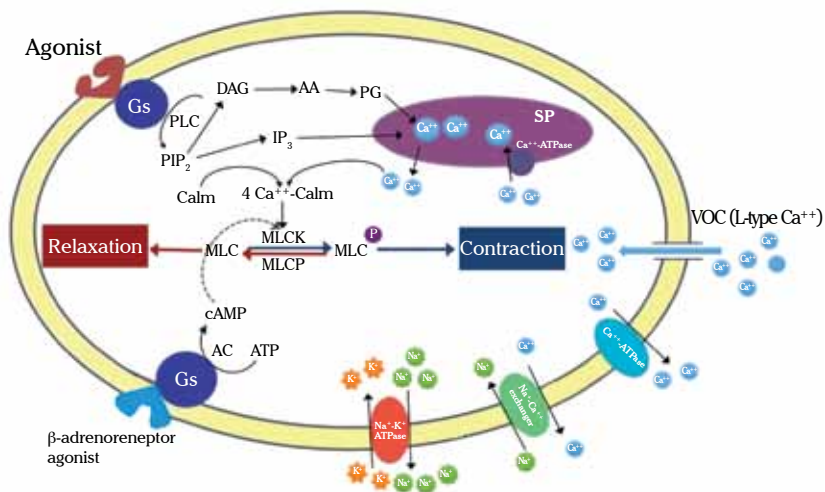




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Fax / Faks : +90 212 217 22 92
E-mail / E-posta: info@avesyayincilik.com

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Aims and Scope

Journal of the Turkish-German Gynecological Association is the official open access publication of the Turkish-German Gynecological Education and Research Foundation and Turkish-German Gynecological Association and is published quarterly on March, June, September and December.

The target audience of Journal of the Turkish-German Gynecological Association includes gynaecologists and primary care physicians interested in gynecology practice. It publishes original work on all aspects of gynecology. The aim of Journal of the Turkish-German Gynecological Association is to publish high quality original research articles. In addition to research articles, reviews, editorials, letters to the editor and case presentations are also published.

It is an independent peer-reviewed international journal printed in English language. Manuscripts are refereed in accordance with "double-blind peer reviewed" process for both referees and authors.

Papers written in English language are particularly supported and encouraged.

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The "Journal of the Turkish German Gynecological Association" is a peer reviewed journal and adheres to the highest ethical and editorial standards. The Editorial Board of the journal endorses the editorial policy statements approved by the WAME Board of Directors. The journal is in compliance with the Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals published by the International Committee of Medical Journal Editors (updated August 2013, www.icmje.org). The editors also adhere to the Committee on Publications Ethics (COPE) recommendations (<http://publicationethics.org>).

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Journal of the Turkish-German Gynecological Association

Editorial



Dear colleagues,

I am delighted to introduce the final issue of the Journal of the Turkish German Gynecological Association (JTGGA) of the year 2013.

Many interesting articles are included in this issue from Turkey and other countries. One of them is an important research article evaluating the correlation between trans-abdominal measurement of the cervix with that of transvaginal measurement in pregnant women between 18 and 26 weeks of pregnancy. In this issue, you will also find a review presenting a critical overview of myometrial functions and focusing specifically on the role of calcium.

Recently we informed you that our journal had been approved to be indexed by **PubMed Central (PMC)**, we are in the final phase of the technical evaluation process and you will be able to display the content of our journal through PMC quite soon.

The web site of our journal (www.jtgga.org) is now going through a renovation and will be available to our readers at the beginning of 2014 with a new and user-friendly interface. You can submit your manuscripts easily through the brand new online submission system of our journal, **ScholarOne**.

I would also like to remind you that **2nd International Research Awards on Obstetrics & Gynecology** will be granted with a total of **\$10.000** to three researchers or research groups who have been able to carry out the best researches in the field of Obstetrics & Gynecology or related subjects and submit them to the JTGGA through the online submission system at www.jtgga.org. The deadline for manuscript submissions is **February 21st, 2014**.

We would like to invite you to join us for our **10th Turkish - German Gynecology Congress** to be held in Antalya on April 30th and May 4th of 2014. We are confident that this global meeting in Antalya will attract many participants. The high standard of the scientific program will be attractive for the international gynecology and obstetrics community world and we look forward to welcoming you to Antalya.

I wish you a Great, Prosperous, Blissful, Healthy, Bright, Delightful, Scientific and Energetic new year...

Best regards,

Prof. Cihat Ünlü, M.D.
Editor in Chief of JTGGA
President of TAJEV

Placental location and pregnancy outcome

Plasenta konumu ve gebelik sonucu

Shumaila Zia

Department of Obstetrics and Gynecology, College of Medicine, King Khalid University, Abha, Saudi Arabia

Abstract

Objective: The purpose of this study was to determine if placental location is associated with adverse pregnancy outcome and to assess whether any association exists between different blood groups and location of the placenta.

Material and Methods: Medical records of women were reviewed retrospectively and placental position as documented in the case notes at routine antenatal (20-38 weeks) ultrasonography was identified. Placental position was categorised as anterior, posterior and fundal. Association of placental location with foeto-maternal outcome and different blood groups was noted.

Results: A total 474 case notes of women were analysed for placental location, foeto-maternal outcome and blood groups. Anterior placenta was found to have a relation with a greater risk of pregnancy-induced hypertension, gestational diabetes mellitus and placental abruption ($p < 0.001$), while posterior placenta had a significant association with preterm labour ($p < 0.001$). Regarding foetal outcome, an anterior placenta was significantly associated with intrauterine growth retardation and intrauterine foetal death ($p < 0.001$). The majority (54%) of women with an anterior placenta were O-positive blood group, while 46% of women in the posterior placenta group were A-positive blood group ($p < 0.001$).

Conclusion: Anterior placental implantation is associated with an increased risk of pregnancy-induced hypertension, gestational diabetes mellitus, placental abruption, intrauterine growth retardation and intrauterine foetal death. Posterior placenta has a significant association with preterm labour and A-positive blood group. Anterior placenta is common in women with O-positive blood group. Placental location may be an important determinant of pregnancy outcome.

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Key words: Placental location, pregnancy outcome, neonatal outcome, antenatal complications

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Özet

Amaç: Bu çalışmanın amacı, plasenta konumunun olumsuz gebelik sonuçları ile ilişkili olup olmadığını belirlemek ve farklı kan grupları ve plasenta konumu arasında herhangi bir ilişki olup olmadığını değerlendirmektir.

Gereç ve Yöntemler: Kadınların tıbbi kayıtları retrospektif olarak incelendi ve rutin doğum öncesi (20-38 hafta) ultrasonografide olgu notlarında dokümanite edilen plasental pozisyon tanımlandı. Plasental pozisyon anterior, posterior ve fundal olarak kategorize edildi. Fetomaternal akıbet ve farklı kan grupları ile plasental konum ilişkisi not edildi.

Bulgular: Kadınlar toplam 474 vaka notu, plasental konum, fetomaternal akıbet ve kan grupları açısından analiz edildi. Posterior plasenta erken doğum ile anlamlı ilişkili ($p < 0.001$) iken anterior plasenta; gebeliğe bağlı hipertansiyon, gestasyonel diabetes mellitus ve plasenta dekolmanı açısından daha büyük bir risk ile ilişkili bulundu ($p < 0.001$). Fetal akıbet gözönüne alındığında bir anterior plasenta intrauterin gelişme geriliği ve intrauterin fetal ölüm ile belirgin ilişkili bulundu ($p < 0.001$). Posterior plasenta grubunda kadınların %46'sının kan grubu A pozitif iken anterior plasentalı kadınların çoğunluğunun (% 54) kan grubu O-pozitif idi ($p < 0.001$).

Sonuç: Anterior plasental yerleşim gebeliğe bağlı hipertansiyon, gestasyonel diabetes mellitus, plasenta dekolmanı, intrauterin gelişme geriliği ve intrauterin fetal ölüm riskinde artış ile ilişkilidir. Posterior plasenta erken doğum ve A pozitif kan grubu ile anlamlı bir ilişkiye sahiptir. Anterior plasenta O-pozitif kan grubuna sahip kadınlarda sık görülür. Plasentanın konumu gebelik sonucunun önemli bir belirleyicisi olabilir.

(J Turkish-German Gynecol Assoc 2013; 14: 190-3)

Anahtar kelimeler: Plasenta konumu, gebelik akıbeti, neonatal akıbet, doğum öncesi komplikasyonlar

Geliş Tarihi: 23 Nisan 2013

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Introduction

In Saudi Arabia, screening ultrasonography (USG) of a large proportion of pregnant women is undertaken and they generally receive at least one obstetric USG for gestational age, amniotic fluid volume, foetal anatomic survey and placental location. Are these implantation sites predictive of an adverse pregnancy outcome? Only a limited number of investigators have dealt with placental implantation site and pregnancy outcome (1-3). Uterine blood supply is not uniformly distributed. The site of implantation and resultant location of the

placenta within the uterus are likely important determinants of placental blood flow and therefore pregnancy success (4). There has been extensive research on low placental implantation because of the importance of detecting placenta previa. Only a few studies have been undertaken on other aspects of placental position and possible impact on pregnancy outcome. These studies reported that placental location might have implications for poor pregnancy outcome including preterm birth (5), small for gestational age (SGA) (4), foetal malposition, malpresentation and the development of pre-eclampsia (1, 6). In theory, lateral placental location could contribute a higher risk of foetal intrauterine growth



Address for Correspondence: Shumaila Zia, Department of Obstetrics and Gynecology, College Of Medicine, King Khalid University, Abha, Saudi Arabia
Phone: +966 535 92 66 58 e-mail: abeeharafique@hotmail.com

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retardation (IUGR). A case-control trial conducted in the USA revealed that women with their placenta located in the fundus carry an increased risk of premature rupture of membranes with all the consequential adverse sequelae (5). Reports on an association between IUGR and placental locations (other than placenta previa) have been conflicting (1, 7, 8).

This study was designed to investigate:

- 1) The association between placental location and foeto-maternal outcome of pregnancy.
- 2) The relationship of different maternal blood groups with placental location.

Material and Methods

This retrospective study was conducted at a Abha General Hospital, Abha, KSA. Our study group included women with singleton pregnancy, delivered vaginally after 28 weeks of gestation, who had prior documentation of placental location on the basis of antenatal USG. The study outcome was the relationship of different placental locations with antenatal foeto-maternal complications, like pregnancy-induced hypertension (PIH), gestational diabetes mellitus (GDM), placental abruption, bad obstetric history (BOH), preterm delivery, intrauterine growth retardation (IUGR), intrauterine foetal death (IUFD) and neonatal outcome. The records of 500 subjects were ascertained. It is our departmental policy to offer a routine scan at 18-20 weeks or later if the booking is late. The details of placental locations are recorded apart from other parameters. We categorised each placenta as anterior, posterior and fundal. Placentas occupying the left or right region of the anterior and posterior uterine walls were considered anterior and posterior, respectively. The following data were collected - maternal age, gravidity, parity, number of miscarriages, gestational age at delivery, maternal blood group, birth weight (BW) of the baby, and 1 minute and 5 minute Apgar scores. The data were analysed using SPSS version 17. The results have been expressed in terms of probability (p) value. A chi squared test was used for categorical data and unpaired t test for continuous data. A p-value <0.05 was con-

sidered statistically significant. The study was approved by our Institutional Research and Ethics Committee.

Results

The study group consisted of 500 cases who delivered vaginally, during November and December 2012. Of these, 10 cases who delivered before 28 weeks, 10 women who came fully dilated without prior documented placental location by USG and six cases that had multiple pregnancies were excluded, leaving a total of 474 women. Table 1 describes the characteristics of the pregnant women according to placental location. There were no differences between baseline characteristics among three placental location categories. Fundal location was noted in 46%, anterior in 28% and posterior in 26% women (Figure 1). Neonatal outcome according to placental locations are shown in Table 2. There was no significant difference in gestational age at birth, mean BW and Apgar scores. Table 3 shows the association of different maternal blood groups with placental location. The commonest blood groups were O-positive (49%, n=236) and A-positive (36%, n=173). The majority (54%, n=72) of women with O-positive blood group had anterior placenta (p<0.001), while A-positive blood group was associated with posterior placenta in the majority of cases (46%, n=57, p<0.001)

Discussion

The blood supply of the uterus is not uniformly distributed and placental location is an important determinant of placental blood flow, as measured by uterine artery Doppler velocimetry (7, 9, 10). There are limited data on the association between placental location, pregnancy complications and perinatal outcome. Some researchers have described that placental location has implications for poor pregnancy outcomes, including preterm birth (5) and small for gestational age (SGA) (4). This study showed a significant association between posterior placenta and preterm labour. In contrast, we did not find any association with SGA. Our finding is consistent with another report (11).

Table 1. Relationship between placental location and maternal characteristics

Characteristic	Fundal N=218	Anterior N=133	Posterior N=123	p value
Past history				
Gravidity (Mean±SD)	5.4±2.2	5.03±1.7	5.5±2.6	0.55
Parity (Mean±SD)	3.8±1.9	3.54±1.6	3.8±2.1	0.54
Miscarriage (Mean±SD)	0.83±1.5	0.63±2.0	0.9±1.0	0.48
Bad obstetric history (%)	2(0.9)	2(1.5)	0	<0.001
Present age & complications				
Maternal age (Mean±SD)	32.9±5.1	31.8±5.2	31.9±4.9	2.45
PIH (%) [†]	7(3.2)	5(3.7)	2(1.6)	<0.001
GDM (%) [‡]	6(2.7)	8(6.0)	2(1.6)	<0.001
Placental abruption (%)	5(2.3)	5(3.7)	0	<0.001
PTL (%) [¥]	0	0	3(2.4)	<0.001
SD: standard deviation; PIH [†] -pregnancy induced hypertension; GDM [‡] - gestational diabetes mellitus; PTL [¥] - pre-term labour				

Table 2. Relationship of foetal outcome with placental location

Variable	Fundal N=218	Anterior N=133	Posterior N=123	p value
Gestational age (Mean±SD)	37.9±1.5	37.2±2	37.8±1.4	2.45
Foetal weight, grams (Mean±SD)	2857±493.4	2808±658.3	2842±503	
APGAR score (mean)				
1 min	6.2	6.1	6.2	2.48
5 min	8.7	8.4	8.8	3.55
IUGR (%)†	0	4 (3)	0	<0.001
Congenital anomalies (%)	3 (1.4)	0	0	<0.001
IUFD (%)‡	3 (1.4)	2 (1.5)	0	<0.001

SD: standard deviation; IUGR†- intrauterine growth retardation; IUFD‡- intrauterine foetal death

Table 3. Association of placental location with blood groups

Blood group N=(474)	Fundal N=218(%)	Anterior N=133(%)	Posterior N=123(%)	p value
O-positive	108 (49.5)	72 (54)	56 (45.5)	<0.001
O-negative	14 (6.4)	4 (3)	0	<0.001
A-positive	70 (32)	46 (34.5)	57 (46.3)	<0.001
A-negative	6 (2.7)	2 (1.5)	0	0.56
B-positive	14 (6.4)	9 (6.7)	10 (8.1)	0.56
B-negative	2 (0.9)	0	0	0.005
AB-positive	0	0	0	0
AB-negative	4 (1.8)	0	0	0.005

Hadley et al. (5) reported that a placenta located in the fundus carries a significantly higher risk of premature rupture of the membrane. They presumed that fundal location of the placenta places the weakest point of the membrane over the cervical os and thus predisposes the women to premature rupture of membrane with all of the consequential adverse sequelae. Contrarily, we found a significant association of posterior placenta with preterm labour. This is probably because placenta located on the posterior uterine wall may be somehow less efficient due to the anatomy of that wall (12). As a result of uneven uterine blood supply (4), the posterior wall of the pregnant uterus is longer (13) and somewhat thicker (14). Each of these factors may affect uterine blood supply, especially as the uterus expands to accommodate the pregnancy. Janewarland et al. (12), in a case-control study, reported that posterior placenta is statistically more likely to result in a still birth. They described that its exact cause is not clear but they put forward three possible hypotheses: the structure of posterior uterine wall is somehow at fault, there may be associated intrauterine factors with the posterior-located placenta, or the pregnant woman's sleeping position is the problem. However, we did not observe such relation. Rather, this study found a significant correlation between fundal and anterior placenta with IUFD (Table 2). The present study showed a statistically significant association of anterior placenta with an increased incidence of PIH, GDM, BOH, placental abruption, IUGR and IUFD. One of the explanations may be non-uniform uterine blood supply or it might be by chance

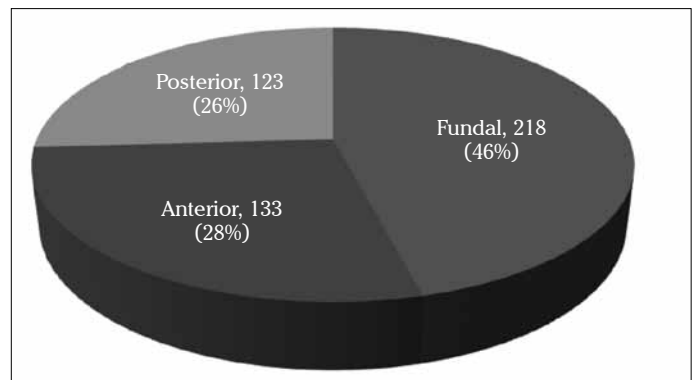


Figure 1. Location of placenta in 474 women

due to the small sample size; further research is needed to verify these findings. In line with Karthika et al. (15), we did not observe a significant difference in mean BW among different placental location groups. The current study showed that IUGR pregnancies had a significant association with anterior placentas. Although the mean BW of anteriorly placed placental pregnancies is low, it is not significant because the number of IUGR pregnancies is only four out of 133 cases. However, Lucy et al. (4) described a positive correlation between IUGR and lateral placentas, rather than anterior and posterior. Kofinas et al. (7) reported that unilateral placentas are more common than central (anterior and posterior) ones in pregnancies with IUGR and/or pre-eclampsia. Consistent with our findings, Booth et al. (16) reported a significant association between fundal placentation and PIH. The present study revealed a significant association of fundal and anterior placentas with PIH and IUGR. In contrast, a recent population-based case-control study of more than 3000 pregnancies (10) reported that the risk of having a foetus with IUGR was not increased by the site of placental implantation. However, that study grouped placental locations in three broad categories (low, high lateral and high fundal) which did not differentiate central (anterior or posterior) placenta. The observation that most of the placentas in this study were located in fundus is not consistent with prior reports (16-18). At least in theory, a placenta which is primarily implanted near the uterine and/or ovarian arteries might receive more blood than one implanted centrally, whether anterior or posterior, and this could account

for poor pregnancy outcome with anterior placenta, as seen in our study. In the three groups of placental location (fundal, anterior and posterior), the mean gestational age and BW were found to be almost the same; however, some have reported the negative impact of fundal location of placenta on these findings. Kalanithi et al. (4) studied the possible influence of placental location on the Apgar scores of newborns. They described the location of the placenta as either fundal, uterine body or lower uterine segment. They found no case of low Apgar score (<4) in the lower uterine segment group, whereas they found that the higher the placenta was situated in the uterus, the greater the incidence of an Apgar score <4 (i.e. 0.6% in the uterine body group and 2.4% in the fundal group). Our study showed no correlation between low Apgar score and placental location. We found no case with Apgar score <4.

We observed that anterior placenta have a strong association with O-positive blood group and posterior placenta with A-positive blood group. Therefore, O-positive blood group women are more prone to antenatal complications, which are commoner in anterior placenta women. To the best of our knowledge, either no work or only small studies have been performed in this regard. Large scale studies are required to confirm these findings. The retrospective nature of this study is a limitation, chiefly because of "observer variation" as a result of different sonographers locating the placental position with variable reporting styles and experience. Nevertheless, a large prospective study, where the placental positions are determined by only one experienced sonographer, would be useful to confirm the findings of this study.

In summary, pregnancies with anterior placenta are complicated by PIH, GDM, placental abruption, IUGR and IUFD as compared to fundal or posterior ones. Anterior placenta is common in O-positive and posterior placenta in A-positive blood group. Women with posterior placenta have a greater risk of premature delivery. This study supports the hypothesis that the location of the placenta is associated with pregnancy success. Therefore, placental location may be an important determinant of pregnancy outcome. Additional research is needed to confirm this observation and to determine whether pregnancies with anterior placenta may benefit from more intensive monitoring.

Ethics Committee Approval: Ethics committee approval was received for the study.

Informed Consent: N/A

Peer-review: Externally peer-reviewed.

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

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Caesarean deliveries by Pfannenstiel versus Joel-Cohen incision: A randomised controlled trial

Joel-Cohen insizyona karşılık Pfannenstiel insizyon ile Sezaryen doğumlar: Bir randomize kontrollü çalışma

Wessam Magdy Abuelghar¹, Gasser El-bishry¹, Lamiaa H. Emam²

¹Department of Obstetrics and Gynecology, Ain Shams University, Cairo, Egypt

²Department of Obstetrics and Gynecology, Ghamra Hospital, Cairo, Egypt

Abstract

Objective: This study was designed to compare the Pfannenstiel versus Joel-Cohen incisions during caesarean deliveries.

Material and Methods: Women undergoing caesarean deliveries (n=153) were randomly assigned to the conventional Pfannenstiel or the Joel-Cohen incision. The outcome measures included postoperative pain, requirement for analgesics, operative time and other post-operative data.

Results: Maternal age, parity, gestational age and indications for caesarean delivery were similar across groups. Total operative time, postoperative recovery duration, time to get out of bed, to walk straight without support, to detect audible intestinal sounds and to pass gases or stools were shorter in the Joel-Cohen group. Postoperative haematocrit decreases and estimated intraoperative blood loss were similar between the two techniques. Moderate and severe pain at 6, 12 and 18 hours post-operatively was less frequent after the Joel-Cohen technique.

Conclusion: Joel-Cohen incision in the non-scarred abdomen may provide a faster technique for caesarean section with less postoperative pain and probably early postoperative recovery in our circumstances. (J Turkish-German Gynecol Assoc 2013; 14: 194-200)

Key words: Caesarean, deliveries, Pfannenstiel, Joel-Cohen, incision

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Özet

Amaç: Bu çalışma sezaryen doğumlar sırasında Joel-Cohen insizyona karşılık Pfannenstiel insizyonu kıyaslamak için tasarlandı.

Gereç ve Yöntemler: Sezaryen doğuma giden kadınlar (n=153) randomize olarak geleneksel Pfannenstiel veya Joel-Cohen insizyon grubuna ayrıldı. Akıbet ölçümlerine postoperatif ağrı, analjezik gereksinimi, operasyon süresi ve diğer postoperatif veriler dahilildi.

Bulgular: Maternal yaş, parite, gestasyonel yaş ve sezaryen doğum endikasyonları gruplar arasında benzerdi. Toplam operasyon süresi, postoperatif iyileşme süresi, yataktan çıkma, destek olmaksızın düz yürüme, duyuabilir bağırsak seslerini saptama ve gaz veya gaita çıkarma zamanı Joel-Cohen grubunda daha kısa idi. Postoperatif hematokrit azalması ve tahmini intraoperatif kan kaybı iki teknik arasında benzerdi. Postoperatif 6., 12. ve 18. saatte orta ve şiddetli ağrı Joel-Cohen tekniği sonrası daha az sıklıkta oldu.

Sonuç: Skar olmayan karında Joel-Cohen insizyon, bizim koşullarımızda Sezaryen kesisi için daha az postoperatif ağrı ve muhtemelen postoperatif erken iyileşme ile daha hızlı bir teknik sağlayabilir.

(J Turkish-German Gynecol Assoc 2013; 14: 194-200)

Anahtar kelimeler: Sezaryen, doğumlar, Pfannenstiel, Joel-Cohen, insizyon

Geliş Tarihi: 29 Haziran 2013

Kabul Tarihi: 07 Ağustos 2013

Introduction

Caesarean section is the most common major abdominal operation performed on women in developed and developing countries; thus, any useful refinement in the operative technique is likely to yield substantial benefits. The surgical technique for caesarean delivery has changed over time, and from surgeon to surgeon, and these changes involve both uterine and skin incisions (1). Rates of caesarean section vary between countries and health services from 3.5% in Africa to 29.2% in Latin America and the Caribbean (2).

There are many possible ways to perform a caesarean section: 77% of Obstetricians use a Pfannenstiel incision for urgent or emergency caesarean sections, 55% use single-layer closure of the uterine incision, 37% use double-layer closure, while 11% use single-layer closure only in women undergoing concomitant sterilisation (3). The Pfannenstiel

incision is a transverse skin incision, two finger-breadths above the symphysis pubis, which is extended in the direction of the anterior superior iliac spine (ASIS) and ends 2-3 cm medial to ASIS on both sides (4). In the Joel-Cohen Incision, the skin incision is placed 3 cm above the original Pfannenstiel incision, the subcutaneous tissue is incised only in the three most medial centimetres, and the lateral tissue is separated manually, before the fascia is divided bluntly with both index fingers inserted in the deep fascial space created by the knife. Then, the abdomen is opened bluntly with fingers, the uterine cavity is incised and the incision is extended laterally by 2 fingers. In both techniques, after delivery of the baby, the placenta is delivered spontaneously (5). The modified Joel Cohen technique is a very attractive surgical option due to its simplicity and its claimed advantages; it is faster to perform, causes less blood loss, less postoperative pain, shorter



Address for Correspondence: Wessam Magdy Abuelghar, Department of Obstetrics and Gynecology, Ain Shams University, Cairo, Egypt.
Phone: +20 122 746 0679 e-mail: dr.awessam@gmail.com

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hospital stay, less postoperative infection, is more economic, and saves more staff time and utilises less anaesthesia (6). This study was designed to compare the Pfannenstiel versus Joel-Cohen incisions during caesarean deliveries.

Material and Methods

This comparative study was carried out over one year from January 2012 to January 2013. One hundred and fifty three (153) women were included in this study after informed consent was taken and the study was approved by the institute ethical committee. One hundred and twenty eight (128) women were finally (25 were lost during follow-up, Figure. 1) included in this study and randomly assigned to either the conventional Pfannenstiel or the Joel-Cohen incisions during caesarean delivery according to the different obstetric indications.

Exclusion criteria included (1) women having experienced previous abdominal operations, (2) women who had received a previous caesarean section, (3) women with any disease that could affect post-operative recovery (cardiac, diabetes mellitus, preeclampsia), and (4) patients who were complicated with unilateral or bilateral extension of the uterine incision during caesarean section.

All recruited women were subjected to history taking, general, obstetric examinations and preoperative investigations according to the hospital labour ward protocol, in particular preoperative haemoglobin and haematocrit analysis.

All caesarean section were done under spinal anaesthesia, by a lecturer of the causality (denoted as someone who had passed the residency program 3 years previously and had at least 3 years of experience as an assistant lecturer, with an MD degree), and were assisted by a registrar of the causality.

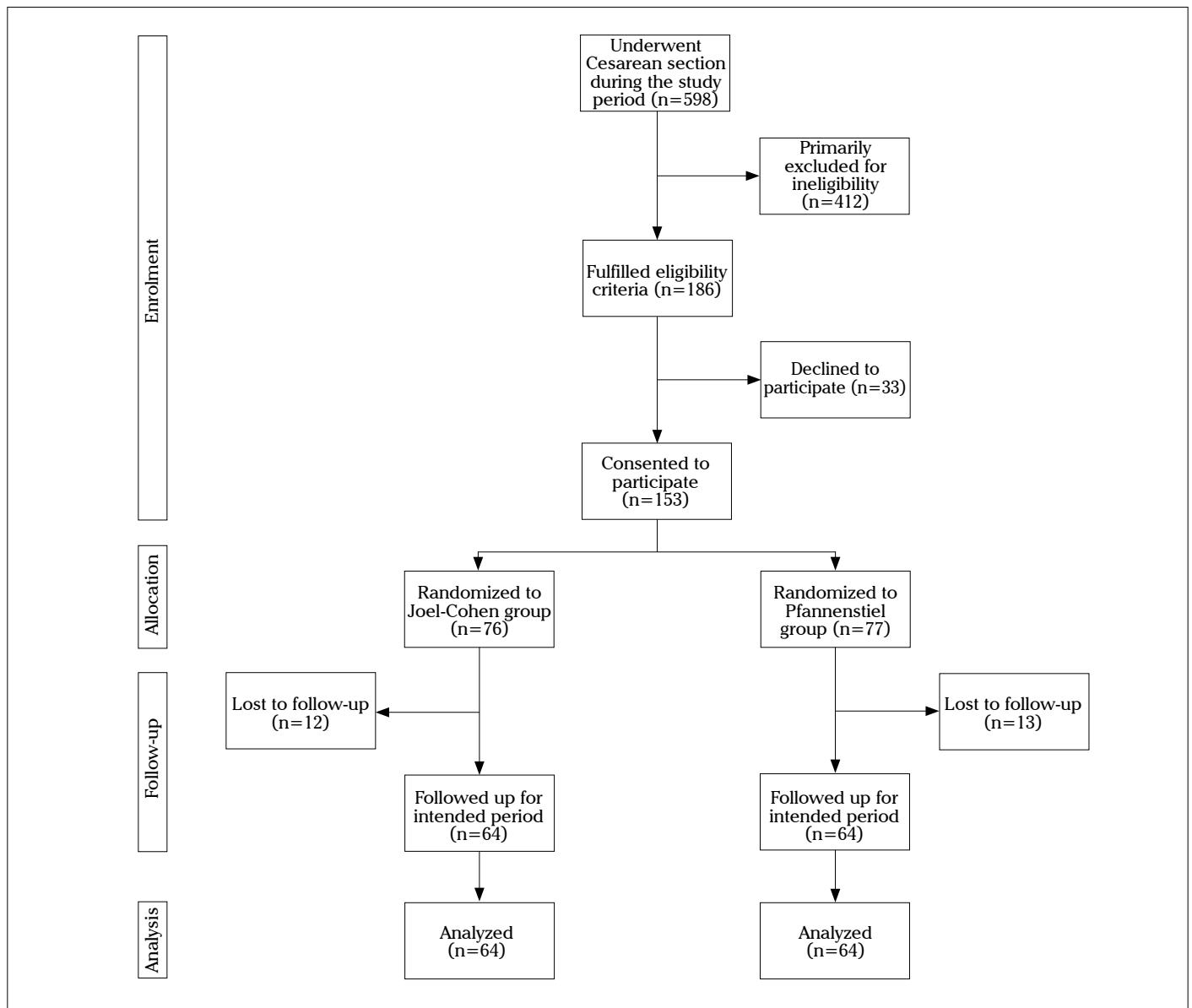


Figure 1. The flow chart of the study design

Randomisation was performed using a computer-generated list of random numbers; the allocation sequence was concealed from the researcher enrolling and assessing participants in sequentially numbered, opaque, sealed and stapled envelopes, which were kept with the labour ward nurse. The envelopes were opened only after the enrolled participants had completed all of the baseline assessments and it was time to allocate the intervention. Once the decision regarding caesarean delivery was taken and after transferring the patient to the operating room, the patient was blinded to the method until a few minutes before the operation where the numbered randomisation envelopes were placed in the preparation room of the obstetric theatre and were consecutively picked by the anaesthetist for each caesarean delivery. The results of randomisation (whether 1 or 2) were known only to the single obstetrician who performed the operation (physicians, nursing staff and the patient were unaware of the randomisation results).

Group 1: The Joel-Cohen abdominal incision was used. This was a straight transverse incision through the skin only, 3 cm below the level of the anterior superior iliac spines (higher than the Pfannenstiel incision). The subcutaneous tissues were opened only in the middle 3 cm. The fascia was incised transversely in the midline then extended laterally with blunt finger dissection; finger dissection was used to separate the rectus muscles vertically and laterally and to open the peritoneum. All layers of the abdominal wall were stretched manually to the extent of the skin incision. The bladder was reflected inferiorly. The myometrium was incised transversely in the midline, without breaching the amniotic sac, then opened and extended laterally with finger dissection.

Group 2: A Pfannenstiel abdominal incision was used. The skin and rectus sheath were opened transversely using sharp dissection. The rectus sheath was dissected free from the underlying rectus abdominus muscles. The peritoneum was opened longitudinally using sharp dissection. The uterus was opened with a transverse lower segment incision. The uterine incision was closed with two layers of continuous sutures and both peritoneal layers were closed with continuous sutures. The fascia was closed with continuous or interrupted sutures. The skin was closed with interrupted or continuous sutures.

Before surgery in both groups, the pubic hair was removed from

the operative field using a razor, and a urinary catheter was introduced before surgery and removed after mobilisation. All patients received the same dose of prophylactic antibiotics, were transferred to the same post-operative ward, received the same medication and were nursed by well-trained nursing staff (the nursing staff were unaware to which group each patient was allocated). Primary outcome measures included postoperative pain using a visual analogue scale (VAS) in the 1st 6th, 12th and 18th hours postoperative; VAS is represented by a 100 mm line with one end labelled as (no pain) and the other as (worst possible pain), in which the patient was asked to put a mark on the line representing the severity of pain she felt (7), (Figure 2).

Secondary outcome measures were operative time (time from skin incision to skin closure), delivery time (time from skin incision to delivery of the baby), delivery to closure time (time from delivery of the baby to closure of skin), the amount of blood loss during caesarean section (which was estimated by the amount of the blood in the suction bottle), postoperative haemoglobin (Hb) & haematocrit drop and postoperative febrile morbidities. Also, secondary outcome measures were the times from the end of caesarean section to getting out from bed and to walking straight without support, time to detecting audible intestinal sounds and to passing gases or stool, and length of postoperative hospital stay.

The same preoperative antibiotics and postoperative analgesics (Pethidine 50 mg IM on request) were given to both groups. Post-operative follow-up was done one week after the caesarean delivery.

Sample size justification

The required sample size was calculated using G* Power software version 3.17 for sample size calculation (*Heinrich Heine Universität; Düsseldorf; Germany), setting the primary outcome as the proportion of patients with severe or very severe pain after surgery as scored on the visual analogue scale (VAS), the α -error probability at 0.05, power (1- β error probability) at 0.95 %, and effective sample size (w) at 0.25.

The effective size (w) was calculated as follows: $w = \sqrt{X^2/N}$ where X^2 is the chi-square test and N is the total sample size. The number of participants needed to produce a statistically acceptable figure was 63 patients in each study group.

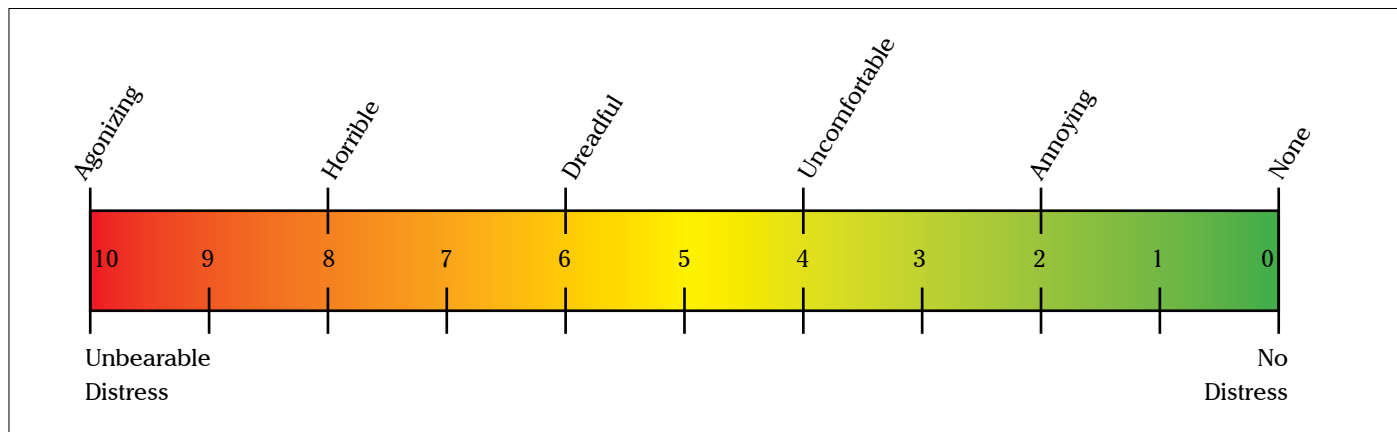


Figure 2. Visual analogue scale (VAS) for pain assessment

Statistical analysis

Data were collected, tabulated and then statistically analysed using the Statistical Package for Social Sciences (SPSS) computer software version 15. Numerical variables were presented as mean and standard deviation (\pm SD), while categorical variables were presented as number and percentage. Chi-square test (χ^2) was used for comparison between groups with regard to qualitative variables. The Student t-test and Mann-Whitney U-test were used for comparison between groups as regard quantitative variables. Relative risks were calculated with respect to intraoperative and postoperative events in both groups, with the corresponding 95% confidence interval (CI). A difference with a p value <0.05 was considered statistically significant.

Results

The mean age of the studied population was 26.64 ± 3.66 years (range: 20–35 years), the mean gestational age at caesarean section was 38.82 ± 1.3 weeks (range: 35.14-42 weeks) and the mean parity was 1 (range: 0-4). There were no significant differences between the Joel Cohen group and Pfannenstiel group regarding mean age (26.75 ± 3.7 versus 26.53 ± 3.65 , respective-

ly), mean parity (1 ± 1.2 versus 1 ± 1.5 , respectively) and mean gestational age (38.86 ± 1.4 versus 38.78 ± 1.2 , respectively) ($p > 0.5$; Chi-square test); Table 1.

Also, there was no significant difference between the two studied groups regarding indications for caesarean section ($p > 0.5$; Chi-square test); Table 2.

The mean VAS score at 6, 12 and 18 hours postoperative were significantly lower in the Joel-Cohen group (52.8 ± 13.0 , 31.5 ± 12.8 and 16.3 ± 6.9 , respectively) compared to the Pfannenstiel group (67.5 ± 12.1 , 43.7 ± 15.4 and 23.1 ± 9.5 , respectively), ($p < 0.001$; independent-samples Student t test); Table 3.

The number of analgesic doses consumed postoperatively was significantly lower in the Joel-Cohen group compared to the Pfannenstiel group (2.4 ± 0.8 versus 3.0 ± 0.8 , respectively), ($p < 0.001$, independent-samples Student t test); Table 3.

Risk analysis was performed to compare the risk of severe pain 6 and 12 hours postoperative in both of the studied groups; the odds and relative risk ratios of severe pain 6 hours postoperative were 0.18 (95%CI 0.08 to 0.38) and 0.43 (95%CI 0.29 to 0.65), respectively, and the risk of severe pain 6 hours postoperative was 0.31 in the Joel-Cohen group compared to 0.72 in the Pfannenstiel group. The Joel-Cohen incision was significantly associated with an absolute risk reduction of severe pain 6 hours postoperative compared to the Pfannenstiel group of 0.41 (95%CI 0.25 to 0.56), ($p < 0.05$); Table 4.

The odds and relative risk ratios of severe pain 12 hours postoperative were 0.15 (95%CI 0.04 to 0.54) and 0.19 (95%CI 0.06 to 0.61), respectively, and the risk of severe pain 12 hours postoperative was 0.05 in the Joel-Cohen group compared to 0.25 in the Pfannenstiel group. The Joel-Cohen incision was significantly associated with an absolute risk reduction of severe pain 12 hours postoperative of 0.20 compared to the Pfannenstiel group (95%CI 0.09 to 0.32), ($p < 0.05$); Table 5.

The secondary outcomes such as total operative time, incision-to-delivery and delivery-to-closure times were significantly shorter in the Joel Cohen group (22.36 ± 2.45 , 2.88 ± 1.12 and 17.86 ± 2.34 minutes, respectively) compared to the Pfannenstiel group (31.59 ± 2.88 , 3.75 ± 1.22 and 24.59 ± 2.51 minutes, respectively), ($p < 0.05$; Independent Student's t-Test). Also, time to get

Table 1. Mean age, parity and gestational age of the two studied groups

Variables	Group 1 (Joel Cohen Incision) (Number=64)	Group 2 (Pfannenstiel Incision) (Number=64)	p value
Age (years) Mean \pm SD (range)	26.75 ± 3.7 (20-35)	26.53 ± 3.65 (20-35)	0.74**
Parity Mean \pm SD (range)	1 ± 1.2 (0-4)	1 ± 1.5 (0-3)	0.80**
Gestational age (Weeks) Mean \pm SD (range)	38.86 ± 1.4 (38-41)	38.78 ± 1.2 (38.5-40.5)	0.73**

** : Non-significant

Table 2. Indication for caesarean section in both groups

Indications for caesarean sections	Group 1 (Joel Cohen Incision) (Number=64)	Group 2 (Pfannenstiel Incision) (Number=64)	p value
Poor progress of labour and CPD	18 (28.1%)	17 (26.5%)	0.88**
Failed induction of labour	9 (14.1%)	10 (15.6%)	0.83**
Malpresentation	8 (12.5%)	6 (9.4%)	0.01**
Foetal distress	5 (6.3%)	5 (4.7%)	1.00**
Oligohydramnios	6 (9.4%)	9 (14.1%)	0.46**
Foetal macrosomia	6 (9.4%)	4 (6.3%)	0.54**
Multiple pregnancy	7 (10.9%)	7 (10.9%)	1.00**
Infertility	1 (1.6%)	2 (3.1%)	0.56**
Pulsating cord prolapse	3 (4.7%)	4 (6.3%)	0.71**
Previous repair of complete perineal tear	1 (1.6%)	0 (0%)	0.22**

** : Non-significant; CPD: Cephalo-pelvic disproportion

out of bed, to walk straight without support, to detect audible intestinal sounds and to pass gas were significantly shorter in the Joel-Cohen group (4.92 ± 1.06 , 7.28 ± 1.25 , 4.82 ± 0.74 and 9.34 ± 1.83 hours, respectively) compared to the Pfannenstiel group (7.13 ± 1.13 , 9.53 ± 1.46 , 6.16 ± 0.71 and 12.14 ± 2.37 hours, respectively), ($p < 0.05$; Independent Student's *t*-Test); Table 6. There was no significant difference between the Joel Cohen and Pfannenstiel groups regarding postoperative haemoglobin decrease (0.35 ± 0.26 versus 0.34 ± 0.21 g/dL, respectively) and haematocrit decrease (0.67 ± 0.29 versus 0.47 ± 0.35 g/dL, respectively), ($p > 0.05$; Independent Student's *t*-Test). The number of patients with a hospital stay of 0-24 hours was 40 (62.5%) in the Joel Cohen group and 44 (68.8%) in the Pfannenstiel

group (statistically insignificant), while the number of patients with a hospital stay of 24-28 hours was 24 (37.5%) in the Joel Cohen group and 20 (68.8%) in the Pfannenstiel group (statistically insignificant), ($p > 0.05$; Chi-Squared Test); Table 6.

Discussion

Caesarean section is a common practice and each institute should study and evaluate the best evidence tailored to its staff and facilities. Caesarean section morbidity is closely related to the precision of opening and closing the abdomen and uterine wall. The modified Joel Cohen technique is a very attractive surgical option due to its simplicity and its claimed advantages. It has already been applied in many parts of the world as it provides more benefits as it is faster to perform, and results in less blood loss, less postoperative pain, earlier ambulation and a shorter hospital stay (6).

This study was designed to compare the Pfannenstiel versus Joel-Cohen incisions during caesarean deliveries, especially in settings with a high flow of patients, as our tertiary referral centre. Several studies have stated that the Joel-Cohen incision at caesarean delivery is a faster method of delivery than both Pfannenstiel incision and mid-line longitudinal incision (8-11). In this study, the total operative time, and incision-to-delivery and delivery-to-closure times in this study were significantly shorter in the Joel Cohen group compared to the Pfannenstiel group. Song & colleagues concluded that the Joel-Cohen incision at caesarean section reduces the operative time, blood loss and postoperative hospital stay (12). Also, the operative time was significantly shorter in the Joel-Cohen technique compared to the Pfannenstiel technique in the studies by Darj et al. (13) and Wallin et al. (14) and the modified Joel Cohen technique

Table 3. Postoperative pain scores and analgesic consumption in the two studied groups

Variables	Group 1 (Joel Cohen Incision) (Number=64)	Group 2 (Pfannenstiel Incision) (Number=64)	p value
VAS at 6 hours postoperative Mean±SD	52.8±13.0	67.5±12.1	<0.001*
VAS at 12 hours postoperative Mean±SD	31.5±12.8	43.7±15.4	<0.001*
VAS at 18 hours postoperative Mean±SD	16.3±6.9	23.1±9.5	<0.001*
Analgesic doses used postoperative Mean±SD	2.4±0.8	3.0±0.8	<0.001*

*: Significant; VAS: Visual analogue score

Table 4. Odds, risk ratios and risk reduction of severe pain 6 hours postoperative in both studied groups

Variables	Value
Odds ratio of severe pain 6 hours postoperative	0.18 (95% CI 0.08 to 0.38)
Relative risk ratio of severe pain 6 hours postoperative	0.43 (95% CI 0.29 to 0.65)
Risk of severe pain 6 hours postoperative in Joel-Cohen group	0.31
Risk of severe pain 6 hours postoperative in Pfannenstiel group	0.72
Absolute risk reduction of severe pain 6 hours postoperative by Joel-Cohen technique	0.41 (95% CI 0.25 to 0.56)
Significance level	$p < 0.0001$

*: Significant; VAS: Visual analogue score

Table 5. Odds, risk ratios and risk reduction of severe pain 12 hours postoperative in both studied groups

Variables	Value
Odds ratio of severe pain 12 hours postoperative	0.15 (95% CI 0.04 to 0.54)
Relative risk ratio of severe pain 12 hours postoperative	0.19 (95% CI 0.06 to 0.61)
Risk of severe pain 12 hours postoperative in Joel-Cohen group	0.05
Risk of severe pain 12 hours postoperative in Pfannenstiel group	0.25
Absolute risk reduction of severe pain 12 hours postoperative by Joel-Cohen technique	0.20 (95% CI 0.09 to 0.32)
Significance level	$p < 0.0001$

*: Significant; VAS: Visual analogue score

Table 6. The secondary outcome in the two studied groups

	Group 1 (Joel Cohen Incision) (Number=64)	Group 2 (Pfannenstiel Incision) (Number=64)	p value
Total Operative Time (minutes) Mean±SD (range)	22.36±2.45 (20-32)	31.59±2.88 (25-36)	<0.001*
Incision-to-delivery time (minutes) Mean±SD (range)	2.88±1.12 (2-5)	3.75±1.22 (2-9)	<0.001*
Delivery-to-closure time (minutes) Mean±SD (range)	7.86±2.34 (12-25)	24.59±2.51 (20-30)	<0.001*
Postoperative haemoglobin drop (g/dL) Mean±SD (range)	0.35±0.26 (0.1-1.4)	0.34±0.21 (0-1.1)	0.734**
Postoperative haematocrit drop (%) Mean±SD (range)	0.67±0.29 (0-10.3)	0.47±0.35 (0-2)	0.099**
Postoperative temperature ≥38°C Number (%)	7 (10.9%)	15 (23.4%)	0.061**
Time to get out from bed (hours) Mean±SD (range)	4.92±1.06 (4-7)	7.13±1.13 (5-10)	<0.001*
Time to walk straight without support (hours) Mean±SD (range)	7.28±1.25 (5-10)	9.53±1.46 (7-13)	<0.001*
Time to detect audible intestinal sounds (hours) Mean±SD (range)	4.82±0.74 (4-6.5)	6.16±0.71 (5-7.7)	<0.001*
Time to pass gases or stool (hours) Mean±SD (range)	9.34±1.83 (7-13)	12.14±2.37 (8-18)	<0.001*
Postoperative hospital stay			
0-24 hours	40 (62.5%)	44 (68.8%)	0.457**
24- 48 hours	24 (37.5%)	20 (31.2%)	
*Significant ** Non-significant			

was recommended by the Royal College of Obstetricians and Gynecology in cases of urgent caesarean delivery due to its speed, non-closure of the pelvic peritoneum and non-closure of subcutaneous tissue (15).

The primary outcome of this study was focused on postoperative pain after caesarean delivery using the visual analogue scale (VAS) in first 6, 12 and 18 hours postoperative. The mean VAS score at 6, 12 and 18 hours postoperative were significantly lower in the Joel-Cohen group (52.8±13.0, 31.5±12.8 and 16.3±6.9, respectively) compared to the Pfannenstiel group (67.5±12.1, 43.7±15.4 and 23.1±9.5, respectively). The number of analgesic doses consumed postoperatively was significantly less in the Joel-Cohen group compared to the Pfannenstiel group (2.4±0.8 versus 3.0±0.8, respectively).

Also, Darj et al. (13) and Ferrari et al. (16) concluded that the postoperative pain was significantly greater in the Pfannenstiel technique compared to the modified Joel Cohen technique due to extensive tissue trauma and increased inflammatory response in the Pfannenstiel technique.

Risk analysis was performed to compare the risk of severe 6 and 12 hours postoperative pain in both of the studied groups; the Joel-Cohen technique was significantly associated with an absolute risk reduction of severe postoperative pain after 6 hours [0.41 (95% CI 0.25 to 0.56)] and 12 hours [0.20 (95% CI 0.09 to 0.32)] compared to the Pfannenstiel technique. A large Cochrane systemic

review was done to evaluate the Joel-Cohen and Pfannenstiel techniques during caesarean deliveries and concluded that the postoperative pain and number of analgesics needed were lower in the Joel Cohen technique compared with the Pfannenstiel technique (17, 18).

Although this study and randomised controlled trials concluded that the time to get out of bed, to walk straight without support, to detect audible intestinal sounds and to pass gases were significantly shorter in the Joel-Cohen group compared to the Pfannenstiel group (6, 9, 19), the Cochrane systemic review concluded that there was no significant difference between the Joel-Cohen and Pfannenstiel techniques regarding time to return of bowel function, time to mobilisation and/or time to the start of breastfeeding (17, 18).

There was no significant difference in this study between the Joel Cohen group and the Pfannenstiel group regarding the postoperative hospital stay, while, Moreira et al. (6) and Popiela et al. (20), concluded that the postoperative hospital stay was significantly shorter in the modified Joel Cohen technique compared to the Pfannenstiel technique.

There was no significant difference in this study between the Joel Cohen group and the Pfannenstiel group regarding the postoperative haemoglobin and/or haematocrit decreases and no blood transfusion or serious complications were recorded; Darj et al. (13) and Wallin et al. (14) concluded that blood loss was less with the

Joel Cohen procedure (448 & 250 mL, respectively) compared to the Pfannenstiel procedure (608 & 200 mL, respectively) due to the short operative time and minimal tissue trauma (13, 14).

The Cochrane systemic review (three trials) reported less blood loss with the Joel-Cohen technique compared to the Pfannenstiel technique and reported more blood transfusion with the Pfannenstiel compared with the Joel-Cohen technique; also, the Cochrane review stated that “the three trials do not provide information on mortality and serious or long-term morbidity such as morbidly adherent placenta and scar rupture” (17, 18).

The limitations of this study include a lack of long-term follow-up, and the fact that women with previous abdominal surgery, women with medical disorders and/or women receiving general anaesthesia were not included in this study.

Based on limitations of this study and Cochrane reviews, further trials with long-term follow-up are needed to provide information on mortality and/or long-term morbidity, such as morbidly adherent placenta and scar rupture after both techniques of caesarean deliveries.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Ain Shams University Maternity Hospital.

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author contributions: Concept – G.E.B., W.M.A.; Design – W.M.A.; Supervision – W.M.A., G.E.B.; Resource – W.M.A., G.E.B.; Materials – W.M.A.; Data Collection&/or Processing – W.M.A.; Analysis&/or Interpretation– W.M.A.; Literature Search – W.M.A., L.H.E.; Writing – W.M.A., L.H.E.; Critical Reviews – W.M.A., L.H.E.

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β -human chorionic gonadotropin assay in vaginal washing fluid for the accurate diagnosis of premature rupture of membranes during late pregnancy

Geç gebelik sırasında erken membran rüptürünün doğru tanısı için vajinal yıkama sıvısında β -human koryonik gonodotropin ölçümü

Orhan Temel¹, Ebru Çöğendez¹, Selçuk Selçuk¹, Mehmet Reşit Asoğlu², Erdal Kaya¹

¹Department of Obstetrics and Gynecology, Zeynep Kamil Training and Research Hospital, İstanbul, Turkey

²The University of Texas MD Anderson Cancer Center, Houston, Texas, United States of America

Abstract

Objective: To determine whether the measurement of beta-human chorionic gonadotropin (β -hCG) levels in vaginal fluid is useful for the diagnosis of premature rupture of membranes (PROM).

Material and Methods: A total of 92 pregnant women between 24 and 40 weeks gestation participated in this study. The patients with fluid leaking from the vagina were designated Group 1, the patients with no fluid leaking from the vagina were Group 2, and those with a suspicion of fluid leaking from the vagina were classified as Group 3. Irrigating the posterior vaginal fornix with 5 mL sterile saline was used to measure β -hCG levels of the patients. Receiver operator curve (ROC) analysis was used to determine the cut-off value for a positive diagnosis.

Results: The β -hCG levels of vaginal fluid were measured as 20.5 \pm 25.0 mIU/mL, 254.6 \pm 346.8 mIU/mL, and 74.3 \pm 100.8 mIU/mL in Group 1, Group 2, and Group 3, respectively. Vaginal β -hCG level was higher statistically significantly in Group 2 than Group 1 and 3 ($p < 0.001$). 100 mIU/mL was accepted as a cut-off value by using the receiver operating characteristic curve. According to 100 mIU/mL, sensitivity, specificity, positive predictive and negative predictive values were calculated as 71.2, 100, 100, and 65.1%, respectively.

Conclusion: The study showed that the measurement of β -hCG level in vaginal washing fluid is an efficient and easy diagnostic test for predicting the amount of fluid leaking from the vagina. However, due to the low negative predictive value of the test, it would not be convenient in daily practice. (J Turkish-German Gynecol Assoc 2013; 14: 201-4)

Key words: Beta-human chorionic gonadotropin, premature rupture of membranes, diagnosis

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Özet

Amaç: Erken membran rüptürünün tanısı için vajinal sıvıda beta-human koryonik gonadotropin (β -hCG) seviyesinin ölçümünün yararlı olup olmadığını belirlemek.

Gereç ve Yöntemler: Gebeliğin 24-40. haftaları arasında olan toplam 92 gebe bu çalışmaya dahil edildi. Vajinadan sıvı geldiği görülen hastalar Grup 1, vajinadan sıvı gelmeyenler Grup 2 and şüpheli sıvı gelişi olan hastalar Grup 3 olarak sınıflandırıldı. Hastaların vajinal sıvıdaki β -hCG seviyelerinin ölçümü için posterior vajinal fornixin 5 mL salin ile elde edilen yıkantı suyu kullanıldı. Receiver operator curve (ROC) analizi yapılarak doğru tanı için gereken eşik seviye belirlendi.

Bulgular: Vajinal sıvıda β -hCG seviyesi Grup 1 için, 20.5 \pm 25.0 mIU/mL, Grup 2 için 254.6 \pm 346.8 mIU/mL, Grup 3 için 74.3 \pm 100.8 mIU/mL olarak ölçüldü. Vajinal β -hCG seviyesi Grup 2 de Grup 1 ve 3'ten istatistiksel olarak daha yüksek bulundu ($p < 0.001$). ROC analizi eğrisi kullanılarak eşik seviye 100 mIU/mL olarak kabul edildi. 100 mIU/mL eşik derece göre; sensitivite, spesifite, pozitif ve negatif prediktif değerler sırasıyla %71.2, %100, %100 ve %65.1 olarak hesaplandı.

Sonuç: Vajinadan sıvı gelişini ön görmede, vajinal yıkama sıvısında β -hCG seviyesinin ölçümünün etkili ve kolay bir tanısal testi olduğu çalışmamızda gösterilmiştir. Bununla birlikte: testin negatif prediktif değerinin düşük olmasından dolayı günlük pratikte kullanımı uygun olmayabilir. (J Turkish-German Gynecol Assoc 2013; 14: 201-4)

Anahtar kelimeler: Beta-human koryonik gonadotropin, erken membran rüptürü, tanı

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Introduction

Premature rupture of membrane (PROM) is shown in 5-15% of all term births and in 20-40% of all preterm births. The most common complication of PROM is infection. Although term births with prolonged PROM are at risk of infection, the

main threat involves preterm cases. Infection risk increases concomitantly with a prolonged latent period (1).

Diagnosis of PROM is easy when there is a demonstration of amniotic fluid leakage from the cervix, but more difficult when there is doubt surrounding whether PROM has occurred. Failure to identify patients with membrane rupture can result in



a failure to implement obstetric measures, while false diagnosis can lead to inappropriate interventions such as hospitalisation or labour induction. The diagnosis of PROM usually depends on a combination of factors, including the patient's history, identification of amniotic fluid index (AFI) pooling and ferning, and the nitrazine test (2, 3). However, in equivocal cases of PROM, the traditional method has been associated with both false-positive and false-negative results (4).

The absence of a non-invasive "gold standard" test for the diagnosis of membrane rupture has led to the search for alternative biochemical markers. Biochemical substances which have high amniotic concentration, e.g. prolactin (5), alpha-fetoprotein (AFP) (6), insulin like growth factor binding protein-1 (7), foetal fibronectin (8), and deaminooxidase (9), have all have been previously studied.

Beta-human chorionic gonadotropin (β -hCG) is produced by trophoblastic tissue, which is present in varying degrees in serum, urine, and amniotic fluid during pregnancy. It is present in AF as well as maternal blood and urine, at concentrations ranging from approximately 2000-70,000 mIU/mL (10). Unfortunately, there is no information available about β -hCG levels in vaginal fluid. Because β -hCG is secreted by cervical glands, a certain level should be present in vaginal fluid. Therefore, we measured and compared β -hCG levels in the vaginal fluid of normal pregnant women, pregnant women with PROM and pregnant women with suspected PROM.

In this study, our aim was to determine the diagnostic value of β -hCG level in vaginal washing fluid for PROM.

Material and Methods

This study was conducted at Zeynep Kamil Education and Training Hospital, İstanbul, Turkey, in the Department of Perinatology, from April 2011 to December 2011. The study was approved by the local ethics committee, and written informed consent was obtained from all participants. The pregnant women in their second and third trimester that had normal foetal development in ultrasound in respect of their last menstruation date were included in this study. A history of preterm labour and PROM, multiple pregnancy, uterine pathology and malformation, cervical dilatation more than 2 cm, vaginal bleeding or placenta previa, vaginal contaminations with urine or faeces, or those with no follow-up were excluded from the study. A total of 92 pregnant women at the 24-40th week of gestation were enrolled in the present study. A power analysis was not used to calculate the sample size in each group.

At admission, all patients underwent a sterile speculum examination. Amniotic fluid pooling with or without valsalva manoeuvre was noted. The patients with negative, positive and suspected pooling were classified as Group 1 (28 patients), Group 2 (52 patients) and Group 3 (12 patients), respectively. Group 1 contained patients with amniotic fluid leaking from the vagina upon speculum examination, Group 2 included patients without complaint of amniotic fluid leaking from the vagina, while Group 3 was composed of those patients who complained of vaginal discharge and/or perineal wetness, and these patients were negative for amniotic fluid pooling with or without valsalva manoeuvre on speculum examination.

After taking the history of patients, vaginal examination with a sterile speculum was performed on all patients. Amniotic fluid pooling, drainage of amniotic fluid, blood, urine, meconium or semen with valsalva manoeuvre and cervical dilatation were evaluated. Subsequently, 5 cc of sterile saline was placed in the vagina through the speculum. After a 20 minute waiting period, 3 cc of vaginal washing fluid was removed using a syringe. The fluid was transported to the laboratory within one hour, and then placed into a biochemistry tube for β -hCG analysis. All of the samples were studied in the same laboratory using the same technique. β -hCG level was measured and interpreted after the samples were centrifuged 5 minutes at 3000 rpm. At the same time, the amniotic fluid index (AFI) of patients was measured with the four quadrant method and recorded. AFI values less than 50 mm were defined as oligohydramnios and values between 50-80 mm were considered as borderline oligohydramnios.

For statistical analysis, SPSS Software Version 19 (IBM, United States of America) was used. In order to analyse parametric data and perform sub-analysis, ANOVA and post-tukey tests were used, respectively. To analyse non-parametric data and perform sub-analysis, Kruskal-Wallis and Mann-Whitney U tests were used, respectively. The chi-square test was utilised to analyse rational data. To determine cut-off values, a receiver operating characteristic (ROC) curve and sensitivity analysis were performed.

Results

Demographic data for each group are shown in Table 1. There were no statistically significant differences between the groups in terms of age, weeks of gestation, AFI and APGAR (Appearance, Pulse, Grimace, Activity, Respiration) score values ($p>0.05$). The birth weight was calculated as 3330.2 ± 478.0 for group 1, 2758.2 ± 953.5 g for group 2, and 2428.8 ± 1105.8 g for group 3. The mean birth weight of group 1 was statistically significantly higher than that of group 2 and 3 (Table 1, $p<0.05$). No significant difference was observed between the groups in terms of number of gravida, parity and abortus numbers ($p>0.05$). The β -hCG levels of group 1, 2 and 3 were measured as 20.5 ± 25.0 mIU/mL, 254.6 ± 346.8 mIU/mL and 74.3 ± 100.8 mIU/mL, respectively. A statistically significant difference was found between the groups for β -hCG levels. On the day of the measurement of hCG, the average gestation age was calculated as 38^{+6} , 36^{+6} and 35^{+1} weeks for groups 1, 2 and 3, respectively. Duration from the day of measurement of hCG to the delivery time was 21 hours for group 1, and 55 hours for groups 2 and 3. All values were found to be statistically significant when β -hCG cut-off levels were accepted as 90, 95, 100, 105 or 110 mIU/mL for predicting certain leakage of fluid from the vagina ($p<0.05$). ROC curve analysis was used to establish the optimal cut-off concentration for vaginal washing fluid for β -hCG levels. The optimal cut-off value was found to be 100 mIU/mL (Figure 1). According to this cut-off point, the sensitivity, specificity, positive and negative predictive value were calculated as 71.2%, 100%, 100% and 65.1%, respectively.

Fluid leaking from the vagina would be considered if the patient's β -hCG value in their vaginal fluid was higher than 100 mIU/mL. Although patients with β -hCG values lower than 100 mIU/mL in

Table 1. Comparison of maternal age, gestation weeks, amniotic fluid index (AFI), birth weight, APGAR (Appearance, Pulse, Grimace, Activity, Respiration) score and β -hCG value between the groups

	Leaking fluid from the vagina			
	Group 1 (n=28) (mean \pm SD)	Group 2 (n=52) (mean \pm SD)	Group 3 (n=12) (mean \pm SD)	p
Age (years)	27.0 \pm 4.5	28.2 \pm 5.4	26.2 \pm 6.3	>0.05
Gestation weeks	38.6 \pm 1.9	36.6 \pm 4.5	35.2 \pm 6.4	>0.05
AFI (mm)	116.5 \pm 47.9	100.5 \pm 44.4	88.3 \pm 43.5	>0.05
Birth weight (g)	3330.2 \pm 478.0	2758.2 \pm 953.5	2428.8 \pm 1105.8	<0.01
APGAR at 1 min	8.4 \pm 0.6	7.4 \pm 2.3	7.2 \pm 2.4	>0.05
APGAR at 5 min	9.5 \pm 0.7	8.7 \pm 2.0	8.2 \pm 3.1	>0.05
Beta-hCG (mIU/mL)	20.5 \pm 25.0	254.6 \pm 346.8	74.3 \pm 100.8	<0.001

ANOVA test was used. p<0.05 was accepted as statistically significant.

the vaginal fluid were more likely to have no probability of fluid leaking from the vagina, water flow was detected in 34.9% of these patients. β -hCG values were found to be lower than 100 mIU/mL in all patients without fluid leaking from the vagina.

Discussion

PROM is associated with infectious morbidity in the mother and foetus, cord accidents, and imminent term or preterm labour. For these reasons, its correct diagnosis is very important. The history of the patient is often sufficient for diagnosis in 90% of cases of suspected PROM. Although an accurate diagnosis can be made with intra-amniotic injections of dye, both patients and doctors are reluctant to go through such an invasive procedure. An ideal laboratory diagnostic technique should be acceptable to both patients and clinicians and should be non-invasive, accurate and rapid. The use of biochemical markers (confirmation of AFI components, such as AFP, foetal fibronectin, or insulin-like growth factor-binding protein-1 in the vaginal fluid) seems to present a reasonable alternative method for diagnosing PROM (6-8). All of these markers have advantages and disadvantages. However, they have not been popular because of their complexity and cost.

The other biochemical marker used for the accurate diagnosis of PROM is β -hCG in vaginal fluid. It does not require additional instruments when a commercial β -hCG kit for pregnancy testing is available. The advantages of the β -hCG test include the low cost and rapid results.

In a study published by Kim et al. (11), β -hCG cut-off value of PROM was estimated in 120 patients and when the cut-off value was accepted as 39.8 mIU/mL, the sensitivity, specificity, positive and negative predictive values were reported as 95.5%, 94.7%, 91.3% and 97.3%, respectively. They showed that the β -hCG values in vaginal washing fluid of patients with pooling was significantly higher than in patients with no pooling, in parallel to our study. However, in contrast to our work, they evaluated preterm and term pregnancies as different groups. Although the cut-off value accepted by Kim et al. (11) was lower than our study, the negative prediction value was higher.

In a study conducted by Mangano et al. (12), 52 patients were evaluated and divided into three groups: patients with clinically confirmed membrane rupture as group 1 (n=21), patients with suspected membrane rupture as group 2 (n=11), and the control group without membrane rupture as group 3 (n=20). In this study, the β -hCG cut-off value in the vaginal washing fluid was detected as 100 mIU/mL with regard to prediction of pooling. In another study, Esim et al. (13) examined 141 patients for β -hCG in vaginal washing fluid; they declared the optimal β -hCG cut-off value to be 65 mIU/mL. According to this, sensitivity, specificity, positive and negative predictive values were calculated as 68%, 95%, 82% and 90%, respectively. Unlike our study, the values of sensitivity and specificity for the second and third trimester were compared separately and sensitivity was found to be higher in the second trimester. Therefore, it was suggested that testing β -hCG in vaginal fluid in the second trimester could be more convenient. Anai et al. (14) evaluated β -hCG as a marker for PPRM and established the vaginal β -hCG concentration ranges of a subset of patients without PPRM in the first, second, and third trimesters. These investigators demonstrated a definitive difference in mean β -hCG concentrations of subjects with PPRM and those without. They considered that there was a significant difference in the second and third trimesters using a vaginal β -hCG threshold concentration of 50 mIU/mL. In a study conducted by Ni et al. (15), β -hCG, AFP and IL-6 markers were investigated in vaginal fluid. According to the ROC analysis, the sensitivity and specificity were 97.7% and 100% for AFP, and 95.1% and 89.5% for β -hCG, respectively. They found that AFP had highest diagnostic value. In the present study, sensitivity and specificity were found to be 72.1% and 100%, respectively, for β -hCG in vaginal fluid.

As can be seen above, different cut-off levels, sensitivities, specificities, positive and negative predictive values for β -hCG in vaginal washing fluid have been reported in various studies for the accurate detection of PROM. These different results could have arisen from reasons such as the existence of a difference in the number of samples, including. In addition, patients with vaginal bleeding were included in some studies.

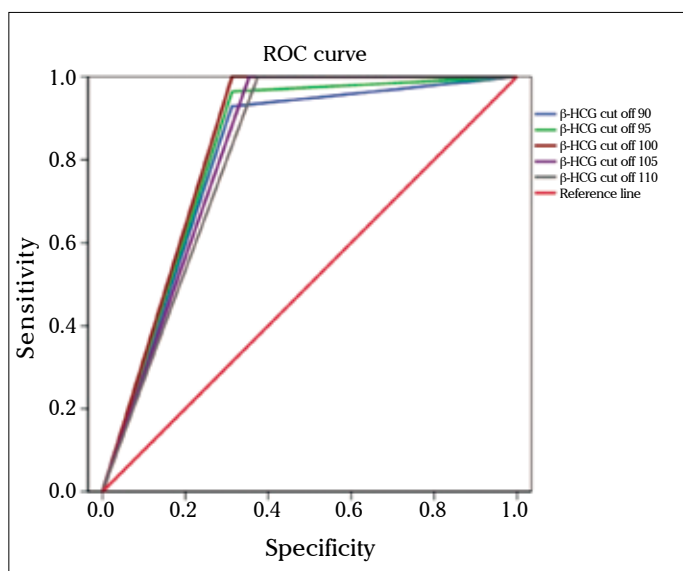


Figure 1. Receiver operating characteristic (ROC) curve analysis

As already known, cut-off values are significantly affected by the number of samples. Also, β -hCG values may vary from laboratory to laboratory and β -hCG level in amniotic fluid of term and preterm pregnancies may vary. In the studies discussed, the term and preterm groups were not homogeneous in terms of pregnancy.

In conclusion, we believe that β -hCG measurements in vaginal fluid would be accurate for diagnostic testing for prediction of PROM. Also, it can be performed quickly and easily. Because it has a low negative predictive value, diagnostic confusion may occur. Extended studies are needed to determine the cut-off value of β -hCG in the diagnosis of PROM.

Ethics Committee Approval: Ethics Committee Approval was obtained from hospital ethics committee

Informed Consent: Informed consent form was obtained from all patients

Peer-review: Externally peer-reviewed.

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The impact of parity on perinatal outcomes in pregnancies complicated by advanced maternal age

İleri maternal yaşla komplike gebeliklerde paritenin perinatal sonuçlara etkisi

Eralp Başer, Kerem Doğa Seçkin, Selçuk Erkıncı, Mehmet Fatih Karılı, İlkin Mahmut Yeral, Oktay Kaymak, Turhan Çağlar, Nuri Danışman

Department of Obstetrics and Gynecology, Zekai Tahir Burak Women's Health Education and Research Hospital, Ankara, Turkey

Abstract

Objective: The purpose of this study was to investigate the impact of parity on perinatal outcomes in pregnancies complicated by advanced maternal age.

Material and Methods: A total of 11 587 pregnancies were reviewed retrospectively from patient medical records. Singleton pregnancies greater than 24 weeks of gestation were included. The study group consisted of women ≥ 40 years old at the time of delivery, and the control group consisted of women aged between 20 and 30 years old. Data regarding age, parity, gestational age, mode of delivery, and obstetric and neonatal complications were collected. Firstly, pregnancies ≥ 40 years and the younger control group were compared altogether with respect to the obstetric and neonatal complications. Secondly, both groups were divided into subgroups according to parity, and a second comparison was made with controls.

Results: Mean maternal age in the study and control groups was 43 ± 2.2 and 24 ± 2.8 years, respectively. In women ≥ 40 years old, all of the investigated obstetric and neonatal complications except postpartum haemorrhage and foetal malformations were higher when compared to younger controls ($p < 0.05$). In the nulliparous ≥ 40 year old group, the most significant complications were preterm delivery (45.3%), low 5-minute Apgar score (15.2%), and neonatal intensive care unit admission (15.2%). On the other hand, in the multiparous group, preeclampsia (16.6%), abruptio placentae (5.1%), foetal demise (7.2%), and macrosomia (9.6%) were found to be significantly higher when compared to controls.

Conclusion: The study suggests that pregnancies of maternal age ≥ 40 years carry increased risks for both neonatal and obstetric complications, and these risks seem to be effected by parity.

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Key words: Advanced maternal age, parity, perinatal outcome, neonatal outcome

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Özet

Amaç: Bu çalışmanın amacı, paritenin ileri maternal yaş ile komplike olmuş gebeliklerde perinatal sonuçlara olan etkisinin incelenmesidir.

Gereç ve Yöntemler: Toplam 11 587 gebeliğe ait takip dosyası retrospektif olarak incelendi. Çalışmaya 24 hafta üzeri tekiz gebelikler dahil edildi. Çalışma grubu doğum sırasında 40 yaş ve üzeri olan gebe kadınlardan, kontrol grubu ise 20-30 yaş arası gebe kadınlardan oluşturuldu. Hastaların yaş, parite, gestasyonel yaş, doğum şekli, obstetrik ve neonatal komplikasyonlara ait verileri toplandı. İlk olarak 40 yaş üzeri gebelerle genç kontrol grubunun tamamı obstetrik ve neonatal komplikasyonlar açısından karşılaştırıldı. Sonrasında, her iki grup da pariteye göre ayrı ayrı (nullipar ve multipar), ikinci bir karşılaştırma yapıldı.

Bulgular: Çalışma ve kontrol grubunda ortalama maternal yaşlar sırasıyla 43 ± 2.2 ve 24 ± 2.8 yıl idi. Kırk yaş üzeri kadınlarda, postpartum kanama ve fetal malformasyonlar dışında incelenen tüm obstetrik ve neonatal komplikasyonlar kontrollere göre daha sıklıkla ($p < 0.05$). Nullipar 40 yaş üstü gebelerde kontrollere göre anlamlı olarak daha sık gözlenen en sık komplikasyonlar preterm doğum (%45.3), düşük 5.dakika APGAR skoru (%15.2), ve neonatal yoğun bakım ünitesine yatış (%15.2) idi. Diğer taraftan multipar grupta preeklampsi (%16.6), ablasyo plasenta (%5.1), fetal kayıp (%7.2) ve makrozomi (%9.6) kontrol grubuna göre daha sıklıkla ($p < 0.05$).

Sonuç: Bu çalışmada, maternal yaşın 40'ın üzerinde olduğu gebeliklerde neonatal ve obstetrik komplikasyonlarda artış olduğu, ve bu risklerin pariteden etkilendiği sonucuna varılmıştır.

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Anahtar kelimeler: İleri maternal yaş, parite, perinatal sonuçlar, neonatal sonuçlar

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Kabul Tarihi: 19 Eylül 2013

Introduction

Delayed childbearing has become increasingly common in the past decades, and this has raised concern for the possible risks for both the mother and the foetus. In numerous previous studies, a maternal age ≥ 40 years has been reported as a proper cut-off to better identify high-risk women with

advanced maternal age (1). The majority of these pregnancies are achieved with assisted reproductive technologies (ART), which also increases the risk of complications.

The prevalence of advanced maternal age within all pregnancies has been previously reported to be around 1.5%; however, these numbers may change according to the population studied (2, 3). Advanced maternal age is well known to be



associated with adverse maternal and foetal outcomes such as gestational diabetes mellitus, preterm delivery, antepartum haemorrhage (4). This study was designed to compare the complications and pregnancy outcomes of women aged 40 years and above with women aged 20-30 years, with special emphasis on the variations of these complications with regards to parity.

Material and Methods

A retrospective patient chart analysis was conducted for pregnancies that were followed-up at a tertiary referral hospital in Ankara, Turkey between January 1, 2011 and January 1, 2013. Institutional ethical and scientific approval was obtained. A total of 11,587 pregnancies were reviewed retrospectively. Singleton pregnancies after 24 weeks of gestation were included, and all gestational ages were confirmed by first or second trimester ultrasound measurements. Pregnant women with multifoetal pregnancies, chronic diseases, and previous uterine surgeries were excluded.

The study group consisted of women ≥ 40 years ($n=190$). Using a 1:3 ratio for cases:controls, the control group consisted of 600 women aged between 20 and 30 years, who were randomly selected. Women with multifoetal pregnancies, chronic diseases, and previous uterine surgeries were also not included in the control group. Data including age, parity, gestational age, mode of delivery and obstetrical and neonatal complications were collected and compared with respect to maternal age and parity. Nulliparity was defined as not having any previous history of deliveries >20 gestational weeks. Multiparity was defined as a previous history of ≥ 1 delivery >20 gestational weeks. Obstetric complications such as placenta previa, placental abruption, hypertension, preeclampsia, gestational diabetes mellitus, preterm delivery, low 1 and 5 minute Apgar scores, neonatal intensive care unit admission, intrauterine growth restriction (IUGR) and foetal demise were recorded for each patient.

Preeclampsia was defined as increased blood pressure $\geq 140/90$ on two or more occasions, and ≥ 300 mg proteinuria in 24-hour urine, after 20 weeks of gestation. The diagnosis for gestational diabetes mellitus was based on the American College of Obstetrics and Gynecology guidelines for diagnosing gestational diabetes mellitus (5). Childbirth before 37 completed weeks (<259 days) was defined as preterm delivery. Postpartum haemorrhage (PPH) was defined as estimated blood loss (EBL) ≥ 500 mL after vaginal delivery, and ≥ 1000 mL after caesarean delivery. Low Apgar scores were defined as a 1 minute Apgar score <7 and a 5 minute Apgar score <9 . The study and control groups were further divided into two subgroups according to parity (nulliparous and multiparous), and the two groups were compared with nulliparous and multiparous controls.

Statistical analyses were performed with IBM SPSS 20.0 (SPSS Inc., Armonk, NY, USA) software. Continuous variables were expressed as mean \pm standard deviation (SD), discrete variables as median (range) and categorical variables as number and percentage. The Kolmogorov-Smirnov test was used to assess normal data distribution. The univariate analyses were inves-

tigated with Chi-square test (with Yates' correction), Fisher's Exact test and *t*-test, where appropriate. Odds ratio (OR) with 95% confidence interval (CI) was calculated for each complication. In addition, crude and adjusted log-linear binomial regression analyses were carried out for each complication separately by maternal age group, to estimate the relative risk ratios (RR). Women aged 20-30 were assigned as the basal controls in this model. P values were considered significant at the 0.05 level (two tailed).

Results

Mean age in the study and control groups were 43 ± 2.2 and 24 ± 2.8 years, respectively. Fifty-two per cent ($n: 408$) of the patients were nulliparous, and 48% ($n: 383$) of the patients were multiparous. The comparisons between the study and control group with regards to perinatal and neonatal outcomes are presented in Table 1. In the study group, the most significant complications that were found at rates higher than in the controls were as follows: preterm delivery (28.9%), preeclampsia (15.8%), gestational diabetes mellitus (6.8%), IUGR (9.5%), placenta previa (3.7%), abruptio placentae (5.8%), and foetal demise (7.8%) ($p < 0.05$). The caesarean delivery rate was also higher in the study group (58.9%) when compared to controls (30.7%) ($p < 0.05$). There were no significant differences between the groups with respect to PPH and foetal malformations ($p > 0.05$). Mean gestational age was lower in the study group as compared to the control group (36.7 ± 2.8 vs. 37.8 ± 2.4 weeks, respectively; $p < 0.05$). Crude and adjusted estimates of the association between maternal age group and parameters of adverse pregnancy outcomes are presented in Table 2.

The two groups were further divided into two subgroups according to parity, as nulliparous and multiparous; the study groups (≥ 40 years) were again compared with controls of similar parity. The comparison of the divided groups in terms of obstetric and perinatal outcomes is given in Table 3. In ≥ 40 year old nulliparous women, there was a trend towards increased obstetric and perinatal complications, including preterm delivery (45.3%), gestational diabetes mellitus (9.1%) and placenta previa (12%) ($p < 0.05$). In ≥ 40 year old multiparous group, preeclampsia (16.6%), abruptio placentae (5.1%), foetal demise (7.2%), caesarean delivery (58%) and macrosomia (9.6%) were higher than in controls. However, there were no statistically significant differences between the ≥ 40 year old multiparous women and controls in terms of preterm delivery, IUGR, placenta previa, postpartum haemorrhage, and foetal malformations ($p > 0.05$). Amniocentesis was performed in 27 patients in the study group, and 8 controls to rule out foetal chromosomal anomalies; all were reported as having a normal karyotype.

Discussion

Advanced maternal age is well known to increase the risk for perinatal complications and adverse pregnancy outcomes when compared to younger women. Current evidence suggests that these risks of advanced age begin to increase after the age of 35 years, and significantly accelerate after the age of 40 (6).

Table 1. Comparison of perinatal and neonatal complications between women aged ≥ 40 years and controls (20-30 years)

	Women aged >40 years (n=190) n (%)	Women aged 20-30 years (n=600) n (%)	OR (%95 CI)	p
Preterm delivery	55 (28.9)	118 (19.6)	1.67 (1.37-1.94)	0.009
Gestational diabetes mellitus	13 (6.8)	18 (3)	5.67 (2.37-4.95)	0.005
Preeclampsia	30 (15.8)	22 (3.6)	4.93 (2.77-8.79)	<0.001
Intrauterine growth restriction	19 (9.5)	30 (5)	2.11 (1.16-3.85)	0.033
Placenta previa	7 (3.7)	3 (0.5)	7.62 (1.95-29.78)	<0.001
Foetal anomaly	8 (4.2)	16 (2.6)	1.71 (0.71-4.11)	0.22
Intrauterine foetal demise	15 (7.8)	13 (2.1)	2.70 (1.45-6.14)	0.005
Ablatio placenta	11 (5.8)	7 (1.2)	5.21 (1.99-13.65)	<0.001
Caesarean delivery	112 (58.9)	185 (30.8)	1.64 (1.46-1.90)	0.011
Postpartum haemorrhage	6 (3.1)	15 (2.5)	1.23 (0.87-3.24)	0.32
Low birth weight	53 (27.9)	124 (20.6)	3.61 (1.91-6.81)	0.020
Macrosomia	21 (11.1)	20 (3.3)	2.14 (0.75-6.10)	<0.001
Neonatal intensive care admission	18 (9.4)	46 (7.6)	2.21 (1.24-3.93)	0.003
Neonatal mortality	12 (6.3)	16 (2.6)	2.46 (1.14-5.29)	0.013
1-minute Apgar score <7	32 (16.8)	47 (7.8)	2.38 (1.47-4.86)	<0.001
5-minute Apgar score <9	34 (17.9)	51 (8.5)	2.35 (1.47-3.75)	<0.001

Table 2. Crude and adjusted relative risks (RR) of association between advanced maternal age (>40 years) and obstetrical-neonatal complications when compared to the control group

	Women aged > 40 years (n=190)	
	Crude RR (95% CI)	Adjusted RR ¹ (95% CI)
Preterm delivery	0.92 (0.82-1.12)	1.08 (0.95-1.12)
Gestational diabetes mellitus	1.84 (1.74-1.91)	1.78 (1.72-1.83)
Preeclampsia	1.88 (1.77-1.98)	1.81 (1.69-1.95)
Intrauterine growth restriction	1.61 (1.53-1.68)	1.34 (1.24-1.47)
Placenta previa	2.12 (2.04-2.21)	1.84 (1.72-1.99)
Foetal anomaly	1.03 (0.92-1.12)	1.06 (0.96-1.11)
Intrauterine foetal demise	1.55 (1.43-1.62)	1.47 (1.39-1.54)
Ablatio placenta	1.79 (1.71-1.87)	1.74 (1.66-1.83)
Caesarean delivery	1.91 (1.83-1.96)	1.86 (1.80-1.91)
Postpartum haemorrhage	1.02 (0.93-1.07)	1.00 (0.91-1.04)
Low birth weight	1.44 (1.37-1.54)	1.51 (1.42-1.58)
Macrosomia	1.71 (1.60-1.77)	1.52 (1.45-1.61)
Neonatal intensive care admission	1.69 (1.59-1.73)	1.61 (1.54-1.69)
Neonatal mortality	1.63 (1.54-1.71)	1.54 (1.42-1.59)
1-minute Apgar score <7	1.38 (1.31-1.47)	1.49 (1.42-1.54)
5-minute Apgar score <9	1.35 (1.28-1.39)	1.46 (1.40-1.51)

¹ Adjusted for parity

In this study, we found that preeclampsia, gestational diabetes mellitus, placenta previa, foetal demise, abruptio placentae, preterm delivery, and IUGR were higher in the women aged ≥ 40 years, when compared to controls. Previous studies have reported similar findings to this study (7, 8). For example, a paper on neonatal outcomes in advanced maternal age reported that maternal age ≥ 40 years was associated with a higher incidence of preterm birth, low birth weight and stillbirth (9). Another study had previously stated that advanced maternal age was a risk factor for abruptio placentae (10). Gestational diabetes mellitus, preeclampsia and preterm delivery were also reported to have a higher incidence among the pregnancies with maternal age over 40 years (4, 11). In the log-linear binomial regression analyses performed in this study, we found that women aged ≥ 40 years had significantly increased RRs for all obstetric and neonatal complications except foetal anomalies and obstetric haemorrhage.

A previous study from Turkey investigated the maternal and foetal outcomes of pregnancies in women aged 35 and older (12). The authors compared 565 women of advanced maternal age (≥ 35 years), with 3,607 controls (< 35 years). Preeclampsia, antepartum bleeding, and caesarean delivery frequency was higher in the advanced maternal age group ($p=0.001$). They also reported that Apgar scores of the infants were lower in women with advanced maternal age. We also found similar results in this study. They reported that newborn weights and NICU admission rates were similar between the two groups in their study. However, in this study, we found higher frequencies of low birth weight infants and higher NICU admissions in women of advanced age. This difference may be due to the fact that our cases of advanced maternal age consisted of women aged ≥ 40 years, while in the study of Üstün et al. (12),

Table 3. Comparison of perinatal and neonatal outcomes between women aged ≥ 40 years and controls, according to parity

Variables	Nulliparous			Multiparous		
	≥ 40 years (n= 33) n (%)	20-30 years (n= 375) n (%)	p	≥ 40 years (n=157) n (%)	20-30 years (n= 225) n (%)	p
Preterm delivery	15 (45.3)	67 (17.9)	0.001	40 (23.4)	53 (23.5)	0.31
Gestational diabetes mellitus	3 (9.1)	14 (3.7)	0.02	10 (6.4)	4 (1.7)	0.018
Preeclampsia	4 (9.4)	14 (3.7)	0.36	26 (16.6)	8 (3.5)	0.00
Intrauterine growth restriction	3 (8.7)	17 (4.5)	0.2	16 (10.2)	13 (5.7)	0.106
Placenta previa	4 (12)	1 (0.26)	0.00	3 (1.9)	2 (0.9)	0.38
Foetal anomaly	2 (6.1)	9 (2.4)	0.21	6 (3.8)	7 (3.1)	0.519
Intrauterine foetal demise	4 (12)	8 (2.1)	0.001	11 (7.2)	5(2.2)	0.009
Ablatio placenta	3 (9.2)	4 (1.1)	0.001	8 (5.1)	3 (1.3)	0.03
Caesarean delivery	21 (63)	147 (39.2)	0.01	91 (58)	38 (16.9)	0.006
Postpartum haemorrhage	1 (3.03)	11 (2.9)	0.24	5 (3.2)	4 (1.8)	0.43
Low birth weight	12 (36.4)	72 (19.2)	0.001	41 (25.7)	52 (23.1)	0.51
Macrosomia	6 (18.2)	11 (2.9)	0.00	15 (9.6)	9 (4)	0.027
Neonatal intensive care admission	5 (15.2)	26 (6.9)	0.002	13 (8.2)	20 (8.9)	0.521
Neonatal mortality	3 (9.1)	5 (1.3)	0.002	9 (5.7)	11 (4.9)	0.72
1-minute Apgar score <7	3 (9.9)	16 (4.3)	0.001	29 (18.5)	31 (13.7)	0.27
5-minute Apgar score <9	5 (15.2)	20 (5.3)	0.000	29 (18.5)	31 (13.7)	0.21

it consisted of women aged ≥ 35 years. In another study from Turkey, 237 advanced maternal age (≥ 35 years) pregnancies were retrospectively analysed and compared with younger age controls for maternal and foetal outcomes (13). The rates of preeclampsia, gestational diabetes, low Apgar scores and intrauterine foetal demise were higher in the advanced age group. On the contrary, caesarean delivery rates were higher in the control group. Rates of prematurity, low birth weight infants and foetal anomalies were similar between the groups. The findings of this study were very similar to our findings, except that the rates of caesarean delivery and low birth weight infants were also higher in the advanced maternal age group in our study.

A very recent study investigated the frequency of postpartum haemorrhage in women with advanced maternal age (14). In this retrospective study, a total of 12,868 women aged ≥ 35 years were compared with 52,200 women aged <35 years. It was reported that, although the risk of postpartum haemorrhage seemed to increase in advanced aged women, this was attributable to factors other than maternal age. Interestingly, it was found that advanced age was found to be associated with less PPH in the multivariate analysis. In our study, the frequency of PPH was similar between advanced age and control groups. In this study, in order to compare women for the aforementioned outcome measures according to parity, we divided the study population into two groups as nulliparous and multiparous. Gestational diabetes mellitus, preterm delivery and placenta previa were found to be significantly higher in nulliparous older women, whereas foetal demise and abruptio placentae were found to be higher in both nulliparous and multiparous women. There was a significantly increased risk of preeclampsia only in multiparous older women compared to young

multiparous controls. These findings are similar to those from the literature, except for those regarding placenta previa and preeclampsia. In a previous study, multiparity was found to be associated with placenta previa (15). On the other hand, Chan et al. (4) also found that an increased incidence of placenta previa existed among mothers ≥ 40 years, in contrast to other studies. Another study also stated that preeclampsia was higher both in nulliparous and multiparous older aged women; however, we could demonstrate this increase only in multiparous advanced maternal age women (16).

In a systematic review, an increased risk of caesarean birth was reported among women at advanced maternal age, compared with both nulliparous and multiparous younger women (16). In this study, nulliparous women ≥ 40 years had an increased risk of caesarean delivery compared to younger nulliparous controls. Although the higher caesarean delivery rate may be attributable to higher obstetric complications, obstetricians might have been prudent when deciding upon the mode of delivery in order to prevent neonatal complications.

In this study, neonatal complications including low birth weight, low Apgar scores and NICU admissions were higher in older nulliparous women. Cleary-Goldman reported that maternal age above 40 years of age was significantly associated with perinatal death and low birth weight (9). The correlation between advanced maternal age and low birth weight might be related to age-related changes in uterine vasculature. Miller et al. (17) published a study on this matter, and claimed that advanced maternal age is an independent risk factor for uteroplacental insufficiency.

Macrosomia was found to be higher in both nulliparous and multiparous advanced aged women in this study. The higher

incidence of macrosomia might be attributable to the higher incidence of gestational diabetes mellitus among advanced age women. Advanced maternal age was previously reported to be a risk factor for having a child with malformations (18). Interestingly, there was no significant difference between advanced age women and controls with respect to foetal anomalies, both in nulliparous and multiparous women. In summary, the results of the current study indicate the increased risk of maternal, foetal and neonatal complications in pregnancies complicated with advanced maternal age. Moreover, the risk was more prominent in nulliparous older women. Obstetricians must be especially cautious for adverse events in this subset of patients.

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Evaluation of mean platelet volume, neutrophil/lymphocyte ratio and platelet/lymphocyte ratio in advanced stage endometriosis with endometrioma

Endometrioma bulunan ileri evre endometrioziste ortalama trombosit hacmi, nötrofil/lenfosit oranı ve trombosit/lenfosit oranının değerlendirilmesi

Ali Yavuzcan¹, Mete Çağlar¹, Yusuf Üstün¹, Serdar Dilbaz¹, İsmail Özdemir², Elif Yıldız¹, Atilla Özkara¹, Selahattin Kumru¹

¹Department of Obstetrics and Gynecology, Düzce University Faculty of Medicine, Düzce, Turkey

²Department of Obstetrics and Gynecology, İstanbul Medicana Beylikdüzü Hospital, İstanbul, Turkey

Abstract

Objective: We compared the preoperative values of mean platelet volume (MPV) and peripheral systemic inflammatory response (SIR) markers (neutrophil/lymphocyte ratio and platelet/lymphocyte ratio) between patients with advanced-stage (stage 3/4) endometriosis having endometrioma (OMA) and patients with a non-neoplastic adnexal mass other than endometrioma (non-OMA).

Material and Methods: Patients who underwent operations with the pre-diagnosis of infertility or adnexal mass and who underwent laparoscopic tubal ligation were included.

Results: Haemoglobin levels, leucocyte count, platelet count, neutrophil count and lymphocyte count were not significantly different between patients with advanced stage endometriosis having OMA, patients with non-OMA and patients in the control group ($p=0.970$, $p=0.902$, $p=0.373$, $p=0.501$ and $p=0.463$, respectively). Patients with stage 3/4 endometriosis having OMA, patients with non-OMA and control patients were also not significantly different in terms of MPV ($p=0.836$), neutrophil/lymphocyte ratio (NLR) ($p=0.555$) and platelet/lymphocyte ratio (PLR) ($p=0.358$). Preoperative cancer antigen 125 (Ca-125) levels were significantly higher in patients with OMA ($p=0.006$). Mean size of the OMAs was significantly lower than non-OMAs ($p=0.000$).

Conclusion: It is very important to determine advanced stage endometriosis and OMAs during preoperative evaluation in order to inform patients and plan an appropriate surgical approach. We demonstrate that MPV, NLR and PLR values are not useful for this purpose in patients with advanced stage endometriosis that are proven to develop severe inflammation at either the cellular or molecular level.

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Key words: Endometriosis, mean platelet volume, neutrophil/lymphocyte ratio, platelet/lymphocyte ratio

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Özet

Amaç: Biz endometrioma bulunan ileri evre endometriozise sahip hastalar (evre 3/4) ve endometrioma dışı non-neoplastik adneksiyel kitle bulunan hastalar arasında preoperatif ortalama trombosit hacmi (MPV) ve periferik sistemik inflamatuvar yanıt (SIR) belirteçlerinin (nötrofil / lenfosit oranı ve lenfosit/trombosit oranı) değerlerini karşılaştırdık.

Gereç ve Yöntemler: İnfertilite veya adneksiyel kitle ön tanısı ile opere edilen hastalar ile laparoskopik bilateral tubal ligasyon yapılan hastalar çalışmaya dahil edilmiştir.

Bulgular: Hemoglobin düzeyi, lökosit sayısı, trombosit sayısı, nötrofil sayısı ve lenfosit sayısı açısından endometrioma saptanan ileri evre endometriosis hastaları (evre 3/4), endometrioma dışı adneksiyel kitle saptanan ve kontrol grubu hastaları arasında anlamlı farklılık saptanmamıştır ($p=0.970$, $p=0.902$, $p=0.373$, $p=0.501$ ve $p=0.463$; sırasıyla). Endometrioma saptanan ileri evre endometriosis hastaları (evre 3/4), endometrioma dışı adneksiyel kitle saptanan ve kontrol grubu hastaları arasında aynı zamanda MPV ($p=0.836$), nötrofil / lenfosit oranı (NLR) ($p=0.555$) ve lenfosit/trombosit oranı (PLR) ($p=0.358$) açısından istatistiksel olarak anlamlı farklılık tespit edilmemiştir. Ameliyat öncesi kanser antijen 125 (Ca 125) seviyeleri operasyonda endometrioma saptanan ($p=0.006$) hastalarda anlamlı olarak yüksek bulunmuştur. Endometriomalarn ortalama boyutu endometrioma dışı kitlelere göre daha düşük tespit edilmiştir ($p=0.000$).

Sonuç: İleri evre endometriozis ve endometrioma bulunan hastaların preoperatif değerlendirme sırasında belirlemek; hastayı bilgilendirmek ve uygun cerrahi yaklaşımı planlamak için çok önemlidir. Bu çalışmada MPV, NLR ve PLR değerlerinin hüresel veya moleküler düzeyde şiddetli inflamasyon varlığı kanıtlanmış olan ileri evre endometriosis hastalarında bu amaç için yararlı olmadığını gösterilmiştir. (J Turkish-German Gynecol Assoc 2013; 14: 210-5)

Anahtar kelimeler: Endometriozis, nötrofil/lenfosit oranı, ortalama trombosit hacmi, trombosit/lenfosit oranı

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Address for Correspondence: Ali Yavuzcan, Department of Obstetrics and Gynecology, Düzce University Faculty of Medicine, Düzce, Turkey.

Phone: +90 532 634 54 31 e.mail: draliyavuzcan@yahoo.com

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Introduction

Endometriosis is defined as the presence of endometrial-like cells in areas outside the uterus (1). Endometriosis is associated with both pelvic pain and infertility. It is prone to progression and recurrence (2). According to the revised scoring system of the American Fertility Association (AFA), the diagnosis of stage 3 endometriosis (moderate) is established if endometriotic cysts referred to as endometrioma (OMA) are found to be 1 cm or larger (3). Apart from endometriotic cysts, deep pelvic invasion, recto-vaginal involvement, partial or incomplete obstruction of the Douglas Pouch, obstruction or fluid collection in tuba uterina signify advanced-stage endometriosis (stage 3/4) (1). Such findings are associated with subfertility, dyspareunia and dysmenorrhoea. On the other hand, abdominal surgery may reveal endometriosis and/or endometrioma in some patients in the absence of remarkable medical history for infertility and in the absence of manifesting symptoms (4). Preoperative serum cancer antigen 125 (Ca-125) level alone is not diagnostic for all patients with endometriosis (5). Endometriosis has been known to be an oestrogen-dependent disease. Inflammatory response, genetic and environmental factors and hormonal regulation are also involved in the aetiopathogenesis of this condition (6). Barrier et al. (7) reported functionally altered immune cells in peritoneal circulation of patients with endometriosis and suggested sterile inflammation occurring in the peritoneal cavity. Based on this inflammatory response in endometriosis, urocortin 2, urocortin 3, high sensitivity c reactive protein (CRP), interleukin 2 (IL-2), interleukin 4 (IL-4), interleukin 10 (IL-10), interferon γ (IFN- γ) and lymphocyte count have been examined alone and in combination with Ca-125 for detecting endometriosis (8, 9).

Neutrophil/lymphocyte ratio (NLR) and platelet/lymphocyte ratio (PLR) in peripheral blood are simple systemic inflammatory response (SIR) markers which are evaluated by blood parameters. NLR possesses diagnostic value in certain pathologies characterised by systemic or local inflammatory response such as diabetes mellitus, coronary artery disease, ulcerative colitis and inflammatory arthritis (10-12). The proportion of these two cell types provides a measure to detect inflammation (13). PLR is used as a marker of endogenous residual anticancer pre-inflammatory and pre-coagulative response which arises in malignancies. PLR is currently considered to be a more sensitive marker and also assumed to be a prognostic factor in breast cancer, and ovarian and colorectal cancers (14). Mean platelet volume (MPV) is a marker of platelet count and platelet activity. Platelets have also been suggested to play important roles in immune and/or inflammatory processes (15). Gasparyan et al. (16) demonstrated the association with increased MPV with cardiovascular and cerebrovascular disorders which are characterised by arterial or venous thrombosis and low grade inflammatory response. MPV levels are lower in high grade inflammatory conditions such as active rheumatoid arthritis, acute attack of familial Mediterranean fever and active chronic obstructive pulmonary disease (16, 17).

Rectovaginal bimanual examination, which can reveal the painful nodularity due to deep infiltrating endometriosis, may be

helpful for the diagnosis of advanced stage disease. The diagnostic method with the highest sensitivity to detect advanced stage endometriosis as recto-vaginal endometriosis in an everyday clinical setting is gynaecological examination. This is followed by rectal endosonography (18). Laparoscopy has been accepted the gold standard for identifying all stages of endometriosis; however, a useful and cost effective peripheral marker for evaluation in preoperative assessment is still under investigation. In this study, we examined preoperative values of MPV and peripheral SIR markers (NLR and PLR) for determining those patients with advanced-stage (stage 3/4) endometriosis having endometrioma (OMA) that have been proven to develop severe inflammation at either the cellular or molecular level.

Material and Methods

Patients who underwent laparotomy or laparoscopic surgery with the pre-diagnosis of infertility or adnexal mass and who underwent laparoscopic tubal ligation in the Department of Obstetrics and Gynaecology between November 2009 and February 2013 were included in this study. All patients were selected among Caucasian, non-pregnant women of reproductive age (16-50 years) with regular cycles and who were all living in the same city. Due to the possibility of interference with serum Ca-125 levels and haematological parameters, patients beyond reproductive age, those who had received a previous medical therapy for endometriosis, patients with a history of past pelvic surgery, those with a history of pelvic inflammatory disease, patients in whom pathologic examination of the operation material revealed myoma uteri, adenomyosis, endometrial polyp, endometrial hyperplasia or borderline ovarian tumour, patients with infectious disease or those patients with chronic or acute inflammatory disease, smokers, patients with autoimmune or systemic disorder, and patients with a gynaecological or non-gynaecological malignancy were excluded. Patients who had OMA measuring less than 10 mm and patients who had benign adnexal mass other than OMA measuring less than 30 mm were also excluded. Patients with OMA and advanced-stage endometriosis (stage 3/4) as described by the revised scoring system of the AFA were included in the study (3). Of these patients, 33 had OMA and 28 had non-OMA. Thirty-three healthy patients, who underwent laparoscopic tubal ligation, constituted the control group. Ninety-four patients meeting the inclusion criteria were included in the study.

Written informed consent was obtained from all patients before the procedure took place. Non-Invasive Clinical Research Ethics Committee of Düzce University School of Medicine granted approval for the present study (Decision Number: 2013/388). Primary infertility was considered when a nulligravid patient had not become pregnant after at least 1 year of unprotected intercourse. All data were retrieved retrospectively from the patients' charts in university hospital.

Three cc of a peripheral venous blood sample was collected into sterile tubes from 61 patients who underwent an operation due to adnexal mass and/or infertility; the blood samples were immediately centrifuged at 3000 rpm for 15 minutes. Serum samples were loaded into an analyser (Roche Hitachi Cobas

6000 E 60, Rotkreuz, Switzerland) for the detection of Ca-125 levels using an electrochemoilluminescence method. The results were expressed in IU/mL. The upper limit of the normal serum Ca-125 levels was set to 35 IU/mL.

Before routine consultation by anaesthesiologists prior to the operation, 5-7 cc of peripheral venous blood was collected into sterile (Ethylenediaminetetraacetic acid) EDTA tubes from total of 94 patients. Haematological parameters were analysed within 30 minutes after collection using a haematology analyser (Abbott CELL DYN 3700, Boston, USA). Leucocyte ($10^3/\mu\text{L}$), neutrophil ($10^3/\mu\text{L}$), lymphocyte ($10^3/\mu\text{L}$) and platelet ($10^3/\mu\text{L}$) counts were recorded. The results were expressed in $10^3/\mu\text{L}$. NLR and PLR were calculated using the results of these parameters. Haemoglobin levels (g/dL) and mean platelet volume (fL) (MPV) were determined. Haemoglobin values were expressed in g/dL and MPV was expressed in fL.

Patients with stage 3 and 4 endometriosis having OMA, patients with non-OMA and controls were compared in terms of age, haemoglobin levels (g/dL), leucocyte count ($10^3/\mu\text{L}$), neutrophil count ($10^3/\mu\text{L}$), lymphocyte count ($10^3/\mu\text{L}$), platelet count ($10^3/\mu\text{L}$), MPV (fL), NLR and PLR. In addition, we compared patients with stage 3 and 4 endometriosis having OMA with those patients with non-OMA with respect to preoperative Ca-125 levels and the size of adnexal mass found during the operation.

Statistical Analysis

All data relevant to the study were analysed using IBM® SPSS® Statistics 19. The data were expressed as mean±standard deviation. Pearson Correlation test was used to evaluate the correlations between the three groups. Correlation analysis for nonparametric variables was conducted using Spearman Rho test. The three groups were compared with each other using One-way and ANOVA tests. Statistical evaluation between two groups was conducted using Independent t test. The level of statistical significance was set at $p < 0.05$.

Results

A total of 94 patients were included in this study. Mean age was 36.21 ± 8.37 years. Patients' demographic and clinical characteristics are shown in Table 1. Of those patients with endometriosis and OMA, 20 (21.2%) were considered to have stage 3 and 13 (13.8%) were considered to have stage 4 disease. Patients with OMA were divided into stage 3 and stage 4 disease groups and then compared with each other. No statistically significant difference was observed via intragroup comparisons of these patients with stage 3 and stage 4 disease in terms of age ($p=0.319$), haemoglobin values ($p=0.726$), leucocyte count ($p=0.779$), platelet count ($p=0.398$), neutrophil count ($p=0.961$), lymphocyte count ($p=0.903$), MPV ($p=0.248$), NLR ($p=0.461$), PLR ($p=0.179$), Ca-125 levels ($p=0.405$) and the size of OMA ($p=0.124$).

Of these patients, 33 (35.1%) had OMA. Mean size of the OMAs was 51.9 ± 22.3 mm (20-110). Twenty-eight patients (29.7%) were found to have a non-neoplastic benign adnexal mass with a mean size 82.6 ± 40.9 mm (30-200). Pathological diagnoses for these non-neoplastic masses other than OMA were mature cystic teratoma in 11 (11.7%), simple serous cyst in 9 (9.5%),

paraovarian cyst in 3 (3.1%), mucinous cystadenoma in 2 (2.1%) and benign mucinous cyst in 1 (1.1%) patient. The control group was comprised of 33 healthy patients (35.1%) who underwent tubal ligation in reproductive age.

Haemoglobin levels ($p=0.970$), leucocyte count ($p=0.902$), platelet count ($p=0.373$), neutrophil count ($p=0.501$) and lymphocyte count ($p=0.463$) showed no significant changes among the patients with stage 3/4 endometriosis having OMA, patients with non-OMA and control patients. Patients with stage 3/4 endometriosis having OMA, patients with non-OMA and control patients were also not significantly different in terms of MPV ($p=0.836$), NLR ($p=0.555$) and PLR ($p=0.358$) (Table 2). Preoperative Ca-125 levels were significantly higher in patients with OMA than non-OMA ($p=0.006$). Furthermore, the mean size of the OMAs found during the surgery was significantly lower compared to the mean size of non-OMAs ($p=0.000$) (Table 2).

Discussion

OMAs are more common in patients with moderate and severe endometriosis (Stage 3/4). In 2004, the American Society for Reproductive Medicine (ASRM) reported a 30-50% infertility rate in patients with endometriosis (19). OMAs are associated with decreased pregnancy rates both through conventional intercourse and *in vitro* fertilisation by compromising pelvic and tubo-ovarian anatomic structures. Redwine et al. (20) suggested that removing only ovarian OMA would be an inadequate treatment for patients with stage 3/4 endometriosis. They claimed that leaving pelvic and possible intestinal endometriotic foci untouched in their location would be an underestimation of the condition (20). In this regard, it is crucial that a surgeon identifies those patients with moderate/severe endometriosis or OMA preoperatively and informs the patient about the possibility of salpingectomy or intestinal resection that the patient might require during surgery.

Kitawaki et al. (5) showed that serum Ca-125 level, which has been the most reliable indicator of endometriosis together with ultrasonography within the last 25 years, measures

Table 1. Demographics and characteristics of all patients

	N (%) / Mean ± SD
Age ^o	36.21 ± 8.37
Nulliparous ^ψ	14 (14.8%)
Multiparous ^ψ	76 (80.8%)
Virginity ^ψ	4 (4.2%)
Infertility ^ψ	10 (10.6%)
Presence of dysmenorrhea ^ψ	17 (18.1%)
Presence of dyspareunia ^ψ	14 (14.9%)
Stage 3 endometriosis ^ψ	20 (21.2%)
Stage 4 endometriosis ^ψ	13 (13.8%)
Total	94 (100%)

^o: Mean ± Standard Deviation
^ψ: N indicates the number of patients and % indicates the percentage

Table 2. Comparison of patients with stage 3/4 endometriosis having endometrioma (OMA), patients with non-OMA with control patients in terms of age, Ca-125 levels, size of adnexal mass and haematological parameters

	Patients with OMA N=33 (35.1%)	Patients with non-OMA N=28 (29.7%)	Control patients N=33 (35.1%)	p value*
Age (years) ^o	34.7±9.0	37.6±9.9	36.2±8.3	0.403
Haemoglobin (g/dL) ^o	11.9±1.6	12.0±1.4	12.0±1.8	0.970
Leucocyte Count (103/ μ L) ^o	7081.5±2170.6	7268.9±2321.7	7311.2±2027.2	0.902
Platelet Count (103/ μ L) ^o	269848± 65202	298964±107813	286484±67636	0.373
MPV (fL) ^o	8.75±1.52	8.56±1.27	8.56±1.27	0.836
Neutrophil Count (103/ μ L) ^o	4.14±1.73	4.68±2.18	4.50±1.57	0.501
Lymphocyte Count (103/ μ L) ^o	2.12±0.87	2.02±0.68	2.25±0.66	0.463
N/L ratio (NLR) ^o	2.40±2.04	2.51±1.37	2.11±0.86	0.555
P/L ratio (PLR) ^o	162.84 ± 141.28	159.14±61.20	132.45±35.74	0.358
Ca-125 levels (IU/mL) ^o	50.8±46.7	22.4±25.3	-	0.006
Size of adnexal mass	51.9±22.3	82.6±40.9	-	0.000

* p values <0.05 were considered statistically significant; ^o: Mean ± Standard Deviation; MPV: mean platelet volume; N/L ratio: Neutrophil/ Lymphocyte ratio; P/L ratio: Platelet/ Lymphocyte ratio

below 20 IU/mL in 10.6% of patients with OMA and in 15.6% of patients with moderate/severe endometriosis in conjunction with adenomyosis and leiomyosis. Mean Ca-125 level in the patients in our study was 50.8±46.7 IU/mL, which was significantly higher compared to patients with non-OMA (p=0.006). The mean size of OMAs was found to be significantly lower than the mean size of non-OMAs (p=0.000). Previous studies have also indicated that patients with OMAs have higher Ca-125 levels and OMAs rarely measuring above 12 cm (2, 4, 21).

Markers of inflammation appear to be useful as diagnostic markers for endometriosis. Serum IL levels, urocortin, or vitamin D binding globulin would bring high costs and have no chance for use in the hospital setting (1, 8, 9). Cho et al. (22) showed that NLR alone or in combination with Ca-125 would offer an inexpensive and practical method for the diagnosis of endometriosis. This analysis is performed in an ordinary haematology analyser found in every hospital. The most significant disadvantage is the impact of age, ethnic origin, nutritional status, haemoglobin concentration and geographic features on the blood parameters (23). We evaluated patients of reproductive age (16-50) of Caucasian origin who were living in the same city. No significant difference was observed between the patients with stage 3/4 endometriosis having OMA, patients with non-OMA and control patients with respect to age (p=0.403), haemoglobin levels (p=0.970) and leucocyte count (p=0.902) in our study. We created a homogeneous group of patients to yield objective results.

The Tissue Injury and Repair (TIAR) mechanism described by Leyendecker et al. (24) has been one of the mainstays of these studies, suggesting the immune system and chronic inflammatory response to be involved in the pathogenesis of endometriosis. According to this theory, local microtrauma is assumed to have occurred in endometrial and myometrial interface due to chronic uterine peristaltic activities (25). In TIAR mechanism, platelets are also involved in chronic inflammatory processes. Both number and MPV increase in the presence of inflamma-

tion (25). In our study, no significant difference was observed between patients with stage 3/4 endometriosis and OMA, those with non-OMA and control patients with respect to platelet count (p=0.373) and MPV (p=0.836). Gasparyan et al. (16) reported increased MPV in low grade inflammatory processes. Bodur et al. (26) showed that MPV is increased in adenomyosis, which is based on similar pathophysiological mechanisms with endometriosis. The study by Bodur et al. (26) was based on the evaluation of hospital records in two different hospitals located in two different cities. The number of patients in this study was similar to that of the study by Bodur et al. (26), and it is considered that studies with a higher number of patients might yield different results.

NLR is increased in most malignancies, particularly in epithelial ovarian cancer, and is characterised by strong SIR (10, 11, 14, 27). Absolute neutrophil count, platelet count and number of platelets have showed an increase in epithelial ovarian cancers in connection with SIR. NLR and PLR indicate advanced stage and extensive ovarian malignancy (27). Azab et al. (28) recently showed that NLR and PLR are also higher in breast cancers that show accelerated progression in the presence of oestrogenic effects. Women with endometriosis are at an increased risk of endometrioid and clear cell ovarian carcinoma. Oxidative stress, inflammation and hyperoestrogenism have been suggested to be the pathways that are involved in endometriosis-related ovarian cancer in 2013 (29). Considering the relationship of endometriosis with the inflammation and ovarian malignancies, we compared NLR and PLR in patients with moderate and severe endometriosis and OMA with those patients with non-OMA and healthy controls. However, we did not observe a statistically significant difference between three groups in terms of NLR and PLR (p=0.555 and p=0.358, respectively).

There are limited studies in the literature investigating the relationship between endometriosis and MPV, NLR and PLR. Our results are not consistent with similar studies about endometriosis (22, 26). On the other hand, Kutlucan et al. (30) showed

that platelet counts and MPV remained unchanged in metabolic syndrome in which SIR is involved as an active player. Altunbaş et al. (31), in contrast to numerous studies conducted so far, found that MPV showed no statistically significant change in preeclampsia, which is a kind of inflammatory disease (32). The number and size of blood elements vary greatly depending on the geographic location and ethnic characteristics (23). This effect could be caused by homogeneous group of patients from Caucasian in the same city in Turkey. Celikbilek et al. (10) found no significant correlation between endoscopically-determined disease activity and NLR in patients with ulcerative colitis in which inflammatory mechanisms are known to play a role in disease aetiology. Similar to the findings of Celikbilek et al. (12), peripheral markers of SIR do not seem to be increased in proportion to the surgical stage of disease in our patients with advanced stage endometriosis and OMA.

Neutrophils are actively involved in systemic and local inflammatory response by releasing pro-inflammatory factors. Their activation and migration functions are triggered by IL-17 released from T helper (Th)17 lymphocytes. It is unknown which types of neutrophils are associated with inflammation in endometriotic tissue. Herington et al. (33) emphasised the need for further investigations in order to elucidate the roles of neutrophils and Th17 lymphocytes in the pathophysiology of endometriosis. It might be anticipated that the number of neutrophil subtypes that play specific roles in endometriosis in proportionate to Th17 lymphocytes might be a better marker in lieu of absolute neutrophil to lymphocyte ratio.

It is very important to determine advanced stage endometriosis and OMAs during preoperative evaluation in order to inform the patient and plan an appropriate surgical approach. More comprehensive studies are needed with homogeneous patient populations for the routine use of MPV, NLR and PLR values as useful and cost-effective markers for this purpose in those patients with advanced stage endometriosis that have been proven to develop severe inflammation at either the cellular or molecular level. It is probable that endometriosis is a local inflammatory process that does not lead to reticulo-endothelial reactions which can be detected by a simple blood count.

Ethics Committee Approval: Ethics committee approval was received from the Non-Invasive Clinical Research Ethics Committee of Düzce University School of Medicine (Decision Number: 2013/388; Decision Date: 28/03/2013)

Informed Consent: Informed consent was received from the participants of this study.

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Is there a link between polycystic ovary syndrome and non-thyroidal illness syndrome?

Polikistik over sendromu ve tiroid dışı hastalık sendromu arasında bir bağlantı var mı?

Melia Karaköse¹, Erman Çakal¹, Oya Topaloğlu¹, Müyesser Sayki Arslan¹, Zeynep Giniş², Mustafa Şahin³, Tuncay Delibaşı¹

¹Department of Endocrinology and Metabolism, Dışkapı Yıldırım Beyazıt Training and Research Hospital, Ankara, Turkey

²Department of Biochemistry, Dışkapı Yıldırım Beyazıt Training and Research Hospital, Ankara, Turkey

³Department of Endocrinology and Metabolism, Ankara University School of Medicine, Ankara, Turkey

Abstract

Objective: The aim of this study was to determine the frequency of non-thyroidal illness syndrome (NTIS) in patients with polycystic ovary syndrome (PCOS).

Material and Methods: During a 6-month period, 52 patients with PCOS were recruited for this cross-sectional study. The control group included 68 age-matched female volunteers. Serum free triiodothyronine (fT3), free thyroxine (fT4), thyroid stimulating hormone (TSH), anti-thyroperoxidase antibody (anti-TPO Ab), and anti-thyroglobulin antibody (anti-Tg Ab) were measured.

Results: The TSH level in the PCOS patients and controls did not differ significantly ($1.9 \pm 1.2 \mu\text{IU/mL}$ vs. $1.8 \pm 0.9 \mu\text{IU/mL}$, $p > 0.05$). Serum fT3 and fT4 levels in the controls were significantly lower than those in the PCOS patients (fT3: $2.7 \pm 0.3 \text{ pg/mL}$ vs. $2.9 \pm 0.3 \text{ pg/mL}$, $p = 0.02$; fT4: $1.0 \pm 0.1 \text{ ng/dL}$ vs. $1.1 \pm 0.1 \text{ ng/dL}$, $p = 0.03$). The Hs-CRP (high-sensitivity C-reactive protein) level in the PCOS patients was significantly higher than in the controls ($3.5 \pm 4.9 \text{ mg/L}$ vs. $1.7 \pm 2.7 \text{ mg/L}$, $p = 0.03$). A statistically significant relationship was observed between Hs-CRP and fT4 ($r = 0.245$, $p = 0.015$). However, NTIS was not observed in either group.

Conclusion: Thyroid function abnormalities could be observed in PCOS; however, NTIS was not noted in the present study despite the inflammatory state of the PCOS patients.

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Key words: Polycystic ovary syndrome, non-thyroidal illness syndrome, inflammation, hormones

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Özet

Amaç: Bu çalışmanın amacı, polikistik over sendromu (PKOS) olan hastalarda tiroid dışı hastalık sendromunun (NTIS) sıklığını tespit etmektir.

Gereç ve Yöntemler: PKOS'lu 52 hasta 6 aylık bir dönemde bu kesitsel çalışmaya alındı. Kontrol grubuna yaş uyumlu 68 gönüllü kadın dahil edildi. Serum serbest triyodotironin (sT3), serbest tiroksin (sT4), tiroid uyarıcı hormon (TSH), anti-tiroperoksidaz antikor (anti-TPO Ab) ve anti-tiroglobulin antikor (anti-Tg Ab) ölçüldü.

Bulgular: PKOS hastalarında ve kontrol grubunda TSH düzeyinde (1.9 ± 1.8 vs. $1.2 \mu\text{IU/mL} \pm 0.9 \mu\text{IU/mL}$, $p > 0.05$) anlamlı fark yoktu. Kontrol grubunda serum sT3 ve sT4 düzeyleri PKOS hastalanninkinden anlamlı olarak daha düşüktü (fT3: $2.7 \pm 0.3 \text{ pg/mL}$ vs. $2.9 \pm 0.3 \text{ pg/mL}$, $p = 0.02$; fT4: $1.0 \pm 0.1 \text{ ng/dL}$ vs. $1.1 \pm 0.1 \text{ ng/dL}$, $p = 0.03$). Hs-CRP (yüksek hassas C-reaktif protein) ve sT4 arasında istatistiksel olarak anlamlı ilişki gözlemlendi ($r = 0.245$, $p = 0.015$). Ancak NTIS iki grupta da gözlemlenmedi.

Sonuç: Tiroid fonksiyon bozuklukları PKOS'ta gözlenebilir ancak PKOS hastalarındaki inflamatuvar duruma rağmen bu çalışmada NTIS tespit edilmedi.

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Anahtar kelimeler: Polikistik over sendromu, tiroid dışı hastalık sendromu, inflamasyon, hormonlar

Geliş Tarihi: 05 Eylül 2013

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Introduction

Polycystic ovary syndrome (PCOS) is probably the most common endocrinopathy in women of reproductive age, and is characterised by anovulation, hyperandrogenaemia, and frequently insulin resistance (IR). It is associated with an increased risk of type 2 diabetes mellitus (T2DM) (1-3). The serum plasminogen activator inhibitor-1 (PAI-1) (4), C-reactive protein (CRP) (5, 6), advanced glycation end-products (AGEs) (7) and endothelin-1 (8) levels are all elevated in PCOS patients. These markers are known to contribute to atherogenesis and chronic inflammation (9-12).

The first study to examine low-grade chronic inflammation in women with PCOS via the measurement of CRP was conducted in 2001 (13). The researchers reported that the CRP concentration was elevated in women with PCOS. PCOS patients were reported to exhibit higher mean serum tumour necrosis factor- α (TNF- α) (14), soluble intracellular adhesion molecule-1 (sICAM-1), and sE-selectin levels (15).

During many chronic illnesses, some aspects of thyroid hormone metabolism may change, which is collectively known as non-thyroidal illness syndrome (NTIS). Non-thyroidal illness is characterised by a decrease in the serum T3 level and it is thought that decreased extrathyroidal conversion of T4 to



Address for Correspondence: Melia Karaköse, Department of Endocrinology and Metabolism, Dışkapı Yıldırım Beyazıt Training And Research Hospital, Ankara, Turkey Phone: +90 312 596 30 93 e.mail: meliakarakose@yahoo.com

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T3 is a primary mechanism underlying the syndrome (16-19). Several pathophysiological mechanisms have been considered and experimental data suggest that pro-inflammatory cytokines play a role in NTIS (20-23).

The most common NTIS hormonal profile is characterised by low peripheral T3 or free T3 (fT3), and an elevated reverse T3 (rT3) concentration; free T4 (fT4) and thyroid-stimulating hormone (TSH) levels are generally normal.

The literature includes detailed reports the on relationship between NTIS and chronic illnesses such as rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), etc. (24, 25); however, to date, no systematic analysis of NTIS in women with PCOS has been undertaken. As such, the present study aimed to investigate the frequency of NTIS in PCOS patients.

Material and Methods

The study included the patients diagnosed as PCOS according to 2003 Rotterdam criteria (26) and followed-up at our Hospital, Department of Endocrinology and Metabolic Diseases, between October 2011 and March 2012. The control group consisted of 68 healthy female volunteers. Patients with a chronic disease other than PCOS, including RA, SLE, DM, hyperprolactinaemia, hypertension, and thyroid illness, and infectious diseases, and hepatic or renal disorders were excluded. Patients that used any drug during the previous 3 months, including oral contraceptive pills, antihyperlipidaemics, and drugs that affect insulin sensitivity were also excluded. All patients and controls underwent anamnesis and physical examination. The study protocol was approved by the Ethics Committee of our hospital and all the participants provided written informed consent.

All patients and controls underwent physical examination, anthropometric measurement and biochemical screening. The waist/hip ratio and body mass index (BMI) were calculated. Fasting blood samples were obtained in the morning between 08:00 and 11:00, during the follicular phase of each participant's menstrual cycle. The fasting serum insulin level was measured using the chemiluminescent immunoassay method (Advia Centaur XP, Siemens Healthcare Diagnostics Inc., Tarrytown, USA). The estimate of insulin resistance was calculated using the HOMA-IR index. TSH, fT3 and fT4 were measured via chemiluminescent microparticle immunoassay (Abbott, Architect i2000, Abbott Laboratories Diagnostics Division, IL, USA). Anti-thyroglobulin antibody (anti-Tg Ab) and anti-thyroperoxidase antibody (anti-TPO Ab) were measured via chemiluminescent competitive immunoassay (Advia centaur XP, Siemens, Tarrytown, USA). Reference limits were as follows: fT3: 1.71-3.71 pg/mL; fT4: 0.7-1.48 ng/dL; TSH: 0.35-4.94 μ IU/mL; anti-Tg Ab: 0-60 IU/mL; anti-TPO Ab: 0-57 IU/mL. Anti-Tg Ab and anti-TPO Ab concentrations >60 IU/mL and >57 IU/mL, respectively, were considered positive.

The statistical analysis was performed with the SPSS statistical software (version 16; SPSS, Chicago, IL, USA). Normality of the variables was tested by Kolmogorov-Smirnov test. Differences between groups were analysed by one way analysis of variance or Mann-Whitney U-test when appropriate. Frequencies were analysed by χ^2 . Correlations between variables were performed

using Spearman's rho correlation coefficient. Results are expressed as mean \pm SD. A probability value of 0.05 was considered to be statistically significant.

Results

The study included 52 PCOS patients (mean age of 24.4 \pm 10.5 years) and 68 controls (mean age of 26.5 \pm 6.5 years). The general characteristics of the patients and controls are presented in Table 1.

There were no significant differences in age, BMI, or waist/hip ratio between the patient and control groups. Fasting blood glucose and HDL-C (high density cholesterol) did not differ significantly between the groups. The total cholesterol, LDL-C (low density cholesterol), and triglyceride levels were significantly higher in the PCOS patients than in the controls. Insulin resistance, as calculated by HOMA-IR (Homeostasis Model of Assessment - Insulin Resistance), was higher in the PCOS patients than that in the controls (4.06 \pm 3.4 vs. 2.3 \pm 1.6, respectively; p=0.0001). The Hs-CRP level in the PCOS patients was significantly higher than that in the controls (3.5 \pm 4.9 mg/L vs. 1.7 \pm 2.7 mg/L, respectively; p=0.03).

The anti-TPO Ab level was measured in all 52 PCOS patients and 67 of the 68 randomly selected controls. Mean \pm SD serum anti-TPO Ab in the PCOS patients and controls was 134 \pm 254 IU/mL and 169 \pm 300 IU/mL, respectively. The serum anti-Tg Ab level was measured in all 52 patients and 66 of the 68 controls. The mean \pm SD of serum anti-TG Ab in PCOS patients and controls was 56 \pm 83 and 70 \pm 77 IU/mL, respectively. There was no significant difference between patients and the control group in terms of anti-TPO Ab levels and anti-TG Ab levels (p=0.49 and p=0.324, respectively).

The control group had a higher prevalence of positive anti-Tg Ab than PCOS (24 vs. 15%); the divergence was not statistically

Table 1. The general characteristics of the PCOS patients and controls

	Patients (n=52)	Controls (n=68)	p
Age (years)	24.4 \pm 10.5	26.5 \pm 6.5	>0.05
BMI (kg/m ²)	26.5 \pm 6.1	24.8 \pm 4.9	>0.05
Waist/hip ratio	0.8 \pm 0.1	0.8 \pm 0.08	>0.05
FBG (mg/dL)	85 \pm 10	82 \pm 12	>0.05
TC (mg/dL)	176 \pm 35	163 \pm 27	0.022
TG (mg/dL)	111 \pm 69	85 \pm 34	0.010
LDL-C (mg/dL)	103.4 \pm 28	92.8 \pm 27	0.044
HDL-C (mg/dL)	53 \pm 14	54 \pm 12	>0.05
HOMA-IR (%)	4.06 \pm 3.4	2.3 \pm 1.6	0.0001
HsCRP (mg/L)	3.5 \pm 4.9	1.7 \pm 2.7	0.030

PCOS: Polycystic ovary syndrome; BMI: Body mass index; TC: Total cholesterol; FBG: Fasting blood glucose; HDL-C: High density cholesterol; LDL-C: Low density cholesterol; TG: Triglyceride; HOMA-IR: Homeostasis Model of Assessment - Insulin Resistance; HsCRP: high-sensitivity C-reactive protein

significant ($p=0.17$). The prevalence of subjects with positive anti-TPO Ab in the patient and control groups was 44 and 73%, respectively; it was significantly higher in control group ($p=0.01$).

NTIS was not observed in either group. The TSH level in the patient and control groups did not differ significantly ($1.9 \pm 1.2 \mu\text{IU/mL}$ vs. $1.8 \pm 0.9 \mu\text{IU/mL}$, $p=0.475$). The serum ft3 and ft4 levels in the control group were significantly lower than in the patient group (ft3: $2.7 \pm 0.3 \text{ pg/mL}$ vs. $2.9 \pm 0.3 \text{ pg/mL}$, $p=0.02$; ft4: $1.0 \pm 0.1 \text{ ng/dL}$ vs. $1.1 \pm 0.1 \text{ ng/dL}$, $p=0.03$). The thyroid tests of the PCOS patients and controls are presented in Table 2.

A statistically significant relationship was found between HOMA-IR and ft3 ($r=0.304$, $p=0.01$), Hs-CRP ($r=0.208$, $p=0.046$), and age ($r=-0.286$, $p=0.03$). A statistically significant relationship was found between Hs-CRP and ft4 ($r=0.245$, $p=0.015$), HOMA-IR ($r=0.208$, $p=0.046$), triglyceride ($r=0.358$, $p=0.0001$) and total cholesterol ($r=0.224$, $p=0.029$).

Discussion

Low-grade chronic inflammation in PCOS is indicated by the elevation of several markers, including the CRP level (5, 13, 15, 27-29), TNF- α (14), inflammatory cytokines (interleukin-6 and interleukin-18) (30), and leukocyte count (31). Data concerning the potential role of deiodinases in the pathogenesis of NTIS are inconsistent. The generally accepted view has been that extra-thyroidal conversion of T4 to T3 is diminished in patients with illnesses due to a decrease in both hepatic/renal D1 activity and skeletal muscle D2 activity (32-34). It was suggested that, together, these modifications in deiodinase expression could be a major factor involved in causing the low T3 concentration that is associated with NTIS. The trigger for these changes in deiodinase expression has been attributed to an increase in pro-inflammatory cytokines, which often occurs in NTIS (35-39).

In the present study, the frequency of NTIS in both groups was the same, and the TSH level in the patient and control groups did not differ significantly; however, serum ft3 and ft4 levels in the controls were significantly lower than those in the patients. Furthermore, the Hs-CRP level in the PCOS patients was significantly higher than that in the controls, and a statistically significant relationship was noted between Hs-CRP and ft4. Martocchia et al. (40) studied ft3, ft4, TSH, and CRP levels in 41 NTIS patients and reported that the serum ft3 level was higher

and the ft4 level was lower in the NTIS patients than in the controls, and that the serum TSH level did not differ between the groups. Moreover, CRP and FT4 concentrations were positively associated ($p<0.01$).

Both anti-TPO Ab and anti-Tg Ab levels were higher in the control group than in PCOS patients; however, the difference was not significant. The prevalence of positivity of anti-TPO Ab and anti-Tg Ab were higher in the control group than in the PCOS group. However, there was a statistically significant difference only in terms of prevalence of anti-TPO Ab positivity ($p=0.01$). Kachuei et al. (41) showed that PCOS patients had higher anti-TPO Ab levels than controls ($p<0.05$), but that serum TSH and anti-Tg Ab levels did not differ significantly. Although the frequency of anti-Tg Ab and anti-TPO Ab positivity was higher in the PCOS patients than in the control group, the difference was not significant ($p>0.05$). Janssen et al. (42) observed that TSH, anti-TPO and anti-Tg levels were significantly higher in PCOS patients than in controls.

In conclusion, the present findings indicate that PCOS is a chronic inflammatory disease associated with elevated Hs-CRP, but, on the contrary, NTIS was not detected. Thyroid function tests which have small deviations should not be considered in relation to the NTIS in patients with PCOS. As a result, other thyroid diseases should be investigated more carefully in such situations.

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Table 2. The thyroid test of the PCOS patients and controls

	Patients (n=52)	Controls (n=68)	p
ft3 (pg/mL)	2.9±0.3	2.7±0.3	0.02
ft4 (ng/dL)	1.1±0.1	1.0±0.1	0.03
TSH (μIU/mL)	1.9081±1.1643	1.7695±0.9	>0.05
Anti-TG Ab Positive (%)	15%	24%	>0.05
Anti-TPO Ab Positive (%)	44%	73%	0.01

PCOS: Polycystic ovary syndrome; ft3: free triiodothyronine; ft4: free thyroxine; TSH: thyroid stimulating hormone; Anti-TG Ab: anti-thyroglobulin antibody; Anti-TPO Ab: anti-thyropoxidase antibody; Values are shown as mean±SD.

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Butorphanol in labour analgesia: A prospective cohort study

Doğum sancısı analjesisinde butorfanol: Bir prospektif kohort çalışma

Ajay Halder¹, Rachana Agarwal²

¹Department of Obstetrics and Gynaecology, Christian Medical College, Vellore, India

²Department of Obstetrics and Gynaecology, Sarojini Naidu Medical College, Agra, India

Abstract

Objective: Parenteral opioids can be administered with ease at a very low cost with high efficacy as labour analgesia. However, there are insufficient data available to accept the benefits of parenteral opioids over other proven methods of labour analgesia. Butorphanol, a new synthetic opioid, has emerged as a promising agent in terms of efficacy and a better safety profile. This study investigates the effect of butorphanol as a labour analgesia to gather further evidence of its safety and efficacy to pave the way for its widespread use in low resource settings.

Material and Methods: One hundred low risk term consenting pregnant women were recruited to take part in a prospective cohort study. Intramuscular injections of butorphanol tartrate 1 mg (Butrum 1/2mg, Aristo, Mumbai, India) were given in the active phase of labour and repeated two hourly. Pain relief was noted on a 10-point visual pain analogue scale (VPAS). Obstetric and neonatal outcome measures were mode of delivery, duration of labour, Apgar scores at 1 and 5 minutes and Neonatal Intensive Care Unit admissions. Collected data were analysed for statistically significant pain relief between pre- and post-administration VPAS scores and also for the incidence of adverse outcomes.

Results: Pain started to decrease significantly within 15 minutes of administration and reached the nadir (3.08 SD0.51) at the end of two hours. The pain remained below four on the VPAS until the end of six hours and was still significantly low after eight hours. The incidence of adverse outcomes was low in the present study.

Conclusion: Butorphanol is an effective parenteral opioid analgesic which can be administered with reasonable safety for the mother and the neonate. The study has the drawback of lack of control and small sample size.

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Key words: Labour analgesia, butorphanol, visual pain analogue scale

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Özet

Amaç: Parenteral opioidler doğum sancısı analjesisinde yüksek etkinlikle, çok düşük bir maliyetle, kolaylıkla uygulanabilir. Bununla birlikte, doğum sancısı analjesisinde diğer kanıtlanmış metotlara göre parenteral opioidlerin faydalarını kabul etmek için ulaşılabılır yeterli veri bulunmamaktadır. Butorfanol, yeni bir sentetik opioiddir, etkililik ve daha iyi bir güvenilirlik profili açısından ümit veren bir ajan olarak ortaya çıkmıştır. Bu çalışma, düşük kaynaklı ortamlarda yaygın kullanımının yolunu açmak için güvenilirlik ve etkililiği hakkında daha fazla kanıt toplamak amacıyla doğum sancısı analjeziği olarak butorfanolün etkisini araştırmaktadır.

Gereç ve Yöntemler: Düşük risk vadeden 100 hamile kadın prospektif kohort çalışmasında yer almak üzere kaydedildi. Butorfanol tartarat 1 mg kas içi enjeksiyonlar (Butrum 1/2mg, Aristo, Mumbai, Hindistan) doğum sancısının aktif fazında verildi ve iki saatte bir tekrarlandı. Ağrı azalması 10 maddelik görsel ağrı analog skalası (VPAS) ile kaydedildi. Obstetrik ve yenidoğan akıbet ölçümleri; doğum şekli, doğum sancısının süresi, 1. ve 5. dakikadaki Apgar skorları ve Yenidoğan Yoğun Bakım Ünitesine kabul durumu idi. Toplanan veriler uygulama öncesi ve sonrası VPAS skorları arasında ağrı gidermede istatistiksel anlamlılık açısından ve ayrıca advers sonuçların insidansı için analiz edildi.

Bulgular: Ağrı uygulamanın 15 dakikası içinde önemli ölçüde azalmaya başladı ve iki saatin sonunda çok az düzeye (3.08 SD 0.51) ulaştı. Ağrı altı saatin sonuna kadar görsel ağrı analog skalasında (VPAS) dördün altında kaldı ve sekiz saat sonra hâlâ oldukça düşüktü. Advers sonuç insidansı bu çalışmada düşüktü.

Sonuç: Butorfanol anne ve yenidoğan için makul güvenilirlik ile uygulanabilen etkili bir parenteral opioid analjeziktir. Bu çalışma, kontrol yokluğu ve örneklem boyutunun küçük olması dezavantajına sahiptir. (J Turkish-German Gynecol Assoc 2013; 14: 221-4)

Anahtar kelimeler: Doğum sancısı analjezi, butorfanol, görsel ağrı analog skalası

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Introduction

Pain experienced by women during labour is considered the worst kind of physical suffering that a human being can undergo in their lifetime (1). Labour analgesia has much to offer in the management of pain in these women. Several non-pharmacological methods have been in use for a long time and still find their place in modern medicine with some

proven benefits (2-8). Pharmacological methods include options like inhaled analgesic gases, opioids and non-opioid drugs, local anaesthetic neuronal block like pudendal and paracervical block, and epidural anaesthesia, including combined spinal epidural (CSE).

Epidural analgesia, including combined spinal epidural and inhalational anaesthesia, has been proven to be beneficial (9), but has side effects like nausea, vomiting and increased



operative deliveries (10). The major factor which limits their use is the costs involved. The data are insufficient to accept the benefits of parenteral opioids over other proven methods of labour analgesia (9). However, the low cost and ease of administration of parenteral opioids has kept the interest of researchers alive as they are the only effective alternative feasible in low resource settings. Butorphanol, a new synthetic opioid which has a partial agonistic action, has emerged as a promising agent in terms of efficacy and better safety profile. This study investigates the effect of butorphanol as labour analgesia to gather further evidence of its safety and efficacy to pave the way for its widespread use in low resource settings.

Material and Methods

The study was conducted in the labour ward of a medical college hospital in the western part of India where consenting low risk term (37 to 41 weeks) pregnant women between the ages of 19 and 35 years were consecutively recruited for the study. Women with known medical risk factors like hypertension, diabetes, obesity (BMI>30), hypothyroidism, asthma, epilepsy, psychiatric disorders, cardiac or renal diseases, or women with anticipated obstetric complications like breech, multiple pregnancies, small for gestation foetus, cephalopelvic disproportion, previous uterine surgeries, caesarean section etc. were excluded. Women in advanced labour who were not able to consent were also excluded. Detailed information about the drug, its benefits and possible side effects were explained to the women before their consent was sought once they came to the labour room for admission either in spontaneous or induced labour. Intramuscular butorphanol tartrate 1 mg was administered at the onset of active labour. Meticulous examination and recording of the vital parameters were done before and every 30 min after the administration. Pain relief was assessed with the 10 point visual pain analogue scale (VPAS) (Table 1). Progress of labour was monitored partographically and foetal surveillance was performed with continuous cardiotocography. The Foetal Heart Rate traces were categorised into *Normal, Suspicious and Pathological* according to set guidelines (11). Further obstetric interventions were done according to the standard protocols. Injections were repeated after 2 hours on demand, but not within 2 hours of anticipated delivery. Women were monitored for 2 hours in the labour ward after vaginal delivery and in the recovery room after caesarean section. Neonates were evaluated by the on duty neonatologist at delivery and Apgar scores at 1 and 5 minutes were noted. The conditions of the mother and baby were followed until discharge.

Table 1. Ten point visual pain analogue scale vs. rupee scale

Visual Pain Analogue Scale	Rupee Scale	Degree of Pain
0-3 cm	4 ana	Minimal pain
4-6 cm	4-8 ana	Mild pain but comfortable
7-8 cm	8-12 ana	Moderate pain with discomfort
9-10 cm	12-16 ana	Severe pain with severe discomfort

Data were collected in a Microsoft Excel (Excel 2007, Microsoft Corporation, Washington, USA) work sheet and analysed for statistical significance. Institutional review board and ethical committee clearance were obtained for the study. The study was funded by the Institute's research grants.

Results

A total of 136 women were approached to take part in the study. Twenty eight women did not fulfil the eligibility criteria and eight women declined to participate. The study was concluded when 100 women were recruited (Figure 1). The majority of women who participated in the study were between the ages of 19 and 25 years (76% vs. 24%) with an almost equal number of primipara and multipara (54% vs. 46%). In ninety percent of cases, normal vaginal delivery could be achieved with another 8% of women having instrumental vaginal delivery (forceps and vacuum delivery). Only two women (2%) underwent caesarean section for non-reassuring foetal status in early labour. Table 2 shows the average duration of labour (from onset of active stage to end of second stage of labour) in each mode of delivery. Eighty six percent of women were given only two doses of butorphanol, 13% were given three doses and only one woman was given a fourth dose. The pre-injection mean VPAS was 8.15 SD 2.04. Pain started to decrease significantly within 15 minutes of administration and reached the nadir (3.08 SD 0.51) at the end of two hours. The pain remained below four on the VPAS for six hours and was still significantly low after eight hours. Figure 2 depicts pre-administration and the relief of pain after periodic injections of butorphanol intramuscularly on VPAS. There was a significant reduction in the mean pulse rate (92.00 vs. 76.88 per minute; p=0.001), mean systolic blood pressure (122.06 vs. 133.53 mm of Hg; p=0.001) and mean respiratory

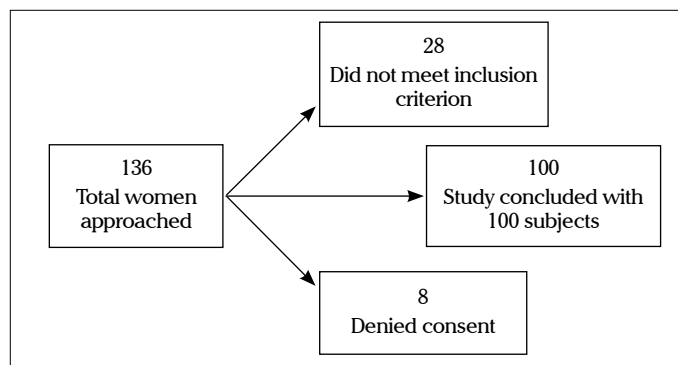


Figure 1. Flowchart for patient recruitment

Table 2. Duration of labour

Mode of Delivery	Number of Cases	Mean Duration of Labour (hrs)
Normal vaginal delivery	39	5.22
Vaginal with episiotomy	51	6.99
Instrumental delivery (Forceps & Vacuum)	8	7.15
Caesarean section	2	8.23

rate (19.06 vs. 15.48 per minute; $p=0.001$). A decrease in the mean diastolic blood pressure did not reach statistical significance. Thirteen percent of women experienced minor side effects like nausea and vomiting. Three women had prolonged sedation for more than four hours after delivery but did not require any ventilator support or antidote (naloxone). No incidence of hypersensitivity to drug or respiratory depression was seen in the study population.

The Apgar scores of the neonates at one and five minutes of life are depicted in Table 3. Nine neonates had Apgar scores of 6 or below at 1 minute and by the 5th minute only two neonates had an Apgar score of 6 or below. Ninety eight percent of the neonates had Apgar scores of more than 6 by the end of 5 minutes. Seven neonates required ICU admission for observation due to meconium stained liquor (5 cases) and transient tachypnoea of newborn (2 cases). No case of hypoxic ischemic encephalopathy or neonatal death was seen in the current cohort until discharge from the hospital. The relationship between the cardiotocographic observations and the neonatal outcome is shown in Table 4.

Discussion

Pain of labour often results in excessive maternal suffering, marked maternal hyperventilation and increased oxygen demand. The natural response to labour pain results in increased catecholamine levels leading to uterine hypoperfusion, foetal hypoxia and acidosis (1). For many years, potent

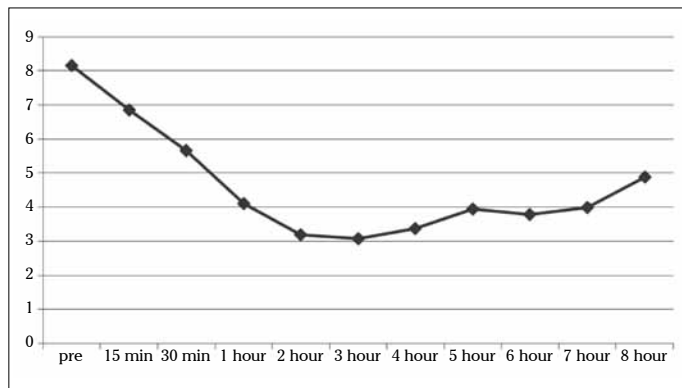


Figure 2. Pain on the Visual Pain Analogue Scale with time

Table 3. Apgar scores

Apgar Score	At 1 min	At 5 min
>6	91	98
6 or less	9	2

Table 4. Cardiotocography observations and neonatal outcome

FHR Trace Categories	n=100	APGAR <6		NICU Admission	
		At 1 min	At 5 min	<24 hours	>24 hours
Normal	63	3	nil	2	nil
Suspicious	32	5	2	4	nil
Abnormal	05	1	nil	1	nil

narcotic agents were used for post-operative pain relief and it seemed as though analgesia, emesis, respiratory depression and addiction potential were inseparable. Diazepam, a benzodiazepine, has been uncommonly used in labour for sedation and anxiolysis. The principle adverse effects of hypotonia, lethargy, decreased feeding and hypothermia in the neonate limits its use (12-13). Opioids commonly used for labour analgesia are meperidine, morphine, fentanyl, nalbuphine and butorphanol. All of these are potent analgesics, but fear of the above side effects may restrict their widespread use. Butorphanol tartrate is a potent analgesic with partial agonist action with minimum side effects (14). Although in radioligand binding studies, butorphanol binds to both μ and κ (kappa) opioid receptors, most of the observed behavioural, pharmacological, and therapeutic effects appear to be due to its lower efficacy agonist actions at μ opioid receptors (15). The κ agonist effects may be revealed in an opioid-dependent or opioid-receptor challenged organism. The major advantage is its low toxicity and low potential for abuse (16). Butorphanol tartrates have been previously studied by several anaesthetists in the context of labour analgesia and have been found to be effective. Maduska et al. (17) compared butorphanol with meperidine in a double-blind randomised control trial and found it to be equally effective and safe. Efficacy and safety of butorphanol in labour analgesia was further established by the works of Atkinson et al. (18) and Quilligan et al. (19). The former compared butorphanol with fentanyl in labour analgesia; they found that butorphanol was more effective in relieving pain early and was equally effective regarding the safety of the mother and newborn. The latter investigators found an increased foetal heart rate in the butorphanol group which was not associated with any adverse neonatal outcome. In a comparison with nalbuphine, pentazocine and butorphanol, acidotic changes in the foetus were most marked with pentazocin, moderate with nalbuphine and minimal with butorphanol (20). Reedy et al. (21) showed that butorphanol was seven times more potent than morphine for pain relief in the post-operative period following major surgeries.

In the present study, there was significant reduction of pain when compared using the VPAS score before and after the administration of butorphanol, which became significant within 15 minutes of administration. The maximum effect was seen by the end of the first hour and this action was sustained for five more hours. Repeated injections were required in 14% of cases. Butorphanol was not found to delay labour. The mean duration of labour was not prolonged in each mode of delivery. There was also no undue increase in the number of caesarean deliveries or instrumental vaginal deliveries. The decrease in the mean pulse rate, respiratory rate and systolic blood pres-

sure was considered a reflection of anxiety alleviation and was deemed a welcome sign. This probably did not reflect any direct effect of the drug.

During intrapartum foetal monitoring, no increased incidence of foetal heart rate abnormalities was seen. Nine neonates had low Apgar scores at 1 minute, which improved by 5 minutes in all but 2 infants who were admitted to the intensive care unit and discharged after observation.

Randomisation was not desired as not offering pain relief by giving placebo was considered unethical. The study group consisted of a small subset of women in labour and the safety of the drug in high risk women needs to be established. However, the concept of risk identification and referral of at risk antenatal mothers to higher centres provides a broader applicability of parenteral butorphanol at peripheral hospitals.

In conclusion, modern day obstetric analgesia has taken centre stage in the management of labouring mothers. Epidural analgesia has become an inseparable part of labour in western countries and resourceful centres in India too. Its safety and efficacy have been proven beyond doubt. It allows near complete analgesia with preserved patient mobility. Side effects are negligible in the hands of expert anaesthetists and obstetricians. However, it is dependent on an elaborate setup and extra personnel for administration and monitoring, maintaining asepsis, closer foetal surveillance and 24 hour operative and intensive care services for obstetric and anaesthetic emergencies, thereby increasing the cost exponentially. In this situation, parental opioids emerge as an effective and low cost alternative in resource-poor settings where anaesthesia and operating theatre facilities are more restrained or even absent. Several research papers including the present paper have shown high potency with better safety profiles among newer synthetic opioids. Butorphanol has higher potency and fewer side effects even in labouring mothers and their neonates, with a low chance of dependency. Although a controlled drug, it can be distributed and stored without special arrangements. If pain relief during labour is given priority at the policy level, butorphanol can serve as a low cost, safe and effective method for the poorest of women delivering at remote places. Therefore, no mother should be denied pain relief in want of resources and leaving her to suffer the worst possible pain when other members of the family are celebrating.

Ethics Committee Approval: Ethics committee approval was received for the study.

Informed Consent: Informed consent was received from the participants of this study.

Peer-review: Externally peer-reviewed.

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Is transabdominal ultrasound scanning of cervical measurement in mid-trimester pregnancy a useful alternative to transvaginal ultrasound scan?

Orta-trimester gebelikte servikal ölçüm için transabdominal ultrason tarama transvajinal ultrason taramaya karşı yararlı bir alternatif midir?

Kalyansree Chaudhury¹, Mrinalkanti Ghosh², Atin Halder¹, Sourav Senapati³, Sudeshna Chaudhury⁴

¹Department of Obstetrics and Gynecology, Burdwan Medical College, Burdwan, India

²Department of Radiodiagnosis, Burdwan Medical College, Burdwan, India

³Department of Gynecology, Kharagpur Subdivisional Hospital, Kharagpur, India

⁴Department of Ultrasonography, The Birth Assisted Conception Institute, Kolkata, India

Abstract

Objective: The aim of this study is to assess the correlation between transabdominal and transvaginal ultrasound measurements of the cervix in pregnancy. If transabdominal ultrasound measurement of cervical length is found to provide effective information, it could be used in patient counselling and when making clinical decisions.

Material and Methods: One hundred and twenty seven pregnant patients between 18-26 weeks of pregnancy were enrolled in this prospective study for measuring cervical length, both by transabdominal and transvaginal ultrasound scan after bladder emptying. Transabdominal and transvaginal measurements were compared and correlated.

Results: In patients with transvaginal ultrasound scan (TVS) cervical length ≤ 32 mm, TVS cervical length was found to be shorter than by transabdominal ultrasound scan (TAS). Most of these patients needed >3 cm of vertical pocket of urine in the bladder for adequate visualisation of the cervix. In patients with TVS cervical length >32 mm, the TVS measurement of the cervix was longer than the TAS measurement of the cervix. In these patients, the cervix could be seen by TAS when there was either ≤ 3 cm vertical pocket of urine in the bladder or an empty bladder. Statistical tests showed that there is a significant difference between TAS and TVS cervical measurements and that there is a significant association between these two measurements.

Conclusion: Most of the patients needed variable degrees of bladder filling for adequate visualisation of the cervix. Although minimal bladder filling does not influence TAS measurements of cervical length, moderate fullness of the bladder does cause an apparent increase in TAS measurements of cervical length. If the cervical length is ≥ 30 mm by TAS, regardless of urine content in the bladder, the patient can be assured vis a vis their risk of preterm labour as far as cervical length is concerned. However, in patients with TAS cervical measurement <30 mm and where the bladder needed a moderate amount of urine for adequate visualisation of the cervix, TVS cervical measurement may be close to the critical value of 25 mm. These patients need to be counselled and offered TVS for better assessment of cervical length. (J Turkish-German Gynecol Assoc 2013; 14: 225-9)

Key words: Cervical length, transabdominal sonography, transvaginal sonography

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Özet

Amaç: Bu çalışmanın amacı, gebelikte serviksin transabdominal ve transvajinal ultrason ölçümleri arasındaki korelasyonu değerlendirmektir. Eğer servikal uzunluğun transabdominal ultrason ölçümü etkin bilgi sağlarsa, hastaya rehberlik ve klinik karar vermede kullanılabilir.

Gereç ve Yöntemler: Gebeliğin 18-26. haftaları arasındaki 127 hamile hasta mesane boşaltımı sonrası hem transabdominal hem de transvajinal ultrason taraması ile servikal uzunluk ölçümü için bu prospektif çalışmaya dahil edildi. Transabdominal ve transvajinal ölçümler karşılaştırıldı ve korelasyonlarına bakıldı.

Bulgular: Transvajinal ultrason taraması (TVS) ile servikal uzunluğu ≤ 32 mm olan hastalarda, TVS servikal uzunluk transabdominal ultrason taraması (TAS)'ndakine göre daha kısa bulundu. Bu hastaların çoğunda, serviksin yeterli görüntülenmesi için mesanede >3 cm'lik vertikal idrar cebi gerekiyordu. TVS serviks uzunluğu >32 mm olan hastalarda, serviks TVS ölçümü serviks TAS ölçümünden daha uzundu. Bu hastalarda mesanede ≤ 3 cm vertikal idrar cebi olduğunda ya da boş bir mesane varlığında serviks TAS ile görülebildi. İstatistiksel testler TAS ve TVS servikal ölçümleri arasında önemli bir fark olduğunu ve bu iki ölçüm arasında anlamlı bir ilişki olduğu gösterdi.

Sonuç: Hastaların çoğunda serviksin yeterli görüntülenmesi için çeşitli derecelerde mesane dolumu gerekiyordu. Minimal mesane dolumunun servikal uzunluk TAS ölçümlerini etkilememesine rağmen, mesanenin orta derece dolgunluğu servikal uzunluk TAS ölçümlerinde belirgin bir artışa neden olmaktadır. Servikal uzunluk TAS ile ≥ 30 mm ise, mesanedeki idrar içeriğine bakmaksızın, servikal uzunluk söz konusu olduğu sürece hastanın erken doğum riski ile karşı karşıya olduğundan emin olunabilir. Bununla birlikte, TAS serviks ölçümü <30 mm olan hastalarda ve serviksin yeterli görüntülenmesi için mesanede orta derecede idrar miktarı gerekli olduğunda, TVS servikal ölçümü 25 mm'lik kritik değere yakın olabilir. Bu hastalara danışmanlık gerekir ve servikal uzunluğun daha iyi değerlendirilmesi için TVS önerilir. (J Turkish-German Gynecol Assoc 2013; 14: 225-9)

Anahtar kelimeler: Servikal uzunluk, transabdominal sonografi, transvajinal sonografi

Geliş Tarihi: 10 Temmuz 2013

Kabul Tarihi: 14 Ağustos 2013



Introduction

Prematurity remains a major cause of perinatal morbidity and mortality (1, 2). Two-thirds of all preterm births are due to preterm labour with or without the rupture of membranes (3). This makes the identification of patients who are at risk of preterm labour and the prevention of prematurity a very important area for study. It is this area where cervical sonography can make a difference. The measurement of cervical length provides an accurate prediction of risk for early preterm delivery (4).

Transvaginal ultrasound scan (TVS) measurement has become the preferred method and is the only ultrasound technique that has been validated in the prediction of spontaneous preterm birth (5). Although TVS is the method that is generally recommended for assessing cervical length in women at high risk of preterm birth, many women in our culture either decline or are not happy to have a TVS during pregnancy.

A series of papers have showed convincingly that transabdominal ultrasound scan (TAS) measurement of the cervix also has utility in the evaluation of women who are at risk for preterm labour (6). Unfortunately, the use of TAS has a number of pitfalls, such as the fact that although filling of the maternal bladder helps with the visualisation of the cervix, excessive bladder filling reportedly spuriously elongates the length of the cervix (7).

As TVS measurement of the cervix needs training and experience and many women in our culture decline to have a TVS during pregnancy, we were interested in investigating whether TAS measurement of the cervix could be used as an effective alternative for TVS measurement. If it is found that TAS has a predictive correlation with TVS measurements of the cervix, it can be effectively employed in patients' counselling.

The aim of this study is to evaluate the correlation between transabdominal measurement of the cervix with that of transvaginal measurement in pregnant women between 18 and 26 weeks of pregnancy.

Material and Methods

Institutional Ethics Committee approval was obtained and this prospective study was conducted between October 2012 and May 2013.

For the purpose of this study, women with a singleton pregnancy, no prior history of cervical operation, including cone biopsy or Large Loop Excision of Transformation Zone (LLETZ), and without a cervical cerclage *in situ*, between 18-26 weeks of gestation were offered enrolment; a total of 127 pregnant patients were recruited following their informed consent.

TAS was done first in the supine position after the patient had emptied her bladder. Thereafter, TVS was done after voiding again, if necessary.

A curvilinear 3.5 Mega Hertz (MHz) transducer was used for transabdominal scan. Transabdominal cervical measurement was obtained with the transducer in the sagittal plane. Bladder filling was noted. The maximum vertical urine pocket in the bladder was measured at the time of TAS. This was done to quantify the amount of residual urine in the bladder. When the cervix was visualised transabdominally, the probe was adjusted

to bring the outline of cervical corpus in sight as well as to demonstrate the length of the cervical canal. Cervical length was measured by placing the callipers at the furthest points where the cervical canal walls were juxtaposed.

A 5 MHz vaginal transducer was used for TVS. The patient emptied her bladder prior to the scan if necessary. The patient was placed in the Lloyd-Davies position to allow easy access to the perineum and easy manipulation of the probe without causing any discomfort to the patient. The Transvaginal (TV) probe was inserted slowly until the cervix was clearly visualised in the sagittal plane with echogenic endocervical mucosa along the length of the canal. The probe was then gently withdrawn until the image blurred, and then reinserted, making sure to avoid excessive pressure. The image was sufficiently enlarged to allow clear identification of the echogenic endocervical mucosa, which was used as a guide to identify the internal os to avoid confusion with the lower segment endometrium. Measurement of the cervical length was taken from the internal os to the external os, incorporating only that length which was bordered by endocervical mucosa.

All of the scans were done by one of the three experienced sonographers who standardised the technique as described on 10 cases initially; the data of these cases were not included in this study. In each instance, both transabdominal and transvaginal scans were obtained by the same sonographer.

All of the measurements were taken in triplicate and the shortest best measurement was recorded for final analysis.

Statistical analysis

A sample size calculation was performed which indicated that 113 patients would be required to detect a 3 mm difference between transabdominal and transvaginal cervical length, with a power of 80% and an α error of 0.05. The tests were 2-sided, and statistical significance was defined as $p < 0.05$.

Paired 'T' test was used to detect the significance of the difference between transabdominal and transvaginal ultrasound measurements. Correlation coefficient was calculated to determine the strength of association between transabdominal and transvaginal measurements.

Results

Both TAS and TVS were performed on 127 pregnant women between 18-26 weeks of gestation. The mean age of the women was 21.80 ± 2.46 years (19-31yrs). 44% were primigravidae. The mean gestational age was 24.23 ± 3.83 weeks (18-26 wks). The minimum and maximum TVS measurements of the cervix were noted to be 22.4 mm and 55.2 mm, respectively. The transvaginal scan measurements were classified into centiles: 25th, 50th and 75th centile values of the transvaginal measurements of the cervix were 30.8 mm, 36.9 mm and 43.9 mm, respectively (Table 1).

Relation between TAS and TVS on cervical length

In patients with up to 25th centile value, where most of the patients needed >3 cm vertical pocket of urine in the bladder for adequate visualisation of the cervix, TAS measurement of

Table 1. Transvaginal scan measurements (in mm) in centiles

	Centile				
	Minimum	25 th	50 th	75 th	Maximum
Transvaginal scan measurements (mm)	22.4	30.8	36.9	43.9	55.2

Table 2. The Mean ± Standard Error (S.E) of all the ‘paired differences’ with their statistical significance

Centile (based on TVS measurement)	Mean (±SE) of all the differences between each paired observations by both TAS and TVS (TAS minus TVS)	p value	Remark
Up to 25 th Centile	3.07 ± 0.80 mm	<0.001	Significant
>25 th to ≤50 th Centile	-2.36 ± 1.24 mm	<0.001	Significant
>50 th to ≤75 th Centile	-2.68 ± 0.29 mm	<0.001	Significant
>75 th to 100 th Centile	-2.90 ± 0.33 mm	<0.001	Significant

the cervix was longer (average 3.07 mm) than the TVS measurement.

Above the 25th centile value in all other centile groups where the patients had either ≤ 3 cm vertical pocket of urine in the bladder or an empty bladder, the TAS measurement was shorter than the TVS measurement. In patients between >25th and 50th centile, TAS was 2.36 mm less, between >50th centile and 75th centile value, TAS was 2.68 mm less, and in patients above the 75th centile, the TAS value was 2.9 mm less than the TVS measurement.

A paired ‘T’ test was used and the difference between TAS and TVS measurements in all centile groups was found to be significant (p<0.001) (Table 2, Figures 1 and 2).

When the data were analysed on the basis of TVS cervical measurements, the following facts were noted:

- In the patients with TVS cervical length ≤32 mm, TVS cervical length was, on average, 2.88 mm (maximum 4.8 mm) less than that by TAS. Most of these patients needed >3 cm of vertical pocket of urine in the bladder for adequate visualisation of cervix; some patients needed up to 5 cm or occasionally even more.
- In the patients with TVS cervical length >32 mm, the TVS measurement of the cervix was longer than the TAS measurement. In these patients, the cervix could be seen by TAS when there was either ≤3 cm vertical pocket of urine in the bladder or an empty bladder.

Again, when we analysed the data on the basis of TAS cervical measurements, the following facts were noted:

- In patients whose TAS cervical measurement was ≥30 mm and the bladder needed a moderate amount of urine (>3 cm and even up to 5 cm of vertical pocket of urine in the bladder) for adequate visualisation of the cervix, TVS measurement of the cervix in these patients, although shorter than the TAS measurement, was longer than the critical value of 25 mm (25 mm is taken as the cut-off length of the cervix for predicting preterm labour).
- In patients whose TAS cervical measurement was ≥30 mm and the cervix could be seen with either an empty bladder or a bladder containing a minimal amount of urine (≤3 cm of vertical pocket of urine), TVS cervical measurement was confidently above 25 mm.

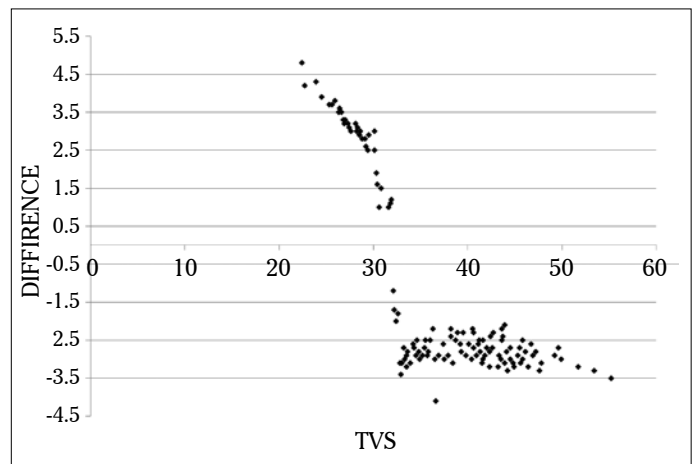


Figure 1. The graph shows the plotting of TAS-TV S differences (in mm on Y axis) against the individual TV S measurements of the cervix (in mm on X axis)

- In patients whose TAS cervical measurement was <30 mm and the bladder needed a moderate amount of urine (>3 cm vertical pocket of urine in the bladder) for adequate visualisation of the cervix, the TVS cervical measurement was shorter than the TAS measurement and was sometimes close to the critical value of 25 mm.

Although there was a significant difference between transvaginal and transabdominal measurements of cervical length in all of the percentile categories, there was a significant association (correlation coefficient r=0.96; p<0.01) between the two (Figure 3).

Relation between visualisation by TAS and bladder volume

When the bladder was empty, the cervix could only be adequately visualised by TAS in 17% of cases. However, the percentage of transabdominal visualisation of the cervix increased as the volume of urine in the bladder increased.

When the bladder had urine with the deepest vertical pocket up to ≤3 cm, the cervix could be adequately visualised by TAS in another 61% of cases.

As the bladder filling increased (up to deepest vertical pocket of 5 cm or occasionally more), it was possible to visualise the

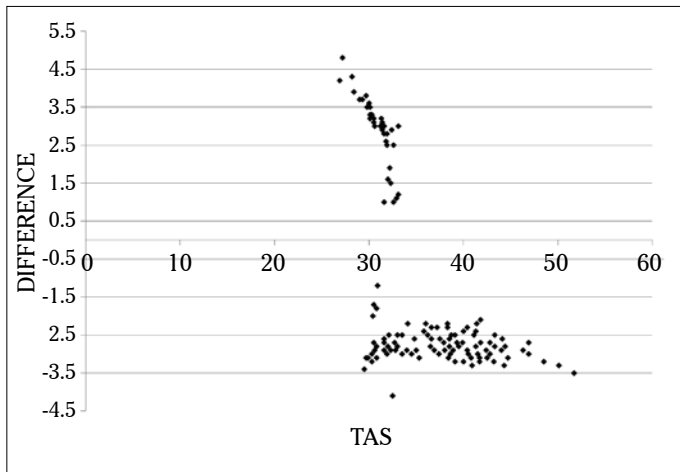


Figure 2. The graph shows the plotting of TAS-TV S differences (in mm on Y axis) against the individual TAS measurements of the cervix (in mm on X axis)

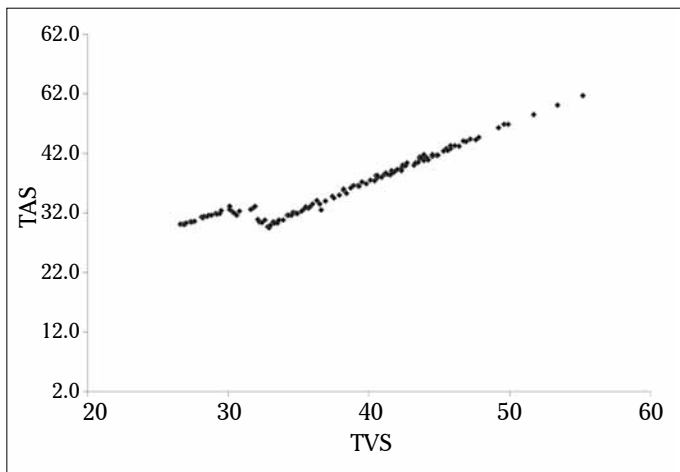


Figure 3. This graph depicts the correlation between transvaginal length (TVS) of the cervix (mm) with that of transabdominal (TAS) length of the cervix (mm)

cervix adequately by transabdominal sonography in the rest of the patients (Figure 4).

Transvaginally, the cervix was satisfactorily visualised in all cases.

Discussion

There is no need to deny the fact that TVS has several advantages over TAS, simply because of the proximity of the probe to the target organ, i.e. the cervix. However, the technique of TVS has a number of difficulties too. First, the variability of the technique has limited the standardisation of measurements. Second, there is a clear need of training for measurement of the cervix by transvaginal ultrasound (8). Finally, and most importantly in our culture, many patients are not happy to undergo TVS. Patient satisfaction is a key factor in patient care. This consideration has been the principal motivating issue to conduct this study.

The data of this study have demonstrated that in only 17% of patients was the cervix visible in the presence of an empty

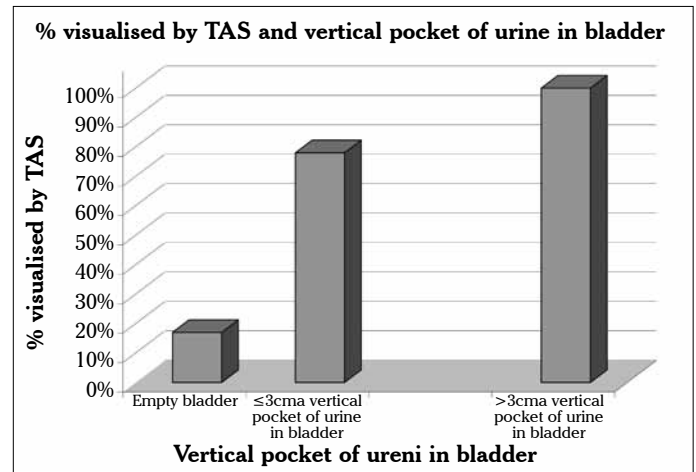


Figure 4. The chart shows the relation between % visualisation of the cervix by Transabdominal Scan with varying depth pockets of urine in the bladder

bladder by transabdominal sonography. In addition, the cervix could only be seen adequately when there was bladder filling with a vertical pocket of urine of up to 3 cm or less in 61% of cases. As the bladder filling increased to a vertical pocket of urine of 5 cm or occasionally more, it was possible to visualise the cervix adequately by transabdominal sonography in the remaining patients.

The fact that TAS cannot demonstrate the cervix adequately in the presence of an empty bladder in most of the pregnant patients and a variable degree of bladder fullness is required to demonstrate the cervix adequately by TAS is vindicated by the studies of Anderson et al. (7) and To et al. (9).

In this study, we observed that in patients with a TVS cervical length of ≤ 32 mm, TVS cervical length was, on average, 2.88 mm (maximum 4.8 mm) shorter than that by TAS. This observation is consistent with the findings of Saul et al. (10). It is noteworthy that, in this study, most of the patients with TVS cervix length of ≤ 32 mm needed >3 cm of vertical pocket of urine in the bladder for adequate visualisation of the cervix.

The probable explanation of the TAS measurement being longer than that of the TVS lies in the fact that bladder filling causes an increase in cervical length.

A number of studies have established the fact that, although a variable degree of bladder filling has an advantage of improving the visualisation of the cervix in pregnant patients by TAS, it causes artificial lengthening of the cervix (7, 9, 11, 12). This may be explained by the fact that the endocervical mucosa cannot be clearly recognised by TAS (in contrast with TVS where the endocervical mucosa can be recognised clearly) and the internal os is falsely thought to be at a higher level than it actually is in reality. Another explanation (for the apparent increase in cervical length with bladder filling) is that the bladder filling may cause the cervix to be progressively more vertical, which results in apparent measurement changes (13).

In this study, in all other patients with a TVS cervical length of >32 mm, in general, the cervical length measurement by TAS is shorter than that by TVS. This finding is consistent with the observation by Stone et al. (14), and can also be explained by

bladder filling. In these patients, the cervix could be visualised by TAS either in an empty bladder or with ≤ 3 cm vertical pocket of urine in the bladder. Thus, the factor of cervical elongation by bladder fullness was minimal.

Although there is a significant difference in TAS and TVS cervical length, this study finding will be useful in clinical practice. This study has found that if TAS cervical length is ≥ 30 mm and the bladder is empty or contains a minimal amount of urine (≤ 3 cm vertical pocket of urine), the patient can be assured that the risk of preterm labour is low as far as the cervical length is concerned (because the TVS cervical length is actually longer than the TAS measurement in these patients). Also, in patients with a TAS cervical length ≥ 30 mm, even though there needs to be a moderate amount of urine in the bladder (>3 cm up to 5 cm vertical pocket of urine) for adequate visualisation of cervix, the TVS cervical length is above 25 mm (taking the critical length of the cervix as 25 mm). Hence, these patients can also be assured that their risk of preterm labour is low.

In patients with a TAS cervical length <30 mm, careful judgement is required, taking bladder fullness in that individual into consideration. In such situations, these patients should be counselled and a transvaginal scan may be offered for the more accurate assessment of cervical length.

In conclusion; a variable degree of bladder filling is necessary for adequate visualisation of the cervix in the large majority of patients.

A minimal amount of bladder filling (≤ 3 cm vertical pocket of urine in bladder) does not influence TAS measurements of cervical length. However, with a moderate amount of bladder filling (>3 cm vertical pocket of urine in bladder), TAS measurement of the cervix appears to be longer than the actual measurement. This information is to be kept in mind while making clinical decisions.

In patients whose TAS cervical measurement is ≥ 30 mm, the patient can be assured, regardless of the urine content in their bladder, that the risk of preterm labour is low as far as the cervical length is concerned.

In patients whose TAS cervical measurement is <30 mm, the patient needs to be counselled and transvaginal scan may be offered for the more accurate measurement of cervical length, particularly when there is a moderate amount (>3 cm of vertical pocket of urine) of urine in the bladder.

Ethics Committee Approval: Ethics committee approval was received for the study.

Informed Consent: Informed consent was received from the participants of this study.

Peer-review: Externally peer-reviewed.

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Processing - K.C., M.G., S.C.; Analysis&/or Interpretation - K.C., S.S.; Literature Search - K.C., S.S.; Writing - K.C., S.S.; Critical Reviews - K.C., A.H.

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A close look at the contraction and relaxation of the myometrium; the role of calcium

Myometriyumun kasılma ve gevşeme mekanizmalarında kalsiyumun rolü

Bilge Pehlivanoğlu, Sibel Bayrak, Murat Doğan

Department of Physiology, Hacettepe University Faculty of Medicine, Ankara, Turkey

Abstract

The function and regulation of the myometrium, especially during pregnancy, labour and birth are important in reproductive physiology. It is crucial to understand the mechanisms that generate and modulate uterine contractility in order to be able to prevent and/or treat the problems related with the myometrium. A limited understanding of the cellular and molecular events underlying these phenomena complicates the situation. Various agonists, hormones, transmitters and/or chemicals are related to the regulation of the functions of the myometrium. Although notable advances regarding the key steps in receptor signalling explaining the actions of these factors have been achieved, a good deal of information is still necessary to understand this vital process. A better comprehension of myometrium physiology and the translation of research findings to clinical settings will help progress in women's health. In this review, we attempt to present a critical overview of myometrial functions and focus specifically on the role of calcium. (J Turkish-German Gynecol Assoc 2013; 14: 230-4)

Key words: Myocytes, contraction, relaxation, calcium, sensitisation

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Özet

Üreme fizyolojisi açısından myometriyumun işlevleri ve bu işlevlerin özellikle gebelik süreci ve doğum sırasında düzenlenmeleri çok önemlidir. Uterus kasılmalarını başlatan ve etkileyen faktörlerin anlaşılabilmesi myometriyumun ilgilendiren patolojik durumların engellenmesi ve/veya tedavi edilebilmesi için çok önemlidir. Ancak bu fizyolojik düzenlemeyi kontrol eden hücrenel ve moleküler olayların tam olarak açıklanamamış olması nedeni ile tablo hala karmaşıktır. Çok sayıda agonistin, hormonların, transmitterlerin ve kimyasal maddelerin myometriyum işlevlerinin düzenlenmesinde rolü olduğu gösterilmiş ve bunların etki mekanizmalarındaki bazı anahtar basamaklar ile ilgili gelişmeler kaydedilmiş olmasına karşın, bu yaşamsal işlevi daha iyi açıklayabilmek için daha fazla bilgiye ihtiyaç vardır. Myometriyumun fizyolojik özelliklerinin anlaşılması, araştırma sonuçlarının klinik uygulamalara yansıtılması kadın sağlığı açısından önemli katkı sağlayacaktır. Bu derlemede myometriyumun işlevlerini ve özellikle kalsiyumun rolünü özetlemeyi amaçladık. (J Turkish-German Gynecol Assoc 2013; 14: 230-4)

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Introduction

The uterus, more specifically the smooth muscle layer of the uterus, the myometrium, is an often overlooked tissue. Even though the myometrium is active throughout a woman's life, not just during labour and delivery, it is rarely considered until things go wrong which may have devastating consequences. However, the uterine myometrium serves life-long by contracting at the right time with exactly the desired amount of force during labour and the postpartum period and remaining relaxed even though distended enormously during the period of pregnancy, as well as maintaining its tonus in non-pregnant, non-menstruating periods. Some of the unwanted but frequently seen results of myometrial dysfunction are untimed contractions leading to abortions or preterm delivery, or stronger than necessary contractions causing foetal distress, hypoxia and even death of the foetus. In addition, dysfunctional labour can be faced and caesarean section may become inevitable when the force of the contractions

are not strong enough and/or contractions are irregular (1, 2). Since the mechanisms that generate and modulate uterine contractility are not fully known, the aberrant patterns of contractile activity remain unsolved (3). Due to these limited answers, the therapeutic or preventive approaches to clinical conditions are not as successful as desired. In this review, we aimed to summarise the current knowledge about the mechanisms of contraction and relaxation of the myometrium and specifically the role of calcium (Ca^{+2}).

Contraction of the Myometrium

Uterine contractility, which occurs throughout the menstrual cycle in non-pregnant and pregnant states, is a complex and dynamic physiological phenomenon (2). Non-pregnant myometrium exhibits different contractions at different phases of the menstrual cycle; the first one is rhythmic, 'wave-like' contractions, which is sometimes known as uterine peristalsis, while the second type of contraction is defined as the 'focal and sporadic bulging of the myome-



Address for Correspondence: Bilge Pehlivanoğlu, Department of Physiology, Hacettepe University Faculty of Medicine, Ankara, Turkey.
Phone: + 90 312 305 15 67-305 15 59 e.mail: pbilge@hacettepe.edu.tr

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trium' (4, 5), leading to sustained contractions. These contractions serve in the sloughing of the endometrium (6) and help the passage of sperm. The myometrium in the pregnant uterus transforms from a silent, non-contracting state to an actively and forcefully contracting organ for a successful delivery. This is achieved by morphological changes and adaptations under the effect of elevated oestrogen and progesterone and the balance between these two hormones; these interactions are reviewed elsewhere as they are beyond the purpose of this review (7, 8). Besides the above-mentioned functional differences, regardless of the presence or absence of pregnancy, uterine contractions are dependent on the contractile activity of the cellular elements, the uterine myocytes. The uterine myocytes are smooth muscle cells exhibiting a phasic contractile pattern which can be summarised as the maintenance of a resting tone superimposed by separate intermittent contractions of varying frequency, amplitude and duration. It is predominantly regulated by intracellular calcium concentration ($[Ca^{+2}]_i$) (1, 2, 8).

Cellular Organisation

The contractile machinery of the uterine smooth muscles involves actin and myosin myofilaments with six times preponderance of actin to myosin. The thin myofilaments composed of polymers of globular actin monomers and thick filaments are made up of myosin helices lying parallel to the longitudinal axis of the cell. In addition, there are intermediate filaments composed of predominantly desmin and vimentin.

Excitation contraction coupling

The excitation contraction coupling is regulated predominantly by $[Ca^{+2}]_i$. Physiologically, the changes in $[Ca^{+2}]_i$ can be considered in three phases leading to differences in contractility: basal concentrations, which are sufficient to maintain the resting tone of the myometrium, increased $[Ca^{+2}]_i$ that occurs with contractile agonist stimulation and the restoration of $[Ca^{+2}]_i$ to the resting state following stimulation.

The contractile machinery of the myocytes involves the interaction of myofilaments, actin and myosin. As in any other muscle, the cross bridge formation and contraction is mediated by elevated $[Ca^{+2}]_i$ and myosin light chain phosphorylation. Irrespective of the triggering stimulus, $[Ca^{+2}]_i$ elevation is essential for contraction (9), which may either enter from the extracellular fluid into the cell across the surface membrane through voltage-gated L-type Ca^{+2} channels and/or be released from intracellular stores in the sarcoplasmic reticulum (SR) (1). Both the release of Ca^{+2} from intracellular stores and the influx of Ca^{+2} from the extracellular space serve to activate the biochemical pathways which lead to actin-myosin cross-bridging and force development (2), i.e. excitation-contraction coupling.

Calcium release from sarcoplasmic reticulum occurs via two mechanisms:

Agonist or inositol triphosphate (IP_3)-induced Ca^{+2} release (IICR) and Ca^{+2} -induced Ca^{+2} release (CICR) via Ca^{+2} release channels (known as ryanodine receptors) on the SR gated by Ca^{+2} (10).

Agonist or IP_3 -induced Ca^{+2} release: Binding of uterine agonists to a specific G-protein coupled receptor (GPCR) in the plasma membrane of uterine myocytes activates trimeric G-protein (11) and turns on a cascade of events starting with membrane phospholipase C (PLC) stimulation (12). Stimulated PLC cleaves phosphatidylinositol bisphosphate (PIP_2) to diacylglycerol (DAG) and IP_3 , the latter of which causes the release of Ca^{+2} from the SR into the cytoplasm, as indicated above (13). The IP_3 -mediated Ca^{+2} release from SR is the major factor adjusting resting membrane voltage (V_{rest}) to the value at which voltage-operated Ca^{+2} (VOC) channels open to trigger an action potential (AP) (14). There are two types of APs recorded in myometrial smooth muscle of various species; simple APs which have depolarisation followed by rapid repolarisation, and complex APs which have an initial depolarisation with a sustained plateau (15, 16). It has been suggested that the shape of $[Ca^{+2}]_i$ transients and contractions triggered by these action potentials may be different (17).

Ca^{+2} -induced Ca^{+2} release in the myometrium: Another mechanism is known as Ca^{+2} -induced Ca^{+2} release, whereby the increasing $[Ca^{+2}]_i$ sensitises other Ca^{+2} channels to open, thus creating a feed-forward loop, although the mechanism of this phenomenon is not yet clear (14).

Extracellular calcium entry

The myometrium contains predominantly voltage-operated, large conductance L-type Ca^{+2} channels (18, 19). The presence of T-type Ca^{+2} channels has been recently shown, although their role has not yet been fully elucidated (20). Massive movement of Ca^{+2} from the extracellular space into the cytosol through these Ca^{+2} channels determines $[Ca^{+2}]_i$ and force generation to a much greater extent than the agonist-stimulated IP_3 -mediated release of Ca^{+2} (13, 21).

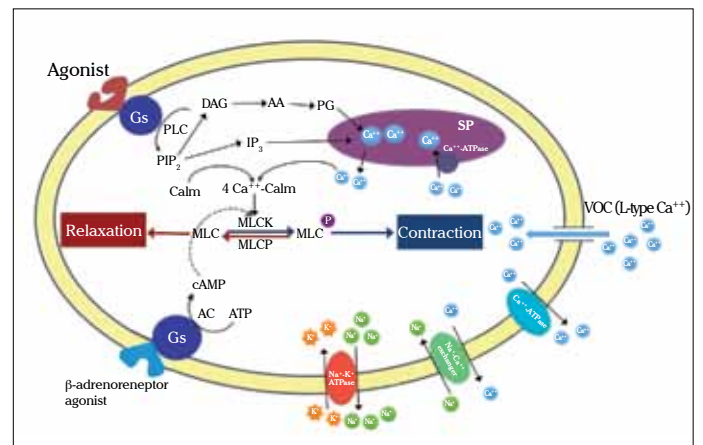


Figure 1. The schematic presentation of the physiological pathways of contraction or relaxation in uterine myocytes

(Calm: calmodulin; MLCK: myosin light chain kinase; MLCP: myosin light chain phosphatase; SR: sarcoplasmic reticulum; Gs: G-protein coupled stimulatory protein; PLC: phospholipase C; PIP_2 : Phosphatidyl inositol diphosphate; DAG: diacylglycerol; IP_3 : inositol triphosphate; AA: arachidonic acid; PG: prostaglandin; VOC: Voltage operated channels)

Taking both mechanisms together, as supported by the experimental data from different species, it is suggested that Ca^{+2} release from the SR is transient and rapidly depleted. For this reason, even under agonist stimulation and IP_3 production, oxytocin is unable to produce force in the uterus if Ca^{+2} entry is inhibited (21). Moreover, when the reuptake of calcium to the SR is inhibited, both $[\text{Ca}^{+2}]_i$ transient and resulting contractions increase due to longer lasting increase in $[\text{Ca}^{+2}]_i$ (21, 22, 23).

Contraction

A prominent increase in $[\text{Ca}^{+2}]_i$ consequently activates a Ca^{+2} -dependent cytosolic protein, calmodulin (CalM), which can bind four Ca^{+2} ions (24). Formation of the Ca^{+2} -CalM complex results in the activation of a key enzyme, myosin light chain kinase (MLCK) and causes an immediate and marked increase in the phosphorylation of myosin regulatory light chain-20 (MLC20) and subsequent cross-bridge cycling (25). Phosphorylation of MLC20 by MLCK is the principal determinant of the amplitude and duration of contraction (26). MLCK contains several phosphorylation target sites for protein kinase A, protein kinase C (PKC) and other kinases (2). Activation of MLCK by CalM translocation of activated MLCK towards the contractile apparatus may be the rate-limiting step of contraction (14) determining the speed of contraction of the myometrium (Figure 1).

Calcium sensitisation

In some conditions, for example after stimulation with an agonist such as oxytocin or PGF_{2a}, a given rise in $[\text{Ca}^{+2}]_i$ will result in a stronger than expected force of contraction (27-29). This physiological phenomenon is known as “ Ca^{+2} sensitisation” (CS) (30). Subsequent experiments have demonstrated that a pathway activated following the stimulation of GPCRs to inhibit myosin light chain phosphatase (MLCP) is the major mechanism controlling CS (31, 32). It can be easily predicted that this pathway involves the small GTPase rhoA and its effector, rhoA-associated kinase (ROK), since CS was shown to be diminished using a specific inhibitor of rhoA (33). The modification of the activity of MLCP (30) with phosphorylation, particularly by ROK, results in decreased activity and in turn increased force at constant $[\text{Ca}^{+2}]_i$, i.e. an increase in Ca^{+2} sensitivity. On the other hand, the dephosphorylation of myosin by MLCP is usually associated with decreased force and relaxation. The ROK pathway is more important in regulating force of contraction during tonic compared to phasic contractions. Despite the large volume of literature demonstrating the relationships between agonist stimulation and CS, the information regarding the physiological role of this mechanism in the uterus is limited (2). These mechanisms may become important therapeutic targets for the regulation of uterine activity, e.g. oxytocin may also act in part by Ca^{+2} sensitisation (34). However, it is clear that further study is necessary to determine the significance of CS in basal or stimulated myometrium function.

Besides the Rho-ROK pathway, PKC and activators or inhibitors of it have also been studied with regards to their potential

involvement in myometrial CS both in pregnant and non-pregnant states; the findings suggest a role via the regulation of MLCP activity (35).

The pregnant myometrium is capable of larger force generation compared to the non-pregnant myometrium per unit of phosphorylated myosin light chain (36), suggesting the presence of a sensitisation system other than CS.

Relaxation of the Myometrium

The myometrium, contracting with increasing $[\text{Ca}^{+2}]_i$, relaxes following a series of events starting with Ca^{+2} dissociation from CalM, in turn inactivating MLCK, which is initiated by a decrease in $[\text{Ca}^{+2}]_i$ (10, 14). Reversal of the Ca^{+2} -CalM-MLCK pathway follows the closure of L-type Ca^{+2} channels and enhanced Ca^{+2} efflux (Figure 1).

Calcium efflux

Calcium efflux in the myometrium is either via primary or secondary active transporters: Ca^{+2} -Adenosine triphosphatase (ATPase) and Na^{+} - Ca^{+2} exchanger, respectively. The affinity of Na^{+} - Ca^{+2} exchanger for Ca^{+2} is low, although it is a high-capacity system. The activity of the Na^{+} - Ca^{+2} exchanger is determined by the transcellular Na^{+} gradient, which is determined by Na^{+} , K^{+} -ATPase pump activity. As a low intracellular Na^{+} concentration is maintained by the activity of Na^{+} , K^{+} -ATPase pump, the exchanger will be activated under physiological conditions of high $[\text{Ca}^{+2}]_i$ and Ca^{+2} will be removed from the cell. The primary active calcium transporter, Ca^{+2} -ATPase, is a high-affinity system that is adjusted to keep intracellular Ca^{+2} low, so that resting Ca^{+2} levels are maintained (37). Intact uterine studies and single myometrial records show that the shares of Na^{+} - Ca^{+2} exchanger and Ca^{+2} -ATPase in the extrusion of increased intracellular Ca^{+2} are 30% and 70%, respectively. The efflux ceases completely when these pathways are both blocked (38, 39).

The SR, acting both as a Ca^{+2} reservoir and a transmission pathway for Ca^{+2} towards two transporters, increases the extrusion rates. Although the SR has a considerably important role in Ca^{+2} signalling in other smooth muscles, its role in lowering intracellular $[\text{Ca}^{+2}]_i$ is not very significant in the myometrium (39).

Being aware of relaxation mechanisms allows researchers and clinicians to modulate uterine contractions. First, stimulating relaxation becomes a therapeutic target to relieve undesired contractions. To achieve relaxation or decrease the force and/or frequency of contractions, Ca^{+2} desensitisation can be used. The phosphorylation of MLCK by several kinases reduces its activity and thus desensitises the contractile machinery (40, 41). Ca^{+2} desensitisation, as described by Sanborn et al. (42), works via the NO-cyclic guanosine monophosphate (cGMP) signalling pathway. Briefly, cGMP-stimulated MLCP removes the phosphate from myosin, thus terminating contraction (42). Secondly, inhibition of relaxation will lead to augmented contraction, which is necessary when labour is not progressing or to achieve a strong enough contraction to prevent postpartum haemorrhage. Agents that are capable of maintaining high intracellular $[\text{Ca}^{+2}]_i$ promote force production. For example, oxytocin, which is widely used to reinforce labour contractions, stimulates calcium entry and release from the

SR, and also inhibits Ca^{+2} efflux (43). In addition, Ca^{+2} -sensitising agonists act mainly by inhibiting MLCP augmentation and/or elongating myometrial contractions. As noted above, ROK-associated phosphorylation of one of the MLCP subunits is the main mechanism in the inhibition of MLCP. Since this mechanism is more prominent in tonic smooth muscles, ROK inhibitors result in a little change in myometrial contractions in the uterus (44). In contrast, MLCP inhibitors acting through different protein kinase pathways have been shown to be more effective in the uterus (45).

Although the role of calcium is undeniable in myometrium relaxation, ligand-mediated relaxation is also important. A myriad of agents to prevent contraction has been tried over the years and only a small number of them have been used as tocolytic agents. The agents that are capable of uterine relaxation may intervene with the pathways which will be summarised briefly.

Nitric-oxide-cyclic nucleotide pathway

Various studies suggest a strong link between nitric oxide (NO) and cyclic GMP production (46). The mechanism of the inhibitory effect of NO/cGMP on uterine contractility, although not clear, is believed to be via decreasing $[Ca^{+2}]_i$ (47). NO alone is also shown to be involved in the activity of potassium channels and the conversion of PGE_2 to PGF_{2a} (48).

G-protein coupled receptors

G-protein coupled receptors mediate the effect of various agonists in the myometrium. Gq-coupled receptors stimulate contraction via phospholipase C, as stated above, whereas Gs-coupled receptors induce relaxation via the activation of adenylyl cyclase (3). A very well-known example is β_2 adrenergic receptors coupled to Gs, which has been used for pharmacological tocolysis (49).

Phosphodiesterases

Phosphodiesterases may attenuate the activity of cyclic adenosine monophosphate (cAMP) or cGMP by contributing to their inactivation; an increased cAMP amount will decrease contractions and lead to relaxation (3). This fact resulted in the extensive use of phosphodiesterase (PDE) inhibitors as tocolytic agents in the 1980s, but this had to be abandoned due to the high incidence of side effects (50).

Conclusion

We tried to summarise the role of calcium both in contraction and relaxation of the myometrium in this review. Major advances in understanding the molecular physiology of the myometrium have been recently achieved. However, there are still key, unanswered questions, mainly concerning the role of the SR, CS and Ca^{+2} -activated ion channels. These issues, together with the action of agonists and antagonists on the myometrium, need further research.

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In vitro maturation may prevent the cancellation of *in vitro* fertilization cycles in poor responder patients: A case report

In vitro matürasyon, zayıf over cevabı veren hastalarda *in vitro* fertilizasyon sikluslarının iptalini engelleyebilir: Vaka raporu

Ender Yalçınkaya¹, Eray Çalışkan², Özcan Budak¹

¹Assisted Reproduction Unit, Faculty of Medicine, Kocaeli University, Kocaeli, Turkey

²Department of Obstetrics and Gynecology, Faculty of Medicine, Kocaeli University, Kocaeli, Turkey

Abstract

In vitro maturation (IVM) is a promising technique that is used for the maturation of immature oocytes in laboratory conditions and preferred for use in patients with a diagnosis of polycystic ovary syndrome (PCOS) as an alternative to conventional *in vitro* fertilization (IVF) treatment. In this report, we present a case who surprisingly showed insufficient response to gonadotrophin stimulation during IVF treatment and whose cycle was retrieved from cancellation by using the *in vitro* maturation technique. As a result, we conclude that IVM may be a good option not only for PCOS patients, but also for poor responders. (J Turkish-German Gynecol Assoc 2013; 14: 235-7)

Key words: *In Vitro* maturation, *in vitro* fertilization, gonadotrophins

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Özet

In vitro matürasyon (IVM), immatür oositlerin laboratuvar koşullarında olgunlaştırılması için umut vadeden bir tekniktir ve çoğunlukla polikistik over (PKO) tanısı koyulmuş hastalarda konvansiyonel *in vitro* fertilizasyon (IVF) tedavisine bir alternatif olarak tercih edilmektedir. Bu raporda, IVF tedavisi sırasında kullanılan gonadotropinlere sürpriz şekilde zayıf over cevabı veren ve aynı siklusu *in vitro* matürasyon tekniği kullanılarak iptal olmaktan kurtarılan bir vakayı sunuyoruz. Bu vakanın sonucu olarak, IVM'in sadece polikistik overli hastalar için değil, aynı zamanda zayıf over cevabı veren hastalar için de iyi bir tedavi seçeneği olabileceği sonucuna vardık. (J Turkish-German Gynecol Assoc 2013; 14: 235-7)

Anahtar kelimeler: *In vitro* matürasyon, *in vitro* fertilizasyon, gonadotropinler

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Introduction

Assisted reproduction programmes frequently use ovulation stimulation protocols in order to increase the number of oocytes available for fertilization. However, ovarian hyperstimulation with exogenous gonadotrophins produces many risks for patients such as ovarian hyperstimulation syndrome or cycle cancellation due to risk of hyperstimulation, delayed response or improper use of drugs by patients. Under these circumstances, *in vitro* maturation (IVM), fertilization and embryo transfer may provide an alternative to cancellation of these cycles. Moreover, the development of the *in vitro* maturation technique could provide a new strategy for assisted reproduction, enabling cost reduction and minimizing concerns about a possible association between the use of ovulation-inducing drugs and their side effects (1).

The IVM technique was first demonstrated by Pincus and Enzmann (1935) and later by Edwards (1969). In the last two decades, many improvements in clinical and laboratory

aspects have been achieved. However, its efficiency is still suboptimal compared to controlled ovarian hyperstimulation cycles in terms of the number of mature oocytes obtained, embryo developmental competence and implantation rates. As success of the technique increases, the indications of IVM are widening to include various diagnoses of infertility (2). In particular, women with polycystic ovaries and those who have a previous history of a hyperstimulation reaction during conventional controlled ovarian stimulation have been considered good candidates for IVM. Diminished ovarian reserve with a poor response to controlled ovarian stimulation is a difficult part of *in vitro* fertilization (IVF) practice to manipulate and yields low success rates. Poor ovarian response in IVF has been characterised as a low number of follicles seen in ultrasound scans, high basal serum follicle stimulating hormone (FSH) concentrations and fewer than five oocytes obtained in a stimulated cycle (3).

Some poor responders appear to respond to stimulation but have a low oestrogen level of a few or slow-growing follicles.



Address for Correspondence: Ender Yalçınkaya, Assisted Reproduction Unit, Faculty of Medicine, Kocaeli University, Kocaeli, Turkey
Phone: +90 533 637 01 15 e.mail: endersu81@gmail.com

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These patients seem resistant to gonadotrophin stimulation and require extended stimulation time and a higher dose of gonadotrophins. Data are limited on *in vitro* maturation treatment of poor responders or patients with retarded follicular development during a conventional stimulation IVF cycle (4).

In this report, we presented a case in which the *in vitro* maturation of oocytes obtained from a patient who showed inefficient response to high doses of exogenous gonadotrophins during an IVF treatment regimen resulted in fertilization and pregnancy.

Case Report

The patient admitted to Kocaeli University IVF Unit with a complaint of diminished ovarian reserve. She was 36 years old and had 1-2 antral follicles in each ovary at the basal ultrasonography. Her basal hormone levels were as follows: FSH, 2.8 mIU/mL; luteinizing hormone (LH), 2.9 mIU/mL; estradiol (E2), 13.06 pg/mL; and prolactin, 4.06 ng/mL. A microdose flare up protocol was planned for the patient. The starting recombinant FSH dose (Gonal F[®], Serono, Italy) was 375 units; however, the dose was increased up to 525 units since the patient's ovaries did not respond adequately to the first applied dose. On day 11, the dose used was 525 units, but the mature follicle was only 11.5 mm in diameter, which was unexpected. Oestradiol level at day 11 was 501 pg/mL, which was not correlated with the mature follicle count. Her doctor offered two choices for the patient. First was the cancellation of the cycle and the other was the collection of the oocytes followed by an attempt to mature them *in vitro*. The patient selected the latter and did not want the cycle to be cancelled. Human chorionic gonadotrophin (hcg) was administered on day 11 and the oocyte collection procedure was performed in the 36th hour of hcg administration and 3 oocytes were collected. The endometrial thickness of the patient was 7.9 mm at the time of oocyte collection. After denudation, it was found that one of the oocytes was metaphase II (MII), one was metaphase I (MI) and the third one was germinal vesicle (GV) stage. Intracytoplasmic sperm injection (ICSI) was performed on the MII oocyte, and the others were incubated in oocyte maturation medium (Sage; CooperSurgical, USA). The fertilization check was done after the 18th hour and it was observed that the mature oocyte was not fertilised. The maturation check was done at the 20th hour and it was observed that the remaining two oocytes were matured to MII phase. Newly matured oocytes were microinjected in the afternoon and the fertilization check was done on the next day (after 18 hour of sperm injection). It was noted that one of the oocytes was 2pn and the other was 3pn. The 2pn zygote was transferred to the patient on the same day. After 13 days, the blood hcg level was measured and it was observed that patient had a hcg level of 136 which indicated pregnancy. After two weeks of hcg measurements, a sac was seen at ultrasonography and a foetal heart beat was seen after two weeks; this was an indicator of a singleton clinical pregnancy.

Discussion

Of the oocytes retrieved after ovulation induction during IVF treatment, approximately 20% are found to be immature (GV

and MI stage). These oocytes are not used for intracytoplasmic sperm injection during routine laboratory applications and are discarded due to their reduced fertilization potential and embryo development under current culture conditions. However, these oocytes are useful for studies that aim to explain the mechanisms of *in vitro* maturation of human oocytes (5). IVM appeared as a theoretically attractive method for obtaining mature oocytes for IVF when it was first announced. However, the efficiency of current IVM techniques are currently thought to be suboptimal in terms of the number of mature oocytes obtained, embryo developmental competence and implantation rates (6), as well as the outcome of fertilization is often poor with standard *in vitro*-matured oocytes (7). Therefore, several clinical alterations such as FSH and hcg priming before oocyte collection, rearrangements in the maturation period and timing of aspiration have been made to improve the quality of IVM oocytes.

To date, several studies have reported the effects of FSH and hcg priming on *in vitro* maturation outcomes and have given conflicting results. In a study by Fadini et al. (8), where oocytes were primed with different gonadotrophin regimens before *in vitro* maturation, it was found that 3-day FSH priming did not result in a higher number of oocytes retrieved. In this study, FSH priming alone did not seem to promote oocyte maturation or improve the fertilization rate. This finding was in accordance with Mikkelsen's study in 1999 (9) in which pre-treatment of patients with recombinant FSH did not increase the number of oocytes retrieved. Accordingly, Lin et al. (10) could not find any beneficial effect of FSH priming on the number of oocytes retrieved, maturation and fertilization rates. Conversely, Suikkari et al. (11) reported that a small dose of FSH in women undergoing regular menstruation might increase the yield of immature oocytes collected. Junk et al. (12) also demonstrated in their study in 2003 that FSH priming improves oocyte maturation, but does not have an effect on subsequent embryonic development.

Studies on the effect of hcg priming on *in vitro* maturation also gave conflicting results. In 1999, Chian et al. (13) reported that giving 10,000 IU hcG 36 hours before oocyte collection as in standard IVF procedures improved the maturation rate of immature oocytes. They postulated that the oocyte maturation period *in vitro* was shortened and the rate of oocyte maturation was increased by priming with 10,000 IU hcg before oocyte collection. On the contrary, the study by Fadini et al. (8) in 2009 was not in favour of hcg priming alone in *in vitro* maturation, since it showed the lowest pregnancy and implantation rates.

In the literature, there are two case reports published in which the cycles were on the edge of cancellation due to the improper use of hcg and ovarian hyperstimulation, but were rescued by IVM application (1,7). Also, Jiayin et al. (4) reported three cases in which *in vitro* matured oocytes retrieved from poor responders undergoing stimulation via *in vitro* fertilization cycles yielded healthy pregnancies and births. IVM was observed to act as a good alternative to cancellation in these cases. Our case seems to be a good example of delayed response to exogenous gonadotrophins and the application of *in vitro* maturation in poor responders.

Although most of the clinical aspects of the technique were studied, the research on the best IVM culture conditions is still ongoing. Since culture conditions and the technique were not optimised adequately, the results of IVM cases are still poorer than conventional IVF, and IVM still stands as a technique that needs to be strengthened. Despite lower clinical outcomes compared to standard IVF techniques, IVM seems to be an attractive method for many patients with many advantages such as lower treatment costs, shorter schedule, no side effects with drugs, no OHSS risk and no patient discomfort (14). Because of these advantages, we believe that IVM could be a good alternative not only for PCOS patients but also for women with different aetiologies when the conditions are optimised.

Ethics Committee Approval: Ethics committee approval was received for this study.

Informed Consent: Written informed consent was obtained from patients who participated in this study.

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Continuous amnioinfusion via an epidural catheter following spontaneous membrane rupture: A case report

Spontan membran rüptürü sonrası epidural kateterle yapılan kontinu amnioinfüzyon: Olgu sunumu

Abdulkadir Turgut¹, Selahattin Katar², Muhammet Erdal Sak¹, Fethiye Gülden Turgut³, Alparslan Şahin⁴, Serdar Başaranoğlu¹, Ahmet Yalınkaya¹

¹Department of Obstetrics and Gynecology, Dicle University School of Medicine, Diyarbakır, Turkey

²Department of Pediatrics, Veni Vidi Hospital, Diyarbakır, Turkey

³Department of Ophthalmology, Diyarbakır Training and Research Hospital, Diyarbakır, Turkey

⁴Department of Ophthalmology, Dicle University School of Medicine, Diyarbakır, Turkey

Abstract

Preterm premature rupture of membranes (PPROM) is seen in 3% of all pregnancies, and is a frequent cause of preterm birth, neonatal mortality and morbidity. The most important complications are maternal and foetal infection, prematurity, umbilical cord compression, hypoxia or asphyxia due to cord prolapse, pulmonary hypoplasia and extremity deformities. The basic approach to PPRM therapy aims to prevent premature birth and the development of foetal distress, and decrease the risk of maternal and foetal infection, and amniotic fluid loss. In compliance with these objectives, alternatives of PPRM therapy demonstrate a wide spectrum, including watchful waiting, amniopatch application, recurrent amnioinfusions and emergency birth. However, repeated amnioinfusions in cases of fluid loss, especially within 6 hours of therapy, provides only minimal benefit. In this case presentation, we attempted to describe a different and cost-effective continuous amnioinfusion technique performed to confer survival benefit for an immature anhydramniotic foetus affected by PPRM at the border of viability.

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Key words: Amnioinfusion, preterm premature rupture of membranes, amniopatch

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Özet

Preterm prematür membran rüptürü (PPROM) tüm gebeliklerin %3'ünde görülür ve preterm doğumun, neonatal ölüm ve morbiditenin en sık nedenidir. En önemli komplikasyonlar maternal ve fetal enfeksiyon, prematürite, umbilikal kord basısı, kord prolapsusuna bağlı hipoksi veya asfiksi, pulmoner hipoplazi ve ekstremitte deformiteleridir. Tedavisinde temel yaklaşım prematüre doğumun önlenmesi, anne ve fetüs te enfeksiyon riskinin azaltılması, amnion sıvı kaybının azaltılması ve fetal distres gelişiminin önlenmesidir. Bu amaçlar doğrultusunda tedavisi de bekleme tedavisi, amniopatch, tekrarlayan amnioinfüzyondan acil doğuma kadar oldukça çeşitlilik göstermektedir. Ancak özellikle de tedavi sonrası 6 saat içinde sıvı kaybının fazla olduğu vakalarda tekrarlayan amnioinfüzyon minimum fayda sağlamaktadır. Bu vaka sunumunda, PPRM nedeniyle anhidramnios olan immatür bir fetusun viabilite sınırını geçmesi için yapılan ve başarılı olan farklı ve ucuz bir kontinu amnioinfüzyon tekniğini anlatmaya çalıştık. (J Turkish-German Gynecol Assoc 2013; 14: 238-41)

Anahtar kelimeler: Amnioinfüzyon, preterm prematür membran rüptürü, amniopatch

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Introduction

Premature rupture of the foetal membranes (PROM) is defined as the rupture of the amniotic membranes and the resultant leakage of the amniotic fluid at least one hour prior to labour contractions. PROM may be subdivided into term PROM (TPROM, i.e. PROM after 37 weeks of gestation) and preterm PROM (PPROM, i.e. PROM prior to 37 weeks of gestation) (1). The incidences of PROM and PPRM are 19.53% and 3%, respectively. It is a frequent cause of preterm birth, neonatal mortality and morbidity (2, 3). The incidence of peri-

natal mortality is 60%, and nearly one-third of these deaths occur in utero. The most important complications are maternal and foetal infection, prematurity, umbilical cord compression, hypoxia or asphyxia due to cord prolapse, pulmonary hypoplasia and extremity deformities (1, 4, 5). The basic approach to PPRM therapy aims to prevent premature birth and the development of foetal distress and to decrease the risk of maternal and foetal infection and amniotic fluid loss. In light of these objectives, PPRM therapy demonstrates a wide spectrum, including watchful waiting, amniopatch application, recurrent amnioinfusions and emergency birth.



Address for Correspondence: Abdülkadir Turgut, Department of Obstetrics and Gynecology, Dicle University School of Medicine, Diyarbakır, Turkey.

Phone: +90 505 483 43 80 e.mail: abdulcadirturgut@gmail.com

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However, repeated amnioinfusions in cases of fluid loss, especially within six hours of therapy, provide only minimal benefit. Major cerebral anomalies, such as cerebral palsy, chronic pulmonary disease, necrotising enterocolitis and blindness, can be seen in infants who survive (3, 6).

In this case presentation, we describe a different and cost-effective continuous amnioinfusion technique performed to confer a survival benefit on an immature anhydramniotic foetus with PPROM at the border of viability.

Case Report

A 37-year-old pregnant woman (gravida 5, para 1, abortus 3) at her 22nd gestational week with antiphospholipid syndrome who had previously given birth to a 27-week premature healthy and still living infant consulted our clinic with a complaint of 'water breaking' amniotic fluid. On ultrasonographic examination (US) (by GE Voluson 730 Pro 4D ultrasound device), the foetus was at nearly the 22nd gestational week, and the amount of total amniotic fluid according to the amniotic fluid index (AFI) was less than 2 cm³ as viewed from all quadrants. PPROM was diagnosed with a speculum, which showed vaginal pooling of the fluid on the posterior fornix, and by a positive alpha microglobulin-1 protein test (Amnisure; Aren Medical, İstanbul, Turkey) of the vaginal fluid. It is probable that the membranes had ruptured much earlier and that the fluid loss had been misinterpreted by the patient as a weakness of the bladder. The cervical length was 25 mm. The patient's treatment started with prophylactic antibiotics, a regimen of bed rest, daily monitoring of inflammation parameters, such as the white blood cell (WBC) and C-reactive protein (CRP), and the monitoring of vital signs, especially temperature. The CRP and WBC measurements were <1 mg/dL and 17,700/mm³, respectively. Prophylactic IV antibiotherapy was initiated with 4x1 g of ampicillin+sulbactam (Sulbaksit; Tüm Ekip İlaç, İstanbul, Turkey). An amniopatch was performed primarily with the use of platelet suspension. The autologous platelet concentrate (PC) was produced by platelet pheresis using the MCS plus[®] blood cell separator (Haemonetics Corporation, Braintree, Massachusetts, USA). The patient's platelet precount of 230x10³/μL was used for programming the device. After rewarming to 37°C, the PC (30 mL) was administered first, followed by 20 mL of cryoprecipitate via a 22-gauge needle (Spinocan; Braun, Mensungen, Germany), directed into an available pocket of amniotic fluid. The amnioinfusion and the amniopatch were performed twice. After application of the amniopatch, the amniotic fluid continued to drain actively. While monitoring the patient, uterine contractions started to develop, prompting initiation of 2 g MgSO₄ (Magnezyum Sulfat %15; Osel, İstanbul, Turkey) IV per hour as a tocolytic agent. Within six hours of each application of the amnioinfusion and the amniopatch, the AFI was less than 2 cm as observed from all quadrants.

Therefore, application of a different and cheaper technique of continuous amnioinfusion was decided upon. Before the procedure, a detailed and undersigned informed consent was obtained from the patient and the family. Continuous amnioinfu-

sion was applied through an epidural catheter (Portex Epidural Minipack System, 18 G, Smiths Medical, USA) (Figure 1). The application procedure was similar to the conventional amniopatch method. Under the guidance of ultrasonography, an epidural catheter was inserted transabdominally into a suitable vertical pocket of amniotic fluid. After withdrawal of the needle, the cannula was left in the uterine cavity, and a portion of the cannula over the body surface was fixed to the abdomen with gauze bandage and non-allergic plaster (Figure 2). After the procedure, 150-200 cc of isotonic fluid was instilled per hour into the uterine cavity. The mean total amount of amniotic fluid was estimated as 5 cm during monitoring. One week later, the CRP values increased to 5.52 mg/dL, which required consultation with a specialist in infectious diseases. No symptoms of chorioamnionitis were detected in the patient. The results of urine and blood culture analysis were not remarkable. Nevertheless, the antibiotherapy was changed, and meropenem therapy (3x1 g IV) (Mopem; Tüm Ekip İlaç, İstanbul, Turkey) was initiated. During follow-up, the CRP values decreased to normal, but the leakage of the amniotic fluid continued. However, owing to continuous amnioinfusion, the AFI did not drop below 5 cm as detected on US examination. At the 24th week of the pregnancy, 12 mg of betamethasone (Celestone; Schering Plough, İstanbul, Turkey) was injected intramuscularly at 12-hour intervals for foetal lung maturation. The patient complained of vaginal bleeding in the 25th gestational week. A physical examination revealed umbilical cord



Figure 1. Epidural catheter set used for the patient



Figure 2. Post-procedural fixation of epidural catheter on the anterior abdominal wall

prolapse, which necessitated an emergency caesarean section. Postoperatively, the mother was in stable health state, and she was discharged on the 4th postoperative day in full health. At one and five postnatal minutes, the Apgar scores of the infant were 5 and 6 points, respectively. The baby was immediately intubated, and 4 mL/kg of surfactant (Survanta; Abbott, North Chicago, USA) was administered through an endotracheal tube, with the diagnosis being respiratory distress. The newborn was connected to a mechanical ventilator. The neonate had a poor general status, weak spontaneous activity, and thin, bright and plethoric skin. The weight was 550 g (<3%), and the height and the head circumference were 27 cm (<3%) and 21 cm (<3%), respectively. The foetal heart rate was rhythmic, and no cardiac murmur was heard. The external appearance of the foetus was of female gender. Her haematocrit was 38%, which necessitated transfusion of an erythrocyte suspension at a rate of 15 mL/kg. Administration of dopamine (Dopmin amp; Orion, Espoo, Finland) and dobutamine (Dobcard; Vem İlaç, İstanbul Turkey) was initiated due to her deteriorated peripheral circulation. As the mother's membrane rupture was present for three weeks, empirical antibiotherapy was started after drawing blood samples for blood culture. The antibiotherapy was discontinued after the absence of any microbial growth on culture media was reported. Parenteral feeding was started on the first day and minimal enteral feeding on the second day. For the relief of symptomatic patent ductus arteriosus, ibuprofen was used. Respiratory support was provided with a mechanical ventilator for nine days and with a nasal continuous positive airway pressure for four days. An ophthalmologic examination detected Stage 1 retinopathy. On a follow-up visit, no progression of the disease was observed. On the contrary, it had regressed to Stage 0. A hearing test was unremarkable. The infant gained weight, and she was 2070 g at discharge on the 128th day. The infant is now six-months old and is fed with breast milk and fortified infant formula. On follow-up visits, her development was found to be in accordance with her gestational age.

Discussion

The current study discussed the use of a relatively cost-effective continuous amnioinfusion technique that can be applied for extended periods in a single session. The method can be used in patients with amniotic fluid loss occurring within less than six hours after undergoing amnioinfusion and an amniopatch who require subsequent repeat applications of these painful procedures and who exhibit foeto-maternal risks.

For the amniopatch application, platelets and cryoprecipitates are usually used because they have been found to be necessary components for a successful and safe therapy for PROM. Sipurzynski et al. (7) did not observe any side effects or complications during autologous platelet pheresis and application of the amniopatch. In cases of PROM occurring after an iatrogenic procedure, such as amniocentesis performed between the 16th and the 24th gestational weeks, the amniopatch is an appropriate procedure in the absence of intra-amniotic infection. An amniopatch was found to be successful in nearly 50% of such patients (4). In amniopatch application, platelets seem to

migrate to the site of the defect and occlude the defective site. Platelet activation and fibrin formation at the site of rupture initiate the healing process (8). However, after amniopatch application, the development of a fibrous band may cause constriction of an extremity or the umbilical cord. In the present case, the failure of the amniopatch application was probably related to a larger membrane defect.

Before 24 weeks of gestational age, PPROM has a predicted perinatal mortality of nearly 90% and amniotic infection is frequently seen. Perinatal outcomes of an iatrogenic PROM like amniocentesis are relatively worse when compared with spontaneous PROM. Repeated amniopatch or saline amnioinfusion techniques can be applied. However serial applications of this method are quite painful and carry important foeto-maternal risks (9, 10).

Tchirikov et al. (11) previously applied a method similar to that reported here. They used an amniotic fluid replacement port. Our system works in a similar way. There were some disadvantages with the system described by Tchirikov et al. (11). The catheter had to be detruncated and reconnected to a metal tube and then to the port capsule. Fluid leakage around the catheter was also detected. Additional disadvantages were important technical problems and the need for anaesthesia (11). Our application technique is independent of gestation weeks. Saline is infused in a method similar to that of Tchirikov et al. (11). The technique did not lead to fluid leakage in the presented case. Moreover, it does not require detailed technical information, and is relatively cost-effective. In addition, it does not necessitate additional procedures, such as skin incision.

Inflammation secondary to microbial invasion of the amniotic cavity is responsible for more than half of cases with preterm birth and PPROM (11). However, in cases with previable PPROM (<22-23 gestational weeks), termination of the pregnancy can be recommended because of poor prognosis secondary to infection and/or pulmonary hypoplasia (3). In the present study, no infection developed, although there was a slight increase in CRP. The infant remained connected to the mechanical ventilator for only nine days and continues to exhibit no pulmonary problems. Continuous intra-amniotic infusion of an isotonic saline solution may be able to protect the patient from the development of amniotic infection syndrome and pulmonary hypoplasia. An isotonic saline solution, which drains from the uterine cavity through the cervical canal, provides continuous irrigation. This might protect the foetus and the mother from ascending infections.

In conclusion, continuous amnioinfusion using an epidural catheter seems to be an appropriate treatment for PPROM in the second trimester of pregnancy. The aim of such treatment is to prevent cord compression secondary to anhydramnios and pulmonary hypoplasia and to enhance the survival potential of the foetus. The risk-benefit ratio and the expectations of the patient should be taken into consideration in the application of the method. Generally, the only wish of the mother is to embrace their baby.

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Informed Consent: Written informed consent was obtained from patients who participated in this study.

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Uterus didelphys with an obstructed unilateral vagina and ipsilateral renal agenesis: A rare cause of dysmenorrhoea

*Tek taraflı kapalı vajen ve aynı tarafta böbrek agenezili didelfik uterus:
dismenorenin nadir nedeni*

Rukset Attar, Gazi Yıldırım, Yücel Inan, Özge Kızılkale, Ateş Karateke

Department of Obstetrics and Gynecology, Yeditepe University Hospital, İstanbul, Turkey

Abstract

Didelphic uterus with obstructed hemivagina and ipsilateral renal agenesis is a rare condition. It usually presents with pelvic pain following the menarche, dysmenorrhoea, and an increase in abdominal volume or a palpable mass due to unilateral haematocolpos. We present the case of a 13-year-old girl who referred with recurrent pelvic pain, mainly at the time of menses, and irregular menstrual cycle complaints in this report. The patient underwent ultrasonography and magnetic resonance (MR) imaging of the pelvis was performed. The diagnosis was uterus didelphys with obstructed hemivagina and ipsilateral renal agenesis. Laparotomy was performed for diagnosis and treatment purposes. Two separated hemiuteri and two cervixes with hematometra and hematocolpos on the right side and ipsilateral renal agenesis were detected. The vaginal septum was excised completely and Strassman metroplasty was performed. Her complaints were resolved and she was absolutely asymptomatic after surgery. Diagnosis and management of this congenital anomaly is challenging due to the complexity of the anatomic structures, nonspecific complaints, and heterogenic presentation. These anomalies must always be considered while working-up female patients presenting with episodic abdominal pain and abdominopelvic mass.

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Key words: Uterus didelphys, vaginoplasty, metroplasty, Müllerian anomalies, renal agenesis

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Özet

Tek taraflı kapalı vajen ve aynı tarafta böbrek agenezisi ile birlikte didelfik uterus nadir görülen bir durumdur. Genellikle menarj sonrasında görülen pelvik ağrı, dismenore, kanın hacminde artış veya tek taraflı hematokolposa bağlı olarak ele gelen kitle şeklinde ortaya çıkar. Bu yazıda özellikle adet sırasında ortaya çıkan pelvik ağrı ve düzensiz adet kanaması şikayetleri ile başvuran 13 yaşındaki bir kız çocuğunun olgusunu sunduk. Hastaya pelvik ultrasonografi ve manyetik rezonans (MR) incelemesi yapıldı. Tek taraflı kapalı vajen ve aynı tarafta böbrek agenezisi ile birlikte didelfik uterus tanısı konuldu. Tanı ve tedavi amaçlı laparotomi yapıldı. İki ayrı hemiuterus, iki serviks ve sağ tarafta hematometra ve hematokolpos ile aynı tarafta böbrek agenezisi tesbit edildi. Vajinal septum tamamen çıkartıldı ve Strassmann metroplastisi yapıldı. Ameliyat sonrasında hastanın bütün şikayetleri geçti ve bulguları tamamen kayboldu. Anatomik yapılarıdaki farklılığa, şikayetlerin özgün olmamasına ve değişik şekillerde ortaya çıkmasına bağlı olarak bu konjenital anomalinin tanısı ve tedavisi güçtür. Dönemsel kan ağrısı ve abdominopelvik kitle ile başvuran bir kadında mutlaka bu bozuklukların da olabileceği düşünülmelidir.

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Anahtar kelimeler: Didelfik uterus, vaginoplasti, metroplasti, Müllerian anomaliler, böbrek agenezisi

Geliş Tarihi: 17 Nisan 2013

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Introduction

Müllerian duct anomalies consist of a set of structural malformations resulting from abnormal development of the paramesonephric or Müllerian ducts. The prevalence of these anomalies ranges from 0.001 to 10% in the general population and from 8-10% in women with an adverse reproductive history (1, 2).

A wide variety of malformations can occur when this system is disrupted. They range from uterine and vaginal agenesis to duplication of the uterus and vagina to minor uterine cavity abnormalities.

Uterine malformations result from a failure in organogenesis or from fusion or reabsorption of the Müllerian ducts.

Approximately 11% of uterine malformations are didelphys uterus (3). Didelphic uterus is associated with unilateral anomalies, i.e., obstructed hemivagina and ipsilateral renal agenesis in 15%-30% of cases, establishing a well-known symptomatic complex (hematocolpos, piocolpos, hematometra, hematosalpinx) that needs an in-depth diagnostic approach as well as surgical treatment with definite anatomic confirmation of the defect type and side (4). This manifestation has been referred to in the literature as the Herlyn-Werner-Wunderlich syndrome (HWWS) as well as the obstructed hemivagina and ipsilateral renal anomaly syndrome (OHVIRA) (5, 6). It is a rare condition and occurs as result of an embryologic arrest simultaneously affecting the Müllerian and metanephric ducts at about 8 weeks gestation.



Address for Correspondence: Rukset Attar, Department of Obstetrics and Gynecology, Yeditepe University Hospital, İstanbul, Turkey.
Phone: +90 537 840 19 00 e.mail: ruksetattar@hotmail.com

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Clinical presentations are variable, depending on the degree of obstruction and the existence of an opening. The most common presenting symptoms are the onset of dysmenorrhoea within the first years after menarche and progressive pelvic pain. Marked rectal pain and constipation secondary to haematocolpos impingement have also been reported as presenting symptoms (7).

In this report, we present a case of a 13-year-old girl who was referred with recurrent pelvic pain, mainly at the time of menses, and irregular menstrual cycles and was diagnosed with uterus didelphys associated with unilateral vagina obstructed by a transverse septum with ipsilateral renal agenesis.

Case Report

A 13-year-old girl presented with recurrent pelvic pain, mainly at the time of menses, and irregular menstrual cycles. The patient's menarche occurred at the age of 11 years. She complained of severe abdominal pain that occurred during each of her menses. An ultrasound examination revealed the existence of two distinct hemiuteruses. The left one was of normal length and the cavity was empty; the right one formed an angle of about 90 degrees with the contralateral and contained fluid in its cavity (haematometra). A cystic mass along the right lateral wall in the upper part of the vagina also was found (haematocolpos). Ultrasound examination of the abdomen confirmed the presence of a single left kidney. Magnetic resonance (MR) imaging of the pelvis was recommended and performed to enable further evaluation. Subsequent computed tomographic examination verified the gynaecologic findings of ultrasound examination and also revealed the accompanying anomalies of ipsilateral renal agenesis (Figure 1).

A diagnostic laparotomy was performed to evaluate the mass and its peripheral extensions with regard to the pelvic anatomy in detail. Laparotomic observation confirmed the diagnosis. We detected two separated hemiuteri and two cervixes with haematometra and haematocolpos on the right side and ipsilateral

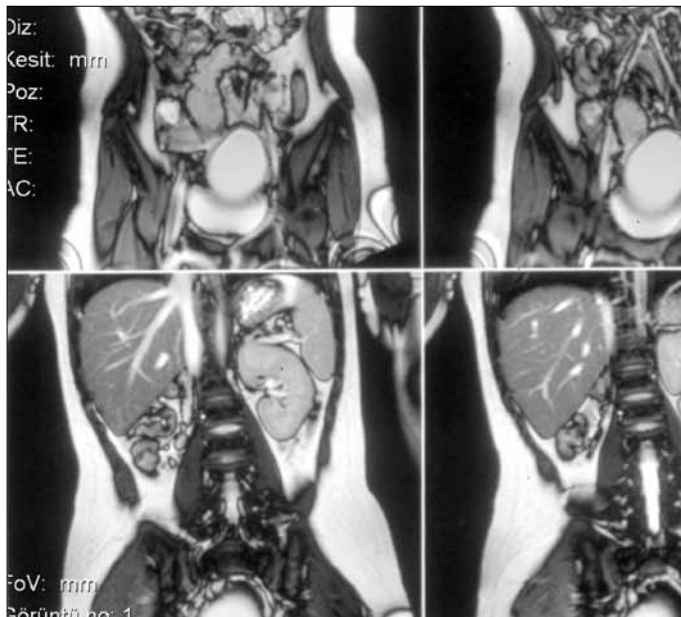


Figure 1. MR image

renal genesis (Figure 2). After an incision on the vaginal septum, a large amount of chocolate-coloured fluid was drained, and the dimensions of the right uterus were diminished after the procedure (Figure 3). Then, the vaginal septum was excised completely and the edges of the septum were marsupialised (Figure 4). As two hemiuteri were hypoplastic, we decided to perform metroplasty by Strassman's method (Figure 5). We made a wedge-shaped incision, deep enough to enter the endometrial cavity on the medial aspect of each uterine horn. The incision extended from the superior aspect of each horn, near the interstitial region of the fallopian tubes, to the inferior aspect of the uterus. Apposition of the opposing myometrium was achieved using interrupted vertical figure-8 sutures along the posterior and anterior uterine walls. The final layer was closed using continuous subserosal sutures, without exposing any suture material to the peritoneal cavity.

The patient was comfortable in the postoperative period. She was followed-up regularly, and she was completely asymptomatic after surgery.



Figure 2. Two distinct hemiuteruses



Figure 3. After an incision on the vaginal septum, a large amount of chocolate-colored fluid was drained

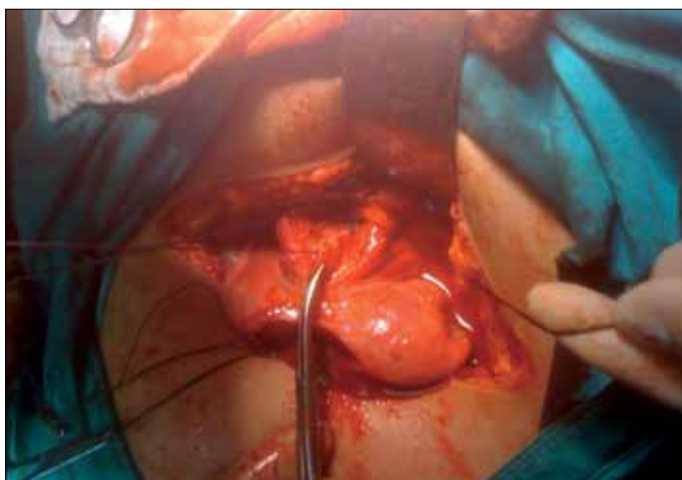


Figure 4. The vaginal septum was excised completely and the edges of the septum were marsupialized



Figure 5. Metroplasty by Strassman's method

Discussion

Congenital Müllerian defects are a fascinating clinical problem, the true incidence of which is hard to determine as most data are derived from studies of patients presenting with reproductive problems, and an accurate diagnosis and complete assessment of the uterine morphology has not always been performed. In many patients, uterine congenital anomalies have been related to infertility, recurrent pregnancy loss, prematurity and other obstetric complications. Although uterine malformations are common, complex malformations are rare. Complex malformations of the female genital tract are often incorrectly identified, treated and reported.

Failure of fusion of the Müllerian ducts can result in a uterine didelphys in some cases, and failure of canalisation or resorption in the uterovaginal canal or urogenital sinus can lead to a vaginal septum (8). OHVIRA is a variant of the broad spectrum of Müllerian anomalies that is being more frequently diagnosed and reported with increasing awareness and advances in radiological imaging.

Diagnosis of this syndrome is a challenge as the complaints are nonspecific and presentations are heterogenic. Patients with this syndrome are frequently asymptomatic, and are often missed in routine gynaecological examinations. A history of pelvic pain following the menarche, dysmenorrhoea and an increase in abdominal volume are complaints that are suggestive of uterine anomalies. Primary amenorrhoea and changes to menstrual flows may also be present (9). Usually, on examination, a unilateral pelvic mass is detected, with the right side affected nearly twice as frequently as the left side (10). Our case showed the right-sided involvement as well.

Ultrasonography, conventional and sonohysterosalpingography, magnetic resonance imaging and three-dimensional computed tomography angiography are useful tools for diagnosing complex Müllerian anomalies. However, haematocolpos frequently distorts the anatomy, leading to radiologic imaging of variable utility. Laparoscopy and laparotomy may be appropriate to aid in the definition of anatomy, and to treat the anomalies and concomitant conditions such as adhesions or endometriosis (11, 12).

Management of this complex congenital anomaly of the female reproductive tract requires careful anatomic consideration. Surgical reconstruction of the internal genitalia with restoration of menses and maintenance of a patent genital tract is challenging. Full excision and marsupialisation of the vaginal septum are the preferred surgical approaches for the treatment of uterine didelphys with obstructed unilateral vagina (13). This can be challenging as haematocolpos causes distortion of the adjacent anatomic structures and there is chronic inflammation. Also, the vagina of many adolescent girls is narrow. Definition of the anatomic structures in detail is a crucial step as sepsis and death have been reported in cervical agenesis cases where vaginoplasty was performed (14, 15).

In this case, we excised and marsupialised the vaginal septum to relieve the obstruction. Also, we performed Strassman metroplasty to preserve future fertility and to prevent obstetric complications such as preterm delivery and recurrent abortus as the size of the two hemiuteri were hypoplastic. Resection of the septum to the level of the cervix that is in close proximity to the uterine vascular supply is a technical challenge while operating on these patients as anatomic variation can lead to ectopic vasculature, especially in the case of asymmetric bicollic. Therefore, careful examination and imaging needs to be performed before surgery to avoid possible haemorrhage in a constricted difficult-to-visualise surgical fields.

In conclusion, a high index of suspicion is necessary to diagnose these disorders, and adequate work-up, careful exam and imaging, as well as careful surgical planning is essential in the management of these anomalies.

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Informed Consent: Informed consent was received from the participant of this case.

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A 34-week ovarian pregnancy: case report and review of the literature

34 haftalık over gebeliği; olgu sunumu ve literatür derlemesi

Elif Meşeci¹, Yılmaz Güzel², Ebru Zemheri³, Semra Kayataş Eser⁴, Şeyma Özkanlı³, Pınar Kumru⁴

¹Department of Obstetrics and Gynecology, Acıbadem Kozyatağı Hospital, İstanbul, Turkey

²Department of Obstetrics and Gynecology, Okmeydanı Education and Research Hospital, İstanbul, Turkey

³Department of Pathology, Göztepe Education and Training Hospital, Medeniyet University, İstanbul, Turkey

⁴Department of Obstetrics and Gynecology, Zeynep Kamil Education and Training Hospital, İstanbul, Turkey

Abstract

Advanced ovarian pregnancy is a quite rare condition. Due to the high maternal and neonatal mortality rates, early and accurate diagnosis is vital. Lack of sufficient data led us to search the literature and compile available data on the topic. A 33-year-old woman presented with acute abdomen at 34 weeks of gestation. She underwent laparotomy, which revealed a live foetus surrounded by an intact amnion membrane located in the left adnexal area. The patient delivered a live female infant. Heavy bleeding from the placenta necessitated salpingo oophorectomy. Histological examination of the removed tissue confirmed the ovarian pregnancy. Because of the substantial risk of adverse outcomes, this condition should be borne in mind, especially in cases presenting with acute abdomen during pregnancy.

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Key words: Abdominal pregnancy, ectopic pregnancy, ovarian pregnancy

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Özet

İkinci ve üçüncü trimester over gebeliği oldukça nadir bir durumdur. Yüksek maternal ve neonatal mortalite oranları nedeniyle erken ve doğru tanı konulması hayat kurtarıcıdır. Karşılaştığımız ender rastlanan olgu ve konu ile ilgili yeterli bilginin bulunmaması bizi ikinci ve üçüncü trimester over gebeliği hakkındaki literatürü irdelemeye yöneltti. Otuz üç yaşında kadın hasta, gebeliğin otuz dördüncü haftasında akut abdomen bulgularıyla kliniğimize başvurdu. Laparatomide sol adneksial alanda intakt amniotik membran ile çevrili, içinde canlı fetusun bulunduğu ekstrauterin gebelik tespit edildi. Canlı bir kız bebek doğurtuldu. Plasental alandaki şiddetli kanama nedeniyle salpingo oofektomi yapıldı. Histopatolojik sonuç over gebeliğiyle uyumlu bulundu. Özellikle ilk trimesterden sonra akut batın bulgularıyla başvuran hastalarda, ayırıcı tanıda over gebeliği akılda tutulmalıdır. (J Turkish-German Gynecol Assoc 2013; 14: 246-9)

Anahtar kelimeler: Abdominal gebelik, ektopik gebelik, over gebeliği

Geliş Tarihi: 06 Kasım 2012

Kabul Tarihi: 23 Ocak 2013

Çevrimiçi Yayın Tarihi: 10 Temmuz 2013

Introduction

Ovarian pregnancy is a specific type of non-tubal ectopic pregnancy, presenting with the same symptomatology. The condition is inherently problematic and challenging. First, it is very rare, which makes it hard to be taken into account during differential diagnosis. Second, reaching an accurate diagnosis is not easy and requires a series of exhaustive procedures ending with surgery in the majority of cases. In situations where routine antenatal follow-up cannot be done during the first and second trimester, the diagnosis of ovarian pregnancy is usually missed. Consequently, presumably a rather high, but unfortunately unknown percent of cases remain undiagnosed. These cases are classified under various other terms such as abdominal, rudimentary horn, cornual pregnancy etc. Third, maternal mortality and perinatal mortality rates are considered to be rather high, although there have

only been a few figures published specific to the condition due to the facts described above. As a consequence, the overall reflection of all these to our current literature is the scarcity of data on the subject.

Hence, early and accurate diagnosis is vital to prevent serious outcomes and to overcome severe complications. Here, we report a case with a live 34-week ovarian pregnancy occurring after spontaneous conception and presenting as an acute emergency. Based on our case, we carried out a literature search and evaluated the risk factors, incidence, symptoms, sonographic findings and management strategy of ovarian pregnancy.

Case Report

A 33-year-old woman gravida 3, para 1 presented to the emergency department with severe abdominal pain, nausea



and vomiting. The pregnant patient was of low socio-economic status and had not visited any obstetrician for prenatal care. Her past medical history included one ectopic pregnancy and one caesarean section with a healthy birth. There was no history of pelvic inflammatory disease, ovulatory induction or intra uterine device (IUD) use.

On physical examination, the abdomen revealed generalised tenderness to palpation in both lower quadrants with guarding and rebound. The foetus was found to be lying in oblique position. Pelvic examination showed a retroverted cervix without dilatation. Her blood pressure was 96/55 mmHg, with a heart rate of 100 bpm. Her complete blood cell count showed a low haemoglobin level of 9.3 g/dL, a slightly elevated white blood cell count of $13.8 \times 10^3/\mu\text{L}$, and a normal platelet count.

The patient was immediately taken for ultrasonographic examination and a 34-week old pregnancy in the abdominal cavity was noted away from the uterus. The patient underwent a laparotomy, which revealed a live foetus surrounded by an intact amnion membrane located in the left adnexal area next to the uterus. The uterus was larger than the normal size, the right ovary and tuba were normal in appearance and there was about 500 mL of haemoperitoneum in the abdominal cavity.

The patient delivered a girl weighing 1920 gr. The newborn's Apgar scores were 4 and 6 at one and five minutes, respectively. She was in the 25-50th percentile, and was intubated immediately after delivery. The baby developed respiratory distress despite the administration of endotracheal surfactant and was followed in intensive care.

The placenta was adherent to the left ovary, uterus, left abdominal sidewall and omentum. The left tuba was elongated, the left ovary was large and oedematous and bleeding was seen in some areas. There was significant bleeding from detached portions of the placenta and the attached ovary, and we had to remove the placenta via salpingo oophorectomy in order to provide haemostasis. The patient was transfused with two units of blood during the operation and she was taken to the recovery room in a stable condition. The postoperative period was uneventful; she was discharged on the 5th postoperative day. The newborn died on the 4th day in the intensive care unit because of respiratory insufficiency and no other congenital malformation was found on autopsy except for pulmonary hypoplasia. Histological examination of the removed tissue confirmed the ovarian pregnancy.

Discussion

The present case is a rare example of an advanced ovarian pregnancy occurring after spontaneous conception.

Although the focus of this review is ovarian pregnancy, some of the figures given below are related to other types of abdominal pregnancies. Due to the scarcity of data specific to ovarian pregnancy, and because all different types present with same symptoms and require the same treatment approach, we believe that these figures could be of help in reaching an overall impression on ovarian pregnancy also.

Ectopic pregnancy represents about 1-2% of all pregnancies with 95% occurring in the fallopian tube. Abdominal preg-

nancies represent just 1% of ectopic pregnancies; ovarian pregnancy accounts for 0.5-3% of all ectopic pregnancies. The overall incidence ranges from 1 in 2100 to 1 in 7000 pregnancies (1-3). To the best of our knowledge, only 11 cases of advanced ovarian pregnancy have been previously reported based on a literature search carried out on PUBMED for the period from 1948 to 2013 (4-14).

The pathogenic mechanism is thought to be fertilisation occurring outside the tube, followed by implantation within the ovary or the failure of follicular extrusion (15, 16). Due to the extreme rarity of ovarian pregnancy, the risk factors are not as well established as in tubal pregnancy. Possible risk factors in the literature include previous ectopic pregnancy, pelvic inflammatory disease, IUD use, endometriosis, previous abdominal surgery, uterine anomalies and assisted reproductive techniques (ART) (15-19).

In a series of 49 cases where ovarian pregnancy was confirmed, the most common risk factors were found to be previous abdominal surgery for 19 cases and endometriosis for 16 cases. Four patients had a history of pelvic inflammatory disease, and only 2 patients had used an IUD. Huge uterine myoma was found in 2 cases, bicornuate uterus was found in 1 case, and arcuate uterus was found in 1 case (20). Our patient had ectopic pregnancy and caesarean section as risk factors. According to the above-mentioned study the most common complaints are abdominal pain (42.9%) and vaginal bleeding (28.6%) (20). The pain is generally nonspecific during early gestation and becomes worse as the pregnancy advances, sometimes culminating in cases of acute abdomen due to rupture of the gestational sac and placental disruption, resulting in haemoperitoneum. In the same study, interestingly, five asymptomatic patients were incidentally discovered to have an ovarian pregnancy during post-*in vitro* fertilisation (IVF) monitoring. The relation with ART was later supported by Ngu et al. (21), who reported that 28.5% of ovarian pregnancies were associated with IVF, indicating the high risk of ovarian pregnancy among women who undergo ART.

The diagnosis of advanced ovarian pregnancy is very challenging. History and physical examination are inconclusive. It is easier to reach a diagnosis during the first trimester using high resolution transvaginal ultrasound, making quantitative measurements of b-human chorionic gonadotropin (HCG) levels and performing laparoscopy; hence, an early diagnosis of an ovarian pregnancy is proposed to be more feasible, as Dr. Huang also concluded in his case report (4). However, as the pregnancy grows, without any suspicion and meticulous examination, a diagnosis of advanced ovarian pregnancy probably can be missed easily. Some authors even argue that ovarian pregnancy is unlikely to be diagnosed preoperatively due to its rarity, a lack of typical presenting symptoms, and a lack of known risk factors (20).

Ultrasonography is the most often used non-invasive diagnostic imaging method in pregnancy. Echographic evidence of a non-gravid uterus alongside a foetus is diagnostic in extrauterine pregnancy. Actually, a preoperative diagnosis of advanced abdominal pregnancy is usually missed, with only 45% of cases being diagnosed preoperatively (22). Observing the entire uter-

ine wall encapsulating the pregnancy and placenta confirms the intrauterine pregnancy. If ultrasonography shows no uterine wall surrounding the foetus, and if foetal parts are very close to the abdominal wall, then the suspected diagnosis would be extrauterine pregnancy. The possibility of extrauterine pregnancy should be strongly suspected, especially in cases of bleeding or non-labour abdominal pain during the third trimester. In addition to these, painful foetal movements, abnormal foetal lie, foetal demise, abdominal mass palpated apart from the foetus, an unusual echographic appearance of placenta, oligohydramnios, the presence of maternal intraperitoneal fluid, and induction failure are all suggestive of abdominal pregnancy; however, neither is accepted to be pathognomonic for ovarian pregnancy (22, 23). Laparotomy findings being at hand, the diagnosis of ovarian pregnancy needs to be confirmed through histopathological work up. Histopathological diagnosis is based upon the worldwide accepted criteria proposed by Spiegelberg, which are as follows: fallopian tubes including fimbria must be intact and separate from the ovary; the pregnancy must occupy the normal position of the ovary; the ovary must be attached to the uterus through the utero-ovarian ligament and there must be ovarian tissue attached to the pregnancy in the specimen. In our case, the final histopathological diagnosis was based on the Spiegelberg criteria (Figure 1).

Once the diagnosis is made, the subsequent steps also continue to be challenging with advanced ovarian/abdominal pregnancy. No absolute consensus exists with regard to the management of abdominal pregnancies. In view of the high maternal mortality and foetal mortality and morbidity, progressive oligohydramnios, a high incidence of malformations, and foetal growth restriction due to placental insufficiency, the majority of investigators agree that abdominal pregnancy should be terminated as soon as it is diagnosed and that the procedure should include complete removal of the foetus and placenta. On the other hand, there are numerous reports of advanced extrauterine pregnancies ending with a viable foetus and a healthy mother. Since the diagnosis is frequently missed preoperatively and adverse foetal and maternal outcomes do not necessarily

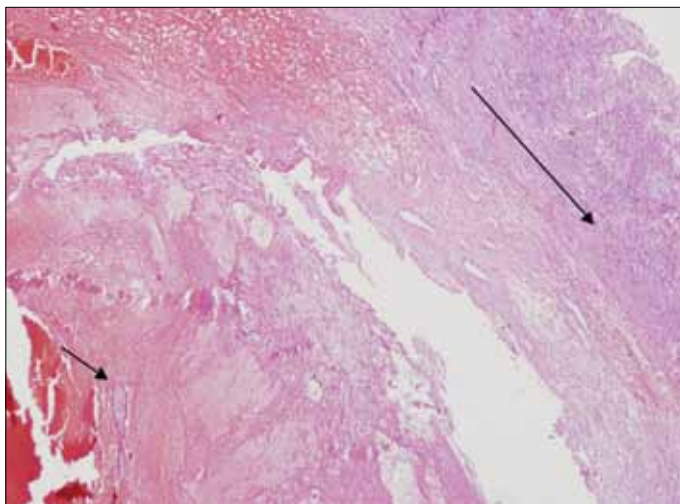


Figure 1. Haemorrhage and chorion villus (*small arrow*) within ovarian stroma (*large arrow*) (H&Ex20)

occur in association with the continuation of pregnancy, one could argue that the termination of an advanced extrauterine pregnancy upon antenatal diagnosis might not be warranted. However, these cases should be followed-up very carefully in order to prevent adverse outcomes (24).

In fact, advanced ovarian pregnancy is diagnosed upon laparotomy in the majority of the cases. The most life-threatening complication of operation is bleeding from the implantation site of the placenta. The most controversial issue in advanced ovarian/abdominal pregnancy during laparotomy is whether or not to remove the placenta. Blood supply to the abnormally implanted placenta is diffuse and the origin is often unidentifiable; consequently, attempts to remove the placenta can provoke bleeding. A placenta left *in situ* might be resorbed spontaneously, but if it does not, the risk of infection, necrosis, and the need for a second surgery is considerable. Most authors agree that the placenta should be removed provided its blood supply is identified and can be ligated without damaging other organs (22). In cases where placental implantation has occurred in vascular areas such as the mesentery and vital organs, it has been recommended that the placenta should be left *in situ*, as surgical excision can result in uncontrollable and life-threatening haemorrhage. If the blood supply cannot be identified, the placenta should be left in place and the patient should be followed-up for paralytic ileus, peritonitis, sepsis, or the formation of abscesses and pre-eclampsia (25). Methotrexate treatment has been proven to be of little value in cases of advanced abdominal pregnancies. When destruction occurs too quickly upon methotrexate treatment, the risk of sepsis and death ensues due to the formation of large amounts of necrotic tissue. This might be avoided by using methotrexate judiciously with the administration of lower doses with less frequent intervals; thereby allowing the slow resorption of the placenta left in the abdominal cavity (26). In the present case, emergency laparotomy was performed because of acute abdomen. The foetus was delivered, and the placenta had to be removed via salpingo-oophorectomy due to heavy bleeding. For the newborn, it is important to rule out congenital malformations. Foetal malformations associated with advanced abdominal pregnancy are as high as 40% and only 50% of these babies survive up to one week post-delivery (23, 27). Pulmonary hypoplasia, pressure deformities, and foetal growth restriction due to placental insufficiency are the most eminent causes leading to neonatal complications. Typical deformities include limb defects, facial and cranial asymmetry, joint abnormalities and central nervous malformation (28). These pregnancies usually do not extend to 37 weeks and usually end up with foetal loss (29). In our case, the newborn died of severe respiratory insufficiency, and pulmonary hypoplasia was found on autopsy. Our case presented as acute abdomen. All of the subsequent procedures were performed under emergency conditions and we were not able to take any ultrasound or intraoperative pictures. This is a weak point of our study.

The diagnosis of advanced ovarian pregnancy is difficult, and treatment is based on surgical approaches. This review describes a very rare case of advanced ovarian pregnancy in a patient with intra-abdominal haemorrhage and acute abdomen

resulting in a live birth, together with a literature review of the topic. In patients with advanced gestational age and abnormal foetus lie, it is important to bear in mind that this may be an abdominal/ovarian pregnancy and the surgeon should be prepared to face various complications during the surgery, such as massive haemorrhage, disseminated intravascular coagulation, pulmonary oedema, bowel perforation, and sepsis. Considerable adverse outcomes are also relevant for the newborn baby. Therefore, the aim of this review was for clinicians to consider abdominal ovarian pregnancy as a differential diagnosis and prepare to manage the patient with a multidisciplinary surgical team, along with the assurance of sufficient blood, and the presence of a newborn intensive care unit; these factors would reduce the high maternal and neonatal mortality rate.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Actbadem University.

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author contributions: Concept – Y.G., E.M., E.Z.; Design – E.M., S.K.E., P.K.; Supervision – E.M., S.K.E., P.K.; Resource – E.Z., Ş.Ö., S.K.E.; Materials – E.Z., Ş.Ö., S.K.E.; Data Collection&/or Processing – E.M., E.Z., S.K.E.; Analysis&/or Interpretation – Y.G., Ş.Ö., P.K.; Literature Search – E.M., E.Z., S.K.E.; Writing – E.M., Ş.Ö., P.K.; Critical Reviews - Y.G., E.M., S.K.E.

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What is your diagnosis?

A 30 year-old female was referred to our hospital with a painless mass of the right inguinal area. The swelling was initially small but gradually increased in size over a period of 10 months. There was no history of trauma, gynaecological problems or previous surgery. On physical examination, a 7x6 cm, rounded, mobile, irreducible swelling was detected superficially in the inguinal area. The volume of this mass increased in standing position, and could be slightly reduced by manual compression. There was no pain on palpation and cough impulse was absent. Sonography was carried out with the patient in prone position. The mass was a



Figure 1. Ultrasonographic appearance of cyst

comma-shaped cyst with a tail directed cranially toward the inguinal canal, measuring 6.4x4.8 cm (Figure 1). There was no vascularity seen in the wall of the cyst on colour Doppler examination. Coronal and axial MR showed a thin walled cystic mass (Figure 2). Considering the clinical symptoms and examination findings, the patient underwent surgical exploration through a lower groin incision. Surgical exploration confirmed the cystic lesion with the patent, fluid-filled canal and the round ligament with a cystic mass was excised (Figure 3). What is your diagnosis?



Figure 3. Intraoperative appearance of cyst

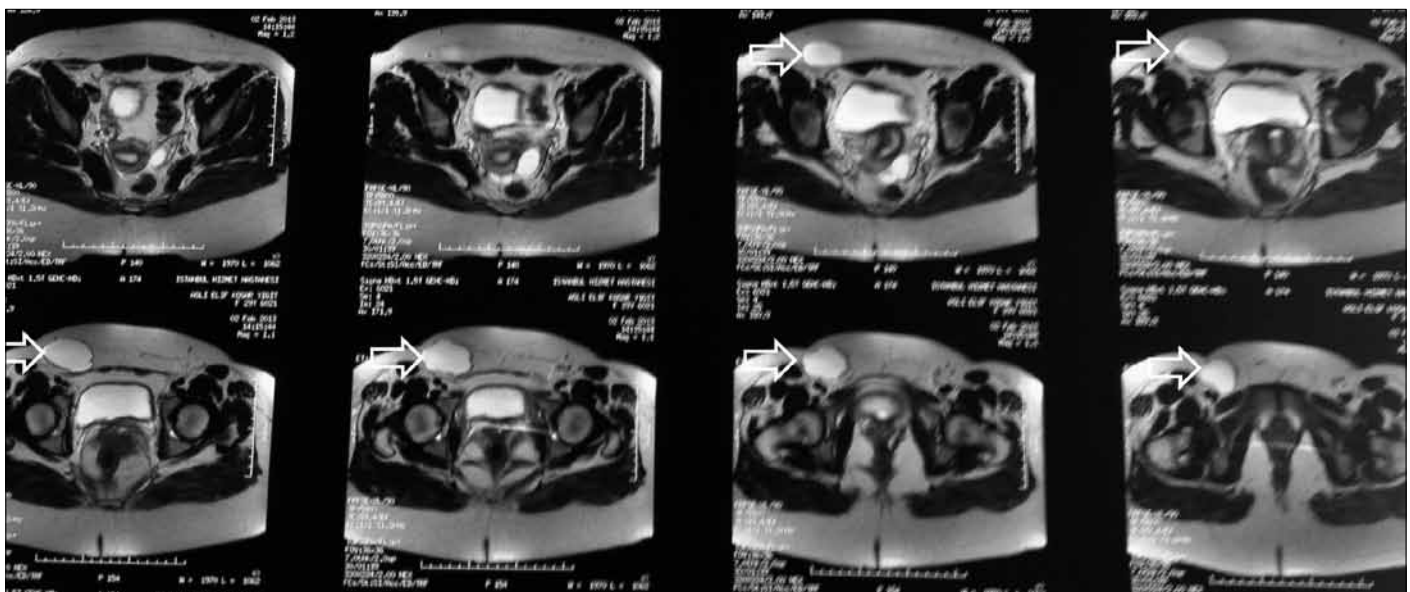


Figure 2. MR appearance of cyst



Answer

Pathologic findings were consistent with a hydrocele of the canal of Nuck. In females, evagination of the parietal peritoneum along with the round ligament through the inguinal ring into the inguinal canal forms the canal of Nuck by 6 months of gestation; this is the female counterpart of processus vaginalis in males (1). Complete obliteration of the canal of Nuck usually occurs by the first year of life (2). If obliteration fails in the distal portion of the canal, a sac containing serous fluid remains, which is the so-called hydrocele of canal of Nuck (3). Hydrocele of the canal of Nuck is a rare condition. Clinically, the hydrocele of the canal of Nuck manifests as a painless swelling in the inguinal area and labium majus. The differential diagnosis for inguinal masses in young adult females includes inguinal hernia, lymphadenopathy, Bartholin's cyst and malignant or benign tumours. In this case, diagnosis was clinical and confirmed with ultrasound and MR. Ultrasound is an easy and accurate preoperative diagnostic procedure; a tubular or oval anechoic lesion in the inguinal area or labium majus is observed (4). MR gives a much more precise image and the hydrocele appears as a simple cyst characterised as hypointense on T1-weighted images and hyperintense on T2-weighted images (5).

The treatment choice is surgical excision; the hydrocele in this case was excised through a lower groin incision. In some

cases, laparoscopic closure of a patent canal of Nuck has been reported (6).

In conclusion, the cyst of the canal of Nuck is a rare developmental disorder, but should be taken into consideration in the differential diagnosis of groin tumours in female patients. Ultrasonography and MR are the imaging modalities of choice for evaluating a cyst of the canal of Nuck.

Cenk Yaşa, Özlem Dural, Ercan Baştu, Aslı Nehir, Samet Topuz
Department of Gynecology and Obstetrics, İstanbul Medical School, İstanbul University, İstanbul, Turkey

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Kaymak ve arkadaşlarının görüntülü sorusu üzerine yazışma

Dear Editor,

We read the paper by Kaymak et al. published in the latest issue of your journal with great interest (1). In this paper, the authors have discussed the benefit of fetal magnetic resonance imaging (MRI) in the differential diagnosis of fluid filled structures over the calvarium. In the first step of evaluation they used 2D transabdominal ultrasonography and detected a cystic mass over the posterior fontanelle. They supposed it to be an encephalocele, until the results of fetal cranial MRI was available. MRI revealed it as a subcutaneous cystic mass with an intact skull.

Meanwhile, we wish to highlight some details regarding the prenatal diagnosis of cephalocele and its differential diagnosis. Cephalocele is the general name of any calvarial defect containing a pouch of cerebrospinal fluid, whether or not it contains the brain tissue. Types of cephaloceles are cranial or occipital meningocele (only dura with cerebrospinal fluid), encephalocele (small amount of neural tissue and cerebrospinal fluid in the dura), encephalomeningocele (cerebrospinal fluid and complete brain without lateral ventricle) and encephalomeningocystocele (whole content of brain including the lateral ventricle in the protruding mass) (2).

Although a cephalocele can be located anywhere in the calvarium, the posterior part of the cranium is frequently involved. The diagnosis requires the demonstration of the bony defect. Unclosed sutures or fontanelles may mimic the defect. Additionally, intracranial anatomy is always distorted except in a small meningocele. Intracranial reflections of encephalocele include ventriculomegaly, frontal bossing and obliteration of the cisterna magna. The differential diagnosis of a meningocele with small osseous defect from the soft tissue masses of skin or subcutaneous tissue may be difficult. The details of sonographic differentiations of these soft tissue lesions from a meningocele of small calvarial defect were clearly stated (2). Observing a normal intracranial anatomy with an intact cranium is strong evidence of non-calvarial pathologies. Neurosonography (multiplanar examination of the fetal head by an experienced operator, using a transabdominal and/or transvaginal transducer) may help to make a proper evaluation of intracranial anatomy (3).

Regarding the information given above, the lesion depicted in picture 1 did not have a neural content and it should

be classified as a “meningocele”, if it is really a neural tube defect. This picture also fails to demonstrate the bony defect. There is no doubt of the value of information provided by fetal MRI, but it is always essential to keep in mind the obstacles involved: such as the cost, availability and necessity of qualified personnel in fetal imaging. We propose to make a neurosonogram with proper image magnification, beam direction and appropriate settings of ultrasound before selecting fetal MRI.

Selim Büyükkurt, Cihan Çetin

Department of Obstetrics and Gynecology, Çukurova University School of Medicine, Adana, Turkey

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Author’s Response

We thank the authors for their interest and comments on our paper. The authors have highlighted some details regarding terminology and sonographical diagnosis of cephalocele. They also have commented on obstacles regarding the use of fetal MRI for diagnosis. We totally agree with our colleagues who have proposed making a proper neurosonogram prior to fetal MRI. It is undoubtedly true that MRI should not be used as an initial assesment tool before complete ultrasonographic examination of the fetal neural axis, which is conveniently performed with transvaginal transducers between 5 and 10 MHz (1). For reasons also stated by our colleagues, the use of fetal MRI to compensate for inadequate fetal neural imaging is unacceptable (2). However due to technical limitations inherent to sonographic instrumentation as well as lack of knowledge about the exact time of development of sonographically



detectable indirect intracranial signs (such as ventriculomegaly); definitive diagnosis of certain CNS pathologies cannot be always possible (3). As stated by our colleagues a meningocele of the cranial vault with a small bony defect is one example (4). Moreover, when a provisional diagnosis of cephalocele without evident bony defect is made at an earlier gestational age, sonographically detectable ventriculomegaly and frontal bossing may appear later. Under such circumstances, reassurance of both physician and patient by fetal MRI may be suitable. Once again we are grateful to our colleagues for their contribution and for the opportunity to address their concerns. The aim of this study was to define a condition in which fetal MRI may be additive to fetal neurosonography. This is now more evident combined with the contributions of our colleagues.

Oktay Kaymak

High Risk Pregnancy Unit, Dr. Zekai Tahir Burak Training and Research Hospital, Ankara, Turkey

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Acknowledgements for the Year 2013

Experts contributed at the review process in 2013 (alphabetical order)

On behalf of the office staff and the editorial board of the Journal of the *Turkish-German Gynecological Association (JTGGGA)*, we would like to extend our thanks to all of our reviewers of the past year for their outstanding contributions. We continue to see an increase in the number of submissions to JTGGGA as well as the quality. JTGGGA is clearly becoming the journal of choice for obstetrics and gynecology healthcare issues in our region. Recently our journal has been accepted for inclusion in Pubmed Central too. We can afford to be somewhat more selective, and our acceptance rate is 50.1% in 2013 and approaches that of other major medical journals. The reviews submitted by you are among the best that we have seen among a number of major medical journals. The office regularly receives letters from authors thanking JTGGGA

for such thorough and helpful reviews, which enables them to produce much better manuscripts.

That fulfills one of our primary missions of teaching authors, especially young authors, how to write better manuscripts.

We have several new and exciting programs under review for implementation during the coming year, and we certainly look forward to your ongoing support, suggestions and recommendations as to how to continue to improve the overall quality of JTGGGA.

To become a JTGGGA peer reviewer, please contact the Editor Cihat UNLU, Prof., M.D., cunlu@ada.net.tr and provide your full contact information and areas of interest

Best regards.

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Saved	0	0	0	0	0	0	0	0	0	0	0	0	0	12	12
Waiting for Secretary	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
At Editor	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
On Review	0	0	0	0	0	0	0	0	0	0	0	0	0	8	8
Reviewed	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1
Minor Revision	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1
Major Revision	0	0	0	0	0	0	0	0	0	0	0	0	0	3	3
Rewriting Needed	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1
Waiting for Final Decision	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Accepted	0	0	0	0	0	0	0	0	0	0	0	0	0	34	34
Rejected	0	0	0	0	0	20	53	61	69	64	73	56	64	78	538
Refused	0	0	0	0	0	0	4	2	10	26	16	8	21	13	100
Withdrawn	0	0	0	0	0	0	12	35	8	5	8	5	21	16	110
Published	15	9	11	46	51	80	73	79	84	48	81	63	64	43	747
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- 5-6 December 2013 **5th Annual Meeting on Laparoscopic, Robotic & Vaginal Hysterectomy with Comprehensive Hands-on Workshop on Laparoscopic Suturing & Knot-Tying with Simulation**
New York, USA
www.aagl.org/event/36/
- 20-23 February 2014 **9th International Congress on Cardiac Problems in Pregnancy**
Venice, Italy
www.cppcongress.com
- 5-8 March 2014 **16th World Congress of Gynecological Endocrinology**
Florence, Italy
www.isge2014.isgesociety.com
- 30 April – 3 May 2014 **XII World Congress on Endometriosis**
Sao Paulo, Brazil
www.endometriosis.ca/world-congress/wce2014
- 7-10 May 2014 **23rd European Congress of Obstetrics and Gynaecology**
Glasgow, Scotland
www.ebcog2014.org
- 9-11 May 2014 **10th Biennial Conference of ALPHA, Scientists in Reproductive Medicine**
Antalya, Turkey
www.alphaconference2014.org
- 26-30 May 2014 **15th World Congress of Cervical Pathology and Colposcopy – IFCPC**
London, UK
www.ifcpc2014.com
- 28-31 May 2014 **13th Congress of the European Society of Contraception and Reproductive Health**
Lisbon, Portugal
www.esrh.eu/events/esc-events/2014

NATIONAL MEETINGS

- 5-6 December 2013 **8th National Menopause Osteoporosis Congress**
İstanbul, Turkey
www.turkiyemenopozosteoporoz.org
- 18-19 January 2014 **Deep Infiltrating Endometriosis Symposium**
İstanbul, Turkey
www.endometriozis2014.org
- 23-26 January 2014 **5th Minimally Invasive Gynecology Symposium**
Bursa, Turkey
www.uludagendoskopisi.org
- 27 February 2014-1 March 2014 **4th Gynecology Days of İstanbul University**
İstanbul, Turkey
www.istanbulkadindogumgunleri.org
- 20-22 March 2014 **6th Egean Gynaecologic Endoscopy Symposium**
İzmir, Turkey
www.egelaparoskopi2014.org
- 30 April – 4 May 2014 **10th Turkish-German Gynecology Congress**
Antalya, Turkey
www.tajev2014.org
www.tajev.org
- 12-19 May 2014 **12th National Gynecology and Obstetrics Congress**
Antalya, Turkey
www.tjod2014.org

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Questions on the article within the scope of CME/CPD

1. Uterine peristalsism is defined as;
 - a) the tonic contractions during labor
 - b) the focal and sporadic bulging of the myometrium
 - c) the rhythmic, 'wave-like' contractions
 - d) the resting tone of myometrium
 - e) excitation-contraction coupling
2. Which one of the followings predominantly regulates contraction of uterine myocytes?
 - a) Extracellular chloride concentration
 - b) Intracellular calcium concentration
 - c) Intracellular sodium concentration
 - d) Extracellular potassium concentration
 - e) Intracellular bicarbonate concentration
3. Which of the followings is not involved in mechanisms of contraction of the myometrium?
 - a) Activation of calmodulin (CaM)
 - b) Formation of Ca^{+2} -CaM complex
 - c) Activation of myosin light chain kinase
 - d) Dephosphorylation of myosin regulatory light chain-20
 - e) Actin-myosin cross-bridging
4. Stimulation of myometrium with an agonist such as oxytocin may result in a stronger than expected force of contraction, this physiological phenomenon known as;
 - a) Excitation contraction coupling
 - b) Summation of contractions
 - c) Rhythmic contractions of the myometrium
 - d) Ca^{+2} -induced Ca^{+2} release
 - e) Ca^{+2} sensitization
5. Which of the followings is/are involved in reducing the intracellular calcium concentration in myocytes?
 - I) Ca^{+2} -ATP'ase mediated efflux
 - II) Na^{+} - Ca^{+2} exchanger mediated efflux
 - III) Closure of L-type calcium channels
 - IV) Ca^{+2} -induced Ca^{+2} release
 - a) Only I
 - b) I and II
 - c) II and IV
 - d) I, II and III
 - e) I, II, III and IV
6. Which of the followings IS NOT related to the relaxation of myometrium?
 - a) Inhibition of myosin light chain phosphatase
 - b) Phosphorylation of myosin light chain kinase
 - c) Ca^{+2} desensitization
 - d) Nitric oxide-cGMP pathway
 - e) Gs-coupled receptor activation

JTGGA CME/CPD CREDITING



Answer form for the articles within the scope of CME/CPD

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