, unlike in our case.

Vitamin D intoxication in infants is not very common and has generally been reported due to high-dose vitamin D intake[9]. Complications due to maternal high-dose vitamin D intake during pregnancy have been reported very rarely[8,10]. In our case, troponin I elevation, hypoxic-ischemic encephalopathy (HIE) and platelet elevation were also observed. In our case, oral alendronate treatment was given and normocalcemia was achieved. In the literature, another patient with transient hypercalcemia due to maternal high-dose vitamin D intake was reported[10]. In recent years, it has been observed that physicians are more interested in possible problems related to vitamin D deficiency during pregnancy[2]. It has been reported that vitamin D deficiency may be associated with problems such as preeclampsia, gestational diabetes mellitus, postpartum depression, preterm birth, and low birth weight in the literature[1,2]. However, excessive and inappropriate doses of vitamin D may cause severe hypercalcemia, which is a life-threatening complication in the neonatal period[8]. In this article, we discuss a case of hypercalcemia due to maternal high dose vitamin D intake in the last trimester of pregnancy and a newborn with HIE, thrombocytosis, and troponin I elevation. Our case is presented to draw attention to the negative effects of maternal high dose vitamin D intake during pregnancy, to prevent its random use, and to emphasize the importance of questioning the history of prenatal/postnatal maternal vitamin D intake in the etiology of hypercalcemia in the neonatal period.

### Ethics

**Informed Consent:** Written informed consent was obtained from the parents of the patient.

**Peer-review:** Internally peer-reviewed.

### Authorship Contributions

Surgical and Medical Practices: G.K.K., M.K., Concept: G.K.K., S.Ç., Design: S.Ç., Data Collection or Processing: Ş.S.E., G.K.K, M.K., S.Ç., Analysis or Interpretation: Ş.S.E., S.Ç., Literature Search: G.K.K., Writing: G.K.K.

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# Endovascular management of episiotomy site hematoma: Two cases and a brief review

## *Epizyotomi bölgesi hematomunun endovasküler yönetimi: İki hasta ve kısa bir inceleme*

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**Abstract**

Episiotomy site hematoma, though uncommon, can be associated with serious maternal morbidity. It arises mostly due to tissue trauma or injury to blood vessels, leading to the formation of a pseudoaneurysm. Sometimes, when surgical management fails, embolization of the bleeding vessel is a lifesaving option. Here, we report two cases of episiotomy site hematoma that required selective arterial embolization for management, following the failure of surgical management. A 28-year-old G6A5 woman underwent forceps delivery following which she developed a 6*6-cm right-sided vulvovaginal hematoma at the episiotomy site. After failed surgical management, arterial embolization was performed and hemostasis was achieved. A 26-year-old P2L2 woman with a history of surgical exploration for episiotomy site hematoma, presented postdelivery on postpartum day seven with profuse vaginal bleeding. Her computed tomography angiogram revealed a pseudoaneurysm of around 2.1*1 cm in length with a vaginal hematoma of 4*5 cm. Selective artery embolization performed and complete hemostasis was achieved with no complications. Selective arterial embolization is a safe therapeutic option for episiotomy site hematoma, especially if surgical management fails.
**Keywords:** Pseudoaneurysm, episiotomy site hematoma, selective artery embolization

**Öz**

Epizyotomi bölgesi hematomu nadir de olsa ciddi maternal morbidite ile ilişkilendirilebilir. Çoğunlukla doku travmasına bağlı olarak ortaya çıkar veya kan damarının yaralanmasına bağlı olarak psödoanevrizma oluşumuna neden olabilir. Bazen, cerrahi tedavi başarısız olduğunda, kanayan damarın embolizasyonu hayat kurtaran bir seçenektir. Burada, cerrahi tedavinin başarısızlığını takiben tedavi için selektif arteriyel embolizasyon gerektiren iki epizyotomi bölgesi hematomlu hasta bildiriyoruz. Yirmi sekiz yaşındaki G6A5 olan hasta forsepsle doğum yaptı ve ardından epizyotomi bölgesinde 6*6 cm boyutlarında sağ vulvovajinal hematom geliştirdi. Başarısız bir cerrahi tedaviden sonra arteriyel embolizasyon yapıldı ve hemostaz sağlandı. Epizyotomi yeri hematomu için cerrahi eksplorasyon öyküsü olan 26 yaşındaki P2L2 olan hasta doğum sonrası yedinci günde bol vajinal kanama ile başvurdu. BT anjiyografide yaklaşık 2,1*1 cm boyutlarında psödoanevrizma ve 4*5 cm boyutlarında vajinal hematom saptandı. Selektif arter embolizasyonu yapıldı ve komplikasyonsuz tam hemostaz sağlandı. Selektif arteriyel embolizasyon, özellikle cerrahi tedavi başarısız olursa epizyotomi bölgesi hematomu için güvenli bir tedavi seçeneğidir.
**Anahtar Kelimeler:** Psödoanevrizma, epizyotomi bölgesi hematomu, selektif arter embolizasyonu

## Introduction

Postpartum vulvovaginal hematomas are potentially life-threatening obstetric complications of vaginal delivery, most commonly presenting with episiotomy site swelling or hemorrhage. The management depends on the size of the hematoma and usually consists of incision and drainage of the hematoma with ligation of the bleeding vessels, followed by packing. Recurrent vaginal hematoma and episiotomy site pseudoaneurysm are rare complications that occur with episiotomy, mainly due to failed surgical management.

Pseudoaneurysms arise from disruption of arterial wall continuity by inflammation or events such as vascular trauma. Pseudoaneurysms differ from aneurysms in that they have a single layer of connective tissue, unlike true aneurysms, which have a three-layer wall[(1)]. Pseudoaneurysms can rupture due to high pressure in the artery, which can cause extravasation of blood through the connective tissue thus, leading to life-

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threatening vaginal bleeding or hematoma. Rapid progression of labor with vacuum or forceps delivery is a probable risk factor for vaginal pseudoaneurysm[2].

Here we report two unusual cases of episiotomy site haematoma following vaginal delivery managed successfully by selective arterial embolization.

## Case 1

A G6A5 28-year-old female with a 38+5 weeks' gestation known case of sickle cell anemia with beta-thalassemia trait and intrahepatic cholestasis of pregnancy came to our emergency department in labor. Her hemoglobin was 8 g/dL, platelet count was $1.4*10^5$, and her coagulation profile was normal at the time of admission. She underwent a forceps delivery and had atonic postpartum haemorrhage after delivery, which was medically managed. Soon she developed a right vulvovaginal hematoma of around 6*6 cm at the episiotomy site. Her hemoglobin dropped to 5.8 g/dL from the 8 g/dL and she had tachycardia of 120 beats/minute.

Surgical exploration of the hematoma was performed under anaesthesia, but immediately after the procedure, she again developed hematoma and bleeding from the episiotomy site. Surgical re-exploration was performed in the same procedure, no active bleeder was found. Accordingly, the dead space was obliterated and hemostasis achieved, but hematoma formed again at the same site. Thus, the decision for selective artery embolization was taken after discussing with the interventional radiologist in view of recurrent hematoma and intractable bleeding from the episiotomy site. Transcatheter embolization was performed on a digital subtraction angiography unit (Artis Zee® Siemens Medical Solutions, Erlangen, Germany). A 5-F diagnostic angiographic catheter was used to access the internal iliac artery. A renal double-curve or Picard catheter (Cook Medical, Bloomington, Indiana) was used to access the contralateral internal iliac artery and a SIM1 catheter was used for accessing the ipsilateral internal iliac artery. A 2.7-F microcatheter (Progreat microcatheter, Terumo Medical, Somerset, NJ) was used for super-selective catheterization of the uterine artery and its branches. A selective angiogram of both internal pudendal artery was performed, but it revealed no active contrast extravasation; however, an abnormal blush was noted, which was embolized using gelfoam (Spongostan, Ferrosan Medical Devices A/S, Søborg, Denmark) and the bleeding stopped immediately after the procedure (Figure 1). The patient was transfused with 3 units of packed red blood cells (PRBC) and 8 units of fresh frozen plasma (FFP) intra and post-operatively. On post-operative day eight, a 3-cm gaping superficial episiotomy was noticed, but conservative management was performed for the patient and she was discharged on day 24 in a healthy condition with a healing episiotomy site, by secondary intention.

## Case 2

A 26-year-old P2L2 woman was referred to our emergency department after an episode of profuse vaginal bleeding on post-partum day seven, following a spontaneous vaginal delivery for further management. She had one previous cesarean section and was diagnosed as having gestational diabetes mellitus in this pregnancy, which was managed with insulin. She had a full-term normal vaginal delivery with right mediolateral episiotomy at a private centre. Three hours after delivery, the patient developed swelling of around 6*6 cm in the right vulvovaginal region at the episiotomy site with profuse vaginal bleeding. As per the records of the hospital from where she was referred, surgical exploration was performed and hemostasis was achieved, she received 6 units of PRBC and 4 units of FFP intraoperatively and was kept in the intensive care unit (ICU) for 2 days.

On post-partum day seven, she again had an episode of profuse bleeding from the episiotomy site, an ultrasound (USG) Doppler was performed, which suggested an arterio-venous (AV) malformation. For immediate management, vaginal packing was performed, 10 PRBC and 10 FFP were transfused and she was transferred to our tertiary care hospital. In our emergency department, the initial evaluation of the patient revealed tachycardia of 112 beats/minute, blood pressure-110/70 mm Hg,

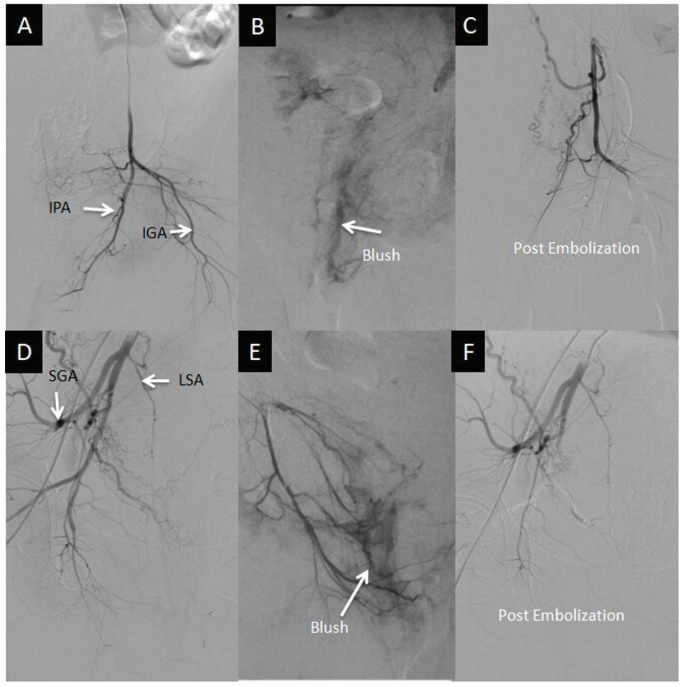


**Figure 1.** DSA spots of both internal pudendal artery angiograms (A, D) showing no active contrast extravasation; however, there was abnormal blush (arrow) noted (B, E), which was embolized using gelfoam. Post embolization angiograms (C, F) showed a significant reduction of the abnormal blush

*IPA: Internal pudendal artery, IGA: Inferior gluteal artery, SGA: Superior gluteal artery, LSA: Lateral sacral artery*

and moderate pallor. All baseline investigations were sent, her hemoglobin was 7.4 g/dL and TLC 24,900/L. One unit of PRBC and three units of FFP was transfused to the patient and she was started on broad-spectrum antibiotics.

Initially, USG Doppler was performed which suggested a pseudoaneurysm, then computed tomography (CT) angiography was performed, which revealed pseudoaneurysm of 2.1*1 cm in relation to the episiotomy site on the right posterolateral wall of the upper vagina, likely from the small branches of the anterior division of internal iliac artery (vaginal artery) (Figure 2A&B). There was a pelvic hematoma of around 4*5 cm just lateral to pseudoaneurysm and the upper vagina was distended with clots (Figure 2A&B), along with the vaginal pack. The decision for embolization was taken in view of the CT pseudoaneurysm findings. Percutaneous thrombin injection into the pseudoaneurysm was attempted, but it was not successful. Hence, transcatheter embolization was performed through the right transfemoral route. A -5F diagnostic angiographic SIM1 catheter (Cook Medical, Bloomington, Indiana) was used to access the ipsilateral internal iliac artery and co-axial microcatheter system (Progreat microcatheter, Terumo Medical, Somerset, NJ) for super-selective catheterization of the vaginal branch of the right internal iliac artery and embolization of pseudoaneurysm was performed using 30% glue injection (Endocryl, Samarth Life Sciences Pvt. Ltd., India) (Figure 2C&D). Post-procedure, the patient was transfused with one unit of PRBC. Post embolization, USG Doppler showed adequate blockage of the supplying artery. The vaginal pack was removed 48 hours after the procedure with no active bleeding. The patient remained hemodynamically stable and was discharged after seven days of embolization.

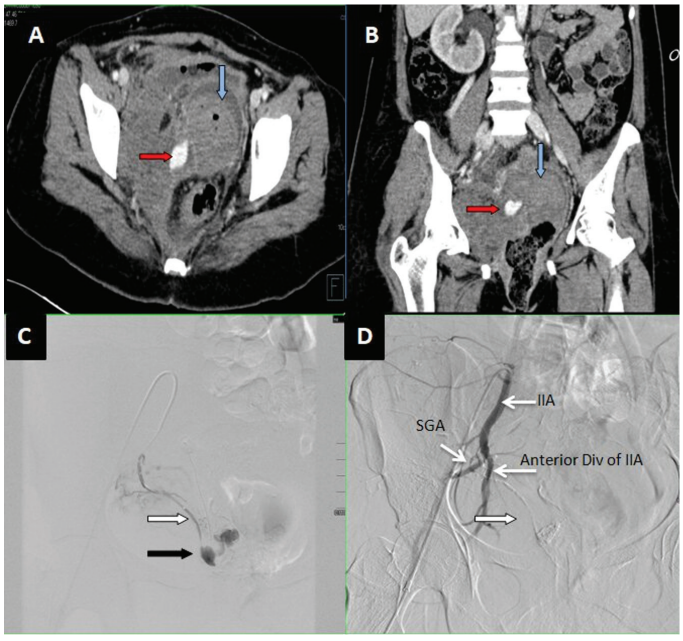


**Figure 2.** CT angiography images (A, B) showing pseudoaneurysm (red arrow) and surrounding hematoma (blue arrow) in the right lateral wall of the vagina. DSA spot images (C, D) of the same patient showing pseudoaneurysm (black arrow) arising from the right vaginal artery (white arrow), which was embolized with a 30% glue injection, and post embolization angiogram (D) showed non-filling of pseudoaneurysm suggestive of successful embolization

*IIA: Internal iliac artery, SGA: Superior gluteal artery, CT: Computed tomography*

## Discussion

Puerperal hematomas most commonly occur due to vascular injury in the lower genital tract, related to operative deliveries or episiotomy. However, hematomas may also result from injury to a blood vessel in the absence of laceration/incision of the surrounding tissue (e.g. pseudoaneurysm, traumatic arteriovenous fistula)[3]. The incidence of puerperal hematomas in the literature is reported as 1:300 to 1:15,000 deliveries. They may present as pain and swelling at the episiotomy site or with profuse vaginal bleeding. There are three main approaches for managing episiotomy site hemorrhage: (1) Conservative management with observation and supportive care, (2) Surgical intervention and (3) Selective arterial embolization, depending on the clinical scenario. Smaller hematomas can be managed with a conservative approach; however, larger ones require surgical exploration. Sometimes, if a surgical repair fails or if there is a recurrent hematoma, embolization is the option for second-line management as in both of our cases. Another indication for which embolization has been used is uncontrolled hemorrhage following delivery due to genital tract injury.

Takagi et al.[4] reported that large and growing hematomas required surgical intervention and hemostasis was mostly obtained by ligation of the bleeding vessels and obliterating the dead space followed by vaginal packing for compression. However, sometimes identification of the bleeding vessel may be difficult leading to excessive bleeding and recurrent hematoma formation, requiring blood transfusion and embolization as a second-line treatment, as happened in our first case where recurrent hematoma formed and no active bleeder was found on surgical exploration[5,6].

In 1979, Brown et al.[7] reported first the case of intractable pelvic hematoma managed by embolization after the failure of three surgical attempts. Villela et al.[8] reported two cases of vulvovaginal hematoma managed successfully by embolization as a second-line treatment. In one case, embolization was performed after a failed surgical management, and in the other, vaginal packing was performed to achieve hemostasis in a hematoma that formed after a vacuum delivery; hemostasis could not be achieved so selective artery embolization was performed, which successfully controlled the bleeding.

In a retrospective review conducted by Lee et al.[9] on 60 patients who underwent embolization primarily due to unmanageable genital tract injury bleeding, post-delivery, it was reported that the clinical success rate was 88% (53/60) after the first embolization and 97% (58/60) after the second embolization.

Some other authors have also reported selective arterial embolization as a first-line treatment for intractable and large hematomas after an evaluation by enhancing CT to identify the location of hematoma and the exact source of bleeding[4,5]. This may help in diagnosing some rare cause of episiotomy site hemorrhage such as AV malformation and pseudoaneurysm, which may present along with hematoma, as in our second case. Pseudoaneurysms are a rare complication that may occur due to inadequate repair of injury to an arterial wall due to trauma, which may be surgical. Most post-partum pseudoaneurysms have been described in the uterine artery, and it is quite rare at other locations such as the vagina. Few cases of vaginal pseudoaneurysm managed by selective artery embolization have been reported involving different arteries such as the vaginal artery, left internal pudendal artery, left obturator artery, and the labial artery[2,3,10]. The definitive diagnosis of pseudoaneurysm is made by angiography; however, both USG Doppler or contrast CT can be useful for its detection, as in our second case, and in monitoring the size of an unruptured pseudoaneurysm. The diagnosis of pseudoaneurysm on USG is based on the presence of a cystic mass showing pulsation and Doppler showing turbulent a blood flow pattern often in association with a to-and-fro waveform pattern[3,11].

In cases of recurrent vaginal hematoma and pseudoaneurysm, the cause is mostly failed surgical management or tissue trauma leading to its friability and inadequate hemostasis as documented in both of our cases. Early diagnosis and intervention in the form of embolization help in decreasing patient morbidity. There is a lack of data in the literature regarding the investigation of choice, at present, however, CT angiography is the investigation of choice to delineate detailed anatomy of pelvic vasculature and to identify any leaking point if present, in cases of episiotomy site hemorrhage[4,10].

## Conclusion

In patients presenting with recurrent episiotomy site hematoma after failed surgical management, the possibility of rupture pseudoaneurysm should be kept in mind and evaluated promptly. Selective artery embolization should be considered as a therapeutic option in such patients after confirmation by a proper imaging technique or instantly in emergencies. It helps in decreasing morbidity of the patient by decreasing surgical complication, the number of blood transfusions, ICU and overall hospital stay.

### Ethics

**Informed Consent:** Retrospective study.
**Peer-review:** Externally peer-reviewed.

### Authorship Contributions

Surgical and Medical Practices: S.S., J.M., S.K., S.G., Concept: S.S., J.M., S.K., S.G., Design: S.S., J.M., S.K., S.G., Data Collection or Processing: S.S., J.M., S.K., S.G., Analysis or Interpretation: S.S., J.M., S.K., S.G., Literature Search: S.S., J.M., S.K., S.G., Writing: S.S., J.M., S.K., S.G.

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