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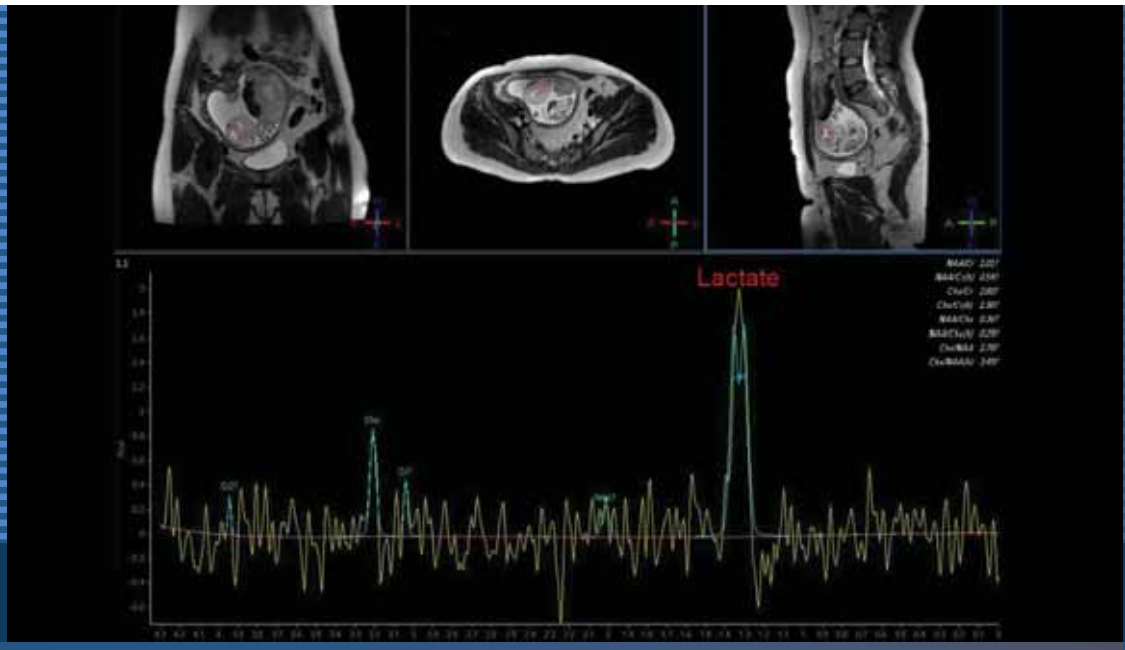

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Aims and Scope

Journal of the Turkish-German Gynecological Association is an official journal of the Turkish-German Gynecological Education and Research Foundation, Turkish-German Gynecological Association and the Turkish Society of Reproductive Medicine and is published quarterly on March, June, September and November.

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.

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State concisely the purpose and rationale for the study and cite only the most pertinent references as background.

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Describe the plan, the patients, experimental animals, material and controls, the methods and procedures utilized, and the statistical method(s) employed. Address "Institutional Review Board" issues as stated above. State the generic names of the drugs with the name and country of the manufactures.

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Present the detailed findings supported with statistical methods. Figures and tables should supplement, not duplicate the text; presentation of data in either one or the other will suffice. Emphasize only your important observations; do not compare your observations with those of others. Such comparisons and comments are reserved for the discussion section.

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Contents

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Editorial

Dear Colleagues,

It is my great pleasure to introduce you to the first issue of the Journal of the Turkish - German Gynecological Association (JTGGA) of 2011. Many interesting articles from different countries have been collected for this issue of our journal.

This issue has a significant importance because it is being published before our traditional Turkish - German Gynecology Congress. Our IX. Congress, which has scored a number of "firsts", is held biennially and stimulates great interest in the National and International Gynecology & Obstetrics community. On May 4th, our congress will begin with the pre-congress courses and hands-on training sessions in different interests. The courses on Colposcopy, Ovulation Induction, Perinatology, Robotic Surgery, Urogynecology and Ultrasound (in collaboration with the International Society of Ultrasound in Obstetrics and Gynecology - ISUOG) are designed to address the expectations of the participants. **Prof. Camran Nezhat**, the honorary president of our IX. Congress will present his opening conference before the opening reception on that day.

Throughout the congress, more than 200 distinguished Turkish and international experts will share their experiences in their field of expertise. The major topics of interest in our congress will be perinatology, oncology, infertility, laparoscopy, embryology, robotic surgery, obstetrics and gynecology. The scientific program is supported by the discussions at the end of the sessions, which enable participants to see the different viewpoints of experts on a specific topic. Some national and international establishments, such as NOGGO, Turkish Society of Menopause & Osteoporosis and Bourn Hall Clinic, will also take part and collaborate in some sessions with our foundation.

More than 300 abstracts have been collected for poster and oral presentations and the best three abstracts will be selected by the scientific secretariat of the congress and financially awarded, in order to encourage young researchers. Satellite symposiums and a 'meet the expert' meeting will also be involved in the scientific program of our congress. We, as the scientific committee of the congress, always place great emphasis on the variety of educational and scientific activities, which makes our congress unique in our field.

I would also like to thank the private sector professionals for their support and collaboration for our congress and the journal. In the current economical situation, their support is crucial for us to continue our scientific projects and congresses.

We look forward to seeing you in Antalya in the Spring of 2011 at the IX. Turkish - German Gynecology Congress and wish you much success in your studies.

Kind regards,

Prof. Dr. Cihat Ünlü
Editor in Chief of the JTGGA
President of TAJEV

Are pregnancy complications increased in poor responders?

Ovaryen stimulasyona kötü yanıt veren hastalarda gebelik komplikasyonları artmış mıdır?

Huriye Ayşe Parlakgümüş, Bülent Haydardedeoğlu, Erhan Şimşek, Tayfun Çok, Cem Yalçınkaya, Cantekin İskender, Esra Bulgan Kılıçdağ

Department of Obstetrics and Gynecology, School of Medicine, Baskent University, Ankara, Turkey

Abstract

Objective: To investigate whether pregnancy complications are increased in poor responders to ovarian stimulation in IVF treatment.

Material and Methods: We reviewed the antenatal follow up and birth records of 26 poor responders to ovarian stimulation and 125 normoresponder patients in an IVF program.

Results: Eighty nine (71.2%) of the normoresponders and 22 (84.6%) of the poor responders had no pregnancy complications. Gestational diabetes was present in 18 (14.4%) of the normoresponders and 3 (11.5%) of the poor responders. Seven of the normoresponders had placenta previa (5.6%). Two of the normoresponders (1.6%) had pregnancy induced hypertension. Two (1.6%) of the normoresponders had preeclampsia. One patient from each group had fetal anomaly (3.8% for poor responders vs. 0.8% for normoresponders). Cholestasis of pregnancy was present in two of the normoresponders (1.6%) and the 2 patients (7.7%) who delivered prematurely also belonged to this group.

Conclusion: Our results revealed that pregnancy complications were not increased in patients with a reduced ovarian reserve when compared to their age matched counterparts.

(J Turkish-German Gynecol Assoc 2011; 12: 1-3)

Key words: Pregnancy complications, poor ovarian reserve, IVF, poor response

Received: 13 August, 2010 **Accepted:** 22 November, 2010

Özet

Amaç: IVF tedavisinde ovaryen stimülasyona kötü yanı veren hastalarda gebelik komplikasyonlarının artıp artmadığını incelemek.

Gereç ve Yöntemler: IVF tedavisinde ovaryen stimülasyona kötü yanıt veren 26 hastanın ve iyi yanıt veren 125 hastanın antenatal izlem ve doğum kayıtları retrospektif olarak incelendi.

Bulgular: İyi yanıt veren hastaların 89'unda (%71.2) ve kötü yanıt veren hastaların 22'sinde (%84.6) herhangi bir gebelik komplikasyonu olmadı. İyi yanıt verenlerin 18'inde (%14.4) ve kötü yanıt verenlerin 3'ünde (%11.5)gestasyonel diyabet vardı. İyi yanıt veren hastaların 7'sinde (%5.6) plasenta previa, 2'sinde (%1.6) gebeliğe bağlı hipertansiyon, 2'sinde(%1.6) preeklampsi vardı. Her gruptan birer hastada fetal anomali mevcuttu (Kötü yanıt veren grupta %3.8, iyi yanıt veren grupta %0.8). İyi vanıt veren gruptaki hastaların 2'sinde (%1.6) gebelik kolastazı vardı ve erken doğum yapan 2 hasta (%7.7) da bu grupta bulunuyordu.

Sonuç: Bu çalışmanın sonuçlarına göre yaşıtlarına kıyasla kötü over rezervi olan hastalarda gebelik komplikasyonları artmamıştır.

(J Turkish-German Gynecol Assoc 2011; 12: 1-3)

Anahtar kelimeler: Gebelik komplikasyonları, kötü over rezervi, IVF, kötü yanıt

Geliş Tarihi: 13 Ağustos 2010 **Kabul Tarihi:** 22 Kasım 2010

Introduction

Advanced maternal age is associated with increased obstetric and perinatal complications. The effects of increasing age occur as a continuum, rather than as a threshold effect. There is an increase in the rates of spontaneous early abortions, chromosomal aberrations, and congenital anomalies with ageing (1). In ongoing pregnancies gestational diabetes, hypertensive disorders and placental problems such as placenta previa and abruption are encountered more often in elderly women (2). Furthermore, pre-existing maternal diseases such as diabetes mellitus, hypertension, cancer and cardiovascular, renal and autoimmune diseases complicate pregnancy more often in these patients (3).

Perinatal mortality and morbidity of babies born to women of advanced age are also increased. This is partly due to diseases complicating pregnancy. Preterm labor and low birth weight babies and unexplained still birth are increased in elderly gravidas (1, 4).

The question of whether this increased incidence of complications in women of advanced age because of ageing of the organism itself or ageing of the ovarian follicles needs to be investigated. Chronological age of the ovaries is not always equivalent to the biological age. Approximately 10% of the women have a diminished ovarian reserve and accelerated ovarian ageing when compared to their age matched counterparts. Chromosomal abnormalities and abortions are proven to be increased in women with advanced ovarian age in the previous studies (5-7). However an impact of ageing of the oocytes on pregnancy complications has not been investigated. In this study we aimed to determine whether pregnancy complications are increased in women with advanced ovarian ageing.

Address for Correspondence / Yazışma Adresi: *Uzm. Dr. Huriye Ayşe Parlakgümüş, Başkent Üniversitesi Seyhan Uygulama Hastanesi, Cemal Paşa Mah. Barajyolu, 01110 Adana, Turkey Phone: +90 322 458 68 68/2203 e.mail: ayseparlakgumus@yahoo.de*

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Materials and Methods

This retrospective study was conducted at Baskent University from December 2004 to April 2008. We reviewed the antenatal follow up and birth records of 26 poor responder and 125 normoresponder patients. Twenty six poor responder women who had undertaken IVF/ICSI cycle treatment and were successfully delivered in Baskent University were eligible for this study. Patients from whom less than or equal to 6 oocytes were collected at the oocyte retrieval, which consisted of germinal vesicle and metaphase I, II oocytes, despite a total gonadotrophin dose over 3000 IU used, were defined as poor responders. Oral contraceptive plus microdose flare-up protocol and GnRH Antagonist protocol were performed on all poor responder women. Patients from whom more than 6 oocytes were collected at the oocyte retrieval, which consisted of germinal vesicle and metaphase I, II oocytes, with a gonadotrophin dose of less than 3000 IU used, were defined as normoresponders. Only long GnRH agonist protocol has been performed on normoresponder 125 women. Women whose gestational follow-up and their deliveries were completed at Baskent University were eligible for this study as well. Exclusion criterias of this retrospective study were pregnancies conceived spontaneously, pregnancies after spontaneous and induced embryo reduction, and multiple pregnancies. Multiple pregnancies were excluded to avoid the confounding effect of increased complications attributed to them. According to our clinical approach, long GnRH agonist protocol is the first choice for expected normoresponder patients.
In this retrospective analysis, we aimed to distinguish the prenatal outcomes of normoresponder women and poor responder women, who had undertaken the IVF/ICSI program.

Statistical analysis

Data were expressed as means±standard deviation (SD) and analyzed with Student's t test, Chi-square test, and Mann-Whitney two sample test (unpaired, nonparametric). $p<0.05$ was considered significant. SPSS for Windows (version 16.0; SPSS, Inc., Chicago, IL) was used for statistical analyses.

Results

Demographic characteristics of the patients are given in Table 1. A total of 113 (74.8%) patients, of whom 93 (74.4%) were from the normoresponder group and 20 (76.9%) were from the poor responder group, did not have any pregnancy complications. Eighteen patients (14.4%) from the normoresponder group and 3 (11.5%) patients from the poor responder group had gestational diabetes. Seven patients from the normoresponder had placenta previa (5.6%). Two patients from the normoresponder (1.6%) group had pregnancy induced hypertension. Two patients (1.6%) from the normoresponder group had preeclampsia. One patient from each group had fetal anomaly (3.8% for poor responders vs. 0.8% for normoresponders). Two patients from the normoresponder (1.6%) group had cholestasis. Two patients from the poor responder group were delivered prematurely (7.6%). There was no preterm labor in the normoresponder group.

Table 1. Demographic characteristics of the patient and data regarding delivery. Data are expressed as means±standard deviations

	Normoresponder (n=125)	Poor responders (n=26)	p
Age (year)	30.68±5.28	32.50±4.51	NS
BMI (kg/m^2)	25.89±4.12	26.13±4.54	NS
Gestational week at delivery	38.00±0.81	37.35±2.16	NS
Birth weight (grams)	3243±421	3074±620	NS

BMI: Body mass index, NS: Non-significant

Discussion

Our results revealed that pregnancy complications were not increased in patients with a reduced ovarian reserve when compared to their age matched counterparts. More than two thirds of the patients had uneventful pregnancies. Gestational diabetes was the most common disease complicating pregnancy. Incidence was similar in both the study and control groups (14.4 vs. 11.8%). In the literature the incidence of gestational diabetes varies between 1.4% and 14% depending on the characteristics of the population studied and the screening method (8). Placenta previa was the second most common complication. Romunstad et al. compared the pregnancies which are conceived spontaneously and via ART in the same mother and reported a three fold increase in placenta previa in IVF pregnancies (9). The incidences of pregnancy induced hypertension and preeclampsia in both groups were somewhat lower than the expected rates of 6% for gestational hypertension (10) and 12-22% for preeclampsia (11). This may be explained by the small size of the groups, mean age of the groups or the singleton pregnancies selected for the study. Preeclampsia is more common in women below 18 and over 35 years of age and in multiple pregnancies. The mean age of the patients was 30.6 years and 32.5 years for normoresponders and poor responders respectively, which may have contributed to the low incidence of hypertensive diseases. The major congenital anomaly rate is reported to be 2.91%. In this study it was lower than the expected rate for the normoresponder group. However, this may be due to the small sample size. Two patients from the normoresponder (1.6%) group had cholestasis. The incidence of intrahepatic cholestasis of pregnancy is reported to be 0.1-15.6% (12). The incidence of prematurity was 7.7% for the normoresponders (Table2). This is lower than the incidence of 13.8%-14.1% reported in the literature (13).
In conclusion, the biological age of the organism seems to determine the outcome of pregnancy. Currently there are no studies on the effects of ovarian ageing on pregnancy in patients aged <35 years. However, there have been some studies on pregnancy outcomes in patients aged ≥35 years and receiving young donor oocytes. Excellent pregnancy outcomes are reported in these pregnancies (14, 15). Porreco et al. compared

Table 2. Pregnancy complications of poor responder and normoresponder women. Data are expressed as percentages (%)

	Normoresponders (n=125) (%)	Poor responders (n=26) (%)	Total (n=151) (%)	p
No complication	93 (74.4%)	20 (76.9%)	113 (74.8%)	NS
Gestational diabetes	18 (14.4%)	3 (11.5%)	21 (13.9%)	NS
Placenta previa	7 (5.6%)	-	7 (4.6%)	-
Pregnancy induced hypertension	2 (1.6%)	-	2 (1.3%)	-
Preeclampsia	2 (1.6%)	-	2 (1.3%)	-
Fetal anomaly	1 (0.8%)	1 (3.8%)	2 (1.3%)	NS
Cholestasis of pregnancy	2 (1.6%)	-	2 (1.3%)	-
Preterm labor	-	2 (7.6%)	2 (1.3%)	-

pregnancies of women older than 45 years who had pregnancies from an oocyte donation cycle with spontaneous pregnancies of women younger than 36 years old. The gamete age was similar in both groups. They reported that mature women over 45 years conceiving largely through ART with donor eggs can expect newborn outcomes similar to younger women cared for in the same setting of a high-risk maternal-fetal practice (16).

Because IVF pregnancies themselves are already at high risk for perinatal complications, we included IVF patients into both the study and the control groups. The limitation of this study is the small size of the poor responder group. In our center, 12.7% of the ART cycles were the poor responder's cycles, which is consistent with the literature. In fact, it has been reported to be 9-26% (17). The low rate of pregnancy, the live birth rate and the high miscarriage rate in poor responder patients may be due to the poor quality of oocytes. Because of the high abortion rates in poor responders, the number of women reaching the first trimester screening is fewer. Besides, only the pregnant women who would have singleton babies were enrolled to avoid the possible confounding effect of multifetal pregnancy on serum markers. Our center is also a reference center to which patients from the neighboring cities present for ART. In addition, most of the patients, when they become pregnant, return home where they attend antenatal care and deliver. For these reasons, a high number of the scheduled poor responder patients did not come to the first trimester screening. Therefore, data of only 26 poor response patients screened in the first trimester were available. All the above mentioned factors caused a small size of the poor responders. This study may be considered a pilot study and a larger study can yield more accurate results.

Conflict of interest

None declared.

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Conservative laparoscopic management of adnexal torsion

Adneks torsiyonunda konservatif laparoskopik yaklaşım

Rana Karayalçın[1], Sarp Özcan[1], Şebnem Özyer[1], Turgut Var[1], Hüseyin Yeşilyurt[1], Hüseyin Dumanlı[2], Sunullah Soysal[1], Leyla Mollamahmutoğlu[1], Sertaç Batıoğlu[1]

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

[2]Department of Radiology, Zekai Tahir Burak Women's Health Education and Research Hospital, Ankara, Turkey

Abstract

Objective: To evaluate our experience with adnexal torsion (AT) in 36 patients and the outcomes of the patients who were managed conservatively via laparoscopy.

Material and Methods: A prospective study was conducted on 36 patients who underwent operations for AT via laparoscopy between January 2008 and December 2009. Data including age, previous history, time of onset of symptoms, time of admission to hospital, gray-scale and color Doppler US findings, time interval between hospital admission and surgery, type of intervention, operative findings and postoperative gray-scale and Doppler US findings were recorded.

Results: In 29 (80.5%) patients, a preoperative diagnosis of AT was confirmed clinically. The mean age of the patients was 26.5, with a range of 11 to 44. Ovarian blood flow was assessed by color Doppler US ultrasonography in 30 patients preoperatively. In 11 (36.6%) patients, this was found to be normal. In 19 (63.3%) patients, ovarian blood flow was found to be pathological or absent. Laparoscopic conservative treatment was performed in 34 patients. In two patients, salpingo-oophorectomy was performed. No thromboembolic complications were seen. Postoperative ultrasonographic examinations confirmed normal ovarian morphology and Doppler blood flow in all patients with no recurrence.

Conclusion: Early diagnosis and treatment are key factors in managing AT. According to the results of the present study, given its demonstrated safety and benefits, in women of reproductive age, a conservative approach of untwisting the adnexa and salvaging the ovary via laparoscopy should be considered in AT cases in which the time from the onset of symptoms to surgery does not exceed 44 hours, regardless of the color and number of twists.

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Key words: Adnexal torsion, laparoscopy, detorsion, conservative management, ultrasonography

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Özet

Amaç: Laparoskopi ile konservatif yaklaşım uyguladığımız 36 adneksiyal torsiyon (AT) hastasının sonuçlarını belirlemek.

Gereç ve Yöntemler: Ocak 2008-Aralık 2009 tarihleri arasında prospektif olarak planlanan çalışmada 36 hastanın verileri (yaş, önceki hikaye, semptom başlangıç zamanı, hastaneye başvuru süresi, USG bulguları, hastenye başvurudan cerrahiye kadar geçen süre,yapılan girişim ve operatif bulgularile postoperatif USG ve Doppler bulguları) belirtilmiştir.

Bulgular: Yirmidokuz hastada (%80.5) klinik olarak AT tanısı konulmuştur. Hastaların ortalama yaşı 26.5. Otuz hastada preoperatif doppler USG yapılmıştır. Onbir hastada doppler normaldir (%36.6). 19 hastada dopplerde patolojik kan akımı veya akım yokluğu gözlenmiştir (%63.3). 2 hastaya salpingoooferektomi yapılmıştır. Tüm vakalarda postoperatif doppler normal olarak bulunmuştur ve rekürrens gözlenmemiştir.

Sonuç: AT da erken tanı ve tedavi over fonksiyonları açısından çok önemlidir. L/S ile overin detorsiyonu semptom başlangıcından sonra 44. saate kadar mümkündür.

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Anahtar kelimeler: Adneksiyal torsiyonu, laparoskopi, detorsiyon, konservatif yaklaşımı, ultrasonografi

Geliş Tarihi: 20 Kasım 2010 **Kabul Tarihi:** 17 Aralık 2010

Introduction

Adnexal torsion (AT), the twisting of an ovary and/or tube on its ligamentous support, is the fifth most common gynecological emergency (1), accounting for 3% of all gynecological surgical emergencies (2, 3). Torsion of the adnexa initially interferes with the venous and lymphatic circulation. If unrelieved, it progresses rapidly to occlusion of the arterial circulation, eventually leading to gangrene and hemorrhagic necrosis (4). It occurs most frequently in adolescent girls and women of childbearing age, most of whom desire future fertility (5). Delay and misdiagnosis of AT are common and can result in a functional loss of the ovary (2).

For approximately 100 years after its initial description in the American literature by J. Bland Sutton, AT was treated by performing a salpingo-oophorectomy without untwisting the adnexa to

Address for Correspondence / Yazışma Adresi: *Uzm. Dr. Rana Karayalçın, Department of Obstetrics and Gynecology, Zekai Tahir Burak Women's Health Education and Research Hospital, Ankara, Turkey Phone: +90 312 310 31 00 e.mail: rkarayalcin@yahoo.com*

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avoid potential thromboembolism from ovarian vein thrombosis (6). However, a significant association between thromboembolism and detorsion of an ischemic pedicle has never been established (7). In the last 15 years, many reports describe minimally invasive surgery with laparoscopy, detorsion, and preservation of the ovary, which has currently shifted the standard approach from oophorectomy to laparoscopy (2, 8-13). As these patients tend to be young, and future fertility is desired, conservative management seems a feasible choice and preferable approach.

The purpose of this study was to evaluate our experience with AT in 36 patients and the outcomes of the patients who were managed conservatively via laparoscopy.

Materials and Methods

A prospective study was conducted on 36 patients who underwent operations for AT via laparoscopy between January 2008 and December 2009. The study was approved by the institutional review board. The demographic data, including age, gravidity, parity, marital status, and previous history, were noted. The time of onset of symptoms, time of admission to hospital, gray-scale ultrasonographic (US) findings, color Doppler US (ALOKA FSSD-5500) findings including the presence of fluid in the Douglas pouch, diameter and appearance of the ovary, presence of hyperstimulation, edema of the parenchyma, presence of an ovarian cyst, time interval between hospital admission and surgery, type of intervention, and operative findings including duration of the operation, size of the ovary and presence of other pelvic pathologies were recorded. All the patients underwent laparoscopic management. Follow-up gray-scale and color Doppler US were performed during the first week and again following the first and sixth month of laparoscopy for patients who were conservatively managed to determine the outcome of the adnexa.

Results

Thirty-six AT cases were managed by laparoscopy between January 2008 and December 2009. In 29 (80.5%) patients, a preoperative diagnosis of AT was confirmed clinically, and a laparoscopy was performed immediately. In the remainder of the patients, the preoperative diagnosis included ovarian cysts, ruptured ovarian cysts and tubo-ovarian abscesses. The mean age of the patients was 26.5±4.82, with a range of 11 to 44 years. The mean gravidity and parity was 2.4±0.98 (0-5) and 1.8±0.6 (0-3) respectively. Twenty-eight of the women were married. Two women had undergone ovarian stimulation during infertility treatments as part of an in vitro fertilization-intracytoplasmic sperm injection (IVF-ICSI) program and became pregnant on their first attempt; torsion occurred in the 11th to 12th week of their pregnancies. The most common presenting signs were lower abdominal pain as well as nausea and vomiting, which were observed in 33 (91.6%) patients and 29 (80.5%) patients, respectively. Leukocytosis was detected in 27 (75%) patients. All patients underwent ultrasonography preoperatively, and a pelvic mass was detected in all cases. The mean diameter of the mass was 7.2±2.21 cm, with a range of 5 to 14 cm. In 23 (63.8%) patients, torsion occurred on the right side. Ovarian blood flow was assessed by color Doppler US in 30 patients preoperatively. In 11 (36.6%) patients, it was found to be normal while in 19 (63.3%) patients, ovarian blood flow was found to be pathological or absent. The average time from the onset of symptoms to operation was 26±6.44 hours, with a range of 8 to 44 hours. The average time from hospital admission to operation was 8.4±3.88 hours. Laparoscopic conservative treatment was performed in 34 patients. In all 34 patients, detorsion of the adnexa and oophoropexy were performed. Oophoropexy was performed by fixing the utero-ovarian ligament to the sacro-uterine ligament, except in two pregnant women, in whom the ligaments were fixed to the pelvic sidewall with two stitches using nonabsorbable 0 prolene sutures Nine patients underwent an ovarian cystectomy. Pathological examination revealed serous cyst, paraovarian cyst and dermoid cyst in four, three and two patients respectively. Pathological surgical findings are listed in Table 1. Demographic data, symptoms, signs, and ultrasonographic and Doppler findings of the patients are summarized in Table 2. In two patients, salpingo-oophorectomy was performed.

Table 1. Pathological surgical findings

Pathological finding	n	%
Serous cyst	4	11.1
Paraovarian cyst	3	8.3
Dermoid cyst	2	5.5
Fibroma	1	2.7
Normal ovary	1	2.7

Table 2. Demographic data, symptoms, signs, ultrasonographic and Doppler findings of patients

Data	
Age (years, mean±SD)	26.5±4.82
Gravidity (n, mean±SD)	2.4±0.98
Married (n,%)	28 (77.7%)
Infertility treatment (n,%)	2 (5.5%)
Symptoms and signs	
Nausea (n,%)	33 (91.6%)
Vomiting (n,%)	29 (80.5%)
Leukocytosis (n,%)	27 (75%)
Ultrasongraphic findings	
Diameter of the mass (cm, mean±SD)	7.2±2.21
Right sided torsion (n, %)	23 (63.8%)
Pathologic or absent blood flow on Doppler US (n,%)	19 (63.3%)
Normal blood flow on Doppler US (n,%)	11 (36.6%)
Time from hospital admission to operation (hr, mean±SD)	8.4±3.88
Time from onset of symptoms to operation (hr, mean±SD)	26±6.44
Conservative treatment (n, %)	34 (94.4%)
Oophorectomy (n,%)	2 (5.5%)

Both of these patients were postmenopausal. Pathological examination revealed normal ovary with hemorrhagic infarction findings in one of these patients and torsioned ovarian fibroma in the other patient. All the patients had uneventful recoveries in the postoperative period. No thromboembolic complications were seen. Patients were discharged one to two days after the laparoscopies. Follow-up gray-scale and Doppler US were performed for all 34 patients in the first week, the first month and the sixth month following surgery. First year controls were completed in 26 patients, which revealed normal US findings. First week controls were performed in 34 patients which revealed a mean ovarian diameter of 5.2 cm on gray-scale US and normal Doppler US findings. First month controls revealed normal ovarian morphology on gray-scale US and normal Doppler US findings in all non-pregnant patients, however gray-scale US revealed a mean ovarian diameter of 5.5 cm at the end of the first month in two pregnant patients. Normal morphology was attained in the third month visit in the pregnant patients. Doppler blood flow was normal in all patients with no recurrence.

Sonographic pictures pre and postoperative ovary are given in Figure 1 and 2 respectively. Figure 1 demonstrates the torsioned ovary with no blood flow and Figure 2 demonstrates the detorsioned ovary revealing normal blood on Doppler US.

In one of the pregnant patients who were treated conservatively due to ovarian torsion, the ovary was observed as completely normal in size and localization during a cesarean section.

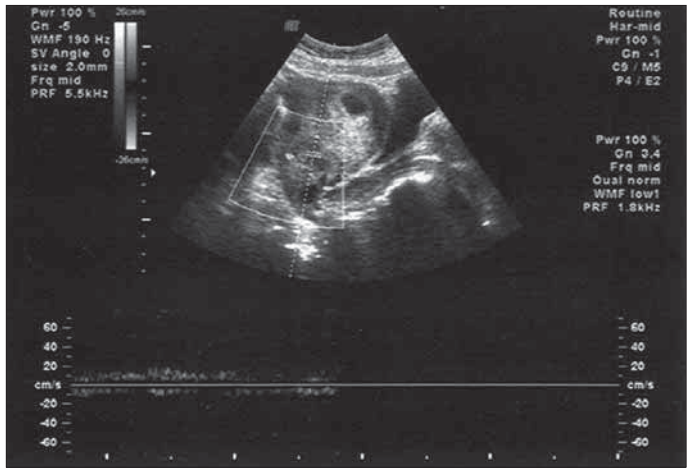

Figure 1. Torsioned ovary with no blood flow on Doppler US

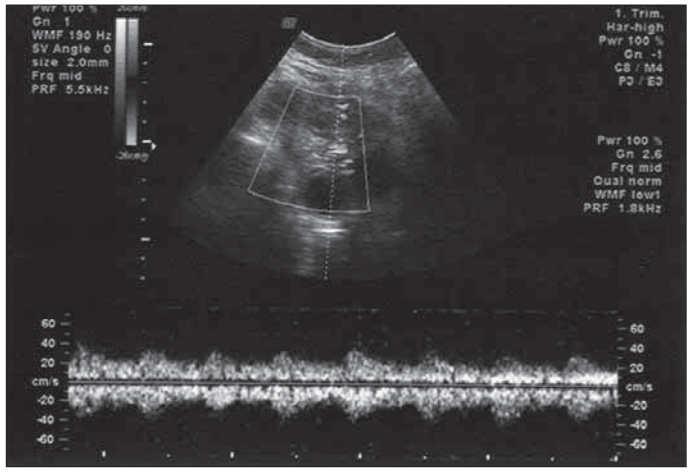

Figure 2. Detorsioned ovary with normal blood flow on Doppler US

Discussion

Because most cases of AT occur in reproductive-age women, prompt diagnosis and treatment is important for the preservation of ovarian function. More than 80% of all cases occur in women under 50. Although cysts and neoplasms account for over 90% of cases, torsion can also occur in ovaries that appear normal (8). Ovulation induction with gonadotropins predisposes the patient to torsion because of ovarian enlargement (3, 14-16).

Delays in diagnosis and surgical intervention are relatively common with AT because there is a non-specific presentation of cases and no absolute clinical profile. The time span from the onset of symptoms to operation reportedly varies from several hours to several days (17). The diagnosis of AT is presently based on clinical symptoms and a physical examination. Blood tests and imaging techniques contribute little to a preoperative diagnosis. The majority of patients present with a sudden onset of lower abdominal pain often associated with nausea and vomiting, adnexal mass, fever, and leukocytosis (8-10, 14). Pain relief observed during observation may be the result of perceptive nerve death and tissue degeneration in the affected ovary (17, 18). Bouguizane et al. reported that 57.8% of patients were diagnosed accurately at the first clinical examination in their study (19). Bar-On et al. found that women who underwent laparoscopies for suspected AT were correctly diagnosed in less than half of the cases (46.1%) (5).

Doppler US studies have been investigated extensively in the diagnosis of AT. A review of surgically diagnosed ovarian torsion cases by Pena et al. demonstrated that normal blood flow was found in 60% of such cases (20). Therefore, the presence of blood flow should not exclude a diagnosis of torsion when there is a high clinical suspicion. Although the absence of Doppler flow is highly specific, it has a very low sensitivity in diagnosing torsion (20, 21). In the Bar-On et al. study, it was found that ovarian blood flow had a low sensitivity (43.8%) and a high specificity (91.7%) for AT (5). In our study, pathological or absent blood flow was found in only 63.3% of the patients. These findings support the continued use of ultrasonographic and Doppler studies as diagnostic aids in cases of suspected AT but warrant caution because of their limited accuracy.

When AT is suspected, an emergency laparoscopy should be performed to establish an accurate diagnosis and avoid ovarian damage. We found that 80.5% of the patients were accurately diagnosed as having AT before undergoing laparoscopy. Many investigators have attempted to define the viable and nonviable appearance of torsioned adnexa during intraoperative inspection. Several studies have shown that the estimation of the degree of necrosis during surgery is inaccurate (22, 23). The color, size, and edema of the twisted ischemic adnexa usually do not reflect the true degree of damage to ovarian tissue. Oelsner et al. demonstrated that the adnexa can retrieve its

functional integrity, which was shown by the ultrasonographic observation of follicular development (91.3%), the normal macroscopic appearance of the adnexa during subsequent surgical intervention (92.4%), and successful oocyte fertilization in all reported cases (13). Taskin et al. investigated adnexal recovery in rodents (24). All rodent adnexa undergoing surgical torsion for 24 hours displayed normal histological findings despite a black-blue, ischemic appearance immediately and for one week after reversal of the torsion. The black-blue appearance was due to an initial lymphatic and venous stasis rather than significant arterial ischemia (24). In various studies in the literature, it has been reported that ovarian function is preserved in 88% to 100% of cases after detorsion of the twisted adnexa (13, 25-28).

In the past, laparotomy with oophorectomy was the standard treatment for AT. Concerns about possible thromboembolism and irreversible ischemic injuries led to the removal of the affected adnexa, regardless of the patient's age or her desire for future fertility. As early as 1946, Way described 16 cases of torsion that were managed by untwisting the adnexa with no serious complications (29). Oelsner et al. reported that none of the patients in their study of 102 AT cases had clinical signs of thromboembolism postoperatively (13). The incidence of pulmonary embolism was reported in 0.2% of cases with adnexal torsion treated by adnexectomy and not more frequently when the adnexa were untwisted (7). No thromboembolic complications secondary to adnexal detorsion were noted in our patients, as reported in the literature. Because there is no effective clinical method of predicting the viability of an ovary exactly by macroscopic appearance, and normal ovarian morphology and follicle formation have been confirmed in many patients, adnexectomy should be avoided. Removing the injured organ is suggested only when there are obvious signs of adnexal disruption, such as ligament detachment or ovarian tissue decomposition (2). In postmenopausal women, the treatment of choice is bilateral oophorectomy.

In the study by Oelsner et al., 5 of 102 patients (4.9%) had retorsion in the same adnexa (13). Surgical management to prevent the recurrence of AT has included triplication of the utero-ovarian ligament (30), in which the ligament is plicated and shortened with a running stitch; ovariopexy, in which the ovary is sutured to the posterior aspect of the uterus or the lateral pelvic wall; and oophoropexy, in which the utero-ovarian ligament is sutured either to the posterior aspect of the uterus or to the lateral pelvic wall. Although oophoropexy has not been evaluated in randomized trials, the procedure has been performed in women of all ages and during pregnancy (8). In our study, we performed oophoropexy in all conservatively managed cases and there were no recurrences of AT.

This is a prospective study consisting of 34 cases of AT managed conservatively by laparoscopy. Normal ovarian morphology and follicle formation were confirmed in all the cases with no recurrences. There were no postoperative complications or apparent adverse effects. Early diagnosis and treatment are key factors in managing AT. According to the results of the present study, given its demonstrated safety and benefits, a conservative approach of untwisting the adnexa and salvaging the ovary via laparoscopy should be considered in AT cases in women of reproductive age in which the time from the onset of symptoms to surgery does not exceed 44 hours, regardless of the color and number of twists.

Conflict of interest

None declared.

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The effect of cell type on surgico-pathologic risk factors in endometrial cancer

Endometrium kanserinde hücre tipinin cerrahi-patolojik risk faktörlerine etkisi

Ahmet Taner Turan[1], Betül Dündar[1], Burcu Gündoğdu[1], Abdullah Boztosun[2], Nejat Özgül[1], Nurettin Boran[1], Gökhan Tulunay[1], Ahmet Özfuttu[3], Mehmet Faruk Köse[1]

[1]*Department of Gynecologic Oncology, Etlik Zübeyde Hanım Women, Ankara, Turkey*

[2]*Department of Gynecology and Obstetrics, Cumhuriyet University, Sivas, Turkey*

[3]*Department of Pathology, Etlik Zübeyde Hanım Women, Ankara, Turkey*

Abstract

Objective: In this study the effect of histologic subtype as a surgicopathologic risk factor in endometrial cancer is evaluated.

Material and Methods: We evaluated 182 patients who underwent systematic lymphadenectomy up to the level of the renal vessels and at least 15 lymph nodes were dissected from the pelvic area and 10 lymph nodes from the para-aortic area. investigation of whether endometrioid and aggressive cell types (serous papillary cell and clear cell) affect the distribution of surgicopathologic risk factors among endometrial cancer cases was carried out.

Results: Patients in the aggressive cell type group were older and the tumor size was significantly smaller. There was no difference between the two groups for the total number of dissected lymph nodes except for the external iliac area. Although the difference is not statistically significant, the total number of lymph nodes dissected in the aggressive group was less (54.3 vs 62.9, p=0.067) than that of the endometrioid cell type group. While the incidence of pelvic lymph node metastasis in the aggressive group was 59.1% the incidence was 15.6% in the endometrioid cell type group (p>0.001). The possibility of lymph node metastasis for aggressive cell type endometrial carcinoma in the para-aortic area was twice the endometrioid cell type group. It was found that the presence and type (stromal/glandular) of cervical invasion, depth of myometrial invasion and presence of lymphovascular space invasion were not affected by cell type.

Conclusion: Aggressive cell types significantly increase the adnexial and lymph node metastasis in endometrial cancer.

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Özet

Amaç: Bu çalışmada endometrium kanserinde hücre tipinin cerrahi-patolojik risk faktörleri üzerine olan etkisi araştırıldı.

Gereç ve Yöntemler: Endometrium kanseri nedeniyle renal damarlar seviyesine kadar sistematik lenf nodu diseksiyonu yapılan 182 hasta retrospektif olarak değerlendirildi. Lenf nodu diseksiyonu yapılan olgularda pelvik bölgeden en az 15 adet, para-aortic bölgeden de en az 10 adet lenf nodu çıkarılmıştır. Hastalar yapılan histolojik değerlendirme sonucuna göre hücre tipine göre endometrioid hücre tipi ve agresif hücre tipi (seröz papiller ve berrak hücreli) olmak üzere 2 gruba ayrıldı.Bu iki grup cerrahi-patolojik risk faktörlerinin dağılımı açısından karşılaştırıldı.

Bulgular: Agresif hücre tipi grubunda yer alan hastaların yaş ortalaması daha yüksekti ve tümör boyutu daha küçüktü. İki grup arasında eksternal iliak bölge dışında diseke edilen lenf nodu sayısı açısından fark olmadığı bulundu. Agresif hücre tipi grubunda çıkarılan toplam lenf nodu sayısı endometrioid hücre tipi grubundan daha azdı fakat fark istatistiksel olarak anlamlı değildi (54.3 vs 62.9, p=0.067). Agresif hücre tipi grubunda pelvik lenf nodu metastazı insidansı %59.1 iken endometrioid hücre tipi grubunda insidans %15.6 olarak bulundu (p>0.001). agresif hücre tipi grubunda para-aortic lenf nodu metastazı olasılığının diğer grubun 2 katı olduğu görüldü. Servikal invazyon ve invazyonun tipinin (stromal/glandüler), miyometrial invazyonun derinliğinin ve lenfovasküler alan invazyonunun hücre tipinden etkilenmediği görüldü.

Sonuç: Endometrium kanserinde agresif hücre tipi adneksiyal alan ve lenf nodu metastazını istatistiksel olarak anlamlı ölçüde arttırmaktadır.

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Anahtar kelimeler: Endometrium kanseri, hücre tipi

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Introduction

Endometrial cancer is the fourth most common cancer among women worldwide (1). More than 80% of the cases are endometrioid type histologically and are associated with a good prognosis (2). Clear cell and serous papillary cell carcinoma, which are the aggressive ones, are quite rare, with an incidence of 1-6% and 1-10%, respectively (3-6).

Serous papillary cell carcinoma of the uterus resembles epithelial ovarian cancer with its aggressive clinical course (7, 8). Clear cell carcinoma of the uterus is another aggressive type of endometrial cancer, which has a similar relapse pattern to uterine serous papillary cell carcinoma and a 5 year survival less than 50% (3, 9). In addition to serous papillary cell and clear cell carcinoma, there is another group with aggressive characteristics called mixed type and is histologically composed of more than 75% serous papillary or clear cells (9). Even if the tumor is only confined to the uterus in the case of an aggressive cell type, adjuvant therapies following surgery are generally recommended (10-13). Because of their aggres-

Address for Correspondence / Yazışma Adresi: *Asistan Betül Dündar, Yeni Etlik Cad., No: 55, Etlik 06010 Ankara, Turkey*
Phone: +90 312 322 01 80 e.mail: mdbetul@hotmail.com
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sive clinical course radical surgical procedures are suggested, and to prevent and control the potential pelvic and extrapelvic disease, radiotherapy and/or systemic chemotherapy are recommended as adjuvant therapies.

Carighead et al. analyzed 103 patients whose histopathologic diagnosis was one of the aggressive variants of endometrial cancer and showed that pelvic radiotherapy reduces pelvic recurrence significantly and increases the overall survival in stage IB, IC, II and III cases (14).

However, in view of the fact that studies on this subject and the number of subjects included in those studies are not sufficient, the most appropriate treatment regimen for clear cell and serous papillary cell carcinoma is still controversial. For this reason, further prospective randomized trials are required to determine the most appropriate treatment method (15, 16). In addition, it is not clearly known that there is a relationship between the aggressive clinical course of the serous papillary and the clear cell carcinoma and the surgico-pathologic risk factors associated with those cell types.However, it is known that extra uterine spread is common among aggressive cell types (7, 13, 14, 17, 18).

In this study we evaluated whether there is an association between the surgico-pathologic risk factors and cell type in endometrial cancer.

Material and Methods

Between 1993 and 2009, a total of 182 patients who had open systematic pelvic and para-aortic lymphadenectomy surgery extending to the renal vessels for endometrial cancer at the gynecologic oncology department were studied retrospectively. Patients who had no other malignancies diagnosed within two years before or after their diagnosis and who had had at least 15 lymph nodes removed from pelvic region and at least 10 lymph nodes removed from para-aortic region were included. All surgical procedures were performed by experienced gynecologic oncologists and frozen sections were studied routinely for all cases, providing information on the grade of neoplasia, histology, depth of myometrial invasion, tumor diameter, sites of extrauterine spread and lymphovascular invasion.

Patients were staged according to FIGO 1988 criteria. In addition to total abdominal hysterectomy and bilateral salphingo-oophorectomy, bilateral pelvic and para-aortic lymph node dissections were performed when one of the following criteria was determined by frozen section examination; (1) Grade 2-3, (2) ≥1/2 myometrial invasion, (3) tumor size >2 cm, (4) adnexial metastasis, (5) cervical involvement and (6) aggressive cell types (clear cell, adenosquamous or serous papillary).

The variations in distribution of surgico-pathologic risk factors according to endometrioid cell type and other aggressive cell types were investigated.

Statistical analyses were performed using 17.0 SPSS programme. χ^2 test and Annova Table tests are used, and $p<0.05$ value is accepted as statistically significant. The study was approved by the Ethical committee in our hospital.

Results

In this study 182 patients with stage IA-IVB endometrial cancer were evaluated. The mean age was 57.3 (35-92). The mean tumor size was 40.6mm with a maximum of 130 mm. There was no tumor in nine patients. The histological subtype was endometrioid in 87.9% of patients. Grade 1 tumor was detected in 61 patients, grade 2 in 68 and grade 3 in 53. There was no myometrial invasion in 14 patients, <1/2 myometrial invasion in 68, ≥1/2 myometrial invasion in 93 and serosal infiltration was present in 11. Ovarian involvement was detected in 22 patients and tubal involvement in 13 patients. In 139 patients the information about lymphovascular space invasion (LVSI) was indicated by the histopathological examination and LVSI was determined in 57 of these patients (Table 1).

The mean of the total number of lymph nodes removed was 61.9 and 42.3 of those were dissected from the pelvic area while 19.6 e were from the para-aortic area.

Lymph node metastasis was found in 43 patients (23.6%). Tumor spread to the pelvic lymph nodes in 38 patients (20.9%) and to the para-aortic lymph nodes in 24 patients (13.2%). Obturator lymph nodes were the most commonly involved area. Details of the surgico-pathologic factors of the patients are shown in Table 1.

The patients in the aggressive cell type group were older and the tumor size in this group was significantly smaller (Table 2). There was no difference between the two groups with regard to the total number of removed lymph nodes except for the external iliac area (Table 2). In the aggressive cell type group, lymph nodes dissected from the external iliac area were significantly fewer in number. Although the difference is not significant statistically, the total number of lymph nodes removed in the aggressive cell type group was also fewer (54.3 vs 62.9, $p=0.067$). However in the aggressive cell type group, pelvic lymph node involvement was greater (59.1% vs 15.6%, $p<0.001$) (Table 3). The possibility of para-aortic lymph node involvement in the aggressive cell type group was twice that in the endometrioid cell type group (22.7% vs 11.9%, $p=0.158$) (Table 3).

Spread of disease to the tuba uterina and ovaries was more common in the aggressive cell type group (Table 3). While the ovarian metastasis was found in 27.3% of patients in the aggressive cell type group, the rate of ovarian metastasis was 10% in the endometrioid cell type group. The rate of tubal involvement was 18.2% and 5.6%, respectively.

It was found that the presence and type of cervical invasion either stromal or glandular,and depth of myometrial invasion and presence of LVSI were not affected by cell type (Table 4).

Discussion

The term clear cell carcinoma of mesonephric origin was first described by Schiller et al. in 1939 to describe clear cell carcinoma of ovarian cancer resembling renal cell carcinoma histologically (19). The descriptive term clear cell carcinoma for tumors originating from the Müllerian duct was first introduced in 1967 by Scully and Barlow (20). The prognostic significance of clear cell histology was recognized in 1970s. Scully and

Table 1. General parameters

Parameter		Mean / n	Range / %
Age (years)		57.3	35-92
Tumor size (mm)		40.6	0-130
Stage	IA	12	6.6
	IB	48	26.4
	IC	49	26.9
	IIA	4	2.2
	IIB	11	6
	IIIA	9	4.9
	IIIB	2	1.1
	IIIC	45	24.7
	IVA	1	0.5
	IVB	1	0.5
Cell type	Endometrioid	160	87.9
	Clear	11	6
	Serous papillary	11	6
Grade	1	61	33.5
	2	68	37.4
	3	53	29.1
Depth of myometrial invasion	Only endometrium	14	7.7
	< ½	68	37.4
	≥ ½	93	51.1
	Serousal infiltration	7	3.8
Peritoneal cytology	Negative	171	94
	Positive	11	6
Ovarian metastasis	Negative	160	87.9
	Positive	22	12.1
Tuba uterina metastasis	Negative	169	92.9
	Positive	13	7.1
Cervical invasion	Negative	141	77.5
	Glandular	8	4.4
	Stromal	33	18.1
Lymphovascular space invasion	Negative	82	45.1
	Positive	57	31.3
	Not reported	43	23.6
Total number of removed lymph nodes		61.9	27-122
Number of lymph nodes removed from pelvic area		42.3	16-81
Number of lymph nodes removed from para-aortic area		19.6	10-49
Lymph node status	Negative	139	76.4
	Pelvic lymph node metastasis	43	23.6
	Para-aortic lymph node metastasis	27	13.2
Pelvic lymph node area	Common iliac lymph node	16	8.8
	External iliac lymph node	19	10.4
	Internal iliac lymph node	16	8.8
	Obturator lymph node	20	11
	Presacral lymph node node	1	0.5

Table 2. Age, tumor size and dissected lymph nodes according to cell types

Cell type		Age	Tumor size (mm)	Total LN	PA LN	Total pelvic LN	CI LN	EI LN	II LN	PS LN	O LN
Endometrioid	Mean	56.7	41.9	62.9	20	43.1	9.71	11.6	5.2	1.74	14.9
	Minimum	35	0	27	10	16	2	2	0	0	0
	Maximum	92	130	122	49	81	26	28	20	8	41
	Median	56	40	58.5	18	40	9	11	6	1	15
Clear cell and serous type	Mean	62.3	31.7	54.3	17.4	37	8.1	9	6.5	1.23	12.2
	Minimum	48	5	32	9	18	2	4	1	0	3
	Maximum	76	60	87	33	59	20	14	15	7	26
	Median	62.5	32.5	50.5	15.5	34.5	8	9	6	0	11
p		0.009	0.029	0.067	0.167	0.068	0.142	0.030	0.119	0.291	0.085

LN: Lymph node, PA: Para-aortic, CI: Common iliac, EI: External iliac, II: Internal iliac, PS: Presacral, O: Obturator

Table 3. Lymph node, ovarian and tubal involvement according to cell type (%)

Cell type	PA LN	Total pelvic LN	CI LN	EI LN	II LN	PS LN	O LN	Ovarian involvement	Tubal involvement
Endometrioid	11.9	15.6	6.9	7.5	4.4	0	8.8	10	5.9
Clear cell and serous type	22.7	59.1	22.7	31.8	40.9	4.5	27.3	27.3	18.2
p	0.158	<0.001	0.014	<0.001	<0.001	0.007	0.009	0.020	0.032

LN: Lymph node, PA: Para-aortic, CI: Common iliac, EI: External iliac, II: Internal iliac, PS: Presacral, O: Obturator

Table 4. Presence of cervical invasion, depth of myometrial invasion and lymphovascular space invasion according to cell type (%)

Cell type	Cervical invasion			Depth of myometrial invasion				LVSI	
	Absent	Glanduler	Stromal	Endometrial	<1/2	≥1/2	Serozal	Negative	Positive
Endometrioid	79.4	4.4	16.3	6.9	37.5	52.5	3.1	79.4	20.6
Clear cell and serous type	63.6	4.5	31.8	13.6	36.4	40.9	9.1	63.6	36.4
p	0.201			0.327				0.098	

LVSI: Lymphovascular space invasion

Kurman reported a series of 21 cases of clear cell carcinoma with an unfavorable clinical course (21).

The concept of uterine serous papillary carcinoma was first brought out by Hendrichson and described as a rare aggressive subtype of endometrioid adenocarcinoma (22). The main histological property of serous papillary carcinoma is the psammoma bodies and the distinct papillary microarchitecture. The serous papillary carcinoma of the uterus, which is a very different clinicopathological entity from endometrioid adenocarcinoma, also differs from the carcinogenesis point of view. The major role in the molecular pathogenesis of uterine serous papillary carcinoma is p53 inactivation (23-25). Overexpression of the p53 gene is observed in 80% of all uterine serous papillary carcinoma cases, while this rate is only 10-25% among all high grade endometrioid adenocarcinoma cases.

The biological behavior of serous papillary malignancies of other tissues, such as the ovaries and the peritoneum, resembles that of uterine serous papillary carcinoma. The reason for this is that the p53 gene inactivation is common in all types of serous papillary malignancies and all of them have the capability to develop aggressively and rapidly instead of undergoing some slow processes of tumor development depending on hormone related mechanisms (23, 25).

In this studywa it is found that the aggressive cell type significantly increases the pelvic lymph node involvement. Pelvic lymph node metastasis was present in 16% of the endometrioid cell type group, while this ratio was 59% among the aggressive cell type group. When the cases were investigated in detail, it was observed that lymph node involvement in all areas of the pelvis was significantly higher among clear cell and serous papillary cell types. In contrast, lymph node involvement in the para-aortic area was found to be independent of cell type.

Typically, uterine serous papillary cell carcinoma differs from the endometrioid adenocarcinoma with its aggressive clinical course associated, with diffuse peritoneal involvement resembling that of ovarian cancer, and it is also associated with deep myometrial invasion and lymphatic involvement (17).

In a study investigating the pattern of metastasis and prognosis among clear cell carcinoma cases; Abeler et al. found that the 5 year survival decreases with myometrial invasion, which is one of the surgicopathologic risk factors. Five year survival was 90% for intramural tumor, while it was 15% in cases with deep myometrial invasion (3).

Xiaohai et al. investigated 310 patients retrospectively to determine the clinicopathological factors other than cell type affecting lymph node involvement (26). As a result of this study, it was found that the presence of LVSI, deep myometrial invasion and cervical invasion were determinants of lymph node involvement. This result is also supported by the results of another study. Fotopoulou et al. found that the presence of LVSI, grade, serous cell type and incomplete resection of the tumor were also associated with lymph node involvement (18). However, in our study there was no significant difference in depth of myometrial invasion, presence of LVSI and cervical metastasis between the aggressive cell type group and endometrioid cell type group. This means that aggressive cell type increases pelvic lymph node involvement independent of depth of myometrial invasion, presence of LVSI and cervical metastasis. Similarly, Goff et al. found in their study that extrauterine disease in uterine serous papillary carcinoma was not associated with depth of myometrial invasion and grade (7). Goff et al. investigated 50 cases of surgically staged uterine serous papillary carcinoma, and lymph node metastasis was observed in 36% of patients without myometrial invasion and 40% of patients with outer one-half myometrial invasion. Among 14 cases in which the tumor was limited to the endometrium, there was lymph node metastasis in 36% and extrauterine disease was present in 43%. In addition, Goff et al. found that the incidence of extrauterine disease was increased with the presence of LVSI (85% of patients), but even if LVSI is not present in these patients, the incidence of extrauterine disease was still found to be high (58% of patients). There are other studies which also reported that myometrial invasion had no prognostic value in uterine serous papillary carcinoma (5, 7, 8).

In this study, ovarian and tubal involvement was found to be higher among the aggressive cell type group. This may explain the higher incidence of pelvic lymph node involvement in the presence of aggressive cell type. In contrast to this, although the adnexial involvement was increased with aggressive cell type, the para-aortic lymph node involvement was not increased with adnexial involvement with the aggressive cell type. Mariani et al. reported that one of the possible ways for para-aortic lymph node involvement in endometrial cancer was the peduncle of ovarian vessels. In their study, there was metastasis in the gonadal vein and surrounding soft tissue in 28% of patients with para-aortic lymph node involvement (27). Mc Meekin et al. also reported similar results and they found that the para-aortic lymph node involvement was present in 11 of 12 patients who have adnexial metastasis and/or positive peritoneal cytology (28). 240 cases of stage I-III endometrial cancer were surgically treated by total abdominal hysterectomy, bilateral salpingo-oophorectomy and retroperitoneal lymph node dissection. They investigated the histopathological factors from the prognostic aspect and found that the incidence of deep myometrial invasion, high nucleolar grade (G3), LVSI and pelvic lymph node involvement were higher among the serous papillary and clear cell carcinoma group compared to the endometrioid cell type group (29). In accordance with that study, we also found that pelvic lymph node involvement and adnexial metastasis was significantly higher among aggressive cell type cases.

For all stages in uterine serous papillary carcinoma, 5-year survival is found to be 30% (6, 30). While 5-year survival for stage I-II cases is 54% and 27% respectively, 5-year survival cannot be predicted in stage III-IV cases (31). Also, unfortunately disseminated disease and death is possible in th case of uterine serous papillary carcinoma even if the tumor is confined to the endometrium (8, 30, 32).

As a result, in this retrospective study we found that the prognostic factors which determine the survival in the aggressive cell type group were poorer. Tubal and adnexial involvement in the aggressive cell type group were significantly higher. However, this situation was independent of depth of myometrial invasion, presence of cervical involvement and LVSI. Also, although it is not statistically significant, para-aortic lymph node involvement in the aggressive cell type group was approximately twice that in the endometrioid cell type group, and adnexial involvement was thought to be responsible for this. In the aggressive cell type group, the treatment plan should be as aggressive as the clinical course.

Since the number of patients included in this study was limited and the study was designed retrospectively, conclusions are restricted. In addition to this, the patients included in our study group were at high risk for lymph node metastasis. For that reason, well designed more prospective studies including all endometrial cancer patients are required for understanding of effect of cell type on variations in surgico-pathologic risk factors.

Conflict of interest

None declared.

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Comparison of ovulation induction and pregnacy outcomes in IVF patients with normal ovarian reserve who underwent long protocol with recombinant-FSH and highly purified-hMG

Normal over rezervi olan ve long protokol uygulanan İVF hastalarında rekombinant fsh ve yüksek derecede saflaştırılmış hmg kullanımının gebelik sonuçlarına etkisinin karşılaştırılması

Cem Çelik[1], Kenan Sofuoğlu[2], Selçuk Selçuk[2], Mehmet Reşit Asoğlu[2], Remzi Abalı[1], Elçin Çetingöz[2], Bahar Baykal[2], Mehmet Uludoğan[2]

[1]Department of Obstetrics and Gynecology, Namık Kemal University, Tekirdag, Turkey

[2]Department of Obstetrics and Gynecology, Zeynep Kamil Training and Education Hospital, Istanbul, Turkey

Abstract

Objective: Gonadotropins used in controlled ovarian stimulation have been increasing in number. Beside the recombinant preparations such as rec-FSH, rec-LH and h-hMG human-derived preparations have entered the market. We decided to compare the effects of rec-FSH and HP-hMG with GnRHa on embryo quality and pregnancy outcome in women undergoing an IVF cycle.

Material and Methods: In this study, data of 87 patients who had applied to our center from 2007 to 2008 and who had met all inclusion criteria, were analyzed. The patients underwent controlled ovarian hyperstimulation with HP-hMG, rec-FSH following down-regulation with a GnRHa in a long protocol, selected according to determined criteria and acquired embryo via IVF transfer.

Results: Of the 87 patients, 44 were stimulated with rec-FSH and 43 with HP-hMG. Distribution of infertility causes was similar between the groups. Duration of gonadotropin administration (p=0.677, Student's t-test) and the total dose of gonadotropin received (p=0.392, Student's t-test) were similar between the two groups. The fertilization rate of the rec-FSH group was significantly higher than the HP-hMG group (p=0.001, Mann-Whitney U test). No significant differences were observed between the study groups in biochemical, clinical and ongoing pregnancy parameters.

Conclusion: The higher oocyte yield with rec-FSH does not result in higher quality embryos. LH activity in combination with FSH activity positively affected the oocyte and embryo maturation. Therefore, when we consider the clinical and ongoing pregnancy rates there is no inferiority of HP-hMG in controlled ovarian stimulation.

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Key words: Ovarian stimulation, rec-FSH, HP-hMG

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Özet

Amaç: Son dekatta ovulasyon indüksiyonu ve kontrollü over stimülasyonu için kullanılan gonadotropinler hızla çoğalmıştır. Çeşitli rekombinant preperatların yanında; rec-FSH, rec-LH, insan kaynaklı gonadotropinlerde pazara girmiştir. Bu çalışmadaki amaç; in vitro fertilizasyon protokolünde yer alan rec- FSH ve HP-hMG'nin elde edilen embriyoların kalitesi ve gebelik sonuçları üzerindeki etkilerinin karşılaştırılmasıdır.

Gereç ve Yöntemler: Çalışmamıza 2007- 2008 tarihleri arasında Zeynep Kamil kadın ve çocuk hastalıkları eğitim ve araştırma hastanesi tüp bebek merkezine başvuran, çalışmaya dahil edilme kriterlerini sağlayan 87 hastanın verileri kullanıldı. Belirlenen kriterlere göre seçilen, ovulasyon indüksiyonu için rec-FSH ve/veya HP-hMG kullanarak uzun protokol agonist tedavi protokolleri uygulanmış; IVF yöntemi ile ovum fertilizasyonu sağlanmış ve elde edilen embriyolarla transfer yapılmıştır.

Bulgular: Olgular rec-FSH (n=44) ve HP-hMG (n=43) olmak üzere iki grup altında incelenmiştir. İnfertilite nedenlerin dağılımı her iki grup arasında benzer olarak bulunmuştur. Gruplara göre olgulara uygulanan total gonadotropin dozları (p=0.677, Student t-test) ve süresi (p=0.392, Student t-test) arasında istatistiksel olarak anlamlı bir farklılık bulunmamaktadır. Rec-FSH grubundaki olguların fertilizasyon sayıları, HP-hMG grubundaki olguların fertilizasyon sayılarından istatistiksel olarak ileri düzeyde anlamlı fazladır (p<0.01). rec-FSH ve HP-hMG gruplarında kimyasal gebelik, klinik ve devam eden gebelik görülme oranları arasında istatistiksel olarak anlamlı bir farklılık bulunmamaktadır.

Sonuç: rec-FSH grubunda yüksek oosit sayısı olmasına rağmen yüksek kalitede embriyo sayısı elde edilmemiştir. FSH aktivitesi ile birlikte LH aktivitesi oosit ve embriyo gelişimini pozitif yönde etkilemiştir. Bu sebepten dolayı klinik ve devam eden gebelik oranları incelendiğinde, HP-hMG grubunda herhangi bir düşüş rastlanılmamıştır.

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Anahtar kelimeler: Ovulasyon indüksiyonu, rec-FSH, HP-hMG

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Address for Correspondence / Yazışma Adresi: *Yard. Doç. Dr. Cem Çelik, Department of Obstetrics and Gynecology, Namık Kemal University, Tekirdag, Turkey*
Mobile: +90 532 420 53 65 e.mail: cemcel@yahoo.com
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Introduction

Controlled ovarian stimulation in infertile women undergoing treatment for in vitro fertilization (IVF) have usually been provided with highly purified human menopausal gonadotropin (HP-hMG), including both luteinizing hormone (LH) and follicle-stimulating hormone (FSH) activity and recombinant FSH (rec-FSH). Decision as to the most effective preparations between HP-hMG and rec-FSH is a common debatable issue (1). Comparing the outcome of rec-FSH and HP-hMG performed in women undergoing pituitary down-regulation with a gonadotropin-releasing hormone agonist (GnRHa), long protocol has been reported in several studies (2). However, the meta-analysis concluded that large randomized trials were needed to precisely estimate any difference between menotrophins and rec-FSH (1).

Results of various studies based on the role of exogenous LH in the process of follicular development, oocyte maturation, and pregnancy rate have raised another argument (3). The concentration of circulating LH that results from the combination of GnRHa and recombinant FSH is much lower than that found in the normal menstrual cycle (4). The lowered basal LH secretion that results from the use of GnRHa, together with the absence of exogenous LH in rec-FSH preparations, may contribute to a decreased PR in IVF (5-8). On the other hand, other studies indicate that very low amounts of LH maintain development of normal follicle and oocyte (9). Moreover, high serum LH during the follicular phase of the menstrual cycle has been associated with lower fertility rates and an increase in the probability of spontaneous abortion (10).

The aim of the present study was to prove the superiority of HP-hMG versus rec-FSH in a relevant clinical setting. We decided to compare the effect of rec-FSH and HP-hMG with GnRHa on embryo quality and pregnancy outcome in women undergoing an IVF cycle. Results were discussed in the light of recent insights on the effects of LH activity on folliculogenesis, embryo quality and endometrial development.

Materials and Methods

The patients underwent controlled ovarian hyperstimulation with HP-hMG, rec-FSH following down-regulation with a GnRHa in a long protocol, selected according to determined criteria and acquired embryo via IVF transfer. Comparing the effectiveness of performed protocols was the retrospective aim. In this study, data of 87 patients who had applied to our center from 2007-2008 and who had met all inclusion criteria, were analyzed.

Inclusion criteria were: primary or secondary infertile women with major indications for IVF, age 20-40 years, body mass index (BMI) 18-29 kg/m^2, regular menstrual cycles ranging from 25 to 35 days, normal basal serum FSH (<13 IU/l) and estradiol (E_2<75 pg/ml) levels determined on day 3 of the cycle, normal basal serum thyroid stimulating hormone (TSH) and prolactin, no uterine (fibroids, adenomyosis, mullerian malformations), ovarian (endometrioma, polycystic ovaries), or adnexal (hydrosalpinx) abnormalities assessed by transvaginal ultrasonograghy.

Exclusion criteria were: patients with a history of recurrent pregnancy loss, history of ovarian hyperstimulation syndrome (OHSS) at previous IVF cycles, previous IVF cycles with unsuccessful fertilization polycystic ovary syndrome, stage 4/5 endometriosis, any significant systemic disease, endocrine, or metabolic disorder.

Cycle cancellation criteria

Unsuccessful fertilization, after ovulation induction, all follicles less than 18 mm in diameter decreasing at serum E_2 level of more than 50% between two control days, existence of OHSS risk: on stimulation day 8; 15 or more intermediate follicles (12-16 mm) or on stimulation day 10 or after; 20 or more large follicles (16-20 mm), and/or serum E_2 level ≥3000 pg/ml.

At the first visit, the obstetric and gynecologic history and menstrual cycle regularity were questioned and pelvic examination was performed. In addition, blood pressure, height, weight, and BMI were measured.

Blood sampling for fasting blood glucose, blood urea nitrogen, aspartate aminotransferase (AST), alanine aminotransferase (ALT), and thyroid function tests were carried out on menstrual cycle day 3.

Blood sampling for endocrine parameters (FSH, LH, hCG, E_2, progesterone, androstenedione, total testosterone, and sex hormone-binding globulin) and basal ultrasonography for assessment of the endometrial thickness, ovarian size, number and diameter of follicles were carried out in the early follicular phase (on menstrual cycle day 2 or 3).

Protocols

All patients underwent controlled ovarian hyperstimulation following down-regulation with a GnRHa in a long protocol. About 44 patients were stimulated with rec-FSH (Puregon; Organon, Holland) and 43 patients with HP-hMG (Menopur, Ferring, Sweden).

All patients received an identical type and dose of concomitant fertility treatment, that is, GnRHa for down-regulation, human chorionic gonadotropin (hCG) for triggering final maturation, and progesterone for luteal support. Pituitary down-regulation using triptorelin acetate, 0.1 mg/day s.c. (DECAPEPTYL; Ferring Pharmaceuticals A/S), was initiated 5-7 days before the estimated start of the next menses and continued until the end of gonadotropin administration. Gonadotropin administration was initiated when down-regulation was confirmed by using transvaginal ultrasonography showing no ovarian cysts, a shredded endometrium with a thickness of <5 mm or serum estradiol <50 pg/ml (0.184 nmol/l). The starting dose of HP-hMG or rec-FSH was 225 IU for the first 5 days, followed by individual adjustments according to the patient's follicular response. The dose could be changed by 75 IU per adjustment and not more frequently than every 4 days. Choriogonadotropin alpha, 250 μg s.c. (OVITRELLE; Serono) was administered to induce final follicular maturation within 1 day of observing three or more follicles of ≥17 mm diameter. Oocyte retrieval took place 36±2 h after hCG administration.

Insemination was done via regular IVF insemination (not ICSI) at 3±1 h after oocyte retrieval. Fertilization was assessed at

20±1 h, and embryo quality was assessed at 28±1 h, 44±1 h, and 68±1 h after oocyte retrieval. A top-quality embryo was defined as four to five cells on day 2 (type A), seven or more cells on day 3, equally sized blastomeres and ≤20% fragmentation on day 3, and no multinucleation. The transfer of one or two embryos of minimum quality, defined as four or more cells with no cleavage arrest (i.e., cleavage must have occurred within the last 24 h and ≤20% fragmentation), was done on day 3 after oocyte retrieval. Vaginal progesterone gel 90 mg/day 8% (CRINONE; Serono) for luteal support was given from the day of embryo transfer until the confirmation of clinical pregnancy (5-6 weeks after embryo transfer) or negative serum β-hCG test (13-15 days after embryo transfer).

Our primary aim was to compare the ongoing pregnancy per started cycle. Positive β-hCG test following embryo transfer was described as chemical pregnancy. Ongoing pregnancy was defined as positive heart beat 10-11 weeks after embryo transfer by ultrasonographic examination. Other outcome parameters assessed were HP-hMG/rec-FSH dose (IU: International Unit), days of gonadotropin stimulation, number of oocytes retrieved, fertilization rate, number of embryos, and ongoing pregnancy.

Statistical analysis

Dates of the study were analyzed by statistical package for social science for window 15.0. Summary statistics were evaluated for all parameters. Differences between groups of normally distributed variables were assessed with the Student's t-test, while not normally distributed variables were compared with the Mann-Whitney U test. Noncontinuous variables were compared with the Chi square test. P<0.05 was considered statistically significant.

Results

Demographics and baseline characteristics of the participants are shown in the Table 1. No difference was observed between the two treatment groups. Distribution of infertility causes was similar between the groups (Figure 1). About 87 cases were reported in this study. Of the 87 patients, 44 were stimulated with rec-FSH and 43 with HP-hMG. Data of 87 patients were analyzed by dividing them into two groups as rec-FSH (n=44) and HP-hMG (n=43) treatments.

Duration of gonadotropin administration (p=0.677, Table 1) and the total dose of gonadotropin received (p=0.392, Table 2) were similar between the two groups. Serum E_2 levels on the day of rec-hCG administration were different between the HP-hMG and rec-FSH group, which was statistically significant. Serum E_2 levels were higher in the HP-hMG group (p=0.041, Table 2). On the day of hCG injection, there was no significant difference in endometrial thickness (p=0.282, Table 2). Oocyte retrieval was performed in 41 (95.3%) patients stimulated with HP-hMG and in 43 (97.7%) patients stimulated with rec-FSH. In the HP-hMG group, 2 patients did not attend the oocyte retrieval visit because of insufficient endometrial thickness (1 patient) and degenerated oocyte (1 patient). In the rec-FSH group, oocyte retrieval was not performed in 1 patient due to endometrial thickness. The mean

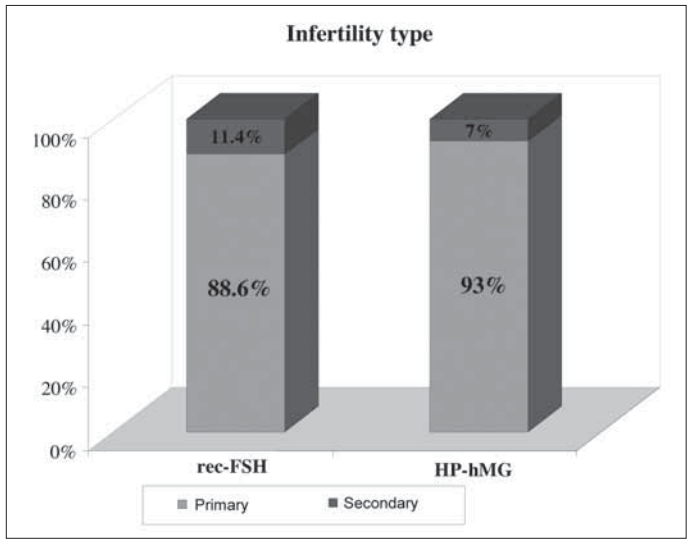

Figure 1. Distribution of infertility type in the groups

Table 1. Demographics and baseline characteristics of patients in the groups

		rec-FSH n (%)	HP-hMG n (%)	p
Age	<35	26 (59.1)	20 (46.5)	0.240
	≥35	18 (40.9)	23 (53.5)	
		mean±sd	mean±sd	
Weight (kg)		63.54±9.54	65.44±9.38	0.353
BMI (kg/m^2)		24.24±4.18	25.17±3.40	0.257
Antral follicles at day 1		10.58±3.98	9.21±3.28	0.087
Duration of infertility (years)		10.53±5.23	10.14±5.00	0.720
FSH (IU/I) at day 3		7.76±2.50	8.09±2.24	0.512
E_2 (IU/I) at day 3		59.97±22.37	59.74±34.04	0.970
Duration of GnRH agonist (days)		22.35±3.60	21.63±3.58	0.354
Duration of Gonadotropin (days)		9.37±1.46	9.51±1.62	0.677

Chi square test was used for age (p<0.05). Student's t-test was used for other parameters (p<0.05

number of oocytes retrieved was lower in the HP-hMG group compared with the rec-FSH group (p=0.029, Table 3). The mean number of oocytes fertilized was also lower in the HP-hMG group compared with the rec-FSH group (p=0.001, Table 3). Between the study groups, there were no significant differences in the number of embryos on day 2 and 3. The number of top-quality embryos did not differ between the patients of the two groups, but the rate of top-quality embryos to total embryos were significantly higher in the HP-hMG group (p=0.006, Table 3). The fertilization rate of rec-FSH group was significantly higher than HP-hMG group (p=0.001, Table 3). Embryo transfer was performed in 40 patients in the rec-FSH group and 28 patients in HP-hMG group. 3 patients in the rec-FSH group and 12 patients

in the HP-hMG group did not have embryo transfer due to lack of embryo. Fertilization failure was the main reason for embryo transfer cancellation. In 64 patients, embryo transfer was easy, while in 4 patients it was difficult.

In conclusion, no significant differences were observed between the study groups in terms of implantation, biochemical and clinical pregnancy, and ongoing pregnancy rates per randomized patient (Table 4).

Discussion

In the last decade, gonadotropins used in controlled ovarian stimulation have been increasing in number. Beside the recombinant preparations such as rec-FSH, rec-LH and h-HMG human-derived preparations have entered the markets. Highly purified human menopausal gonadotropin (HP-hMG) has been the last preparation that was used for infertility (11). The aim of this study was to compare the effect of rec-FSH and HP-hMG in the IVF protocol on the quality of acquired embryo and pregnancy outcome. Factors that can influence the outcomes were limited with the intention of providing homogenization in the study groups. In the latest meta-analysis, the ongoing pregnancy rate was 5% higher in the patients treated with HP-hMG than rec-FSH. The ongoing pregnancy rates were 27% with HP-hMG and 22% with rec-FSH, but no statistical difference was established (12). The first study to evaluate the quality of embryo in the study groups stimulated with rec FSH and HP-hMG was carried out by Ziebe et al. They observed the positive effect of gonadotropin with LH activity on the number of blastomeres and degree of fragmentation (13). In this study, the ongoing pregnancy rates were 38.9% in the rec-FSH group and 25.3% in the HP-hMG group. There was no statistical difference between the two groups ($p>0.05$) (Table 4).

Our study included only patients suitable for in vitro fertilization. The patients requiring Intra Cytoplasmic Sperm Injection (ICSI) were excluded. Furthermore, the patients who did not have embryo transfer were suitable for cancellation cycle criteria. These criteria included poor ovarian response and lack of qualified embryo. Andersen et al. found that the rate of embryo transfer in patients stimulated with rec-FSH and HP-hMG was 82% (14). In our study, the rate of embryo transfer was 90% in the rec-FSH group and 90.3% in the HP-hMG group. Between the two groups, no statistical difference was observed. Our outcomes are compatible with other studies (Table 3). Another argument is the effect of LH activity on ovarian response. There is insufficient information regardingt the number and development potential of retrieved oocytes. In 2004, Platteau et al. reported that the number of retrieved oocytes was higher in the patients stimulated with rec-FSH than HP-hMG. Interestingly, the number of top-quality embryo was higher in the HP-hMG group, while the number of retrieved oocytes was higher in rec-FSH group. According to this finding, the positive effect of LH activity on development and quality of oocytes was stated (5). Ziebe et al. reported that the mean number of retrieved oocytes was 11.8 in the rec-FSH group, whereas this was 10 in the HP-hMG group. The difference between the two groups were significant statistically ($p<0.001$). Also, they found

Table 2. Clinical parameters during stimulation in the groups

	rec-FSH (mean±sd)	HP-hMG (mean±sd)	p
E_2 (nmol/l) in day of hCG	2018.63±1083.77	1562.44±948.94	0.041*
Endometrial thickness (mm) in day of hCG	10.48±2.21	9.92±2.57	0.282
Total dose (IU)	3287.79±1012.97	3471.72±1121.80	0.427
Avarage daily dose (IU)	348.95±86.46	365.09±87.60	0.392
Student's t-test was used (*p<0.05)			

Table 3. Oocyte and embryo parameters after stimulation in the groups

	rec-FSH mean±sd	HP-hMG mean±sd	p
Oocytes retrieved	9.24±5.50	6.88±5.08	0.029*
Mature oocytes	7.88±4.95	5.24±4.10	0.010*
Number of oocytes fertilized	4.22±3.57	1.87±1.96	0.001*
Embryos on day 3 (total)	6.41±4.03	3.43±3.15	0.116
Embryos Transferred	2.25±0.80	2.18±0.90	0.825
Top quality embryos count in embryos on day 3 (total)	2.84±3.36	2.44±2.00	0.865
Top quality embryos/Total embryos	45.89±37.95	71.31±34.63	0.006*
	n (%)	n (%)	
Fertilization rate (%)	40 (90.9)	25 (58.1)	0.001*
Embryos transferred (%)	40 (90.9)	28 (90.3)	1.000
Mann-Whitney U test was used (*p<0.05)			

Table 4. Efficacy end points in the groups

		rec-FSH n %	HP-hMG n%	p
Biochemical pregnancy	+	10	8	0.839
		26.3	28.6	
	-	28	20	
		73.3	71.4	
Clinical pregnancy	+	8	6	0.812
		25.8	23.1	
	-	23	20	
		74.2	76.9	
Ongoing pregnancy	+	7	6	0.826
		38.9	35.3	
	-	11	11	
		61.1	64.7	
Chi square test was used (p<0.05)				

that the fertilization rate was 51.6% in the HP-hMG group and 52.6% in the rec-FSH group (p=0.065) (13). In the same study, the mean numbers of cells with 2 pronucleus at the 20th hour were 5.1±4.0 in the HP-hMG group, 6.0±4.3 in the rec-FSH group (13). In our study, the proportion of fertilization rate was 90.9% in the rec-FSH group, 58.1% in the HP-hMG group. There were significant statistical differences (p=0.001, Table 3). The mean numbers of cell with 2 pronucleus at the 20th hour were 1.87±1.96 in the HP-hMG group and 4.22±3.57 in the rec-FSH group. Between the two groups, patients stimulated with rec-FSH have a statistically higher fertilization number (p<0.01). The mean number of oocytes retrieved was significantly lower in the HP-hMG group compared with the rec-FSH group (p<0.05, Table 3). The numbers of mature oocytes differ between the treatment groups, and was found higher in the HP-hMG group than the rec-FSH group (p<0.005), but the proportion of mature oocytes to total oocytes retrieved was similar in the two groups (p=0.05, Table 3). The mechanisms whereby the LH activity could mediate improvements in some oocyte/embryo quality parameters in IVF cycles are not yet fully understood. Cumulus cells are considered an ideal surrogate for assessment of oocyte development potential. It is speculated that a set of cumulus genes may determine oocyte maturation, fertilization potential, and embryo quality (15). Magier et al. detected that cumulus cells have a positive effect on embryo development (16). Furthermore, cumulus cells and cytoplasmic maturation of oocytes that may be directed with LH activity was considered in some studies (5). Ziebe et al. obtained a higher percentage of top-quality embryos per oocyte retrieved from stimulation with HP-hMG. The subgroup of top-quality embryos obtained from HP-hMG-treated women was associated with increased ongoing implantation and pregnancy rates in comparison with rec-FSH-treated women (13). Formerly, articles had declared that LH activity with the effect of Rec-FSH increased the rates of implantation and pregnancy (17). In our study, the proportion of top-quality embryos per obtained oocyte in patients treated with HP-hMG and rec-FSH was 28.4% and 20.37%, respectively. We did not observe a statistical difference between the two groups (p>0.05). The rate of top-quality embryo to total embryo was 45.8% in rec-FSH and this rate was 71.31% in HP-hMG group. The higher proportion of HP-hMG group was significant statistically (p<0.001, Table 3). Information on ongoing pregnancy rate was not relevant between the rec-FSH and HP-hMG groups. In their study, Andersen and Coworkers conducted a research in which the ongoing pregnancy rate was 27% in the HP-hMG group and 22% in the rec-hMG group (14). In our study, the clinical pregnancy rates were 25.8 in the rec-FSH and 23.1 in the HP-hMG groups and the ongoing pregnancy rates were 38.9 and 35.3, respectively. However, the superiority of rec-FSH on the clinical and ongoing pregnancy rates are not shown statistically (p>0.05).

In conclusion, the higher oocyte yield with rec-FSH does not result in more high quality embryos. LH activity with the combination of FSH activity positively affected the oocyte and embryo maturation. Therefore, when we compare the clinical and ongoing pregnancy rates, there is no inferiority of HP-hMG in controlled ovarian stimulation.

Conflict of interest
None declared.

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Surgical second-look in epithelial ovarian cancer: high recurrence rate after negative results and lack of survival benefit limits its role in standard management

Epitelyal over kanserlerinde ikinci-bakı operasyonu: Negatif sonuçlardan sonra yüksek nüks oranı ve sağkalıma katkısının olmaması prosedürün standart yaklaşımdaki yararını sınırlamaktadır

Salih Taşkın, Mete Güngör, Elif Aylin Taşkın, Fırat Ortaç

Department of Obstetrics and Gynecology, Medical School, Ankara University, Ankara, Turkey

Abstract

Objective: To evaluate the role of surgical second look (SSL) in epithelial ovarian cancer.

Material and Methods: One hundred and seventy-one patients clinically free of disease were assessed retrospectively. Ninety-eight (57.3%) patients underwent SSL and 73 (42.7%) were observed. Fifty-one (52.0%) of the SSL operations were negative, 31 (31.6%) microscopically positive, and 16 (16.3%) macroscopically positive. Cytoreduction and/or chemotherapy were administered after positive SSL. Negative SSL and observation group patients were observed without treatment until recurrence was detected. Disease free survival (DFS), overall survival (OS) and clinical characteristics of groups were compared.

Results: While DFS and OS of negative SSL group were better than the observation , microscopic and macroscopic positive SSL groups ($p<.01$), no significant difference was found between positive SSL and observation groups ($p>.05$). However, DFS and OS of the microscopic positive SSL group were significantly longer than the macroscopic positive SSL group ($p<.01$). Thirty-two patients have had recurrences (62.8%) after negative SSL. Only the use of paclitaxel as first-line chemotherapy was seen to prevent recurrence after negative SSL ($p<.05$). Recurrence after negative SSL was not affected by stage, grade, age, CA-125 level, ascites volume, histologic type or optimal cytoreduction.

Conclusion: Rate of recurrence after negative SSL remains high, and secondary efforts following positive SSL could not lead to an obvious survival benefit. Therefore, routine use of SSL seems ineffective and unnecessary. (J Turkish-German Gynecol Assoc 2011; 12: 21-5)

Key words: Surgical second-look, ovarian cancer, recurrence, survival

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Özet

Amaç: Cerrahi ikinci-bakı'nın (CİB) epitelyal over kanserindeki rolü araştırılmıştır.

Gereç ve Yöntemler: Klinik olarak hastalıksız olan 171 hasta retrospektif olarak değerlendirilmiştir. 98 (%57.3) hastaya CİB uygulanmış ve 78 (%42.7) hasta takip edilmiştir. CİB yapılanların 51 (%52.0)'inde hastalık saptanmazken, 31 (%31.6) mikroskopik pozitif ve 16 (%16.3) makroskopik pozitifti. Pozitif CİB sonucu olanlara sitoredüksiyon ve/veya kemoterapi uygulanmıştır. Negatif CİB ve gözlenen grup ise nüks saptanana kadar tedavisiz takip edilmiştir. Gruplar hastalıksız sağkalım, toplam sağkalım ve klinik karakteristikler açısından karşılaştırılmıştır.

Bulgular: Hastalıksız sağkalım ve toplam sağkalım negatif CİB grubunda gözlem grubuna, mikroskopik ve makroskopik gruplara göre daha iyi olsa da ($p<.01$), pozitif CİB grubu ile gözlem grubu arasında fark yoktu ($p>.05$). Ancak hastalıksız sağkalım ve toplam sağkalım oranları mikroskopik CİB grubunda makroskopik pozitif CİB grubuna göre anlamlı düzeyde uzundu ($p<.01$). 32 hasta (%62.8) negatif CİB sonucundan sonra nüksetmiştir. Sadece ilk kemoterapide paklitaksel kullanımı negatif CİB sonucundan sonra daha az nüks oranıyla ilişkilidir ($p<.05$). Negatif CİB sonrası nüks ile evre, grade, yaş, CA-125 düzeyi, asit hacmi, histolojik tip ve optimal sitoredüksiyondan etkilenmemektedir.

Sonuç: Negatif CİB sonrası nüks oranı halen yüksek olup, pozitif CİB sonrası ikincil çabalar sağkalım için net bir yarar sağlamamaktadır. Bu nedenle rutin CİB uygulaması etkin ve gerekli değildir.

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Anahtar kelimeler: Cerrahi ikinci-bakı, over kanseri, nüks, sağkalım

Geliş Tarihi: 04 Kasım 2010 **Kabul Tarihi:** 17 Kasım 2010

Introduction

Surgical second-look (SSL) was introduced to evaluate response of an ovarian malignancy to primary surgery and chemotherapy four decades ago. However, its incorporation to standard management of epithelial ovarian cancers is still controversial. SSL is offered to patients clinically free of disease, based on physical examination, CA-125 and imaging studies, in order to define actual disease status, obtain prognostic information, identify the patients who might benefit from additional therapy such as chemotherapy or secondary cytoreduction finally resulting in improvement in survival. Noninvasive techniques remain unreliable to determine "complete response", so that nearly half of these patients turn out to be "positive" either macro- or microscopically after SSL, which is the gold standard for identifying residual disease (1).

Address for Correspondence / Yazışma Adresi: *Dr. Salih Taşkın, Ankara Üniversitesi Tıp Fakültesi, Kadın Hastalıkları ve Doğum Anabilim Dalı, 06100 Cebeci, Ankara, Turkey*
Phone: +90 312 595 78 69 e.mail: salihtaskin@yahoo.com
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On the other hand, recurrence rate approximates 50% after a negative SSL (2). Furthermore, a salvage chemotherapy proven to be effective is unfortunately absent for the cases shown to have persistent or progressive disease in SSL. Therefore, whether SSL provides either reliable prognostic information or survival benefit is questionable. In this study, we evaluated our experience with SSL in order to assess survival benefits of SSL and recurrence risk after negative SSL.

Patients and Methods

A total of 171 patients with epithelial ovarian cancer who underwent comprehensive staging surgery and treatment with platinum-based chemotherapy between January 1991 and December 2004 at Ankara University Faculty of Medicine, Department of Obstetrics and Gynecology, Gynecologic Oncology clinic were enrolled to this study and grouped into observation (n=73) and SSL (n=98) arms after their informed consents were obtained. According to the classification of the International Federation of Gynecological and Obstetrics (FIGO), 15 cases were classified as stage I, 11 as stage II, 142 as stage III and 3 as stage IV. Using World Health Organization criteria, 22 of the carcinomas were grade 1, 51 were grade 2, and 98 were grade 3. All patients were clinically disease-free based on physical examination, imaging studies and CA-125 levels at the time of enrollment. Optimal and suboptimal primary cytoreductions were defined as residual disease ≤1 cm and >1cm, respectively. Second-look surgery was performed by a gynecologic oncologist, 4 to 6 weeks after completion of primary chemotherapy. The second-look operations were standard second-look laparotomy or laparoscopy. SSL was performed according to previously defined standards (1). Secondary cytoreductions were performed in cases where tumor removal seemed technically possible.

Three pathologic response categories were defined based on SSL findings and pathologic examination (1). Negative SSL: no evidence of gross disease and negative pathology specimens and peritoneal washing (2). Macroscopic positive SSL: grossly visualized disease confirmed by pathologic examination and (3) Microscopic positive SSL: no macroscopic disease but positive biopsies or positive peritoneal washing.

Patients in the observation arm were treated if disease recurred during follow-up. Patients with negative SSL received no further therapy unless they subsequently relapsed. Microscopic or macroscopic positive SSL cases received salvage chemotherapy, which were individualized on the basis of prior treatment and surgical findings.

Overall survival (OS) and disease free survival (DFS) were defined as the time from the date of primary surgery to either death or recurrence, respectively, or date of last contact. Additionally, patients who died without clinical recurrence were censored.

Statically analyses

The Kaplan-Meier method was used to estimate the OS and DFS curves. The difference in curves was determined by the log rank method. All indicated P-values are based on two sided significance tests. P values smaller than 0.05 were reported as statically significant.

Results

Clinical characteristics of patients were summarized in Table 1. Out of 171 patients, 98 (57.3%) underwent second-look surgery by laparotomy or laparoscopy (SSL group) and 73 (42.7%) were observed (observation group). Mean age, histologic type and grade, ascites, optimal cytoreduction rate in primary surgery, and CA125 level at diagnosis were similar in two groups. Advanced stage disease and the use of paclitaxel in first-line chemotherapy were more common in the SSL group than the observation group (p<.01). The majority of SSL were performed by laparotomy (81 cases) and 17 cases by laparoscopy. Fifty-one (52.0%) of the SSL operations had negative results, 31 (31.6%) microscopically positive, and 16 (16.3%) macroscopically positive. The mean follow-up intervals of the SSL and observation groups were 42.28 and 25.61 months, respectively. Currently, 78 (45.6%) of all patients have died, while 93 (54.4%) are alive. In the negative SSL group,

Table 1. Patient characteristics

	SSL (n=98)	Observation (n=73)	p
Age, mean (years)	53.2	54.5	NS
Stage (n, %)			0.001
I	3 (3.1)	12 (16.4)	
II	3 (3.1)	8 (11.0)	
III	90 (91.8)	52 (71.2)	
IV	2 (2.0)	1 (1.4)	
Grade (n, %)			NS
1	10 (10.2)	12 (16.4)	
2	34 (34.7)	17 (23.3)	
3	54 (55.1)	44 (60.3)	
Histologic type (n, %)			NS
Serous	83 (84.7)	55 (75.3)	
Mucinous	4 (4.1)	9 (12.3)	
Endometrioid	6 (6.1)	6 (6.1)	
Clear cell	2 (2.0)	3 (4.1)	
Mixed	1 (1.0)	2 (2.7)	
Undifferentiated	2 (2.0)	2 (2.7)	
CA-125 (IU⁄ml)	496	707	NS
Ascites (ml)	1713	1432	NS
Paclitaxel use (n, %)	67 (68.4)	34 (46.6)	0.004
Optimal cytoreduction (n, %)	67 (68.4)	54 (73.9)	NS
Alive (n, %)	51 (52.0)	42 (57.5)	NS

Note: Percentage of total given in parentheses. SSL: Surgical second-look. NS: Not significant

18 are alive with no evidence of disease, 18 patients are alive with disease, 14 have died of disease and 1 has died (undefined cause). In the positive SSL group (microscopic or macroscopic positive) 3 patients are alive with no evidence of disease, 12 are alive with disease, and 32 have died of disease.

The Kaplan-Meier 2-, 3-, and 5-year OS for the SSL group were 85.5%, 65.4%, and 48.6%, respectively, compared to the observation group with 69.1%, 46.8%, and 29.0% (Figure 1, $p>0.05$). No significant difference was observed in DFS for the SSL and observation groups. While DFS and OS of the negative SSL group were better than the observation group, microscopic and macroscopic positive SSL groups ($p<.01$), no significant difference was found between positive SSL and observation groups ($p>.05$). However, DFS and OS (Figure 2) of the microscopic positive SSL group were significantly longer than the macroscopic positive SSL group ($p<.01$).

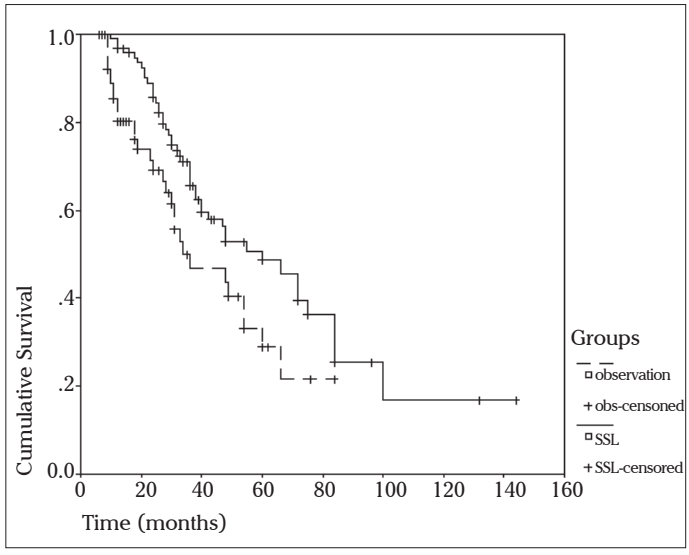

Figure 1. Overall survival for surgical second-look and observation groups (p:not significant)

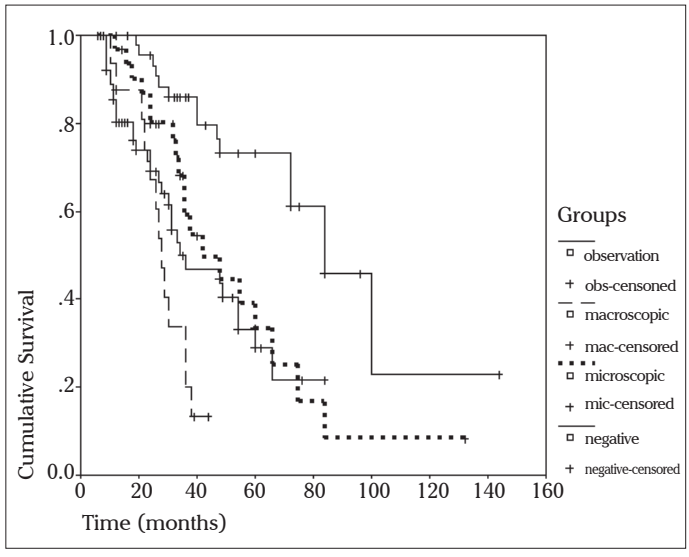

Figure 2. Overall survival of microscopic positive SSL group were significantly longer than macroscopic positive SSL group

Table 2 demonstrates clinical characteristics of the negative and positive SSL groups. While histologic grade, age and ascites volume at the primary surgery were significantly higher in the positive SSL group ($p<.05$), optimal cytoreduction rate was higher in the negative SSL group. No significant difference was found for other variables.

Clinical features of patients with negative SSL, with and without recurrence, are summarized in Table 3. Thirty-two patients recurred (62.8%) after negative SSL and 3.1%, 40%, and 68.7% of recurrences occurred in 1-, 2-, and 3-years after SSL, respectively (Follow-up: mean=34.09 months, median=27 months, range=12-120 months). Only the use of paclitaxel at first-line chemotherapy was seen to prevent recurrence after negative SSL ($p<.05$). Recurrence after negative SSL was not affected by stage, grade, age, CA-125 level, ascites volume, histologic type or optimal cytoreduction.

Discussion

SSL remains the best means in hand to evaluate the actual disease status in an ovarian cancer patient clinically free of disease after primary surgery and chemotherapy. Nearly half of these patients turn out to be positive after SSL. Negative SSL rates remain nearly constant for years, ranging from 35% to 55.1% (3, 4). The 52.0% incidence of negative SSL in this study is also similar. This result demonstrated once more that clinically complete response does not reflect actual disease status after primary therapy,in approximately half of the patients.

Recurrence rates following negative SSL remain unacceptably high, and reported to range between 27.9 and 61% (2, 4-6). Therefore negative SSL does not mean a cure. Inadequate sampling, or recurrences hard to visualize, e.g. hindered by adhesions, located in the retroperitoneum or lesser sac, are proposed as possible reasons underlying “false negativity”. In our series, 62.8% recurred after negative SSL. All recurrences were identified at least 1 year after SSL, and 2/3 of the cases between 1st and 3rd years. Previously, half of the recurrences following negative SSL were reported to occur in the first 2 years (6). Thus, negative SSL does not seem to be a precise indicator for discontinuation of chemotherapy. Barakat et al. (7) compared recurrence rates following negative SSL in stage II-IV patients in consolidation chemotherapy (intraperitoneal cisplatin and etoposid) and observation arms as 39 and 54% respectively. Similarly Tournigand et al. (8) reported survival benefit with use of intraperitoneal chemotherapy for consolidation. On the other hand, Gadducci et al. (2) and Varia et al. (6) could not detect any survival benefit between observation and consolidation chemotherapy after negative SSL. Therefore, more efficient new consolidation chemotherapy protocols should be investigated and may be reserved for patients under high recurrence risk after negative SSL (9, 10). Patients with negative SSL may constitute suitable randomization groups for these investigations.

Stage, histologic grade, amount of residual disease after first operation (5), age, chemotherapy protocol (11, 12) and initial disease in the omentum (6) were among the proposed risk factors for recurrence after negative SSL. Neither these, nor ascites, optimal cytoreduction at primary surgery or CA-125 at

Table 2. Comparison features of patients with Negative and Positive SSL results

	Negative SSL (n=51)	Positive SSL* (n=47)	p
Age, mean (years)	50.8	55.8	0.03
Stage (n, %)			NS
I	2 (3.9)	1 (2.1)	
II	3 (5.9)	0	
III	45 (88.2)	45 (95.7)	
IV	1 (2.0)	1 (2.1)	
Grade (n, %)			0.03
1	9 (17.6)	1 (2.1)	
2	18 (35.3)	16 (34.0)	
3	24 (47.1)	30 (63.8)	
Histologic type (n, %)			NS
Serous	42 (82.3)	41 (87.3)	
Mucinous	2 (3.9)	2 (4.3)	
Endometrioid	4 (7.8)	2 (4.3)	
Clear cell	1 (2)	1 (2.1)	
Mixed	0	1 (2.1)	
Undifferentiated	2 (3.9)	0	
Ascites (ml)	1229	2239	0.02
CA-125 (IU/ml)	445	551	NS
Paclitaxel use (n, %)	19 (37.3)	12 (25.5)	NS
Optimal cytoreduction (n, %)	40 (78.4)	27 (57.4)	0.03

Note: Percentage of total given in parentheses. SSL: Surgical second-look. *:Total of microscopic and macroscopic positive SSL cases. NS: Not significant

Table 3. Recurred and no recurred cases after Negative SSL result

	No recurrence after negative SSL (n=19, 37.2%)	Recurrence after negative SSL (n=32, 62.8%)	p
Age, mean (years)	50.3	51.1	NS
Stage (n, %)			NS
I	1(5.3)	1 (3.1)	
II	1 (5.3)	2 (6.3)	
III	17 (89.5)	28 (87.5)	
IV	0	1 (3.1)	
Grade (n, %)			NS
1	4 (21.1)	5 (15.6)	
2	6 (31.6)	12 (37.5)	
3	9 (47.4)	15 (46.9)	
Histologic type (n, %)			NS
Serous	16 (84.2)	26 (81.2)	
Mucinous	0	2 (6.3)	
Endometrioid	2 (10.5)	2 (6.3)	
Clear cell	1 (5.3)	0	
Undifferentiated		2 (6.3)	
Ascites (ml)	921	1412	NS
CA-125 (IU/ml)	403	470	NS
Paclitaxel use (n, %)	11 (57.9)	8 (25.0)	0.01
Optimal cytoreduction (n, %)	16 (84.2)	24 (75.0)	NS

Note: Percentage of total given in parentheses. SSL: Surgical second-look. NS: Not significant

diagnosis, were identified as associated with recurrence after negative SSL in our study. However paclitaxel administration in first-line chemotherapy is more common among patients in whom disease did not recur after negative SSL (57.9% versus 25.0%, p=0.01). This result conflicts with Friedman et al. (4) and Varia et al. (6) who detected no association with paclitaxel use in first-line chemotherapy and recurrence after negative SSL.

There are conflicting results in the literature on whether SSL provides survival benefit or not. While some authors state that SSL does not improve DFS or OS (11, 13-16), some others (17, 18) advocate the opposite. According to our results, DFS and OS are longer in patients with negative SSL than patients in the observation arm. Among those with positive SSL, disease-free and overall survival of microscopic positive cases was longer than macroscopic-positive cases. Also, no significant difference at DFS and OS was determined when the positive SSL group, either micro- or macroscopic, is compared to the observation group. So we can conclude that neither second-line chemotherapy protocols, nor secondary cytoreduction can improve survival up to the negative SSL group status, and information gained with SSL does not lead to a survival benefit (when compared to observation). DFS and OS of the negative SSL group is better when compared to the observation group, however SSL did not result in a change in management of this group of patients.

Histological grade, age, and ascites at primary surgery were higher and optimal cytoreduction rate was lower in the positive SSL group, when compared to the negative SSL. Therefore these parameters might have a prognostic significance to predict SSL results, and every effort should be made at initial surgery to resect the tumor as completely as possible. In contrast to its possible association with recurrence after negative SSL, paclitaxel use at first-line chemotherapy was also similar in both negative and positive SSL groups. In addition, stage, histological type, and CA 125 level were also similar. Friedman et al. (4) also reported that paclitaxel use was not associated with negative or positive SSL, in contrast to age and ascites volume which were determined to be risk factors for positive SSL.

Currently there is no better method or marker than SSL to evaluate the response to primary treatment in epithelial ovarian cancer. Nevertheless, the rate of recurrence after negative

SSL remains high, and secondary efforts following positive SSL could not lead to an obvious survival benefit. Therefore, according to results of this and many other studies, routine use of SSL in the management of epithelial ovarian cancers seems ineffective and unnecessary.

Conflict of interest
None declared.

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Preeclampsia and eclampsia incidence in the eastern anatolia region of Turkey: the effects of high altitude

Türkiye'nin Doğu Anadolu Bölgesinde preklampsi ve eklampsi insidansı: Yüksek rakımın etkileri

Yakup Kumtepe[1], Onur Dündar[2], Kadir Çetinkaya[3], Metin İngeç[1]

[1]Department of Obstetrics and Gynecology, Faculty of Medicine, Atatürk University, Erzurum, Turkey

[2]Department of Obstetrics and Gynecology, Trabzon Women's Hospital, Trabzon, Turkey

[3]Department of Obstetrics and Gynecology, Ankara Oncology Education and Research Hospital, Ankara, Turkey

Abstract

Objective: Hypertensive disorders of pregnancy remain a leading cause of maternal and perinatal mortality and morbidity. The purpose of this study was to determine the distribution map related to pregnancy toxicosis of provinces in our region and the effects of altitude on hemolysis, elevated liver enzymes, low platelets (HELLP) syndrome and eclampsia.

Materials and Methods: Patients who were admitted to Atatürk University, Obstetrics and Gynecology Department with preeclampsia, eclampsia and a diagnosis of HELLP syndrome for the 5 years between1998-2002 were chosen. The birth rate was obtained from the health directorate of provinces in our area during the same period. Provinces were divided into two groups by altitude: less than and more than 1500 m above sea level.

Results: The rates of HELLP syndrome and eclampsia diagnoses were 1.4 per 10.000 patients living above 1500 m altitude. However, this rate was 0.96 per 10.000 patients living below 1500 m altitude ($p < 0.01$). The highest rate of eclampsia and HELLP syndrome was seen in the Ardahan province, in 36 patients per 10,000 births, whereas the lowest rate was seen in the Iğdır province, 9.9 patients per 10,000 births.

Conclusion: Altitude contributes to occurrence of HELLP syndrome and eclampsia. Since the rate of pregnancy related hypertension is higher at high altitude, it is vital that these patients should be diagnosed during the early stages of the diseases in order to decrease complications.

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Key words: Preeclampsia, eclampsia, HELLP syndrome, high altitude

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Özet

Amaç: Gebeliğin hipertansif hastalıkları maternal ve perinatal mortalite ve morbiditenin önde gelen sebebi olmaya devam etmektedir. Bu çalışmanın amacı, bölgemizdeki illere gore gebelik toksikozu dağılım haritası çıkarmak ve hemoliz, yükselmiş karaciğer enzimleri, düşük platelet (HELLP) sendromu ve eklampsi üzerine yüksek rakımın etkilerini belirlemektir.

Gereç ve Yöntemler: Atatürk Üniversitesi, Kadın Hastalıkları ve Doğum bölümüne 1998-2002 yılları arasında 5 yıllık bir dönemde preeklampsi, eklampsi ve HELLP tanısı ile başvuran hastalar seçildi. Aynı dönemde, il sağlık müdürlüklerinden doğum hızları temin edildi. Deniz seviyesine göre 1500 m altında ve üstünde olmak üzere iller iki gruba ayrıldı.

Bulgular: HELLP sendromu ve eklampsi tanıları 1500 m üzerinde 10.000 doğumda 1.4 izlenirken, 1500 m altında 0.96 izlenmiştir ($p<0.01$). En yüksek HELLP sendromu ve eklampsi Ardahan ilinde 10.000 doğumda 36 izlenirken, en düşük Iğdır ilinde 10.000'de 9.9 olarak izlenmiştir.

Sonuç: Rakım, HELLP sendromu ve eklampsi oluşumunda rol alır. Yüksek rakımda yaşayanlarda gebelik ile ilişkili hipertansif hastalıkların daha yüksek oranda izlendiği için komplikasyonların azaltılabilmesinde hastalığın erken dönemlerinde tanı alması hayati önem taşımaktadır.

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Anahtar kelimeler: Preeklampsi, eklampsi, HELLP sendromu, yüksek rakım

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Introduction

There is a prominent increase in all arterial flow (consequently, uterine artery blood flow), a decrease in the vasoconstrictor response of the vascular system, and an increase in the vasodilator response during normal pregnancy (1). The results of animal-based studies have shown that there is a decreased response to alpha-adrenergic stimulation of the vascular system and an increase in endothelium-dependent vasodilatation caused by increased basal and stimulated endothelium-derived nitric oxide (2, 3). However, in pregnancies developing preeclampsia at a later stage, there is evidence of vasoconstriction, increased vascular tone, platelet aggregation, and an alteration in the thromboxane-to-prostacyclin ratio (4). Maternal and fetal morbidity and mortality rates increase in hypertensive disorders of pregnancy (5).

Preeclampsia is seen in 2-7% of all pregnancies, and its frequency is higher in primigravid than in multigravid women

Address for Correspondence / Yazışma Adresi: *Dr. Kadir Çetinkaya, Yaşamkent Mahallesi, 3251. Cadde, Kozluevler No: 2/28, Yaşamkent, Yenimahalle, Ankara, Turkey*
Mobile: +90 505 388 44 13 Fax: +90 312 336 34 39 e.mail: kacetinkaya@gmail.com
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(6, 7). It is also more frequently seen in women carrying more than one fetus, older women, women with genetic factors, hyperlipidemia, thrombophilia, obesity, and diabetes mellitus, women experiencing preeclampsia during a previous pregnancy, and those living at high altitudes (8-13).

Preeclampsia is a multisystem disease that affects both mother and fetus. There is a progressive loss of musculoelastic tissue on spiral arteries in normal placental development, because extravillous cytotrophoblasts migrate up the spiral arteries and cause an erosion of the vascular smooth-muscle layer of the maternal spiral arteries, resulting in a loss of vasoactivity, subsequent dilatation, and a decrease in uteroplacental vascular resistance (9). Thus, uterine blood flow increases approximately 25% throughout the first trimester. However, in women living at high altitude, hypoxia inhibits the transition of the trophoblast from a resting, proliferative phenotype to an invasive phenotype and, hence, may inhibit arterial remodeling (10). As a result, maternal arterial oxygen pressure and uterine blood flow decrease at high altitude (11). This physiological dilatation does not occur in patients prone to preeclampsia, because placental trophoblastic cells do not wrap up spiral arteries, therefore spiral arteries are tightened and shortened, and uteroplacental blood flow decreases (14). Because of increased hypoxia, living at high altitude causes important health problems. Studies have revealed that intrauterine growth restriction (IUGR), preterm labor, abruptio placentae, and preeclampsia increase with increasing altitude (12, 15). Hemolysis, elevated liver enzymes, and low platelet count (HELLP) syndrome were first reported by Weinstein (16) in 1982, and immediate termination of pregnancy was proposed because of high maternal and perinatal mortality rates. However, Weinstein did not announce a cut off value of parameters. The cut off values for HELLP syndrome that are used now were defined by Sibai (17) in 1990. Eclampsia and preeclampsia are serious problems and account for 10% of maternal mortality worldwide (18). HELLP syndrome can be considered a serious variant of preeclampsia, and it occurs in 0.90% of all pregnancies and in 10-20% of cases with severe preeclampisa (19). Associated with liver, kidney, and serious coagulation disorders, HELLP syndrome carries significant maternal and perinatal risk, because disseminated intravascular coagulation (DIC), abruptio placenta, acute renal problems, pulmonary edema, subcapsular liver hematoma, and retinal detachment are frequently seen in HELLP syndrome (4). The purpose of the present study was to determine the rates of HELLP syndrome, preeclampsia, and eclampsia in association with altitude.

Material and Methods

The study was carried out retrospectively by medical record examination, in patients with preeclampsia-eclampsia who had been admitted to Atatürk University, Faculty of Medicine, Department of Obstetrics and Gynecology during the period between 1998-2002. The total number of births that took place in the Eastern Anatolia Region of Turkey during this 5-year-period was obtained from the Health Directorate of Provinces. During the same time, the numbers of births and patients with preeclampsia, eclampsia, and HELLP syndrome were recorded. Patients from the city of Erzurum and its provinces and neighboring cities were divided into 2 groups according to altitude (Table 1). Group 1, patients living at over 1500 m, included Karaçoban (1945 m), Köprüköy (1747 m), Tortum (1772 m), Pasinler (1660 m), Aşkale (1700 m), Narman (1830 m), Çat (1920 m), Karayazı (2260 m), and Hınıs (1795 m) provinces and Bayburt (1680 m), Ağrı (1738 m), Kars (1859 m), Ardahan (1929 m), Erzurum (1864 m) city centers. Group 2, patients living at under 1500 m, included Ispir (1222 m), Olur (1300 m), Uzundere (1300 m), and Oltu (1229 m) provinces and Artvin (628 m), Iğdır (758 m), Bingöl (1177 m), Erzincan (1058 m), and Muş (1224 m) city centers.

Preeclampsia was defined in accordance with the criteria of the American College of Obstetrics and Gynecology (20). Mild preeclampsia was diagnosed if systolic blood pressure was ≥140 mmHg, diastolic blood pressure was ≥90 mmHg, and proteinurea was ≥0.3 g/L in a 24-hour urine sample. Severe preeclampsia was diagnosed when one of the following criteria was present: (1) blood pressure ≥160 mmHg systolic or ≥110 mmHg diastolic on two occasions at least 6 hours apart with the patient on bed rest, (2) proteinurea ≥5 g in a 24-hour urine collection or ≥3+ on dipstick in at least two random clean-catch samples at least 4 hours apart, or (3) eclampsia. Eclampsia was diagnosed if the patient who had previously been diagnosed with preeclampsia had convulsions, once other causes of convulsions had been ruled out.

To determine mean hypertension, mean arterial pressure (MAP) was calculated [MAP = (2×diastolic pressure + systolic pressure)/3] after admission and before treatment for each patient. HELLP syndrome was diagnosed according to strict Sibai criteria (17) as follows:

Table 1. Altitudes of provinces and districts

Group 1 (>1500 m)		Group 2 (<1500 m)	
Province/district	**Altitude (m)**	**Province/district**	**Altitude (m)**
Erzurum (Karaçoban)	1945	Artvin	628
Erzurum (Köprüköy)	1747	Iğdır	758
Erzurum (Tortum)	1772	Bingöl	1177
Bayburt	1680	Erzincan	1058
Ağrı	1738	Erzurum (İspir)	1222
Erzurum (Aşkale)	1700	Erzurum (Uzundere)	1300
Erzurum (Narman)	1830	Erzurum (Olur)	1300
Erzurum (Hınıs)	1795	Muş	1224
Kars	1859	Erzurum (Oltu)	1229
Ardahan	1929		
Erzurum (Centre)	1864		
Erzurum (Çat)	1920		
Erzurum (Karayazı)	2260		
Mean	1849.2±150.7	Mean	1099.6±243.5

1. Hemolysis: characteristic appearance of peripheral blood smear and serum LDH ≥600 U/L or serum total bilirubin ≥1.2 mg /dL.
2. Elevated liver enzymes: AST concentration ≥70 U/L.
3. Low platelet count: <100,000 cells/μL.

The patients who had all these 3 indications and those who had 1 and/or 2 of these indications were categorized as complete and partial HELLP syndrome.

Our database included only the patients with HELLP syndrome and eclampsia. Maternal age, gravidity, parity, and gestational age were recorded in patients with HELLP syndrome and eclampsia in both groups. Numbers of Cesarean births were obtained for an evaluation of birth position for both groups. Fetal or live birth numbers and birth weights were recorded to evaluate the fetal situation. Platelet count as well as aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactate dehydrogenase (LDH), bilirubin, and uric acid levels in blood were analyzed to evaluate the incidence rate of HELLP syndrome.

Statistical analyses were performed using the Minitab Packed program, and differences between groups were determined by the Mann Whitney U test. Data are given as mean ± standard deviation.

Results

The total number of births was 114,819 in group 1 and 81,454 births in group 2 over the 5-year period (1998-2002) (Table 2). In group1, there was a total of 164 diagnosed patients (HELLP+ eclampsia) and 75 of these had eclampsia (54 patients accompanied by HELLP syndrome and 21 patients accompanied by preeclampsia). In group 2, there was a total of 78 diagnosed patients (HELLP+eclampsia) and 45 had eclampsia (33 patients accompanied by HELLP syndrome and 12 patients accompanied by preeclampsia) (Table 3).

There were no differences in the two groups for age, gravidity, parity, gestational age, normal birth rate, and fetal weight. Cesarean births in groups 1 and 2 were 94 (57%) and 44 (56%), respectively. Platelet count and concentrations of AST and LDH were 87.648±109.970/μl, 172±237 IU/L, and 1366±1293 IU/L, respectively in patients in group 1 (>1500 m altitude) and 96.347±109.970/μl, 146±109 IU/L, and 1208±755 IU/L, respectively in patients in group 2 (<1500 m altitude) (Table 4).

During this study, 8100 births occurred in our clinic, and in 582 cases preeclampsia and eclampsia were diagnosed (7.2%). A total of 242 patients were evaluated for HELLP syndrome and eclampsia, and 10 patients were excluded from the study because of a high level of liver enzymes suggesting viral hepatitis in 4 patients, DIC owing to an intrauterine dead fetus in 3 patients, and hepatotoxic medicine usage in 3 patients. In group 1, of 144 patients who were suspected of having HELLP syndrome, there were 69 (48%) with complete and 75 (52%) with partial HELLP syndrome. Of 75 patients with partial HELLP syndrome, AST level was >70 IU/L in 38 patients, AST level and platelet count were >70 IU/L and <100,000/μl in 19 patients, and the platelet count was <100,000/μl in 17 patients. When parity and maternal age in patients with complete and partial HELLP syndrome were considered in group 1, maternal age and parity in patients with complete and partial HELLP syndrome were 32.6±5.6 and 3.6±3.8 and 27.0±4.3 and 3.4±3.2, respectively. In group 2, of 66 patients suspected as having HELLP syndrome, patients with complete and partial HELLP syndrome were 27 (40.9%) and 39 (59.1%), respectively. Of 39 patients with partial HELLP syndrome, the AST level was >70 IU/L in 12 patients, and AST and platelet count were >70 IU/L and <100,000 /μl in 19 patients, respectively. The platelet count was <100,000/μl in 5 patients. Parity and maternal age in patients with complete and partial HELLP syndrome were 2.9±1.6 and 26.7±5.3 and 2.4±1.6 and 25.5±5.2, respectively.

The rates of HELLP syndrome and eclampsia per 10,000 births in provinces are shown in Figure 1. When the incidence rate of HELLP syndrome and eclampsia were evaluated, the highest rate was seen in the Ardahan province (36 per 10,000 births). With 28 per 10,000 births, Artvin had the second-highest rate, and Erzurum, Kars, Ağrı, Bayburt, Muş, Bingöl, Erzincan, and Iğdır followed these provinces.

Table 2. Birth numbers in subject populations

Groups	Year					
Group 1 (altitude >1500 m)	**1998**	**1999**	**2000**	**2001**	**2002**	**Total**
Ağrı	5746	7984	7885	7853	7950	37418
Ardahan	210	1082	1532	974	1071	4869
Bayburt	1215	1563	1308	1197	1092	6375
Erzurum+	15200	13813	14689	12969	7517	50108
Kars	3028	2896	2600	3208	4317	16049
Grand Total						114819
Group 2 (altitude <1500 m)						
Artvin	1816	1749	1775	1339	1377	8056
Bingöl	2634	2508	2550	2561	1921	12174
Erzincan	4363	5658	6009	5039	3521	24590
Iğdır	2118	1739	1093	1369	1547	7866
Muş	2234	3050	3309	3479	2616	14688
Erzurum++	2852	2951	2742	2789	2746	14080
Grand Total						81454

+Erzurum centre and Aşkale, Hınıs, Çat, Karayazı, Karaçoban, Horasan, Pasinler, Köprüköy, Tortum, and Şenkaya districts.
++Oltu, Olur, İspir, and Uzundere districts

Table 3. Patients with HELLP syndrome and eclampsia

Diagnosis	Group 1 (altitude >1500 m)	Group 2 (altitude <1500 m)
Total patients	164	78
Total HELLP	143	66
Eclampsia	75	45
Eclampsia accompanied by HELLP	54	33

Table 4. Comparison of parameters in subject populations

Parameter	Group 1 (n:164) (altitude >1500 m)	Group 2 (n:78) (altitude <1500 m)	p
Altitude (m)	1040±287	1736±122	<0.01
Age (years)	28.6±7.3	26.0±6.0	ns
Gravidity (n)	2.8±2.6	2.7±2.6	ns
Parity (n)	1.6±2.0	1.4±2.1	ns
Gestational age (year)	35.2±5.4	34.0±5.1	ns
MAP (mmHg)	124.4±9.2	118.4±8.6	ns
Hb (g/dl)	12.9±2.2	11.7±2.2	ns
Thrombocyte (/μl)	87,648±109.9	96,347.0±107.0	<0.05
AST (IU/L)	172.0±237.0	130.5±150.9	<0.01
ALT (IU/L)	286.0±91.0	111.7±208.0	0.01
LDH (IU/L)	1208.0±755.0	1366.0±1293.0	ns
Uric acid (mg/dl)	7.2±2.4	6.7±2.7	ns
Birth weight (g)	2031±964	2197±893	ns
Cesarean rate (%)	57	56	ns
Fetal death (%)	38	17	<0.01

ns=not significant

Discussion

Women living at high altitude have low uterine blood flow (21) and a high rate of IUGR (22). The maternal arterial system is normally insensitive to pressor agents in the circulation (23). However, in the case of a deterioration of insensitivity due to uteroplacental ischemia resulting from extreme vasoconstriction, hypoxia develops and this causes IUGR, maternal hypertension, and endothelial cell damage. Indeed, hypoxia deteriorates the arterial structure causing decreased sensitivity against vasoconstriction in pregnancy (24). These suggest that, because of increasing hypoxia, a higher rate of damaged placenta is the reason for increasing rates of preeclampsia at high altitudes.

Barometric pressure decreases with increasing altitude; pressure at sea level is 760 mmHg and this decreases to 490 mmHg at 4000 m altitude (25). Besides, arterial PO_2 and hemoglobin O_2 saturation, which are 95 mmHg and 87% at sea level, decline to 50 mmHg and 80%, respectively, at high altitude (25). Hypoxia causes venous damages which is associated with low birth weight, thrombosis, and preeclampsia (25, 26). Kametas et al. (27) observed a 15% decrease in plasma volume in pregnancy as altitude increased. The increased erythrocyte mass and decreased plasma volume cause hemoconcentration and hyperviscosity, and consequently a decrease in fetoplacental blood flow which could lead to IUGR and preeclampsia (28).

Sibai et al. (29) reported that mean maternal age was 27.4±6.7 in their study. In the present study, in patients with HELLP syndrome, maternal ages were 28.6±7.3 in group 1 and 26.0±6.0 in group 2. In this study, maternal age, gravidity, parity, and gestational age were insignificant, but hemoglobin levels increased with altitude (12.9 vs. 11.7 g/L in Group 1 and 2; p<0.01). Palmer et al. (12) revealed that the incidence of preeclampsia at 3100 m and 1260 m was 16% and 3%, respectively, and it increased with increasing altitude. In the present study, overall preeclampsia and eclampsia incidence rate was 7.2% (n=582) during the last 5 years, which is in agreement with the literature (6, 7). Taking patients with HELLP syndrome and eclampsia into consideration, we aimed to determine the present situation in the Eastern Anatolian region. With 209 cases in the past 5 years, HELLP syndrome occurred in 2.6% of total births and 36% of preeclamptic patients in our clinic. It was reported that HELLP syndrome progressed in 4-12% of preeclamptic patients (30). In the present study, the rates of HELLP syndrome are 3-9 times higher than literature findings. This could be due to the fact that preeclamptic patients seek health care only when their health status is complicated by conditions such as HELLP syndrome and eclampsia.

Total birth number and the number of cases of HELLP syndrome and eclampsia in the last 5 years were 114,899 and 164, respectively, in places higher than 1500 m altitude. The rate of HELLP syndrome and eclampsia was 0.14%, in places lower than 500 m altitude, the total birth number was 81,374, and the rate of cases of HELLP syndrome and eclampsia was 0.096% (p<0.01). When the rate for HELLP syndrome and eclampsia is combined, the rate in places higher than 1500 m altitude was much higher than in places below 1500 m altitude. The highest rate was seen in Ardahan (36 cases per 10,000 births), and the lowest rate was seen in Iğdır (9.8 cases per 10,000 births).

When HELLP syndrome and eclampsia rates were considered, it could be clearly seen that provinces with similar altitudes have similar rates; for example, 22.9 in Erzurum (1864 m.), 18.8 in Kars (1875 m.) and Ağrı (1732 m.), and 18.0 in Bayburt (1684 m.). Although the Ardahan province has a similar altitude (1929 m.), the rate in this province was 36. Likewise, Artvin is located at low altitude, the rate, 28 per 10,000 births, was much higher than the group mean (11.5). This could be related to other nutritional and environmental factors that could contribute to preeclampsia. On the other hand, with 9.9 and 10 cases per 10.000 births, Iğdır and Erzincan in group 2 (<1500 m altitude) had the lowest rates among the other provinces.

Liver impairment could result in serious problems in HELLP syndrome and plays a vital role in mortality; it is the cause of 1 out of 6 maternal mortalities (4). Elevations in enzyme levels, especially AST, indicate liver impairment. Leakage of enzymes from cell membranes to the blood is the reason for high enzyme levels in HELLP syndrome. With 172.0±237.0 IU/L (72-1061), AST levels in group 1 were significantly higher (p<0.01) than those in group 2, 130.5±150.9 IU/L (82-1064). It could be inferred that, with increasing altitude, a higher rate of HELLP syndrome was seen.

With 166 g difference, fetal weight was found to be lower in group 1 than group 2 (2031±964 g in group 1 and 2197±893 in group 2). Palmer et al. (12) reported that with 285 g difference, people living at 3100 m altitude had a lower fetal weight than those at 1260 m altitude. At 38%, (62 cases), the fetal death rate in group 1 was higher than that in group 2 with 18% (14

cases), but no studies of high fetal death rates at high altitude could be found in the literature. However, it is clear that, in our study, death rate of preeclamptic babies at high altitude is about twice that at lower altitude. The eclampsia rate is about 1 in 2000 pregnancies in developed countries (31), whereas this rate was determined to be 1 in 100-1700 pregnancies in developing countries, and eclampsia is still the reason for 10% of maternal mortalities (18). Chen et al. (32) reported that this rate in Singapore is 6.7 per 10,000 pregnancies. With 45 cases, our eclampsia rate is similar to rates found in that study. The etiological relation of HELLP syndrome and eclampsia to preeclampsia is not well known. Moreover, it was previously thought that abnormal trophoblast invasion of uterine arteries, immunological intolerance between fetoplacental and maternal tissue, maladaptation to cardiovascular changes of pregnancy, dietary deficiency, and genetic abnormalities could affect these illnesses (33).

Our study demonstrated a greater incidence of eclampsia accompanied by complete and/or incomplete HELLP syndrome among women living at high altitude (>1500 m). However, our results have certain limitations that probably contribute to this illness, such as economical and nutritional status, diagnosis time relative to disease onset, and interactions among these and other unmentioned causes.

Conflict of interest

None declared.

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Comparison of two WHO partographs: a one year randomized controlled trial

İki DSÖ partografının karşılaştırılması: Bir yıllık randomize kontrollü çalışma

Swamy Mallaiah Kenchaveeriah, Kamal Prakash Patil, Tania Gurudeep Singh

Department of Obstetrics and Gynaecology, Kle University, Jawaharlal Nehru Medical College, Belgaum, Karnataka, India

Abstract

Objective: To compare two World Health Organization (WHO) partographs - a composite partograph including the latent phase with a simplified one without the latent phase in women with uncomplicated pregnancy.

Material and Methods: This was a randomized controlled trial conducted at a tertiary hospital at Belgaum, India. 743 women with term, singleton, vertex gestation, in spontaneous labor were included in the study over a period of one year. Either of the partographs was used on laboring women. The following outcomes were compared: labor crossing the alert and action line, augmentation of labor, rate of cesarean section, perinatal outcome, user friendliness and maternal complications. Statistical analysis was done using Chi-square test.

Results: Labor values crossed the alert and action lines significantly more often when composite partograph was used ($p<0.001$) in each, with increased number of augmentations ($p<0.001$). The number of vaginal deliveries were high ($p<0.005$) in the simplified group. There was no significant difference in the rate of cesarean deliveries due to non progress of labor in both groups ($p=0.68$). NICU admissions were higher in the composite group ($p=0.035$). Most resident doctors (93%) experienced difficulty with the composite partograph, but no resident doctor reported difficulty with the simplified partograph. The mean SD user friendliness score was lower for the composite partograph (2.87 ± 1.86 vs 10.67 ± 1.61; $p<0.005$).

Conclusion: The WHO simplified partograph is easier to use and is a better option for both the laboring women and the user, when compared to composite partograph.

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Key words: World Health Organization, partograph, latent phase, action line, alert line, user friendliness

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Özet

Amaç: İki Dünya Sağlık Örgütü (DSÖ) partografını karşılaştırmak - komplike olmamış gebeliği olan kadınlarda latent fazı içeren bileşik bir partograf ile latent fazı olmayan basit bir partograf.

Gereç ve Yöntemler: Bu çalışma Belgaum, Hindistan'da üçüncü basamak bir hastanede yapılmış randomize kontrollü bir çalışmadır. Çalışmaya bir yıllık süre içinde termde, tekil gebeliği, baş gelişi ve spontan doğum sancısı olan 743 kadın dahil edildi. Doğum sancısı olan kadınlarda partograflardan biri kullanıldı. Aşağıdaki sonuçlar karşılaştırıldı: alarm ve eylem çizgisini geçen doğum sancısı, suni sancı, sezaryen doğum oranı, perinatal sonuç, kullanım kolaylığı ve maternal komplikasyonlar. İstatistiksel analiz Ki-kare testi kullanılarak yapıldı.

Bulgular: Bileşik partograf kullanıldığında doğum sancısı değerleri alarm ve eylem çizgilerini daha sıklıkla geçti ($p<0.001$) ve hepsinde suni sancı sayısı arttı ($p<0.001$). Basitleştirilmiş grupta vajinal doğum sayısı yüksekti ($p<0.005$). Her iki grup arasında doğumun ilerlememesi nedeniyle yapılan sezaryen doğum oranı açısından anlamlı farklılık yoktu ($p=0.68$). YYBÜ'ne yatışlar bileşik grupta daha fazlaydı ($p=0.035$). Asistan doktorların çoğu (%93) bileşik partograf ile zorluk yaşadı ancak asistan doktorların hiçbiri basitleştirilmiş partograf ile bir zorluk bildirmedi. Ortalama SS kullanım kolaylığı skoru bileşik partograf için daha düşüktü (2.87 ± 1.86'ya karşılık 10.67 ± 1.61; $p<0.005$).

Sonuç: DSÖ basitleştirilmiş partografının kullanımı daha kolaydır ve bileşik partografa kıyasla hem doğum sancısındaki kadın hem de kullanıcı için daha iyi bir seçenektir.

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Anahtar kelimeler: Dünya Sağlık Örgütü, partograf, geç faz, eylem çizgisi, alarm çizgisi, kullanım kolaylığı

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Introduction

Partograph is a Greek word meaning "Labor Curve"(1). It is a graphic recording of progress of labor and salient features in the mother and fetus. It detects labor that is not progressing normally, indicates when augmentation of labor is appropriate and recognizes cephalo-pelvic disproportion long before labor becomes "obstructed". It serves as an early warning system and assists in early decision making on transfer, augmentation and termination of labour (2).

Obstructed labor remains an important cause of not only maternal death but also short and long term disability. India has a high maternal mortality of about 300-500 per 100,000 births, of which 10% are due to obstructed labor (3-5). To reduce the maternal mortality rate, the problem of obstructed labor will need to be addressed effectively. Improved outcome after obstructed labor requires early detection of abnormal progress of labor, which can be easily identified with the use of a partograph.

The development of a partograph started in 1970, when Philpott's partograph was developed from the original cervi-

Address for Correspondence / Yazışma Adresi: *Prof. Dr. Swamy Mallaiah Kenchaveeriah, Department of Obstetrics and Gynaecology Belgaum, India*
Phone:00 91 831 2470147 e.mail: mkswamy53@yahoo.co.in
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cograph of Friedman (6). But its use was only rigorously evaluated 20 years after its introduction (7). It was only in 1994 that WHO devised the composite partograph. It included a latent phase of 8 hours. It was an adaptation of the one formulated and described by Philpott and colleagues (8).

Since the first publications on cervicography, the issue of the latent phase has been controversial, (9) as there is always a risk of inappropriate interventions if undue attention is paid to the latent phase (10). Subsequently, in 2000 the WHO produced the modified partograph where the latent phase was removed, to make it simpler and easier to use (11).

In India, the use of the partograph has not been incorporated and practiced widely, even at the tertiary level. There is very limited data available in Indian literature, comparing the two WHO partographs. Comparison of the two WHO partographs (a composite one with a latent phase and a simplified one without a latent phase) can tell which partograph is associated with better maternal and perinatal outcomes and is more user friendly. Hence, the present study was undertaken to highlight the efficacy of either WHO partograph, so that the partograph becomes a routine practice in our setup.

Materials and Methods

This randomized controlled trial was conducted at a tertiary care hospital, Belgaum, India, from November 2008 to October 2009, after having obtained clearance from the institutional ethical committee. All women with uncomplicated, singleton, term, vertex gestations, in spontaneous labor and those willing to participate after informed and written consent, were included in the study.

The sample size was calculated using the formula $N=(Z\alpha+Z\beta)^2 \times 2p(1-p)\div d^2$,taking the level of significance as 5%, $Z\alpha=1.96$ and power of the test as 80%, $Z\beta=0.84$. $p=0.113$. A sample size of 65 in each group was calculated. However, since the study was conducted over a period of one year, all women meeting the inclusion criteria were included. Hence a total of 743 women were studied. Either partograph was used according to computer generated random number table.

Exclusion criteria included women with short stature (<140cm.), antepartum haemorrhage, severe preeclampsia / eclampsia, anaemia (haemoglobin <10g), malpresentations, multiple pregnancy, previous caesarean section, preterm labor, fetal distress and intrauterine death. The partograph was started after establishment of true labor defined as the presence of uterine contractions with show with or without cervical changes. A total of 31 resident doctors working in 12 hour shifts at this teaching hospital were instructed to use both the partographs.

The plotting of the composite partograph was started as soon as the woman was in labor. In the simplified partograph, the plotting of the partograph was started with ≥4 cm of cervical dilatation. Labor was monitored until delivery. The outcome was reported at the bottom of each partograph. The outcomes noted were labors crossing the alert and action line, augmentation of labor, rate of cesarean section, perinatal outcome, user friendliness and maternal complications.

Analysis was made using Chi-square test and p value less than 0.05 was considered significant.

Non progress of labour was defined as labour crossing the alert line after four hours. Cephalo pelvic disproportion (CPD) was defined as disproportion between the fetal head and the pelvis in active labour (non descent of the head at 4cm of cervical dilatation after rupture of membranes). Failed ventouse was defined when vaginal delivery did not occur after 3 pop offs. Prolonged labour was defined when the woman was in labour for more than twelve hours in the active phase.

Results

The total numbers of deliveries were 3110, of which 743 women fulfilled the inclusion criteria and were enrolled in the study. Out of 350 patients in thecomposite group, 192 were primigravidae and 158 were multigravidae. 204 primgravida and 189multigravida were enrolled in the simplified partograph group as shown in Table 1.

In this study labor values crossed the alert and action lines significantly more often when the composite partograph was used ($p<0.001$) each with an increased number of augmentations ($p<0.001$). The number of vaginal deliveries were high ($p<0.005$) in the simplified group. There was no significant difference in rate of cesarean deliveries due to non progress of labor in the two groups ($p=0.68$).

Labor crossed the alert line in 98 cases monitored by the composite partograph and 55 cases monitored with the simplified partograph. Labor crossing the action line was found in 40 patients for whom the composite partograph was plotted whereas in patients monitored with the simplified partograph, labor crossed the action line in 8 cases ($p<0.05$) as shown in Table 2.

Augmentation of labor was required in 126 cases who were randomized to the composite partograph and in 65 patients subjected to the simplified partograph ($p<0.05$). One important association which was found in the current study was that augmentation was higher in patients in whom labor had crossed the alert and action lines. 265 women in the composite partograph group and 351 women in the simplified group delivered vaginally ($p<0.05$). Out of these, almost the same number of patients, 24 in the composite group and 26 in the simplified group, had instrumental delivery.

Of the patients randomized to the composite partograph, 83 underwent cesarean section. In patients with the simplified par-

Table 1. Patient characteristics

Variable	Composite n=350	Simplified n=393	P value
Age	24.60±3.46	24.66±3.57	t=0.05 DF=98, p=0.932
BMI	25.64±3.27	24.99±3.29	t=1.401 DF=98, p=0.164
Primigravida Multigravida	192 (54.8%) 158 (45.14%)	204 (51.90%) 189 (48.09%)	$x^2=0.646$ DF=1, p=0.421

tograph, cesarean section was performed in 39 cases ($p<0.05$) as shown in Table 2. The indication for cesarean section in the majority of patients in both groups was fetal distress (Table 3). Only 3.41% in thecomposite and 2.54% in the simplified group underwent cesarean section for non progress of labor. There were no cases of obstructed or prolonged labor in either of the groups. Maternal complications such as postpartum hemorrhage was observed in 1 case in each partograph group respectively. No woman suffered from puerperal sepsis.

NICU admissions were statistically significant in the composite partograph group 68 (19.4%) as compared to 35 (8.90%) in the simplified group ($p<0.05$) as depicted in Table 4. However it was not related directly to monitoring of labor.

Resident doctors scored the two partographs for each of the following categories: teachability, overall usefulness, interpretation and overall rating. The mean (S.D.) user friendliness score was lower for the composite partograph (2.87 ± 1.86 vs 10.67 ± 1.61; $p<0.005$). Most of them (93%) experienced difficulty with the composite partograph, but none reported difficulty while plotting the simplified partograph, as shown in Table 2.

Table 2. Comparison of labor outcomes and user satisfaction

Variable	Composite (n=350)	%	Simplified (n=393)	%	P value
Labour crossing the alert line	98		55		
Primiparous	63	18%	33	8.39%	0.0001
Multiparous	35	10%	22	5.59%	0.0080
Labour crossing the alert line	40		8		
Primiparous	28	8%	7	1.78%	0.005
Multiparous	12	3.42%	1	5.59%	0.005
Augmentation of labour	126		65		
Primiparous	76	21.7%	37	9.41%	<0.0001
Multiparous	50	14.2%	28	7.12%	0.0004
Vaginal Delivery	265		351		
Primiparous	130	37.14%	170	43.2%	0.0055
Multiparous	135	38.57%	181	46.05%	0.0007
Instrumental delivery	24		26		
Primiparous	23	6.57%	23	5.85%	0.98
Multiparous	1	0.28%	3	0.76%	0.74
Cesarean Section	83		39		
Primiparous	62	17.71%	33	8.39%	0.0010
Multiparous	21	6.00%	6	1.52%	0.0007
Admission to NICU	69		42		
Primiparous	39	11.14%	23	5.85%	0.040
Multiparous	30	8.57%	19	4.83%	0.028
Apgar score <7 at 5'	4		6		
Primiparous	3	0.85%	5	1.27%	0.67
Multiparous	1	0.28%	1	0.25%	0.55
User friendliness score	2.87 ± 1.86		10.76 ± 1.61	<0.005	
Difficulty in using the partograph	93%		0%		

Table 3. Indications for Cesarean Section

Indications for C.S.	Composite (n=350)	%	Simplified (n=393)	%	P value
Fetal distress	65	18.6%	15	3.82%	0.001
CPD	1	0.30%	3	0.76%	0.72
Non progress of labor	12	3.41%	10	2.54%	0.68
Deep transverse arrest	3	0.86%	5	1.30%	0.51
Failed ventouse	2	0.57%	5	1.30%	0.43
Obstructed labor	0	0%	0	0%	0.0
Total	83	23.7%	38	9.7%	0.001

Discussion

Maternal mortality reduction is one of India's developmental priorities. One of the challenges in this respect is the quality of obstetric practice, comma should not be there before and failure to use the partograph in the monitoring of labor reflects inadequate process of care. The WHO partographs are the best known partographs in low resource settings (11). In India, the partograph is not widely incorporated in our day to day practice as there is a lack of awareness and very few reports available comparing the two WHO partographs. The present study was conducted at a University teaching hospital to compare the two WHO partographs and its user friendliness.

In the present study, labor crossing the alert line was found in 28.2% of patients in the composite partograph group and 13.7% of patients in the simplified partograph group ($p=0.0001$). Similar study done at Vellore, India reports 17.7% and 15.1% in the two groups respectively (12). A study done in Pakistan showed 11.6% of labors to cross the alert line in the simplified partograph group (13). 23.6% of patients crossed the alert line when the composite partograph was plotted in a study conducted in Medan, Indonesia (14).

Labor crossing the action line was observed in 10.8% and 1.96% parturients in the composite and simplified group respectively ($p=0.005$). Almost similar observations were made by the study done at Vellore where labor had crossed the action line in 7.0% in the composite group as compared to 1.0% in the simplified group (12). Action line was crossed in 38% of cases in the composite partograph group at a study done in Liverpool (15).

One important association which we found in the current study was that augmentation was higher in patients in whom labor

Table 4. Indication for admission to NICU

Indications for admission	Composite (n=350)	%	Simplified (n=393)	%	P value
Hyperbilirubinaemia	29	8.2%	14	3.56%	<0.05
Meconium aspiration syndrome	8	2.2%	3	0.76%	0.55
Sepsis	5	1.4%	4	1.01%	0.64
Asphyxia	1	0.28%	3	0.76%	0.57
Low birth weight	14	4%	6	1.52%	<0.05
Others	11	3.14%	5	1.27%	0.05
Total	68	19.4%	35	8.90%	0.035

had crossed the alert and action lines. Similar results were noted in a study done in Belgium where 26% had crossed the action line even after augmentation, when the composite partograph was used (16). The present study was again in accordance to a study done in Leeds, UK where they had intervened actively when the latent phase of the partograph was used (10). The success rate in terms of vaginal delivery in our study was 76.08% in the composite group and 89.9% in the simplified partograph group.A study done in Calcutta had 80.6% of cases who delivered vaginally in the composite group and 82.7% in the simplified group (1).

23.9% and 10.08% in thecomposite and simplified groups respectively underwent cesarean section (p=0.001). A study from Calcutta had similar results, where it was 10% and 8.9% in each (1). Published literature from Dublin, Ireland, highlights 5.4% of patients undergoing cesarean section in the composite partograph group, (17) but a study from Vellore showed only 8.8% and 2.35% of parturients undergoing cesarean section (12).

Another aspect of the study was observation of the neonates of these parturients. We detected no statistically significant difference in the number of infants with Apgar score <7 at 5 minutes in both the groups where it was 1.24% and 1.68% (p=0.678 and p=0.555 in primigravidas and multigravidas respectively).The study at Vellore had similar results of 2% in each group (12). The Liverpool study had 1.6% of cases in the composite group (15). However, results varied with the study in Indonesia, where an Apgar score of <7 at 5 minutes was observed in 7.0% of cases in the composite group (14).

19.8% and 10.92% of the babies born to mothers monitored by composite and simplified partographs respectively were admitted to NICU (p=0.035).

The majority of admissions were due to hyperbilirubinaemia and low birth weight. Although the difference between the two groups was statistically significant, it was not related directly to monitoring of labor with the composite partograph. Meconium aspiration syndrome, sepsis and birth asphyxia were other important causes. The Vellore study had similarities with our results, where the admissions to NICU care were 20% in the composite group and 16% in the simplified group (12).

In the present study, we observed that labor can be managed without the latent phase being plotted on the partograph. However, a labor management protocol for the latent phase should be instituted with clear guidelines. The interventions were higher when the latent phase was included, with a larger number of cesarean sections. The residents had difficulties in transferring from latent to active phase when the composite partograph was used. Our study favors the use of the WHO simplified partograph, which should become routine practice in monitoring labor for better maternal and perinatal outcome.

Conflict of interest

None declared.

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Effect of lycopene in prevention of preeclampsia in high risk pregnant women

Yüksek riskli gebe kadınlarda preeklampsinin önlenmesinde likopen'in etkisi

Ramalingappa Antartani[2], Kiran Ashok[1]

[1]Helios Clinics, Schwerin, Germany [2]Department of Obstetrics and Gynecology, Karnataka Institute of Medical Sciences, Hubli, India

Abstract

Objective: To evaluate the effect of pre-natal supplementation of antioxidant Lycopene in prevention of pre-eclampsia in the high risk pregnant women. We also assessed the effect of lycopene supplementation on intra-uterine growth restriction and the perinatal outcome in women at high risk of developing pre-eclampsia.

Materials and Methods: A total of 54 women between 14-28 weeks of pregnancy who were at high risk of developing pre-eclampsia were considered for the study. Inclusion criteria were women with a previous history of preeclampsia, a growth-retarded fetus, perinatal death, multifetal gestation and chronic hypertension. Of the total of 54 women, 30 women were randomized to receive Lycopene in a dose of 2 mg twice daily starting from the date of entry and were instructed to continue the drug regularly until delivery. The other 24 women were randomized to the control group and they did not take lycopene. The controls were matched to cases with respect to the risk factors for the development of preeclampsia. Both groups were followed at monthly intervals. In addition, a Doppler assessment for evidence of intrauterine growth retardation was done at around 28 wks of gestation. Data regarding development of preeclampsia, period of gestation during delivery, mode of delivery, fetal weight and perinatal outcome were recorded and subjected to statistical analysis.

Results: Of the 30 women randomized to receive the drug, ten women were lost to follow-up. Thus only 20 women in the treatment group completed the study. All the 24 women in the control group completed the study. Lycopene was not found to decrease the incidence of pre-eclampsia in high risk women. Women in the lycopene supplementation group had significantly lesser incidence of growth restricted babies and had a significantly better perinatal outcome compared to women in the placebo group.

Conclusion: Lycopene supplementation does not decrease the incidence of preeclampsia in high risk women. However lycopene supplementation does seem to help in reducing the incidence of intrauterine growth restriction.

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Key words: Preeclampsia, anti-oxidants, intrauterine growth restriction

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Özet

Amaç: Yüksek riskli gebe kadınlarda preeklampsinin önlenmesinde antioksidan Likopen'in prenatal takviye edilmesinin etkilerini değerlendirmek. Biz ayrıca preeklampsi geliştirme riski yüksek olan kadınlarda likopen takviyesinin intra-uterin büyüme kısıtlılığı ve perinatal sonuçlar üzerindeki etkisini değerlendirdik.

Gereç ve Yöntemler: Çalışma için preeklampsi geliştirme riski yüksek olan 14-28 gebelik haftası arası toplam 54 kadın irdelendi. Çalışmaya dahil etme kriterleri önceki preeklampsi öyküsü, önceki büyüme geriliği olan fetüs öyküsü, önceki perinatal ölüm öyküsü, çoğul gebelik ve kronik hipertansiyondu. 54 kadından 30'u, çalışmaya girdikleri tarihte başlamak üzere günde iki kez 2 mg dozunda Likopen alacak şekilde randomize edildi ve doğuma kadar ilaca düzenli şekilde devam etmeleri istendi. Diğer 24 kadın kontrol grubuna randomize edildi ve likopen almadılar. Kontroller preeklampsi gelişimi için risk faktörleri açısından olgularla eşleştirildi. Her iki grup aylık aralarla takip edildi. Ayrıca gebeliğin 28. haftası civarında intrauterin büyüme geriliğinin bir kanıtı olarak Doppler değerlendirmesi yapıldı. Preeklampsi gelişimi, doğumdaki gebelik süresi, doğum şekli, fetüs ağırlığı ve perinatal sonuçlar gibi veriler kaydedildi ve istatistiksel analize tabi tutuldu.

Bulgular: İlacı almak üzere randomize edilen 30 kadından onu takipten düştü. Böylece tedavi grubunda yalnızca 20 kadın çalışmayı tamamladı. Kontrol grubundaki 24 kadının hepsi çalışmayı tamamladı. Likopenin yüksek riskli kadınlarda preeklampsi insidansını düşürmediği bulundu. Plasebo grubundaki kadınlara kıyasla likopen takviyesi grubundaki kadınlarda büyüme kısıtlılığı olan bebek insidansı anlamlı şekilde daha düşüktü ve perinatal sonuçları anlamlı şekilde daha iyiydi.

Sonuç: Likopen takviyesi yüksek riskli kadınlarda preeklampsi insidansını düşürmemektedir. Ancak, likopen takviyesi intra-uterin büyüme kısıtlılığı insidansını düşürmeye yardımcı oluyor gibi görünmektedir.

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Anahtar kelimeler: Preeklampsi, anti-oksidan, intra-uterin büyüme kısıtlılığı

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Address for Correspondence / Yazışma Adresi: *Yard. Doç. Dr. Kiran Ashok, Pes Medical College, kuppam, Chittor Dist Kuppam, India*
Phone: +919964015207 e.mail: drkirana@gmail.com
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Introduction

Preeclampsia complicates 5% to 8% of all (10% of all pregnancies at our set up) pregnancies. In developing countries, where prenatal care is inadequate, preeclampsia-eclampsia accounts for 40-60% of maternal deaths, an estimated 50,000 per year. Infants of women with preeclampsia have a 5-fold increase in mortality compared with infants of mothers without this disorder.

Lycopene is a bright red carotenoid pigment present in tomatoes and other red fruits and vegetables. Structurally, Lycopene is a tetraterpene with eleven conjugated double bonds, which is responsible for the red color and its antioxidant activity. Lycopene is one of the most potent antioxidants found in the human body, having 100 times the antioxidant potency compared to vitamin E and C. The antioxidant property of Lycopene is believed to be of protective value in many chronic diseases like atherosclerosis and many types of cancer (1).

In this study we studied the effect of lycopene in the prevention of preeclampsia in women who are at high risk of developing preeclampsia. We also study the effect of lycopene supplementation on the perinatal outcome in these groups of women. We searched the Medline and the highwire-press database for similar studies. To our knowledge, no study has been conducted on the effect of lycopene for preventing preeclampsia in high-risk women.

Materials and Methods

A total of 54 women at high risk of developing pre-eclampsia, who attended antenatal clinic at KIMS, Hubli were considered for the study. A written and informed consent was taken from all women who were to undergo the trial. The ethical review committee of KIMS, Hubli approved the study.

Inclusion criteria: Pregnant women between 14-28 weeks of pregnancy at high risk of developing preeclampsia were included. These are women with a previous history of preeclampsia, a growth-retarded fetus, perinatal death, multifetal gestation and chronic hypertension.

Of the total 54 women, 30 women were randomized to receive Lycopene in a dose of 2 mg twice daily starting from the date of entry and were instructed to continue the drug regularly until delivery. We used the preparation Lycored® (Jagsonpal Pharma, India). The other 24 women were randomized to the control group and they did not take lycopene. We did not use a placebo in the control group due to logistic constraints. The controls were matched to cases with respect to the risk factors for the development of preeclampsia. The alternate women were assigned to cases and controls. Preliminary investigations were conducted in both the groups namely, weight, BP, measurement of urine for protein and obstetric ultrasound. Both cases and controls were supplemented with prenatal iron and calcium supplements.

Both groups were followed at monthly intervals with measurement of the above parameters. In addition, a Doppler assessment for evidence of intrauterine growth retardation was done at around 28 wks of gestation. Data regarding development of preeclampsia, period of gestation during delivery, mode of delivery, fetal weight and perinatal outcome were recorded and subjected to statistical analysis. Intrauterine growth retardation was diagnosed when the abdominal circumference after 28 weeks was less than the 2.5th percentile for the given gestational age and an amniotic fluid index of less than 5.

Results

Of the 30 women randomized to receive the drug, ten women were lost to follow-up. Thus, only 20 women in the treatment group completed the study. All the 24 women in the control group completed the study. We analyzed data pertaining only to those women who completed the study.

Table 1 shows the characteristics of the women in the two groups. With respect to age, both groups were similar. When parity is considered, the control group had a larger number of women with parity 1 compared to the treatment group. The treatment group had more multiparous patients compared to the control group. Since the recurrent rate of preecalmpsia in subsequent pregnancies is greater with increasing parity, the above distribution of women may not affect the results of the study with respect to development of preeclampsia. As can be inferred from Table 1, both the groups were similar with respect to the risk factors for subsequent development of preeclampsia. More women in the control group had preterm deliveries compared to the women receiving lycopene. However the difference is not statistically significant.

Table 2 shows the principal out the come of trial, which is the development of preeclampsia in both the groups. Thus, although not statistically significant, Lycopene reduces the risk of developing preeclampsia. The odds ratio for developing preeclampsia in

Table 1. The characteristics of women in the two groups

Characteristics	Cases n=20	Percent	Controls n=24	Percent
Maternal age in years				
18-23	10	50	16	66
24-28	6	30	4	16.66
>28 yrs	4	20	4	16.66
Parity				
Nullipara	1	5	0	0
P1	9	45	17	70.83
P2	7	35	5	20.83
P3	3	15	2	8.33
Risk factors				
Previous preeclampsia	19	95	22	91.66
Multifetal gestation	1	5	2	8.4
Gestational age at delivery				
Less than 28 weeks	1	5	3	12.5
28-37 weeks	8	40	10	41.66
More than 37 weeks	11	55	11	45.83

the control group is 2.3 when compared to the Lycopene using group (Table 2). Thus supplementation with lycopene appears to be 2.3 times more protective than non-supplementation with respect to development of preeclampsia. Table 4 shows the perinatal outcome in the two groups. The perinatal outcome in terms of babies alive at discharge was significantly better in the treatment grocompared to controls.

Discussion

Preeclampsia can be considered a 2-stage disease, and the linkage of these two stages remains the focus of preeclampsia research (2, 3). The first stage of preeclampsia involves abnormal placentation. The failure of the spiral arteries to transform to dilated flaccid tubes with a four-fold increase in diameter, and the frequent finding of atherosis, leads to reduced placental perfusion. The hypoxic placenta releases soluble factors into the maternal circulation, which induces systemic endothelial dysfunction. This causes the second stage of the disease: the maternal syndrome.

The identification of circulating factors mediating endothelial dysfunction has been the source of great research interest for decades. One hypothesis receiving increased attention is that placental and maternal free radical reactions promote a cycle of events that compromise the defensive function of the vascular endothelium in preeclampsia. Recent information indicated that uncontrolled lipid peroxidation may contribute to certain disease processes via disruption of membrane lipids and other cell components.

Markers of lipid peroxidation, including Malondialdehyde and 8-epiprostaglandin F2α are increased in the plasma of women with preeclampsia, and the low concentration of water-soluble and lipid-soluble antioxidants in the plasma and the placenta (4, 5) further suggest a state of oxidative stress. These observations have led to the hypothesis that early supplementation with antioxidants may be effective in decreasing oxidative stress and improving vascular endothelial function, thereby preventing, or ameliorating, the course of preeclampsia.

There is evidence that protective antioxidant systems are deficient in preeclampsia and maternal serum carotenoid levels such as β–carotene, lycopene and canthaxanthin levels are low in placental tissue and maternal serum (6). Chappel LC et al. (7) studied the effect of antioxidants vitamin C and vitamin E on the plasma markers of endothelial activation (plasminogen activator inhibitor PAI-1) and placental dysfunction (PAI-2) and found that antioxidant supplementation decreased the PAI1/PAI2 ratio by 21%. Sharma JB et al. (8) studied the effect of lycopene on preeclampsia and IUGR in primigravidas and found that lycopene reduces the development of preeclampsia and IUGR in primigravida. In our study Lycopene was started after the 14th week of pregnancy, as the safety of Lycopene in the first trimester is not known.

Pre-eclampsia occurred in 30% in the treatment group compared to 50% in the control group. The relative risk of developing preeclampsia is reduced by lycopene (RR=0.6). However, the difference in outcomes between the two groups in terms of developing pre-eclampsia did not reach statistically significant

Table 2. The principal outcome of trial-the development of preeclampsia in both groups

Development of preeclampsia	Cases n=20	%	Controls n=24	%
Preeclampsia occurred	6	30	12	50
Pre eclampsia not developed	14	70	12	50

By applying Fischer's exact test
p=0.2268
p>0.05 not significant
Preeclampsia development in Lycopene group compared to control group Relative risk=0.6
Preeclampsia development in control compared to lycopene group Odds ratio=2.3

Table 3. Incidence of IUGR

Growth parameter	Cases n=20	%	Controls n=24	%
IUGR	1	5	8	33.3
No IUGR	19	95	16	66.67

By Fischer's exact test
p=0.0271
p<0.05 significant.
Relative risk=0.20

Table 4. Perinatal outcome

Outcome	Cases n=20	%	Controls n=24	%
Babies alive at discharge	19	95	18	75
Perinatal death	1	6	6	25

Test of proportions
z=1.98
p=0.05 significant

levels. The risk of development of preeclampsia following a history of preeclampsia in the first pregnancy was studied by Sibai et al. They reported the recurrence rate of preeclampsia in the second pregnancy to be 46.8%. Sibai et al. (9) in 1991 reported that women with severe preeclampsia which develops in the second trimester are at very high risk of severe preeclampsia in a subsequent pregnancy. In such women, 65% of all subsequent pregnancies were complicated by preeclampsia. Thus, comparing the pregnancy outcome with lycopene with the above studies, it can be said that lycopene may be modestly effective in preventing recurrence of preeclampsia in the high risk group. However, as the number of subjects in this study is very small we recommend further multicentric studies with large number of subjects for further verification of the results of our trial.

The incidence of IUGR was significantly lower in the study group compared to controls. The incidence of IUGR in the treatment group was 5% compared to 33% in the control group (p<0.05). Also, the perinatal outcomes in terms of babies alive at discharge and perinatal death, were better in the lycopene group than controls. There was only one perinatal death in the lycopene-supplemented group, compared to 6 perinatal deaths in the control group. (p<0.05). Cause of death in the lycopene group was preterm with respiratory distress. All deaths in the

control group were due to either complications of preterm delivery or to severe IUGR and fetal asphyxia. Thus, we can hypothesize that although lycopene may not prevent the root cause of pre-eclampsia, it might be effective in reducing the complications of pre-eclampsia such as IUGR and perinatal mortality.

The above results could be explained as follows: The exact nature of the initial pathology in pre-eclampsia is not known. Some initial (genetic/fetal/placental factors) event causes the production of free radicals, leading to lipid peroxidation thus setting up a self-perpetuating chain reaction of lipid peroxidation. Antioxidants cannot prevent formation of free radicals and hence cannot alter the basic pathophysiology of pre-eclampsia. However, they might absorb the circulating and tissue free radicals and lipid peroxidation products and limit further damage caused by the lipid peroxidation chain reaction. They might stop the lipid peroxidation chain reaction.

This study shows that antioxidant lycopene, although it may not prevent pre-eclampsia., might help in mitigating fetal complications. This may be due to selective improvements in the fetoplacental circulation compared to the general circulation.

However, large trials with numbers >1000 are needed to confirm the findings of the trial.

At present, it might not be possible to prevent preeclampsia at its source, but at least we are able to lessen the burden of its complications on the mother and fetus. With the introduction of magnesium sulfate, an important maternal complication of preeclampsia i.e. eclampsia was prevented. Now hopefully antioxidants will help prevent the fetal complication such as IUGR, fetal asphyxia, and perinatal mortality.

Conflicts of interests: None.

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Fetal magnetic resonance imaging in obstetric practice

Fetal manyetik rezonans görüntülemenin obstetri pratiğindeki yeri

Aydın Köşüş[1], Nermin Köşüş[1], Betül Usluoğulları[1], Müzeyyen Duran[1], Nilgün Öztürk Turhan[1] Mehmet Tekşam[2]

[1]*Department of Gynecology and Obstetric, Fatih University, Ankara, Turkey*

[2]*Department of Radiology, Fatih University, Ankara, Turkey*

Abstract

Ultrasonography (USG) is the primary imaging method for prenatal diagnosis of fetal abnormalities since its discovery. Although it is the primary method of fetal imaging, it cannot provide sufficient information about the fetus in some conditions such as maternal obesity, oligohydramnios and engagement of the fetal head. At this stage, magnetic resonance imaging (MRI) facilitates examination by providing more specific information. The need and importance of fetal MRI applications further increased by the intrauterine surgery which is currently gaining popularity. Some advantages of fetal MRI over USG are the good texture of contrast, a greater study area and visualization of the lesion and neighbourhood relations, independence of the operators. Also it is not affected by maternal obesity and severe oligohydramnios. However, MRI is inadequate in detecting fetal limb and cardiac abnormalities when compared to USG. MRI is not used routinely in pregnancy. It is used in situations where nonionizing imaging methods are inadequate or ionizing radiation is required in pregnant women. It is not recommended during the first trimester. Contrast agent (Godalinium) is not used during pregnancy. It is believed that MRI is not harmful to the fetus, although the biological risk of MRI application is not known. MRI technique is superior to USG in the detection of corpus callosum dysgenesis, third-trimester evaluation of posterior fossa malformations, bilateral renal agenesis, diaphragmatic hernia and assessment of lung maturation. Especially, it is the method of choice for evaluation of central nervous system (CNS) abnormalities. Fetal MRI has a complementary role with USG. It provides important information for prenatal diagnosis, increases diagnostic accuracy, and in turn affects the prenatal treatment, prenatal interventions and birth plan.

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Özet

Ultrasonografi (USG) keşfedilmesinden günümüze kadar fetal anomalilerin prenatal tanısında primer görüntüleme yöntemidir. Fetal görüntülemede USG primer yöntem olmasına rağmen fetus hakkında yeterli bilgi veremediği obezite, oligohidramnioz, fetal başın angajmanı gibi durumlar vardır. Bu aşamada manyetik rezonans görüntüleme (MRG) daha fazla spesifik bilgi sağlayarak bize yardımcı olmaktadır. Günümüzde giderek yaygınlaşan intrauterin cerrahi, fetal MRG uygulamalarına olan ihtiyacı ve önemini daha da arttırmaktadır. MRG'nin doku kontrastını iyi verebilmesi, inceleme alanının büyük olması ve böylece lezyon ile olan komşulukların ilişkisinin gösterilebilmesi, operatörden bağımsız oluşu, maternal obezite ve ciddi oligohidramnioz durumundan etkilenmemesi USG'ye olan üstünlüklerindendir. Ancak fetal ekstremite değerlendirilmesi ve fetal kardiyak anomali tesbitinde MRG, USG'ye göre yetersiz kalmaktadır. MRG gebelikte rutin olarak kullanılmaz. Noniyonize görüntü yöntemleri yetersiz kaldığında veya iyonoze radyasyon gerektiren durumlarda gebe kadınlarda MRG kullanılır. İlk trimesterde önerilmemektedir. Kontrast madde (Gadolinium) kullanılmaz. MRG uygulamasının biyolojik riski bilinmemekle birlikte fetusa zararlı etkisi olmadığına inanılmaktadır. Kopus kallozum disgenezisi, üçüncü trimesterde posterior fossa malformasyonlarının değerlendirilmesi, bilateral renal agenezi, diyafram hernisi ve akciğer maturasyonu saptamada MRG tekniği USG'ye üstündür. Özellikle santral sinir sistemi (SSS) anormalliklerinin değerlendirilmesinde sıklıkla kullanılan bir yöntemdir. Fetal MRG, USG'yi tamamlayıcı bir rol üstlenmekte ve prenatal tanıda önemli bilgiler sağlayarak tanı doğrulunu, prenatal tedaviyi, prenatal girişimi ve doğum planını etkileyebilmektedir.

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Anahtar kelimeler: Fetal manyetik rezonans görüntüleme, fetal ultrasonografi

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Introduction

Ultrasonography (USG) has been the primary imaging method in diagnosing fetal anomalies since its discovery (1). USG has been used since the 1950's. With the progression of technological improvements with time, imaging with real-time USG, color Doppler, power Doppler, 3 and 4 dimensional USG has taken its place in fetal evaluation. Although USG is the primary method in fetal imaging, in situations where it cannot give sufficient information about the fetus, magnetic resonance imaging (MRI) helps us by providing more specific information (2). Nowadays the increasing intrauterine surgery has further increased the need and importance of fetal magnetic resonance imaging. In this article, the position

Address for Correspondence / Yazışma Adresi: *Asistan Müzeyyen Duran, Hürriyet Cad. 162/8 Dikmen, Ankara, Turkey*
Mobile: +90 505 757 78 71 e.mail: drmuzbur@yahoo.com.tr
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of magnetic resonance imaging in obstetric practice has been presented within the frame of the literature.

History

Evaluating the fetus with MRI is not a very new method. The first definition of Fetal MRI was described by Smith and his colleagues in 1983 (3). In their early stage studies, fetal movements prevented the evaluation of fetal morphology. The suggestion was to perform this technique in cases where limited images were obtained in the late pregnancy period or in cases where the fetal movement was limited by oligohydramnios (4). Some of the researchers performed imaging by sedating the gravida with benzodiazepine or directly injecting curare into the fetus to decrease movement (5). Despite all these difficulties, MRI was accepted as an important method in evaluating fetal anomalies (6). MRI was previously used only in the evaluation of the CNS, but with the development of fast sequences completed in less than 20 seconds, the anatomy and malformations of the fetus can be imaged without using any premedication. With its ease of application and high resolution, the MRI techniques increasing popularity will obviously be helpful for obstetricians in future prenatal diagnosing.

Reliability

The biological risk of magnetic resonance imaging is unknown, but it is believed not to have a harmful effect on the fetus (7). Despite the high magnetic field in the conducted animal studies, no negative effects could be shown on fetal development (8). At the same time, a study conducted with pregnant women working in the MRI unit showed no difference from the control group in terms of pregnancy outcomes (9). Also, children undergoing fetal magnetic resonance imaging were monitored for two years and no increase in disease rates could be shown (10). Despite all these, the Food and Drug Administration (FDA) requires that the statement 'the effect on the fetus has not yet been proven' be shown on MRI devices. However, the Society of Magnetic Resonance Imaging has stated that MRI is indicated in pregnant women when other non-ionizing imaging methods are insufficient or in situations where ionizing radiation must be used (11).

There are some points that must be paid attention to when performing magnetic resonance imaging on pregnant women. It must not be used routinely in pregnancy. It is performed when cases cannot be diagnosed with ultrasonography. It is not recommended in the first trimester. Contrast material (Godolinium) must not be used. Pregnant women must be informed about the examination with a disclosure form and must give their approval before the procedure.

Advantages and Disadvantages

Ultrasound is a fetal evaluation method that has been proven to be reliable, is widely used, and is not expensive. It simultaneously provides fetal monitoring and an evaluation of the fetus' well-being. Fetal and placental blood flow evaluation is another advantage of ultrasound (12).

As well as its advantages, ultrasound also has disadvantages. First of all, it is an operator dependent method. In addition, it gives us only a small sampling area of the fetus; we cannot observe the fetus as a whole after the second trimester; the image resolution differs highly whether the examined tissue is soft tissue or bone; and as a result of the bone structures, the image quality decreases when evaluating the cranial structure. Also, the fetal position is another parameter that affects image quality. Evaluating the anatomical details in breech presentation in the prone position is very difficult. The image quality is also very low in situations like obesity, oligohydramnios and engagement of the fetal head (12-15).

In situations like these, where we cannot obtain sufficient information about the fetus, MRI does not get seriously affected It does not contain ionizing radiation. It differs from ultrasound with its high soft tissue resolution, which provides the distinction of maternal and fetal organs. The fetus can be examined three dimensionally (12, 16). It is a perfect method for imaging intracranial and spinal anatomy. At the same time, it is very useful in measuring organ volumes, such as the lungs. Its other advantages are not being operator dependent and obtaining more than one image. Its disadvantages can be listed as its high cost, being a method which is difficult to obtain, and the fetal-maternal-amnion fluid and extremity movements cause artifacts. This is why maternal sedation could be necessary in fetuses that move a lot. Although a distinct fetal effect has not been determined up to today, long term results are still unknown (7, 9, 10, 17-26). Therefore it is not recommended for use in pregnancies earlier than the eighteenth week (2). Also, it cannot be usd for people who suffer from claustrophobia.

Technique

The fetus must be evaluated in terms of position and fetal cardiac activity (for medicolegal reasons) before MRI. Fetal MRI is applied to the pregnant woman in the supine position. Images are obtained in sagittal, transverse and coronal planes with a T2 weighted sequence. Due to its placental transition, contrast material is not used in examinations. The nasopharynx, oropharynx, trachea and lungs are observed as hyperintense because they are filled with amniotic fluid. The aorta, pulmonary vessels and heart have hypointense signals. For this reason, we cannot differentiate the fetal heart chambers with MRI. While the thyroid gland is observed in equal intensity with its surrounding tissues in T2 weighted sequences, it can be easily distinguished from its neighboring structures in T1 weighted sequences, where it is clearly hyperintense. The stomach, small intestinal loops and colon are selected as hypointense in T2 weighted sequences because of their meconium content. The liver, spleen and kidneys have a mean signal character. The gallbladder is observed as a cystic structure next to the lower edge of the liver. The urinary bladder is a liquid filled structure that can be easily recognized in the pelvis. The scrotum and penis are frequently observed in the male fetus but the female genital organs mostly cannot be selected.

Indications

Fetal MRI can be used in the following cases (1, 2, 12, 15):
Situations where USG is limited:

- In the presence of maternal obesity,
- Decreased amniotic fluid cases (oligohydramios, membrane rupture),
- Third-trimester evaluation of the posterior fossa,
- The fetus position unsuitable for the evaluation with ultrasound.

Fetal assessment:

- Detailed diagnosis and analysis of anomalies that require termination of pregnancy,
- The evaluation of conditions associated with multiple anomalies,
- Intracranial and spinal malformations,
- Facial malformations such as cleft lip and palate,
- Pathology of multiple pregnancy (twin-twin transfusion, acardiac twin, etc.),
- Fetal masses,
- Thoracic lesions, evaluation of anomalies of the neck that cause compression of the airway,
- Abdominal wall defects,
- Skeletal dysplasias,
- Placenta and cord abnormalities,
- Cases where fetal surgery is planned,
- The method of birth and determining if neonatal support is needed.

The MRI technique is superior to USG in detecting corpus callosum dysgenesis, third-trimester evaluation of posterior fossa malformations, bilateral renal agenesis, diaphragmatic hernia and lung maturation. It is a frequent method used in evaluating especially central nervous system (CNS) anomalies.

Fetal Central Nervous System Anomalies

Although MRI and USG are complementary methods in evaluating the fetal central nervous system, fetal MRI provides increased contrast resolution that increases anatomical detail, and sometimes can change the diagnosis. In the evaluation of the fetal CNS with USG, there are conditions for which imaging is insufficient, such as maternal obesity, oligohydramnios and poor fetal position. Magnetic resonance imaging is less affected by these conditions (27). In 40 percent of the CNS anomalies diagnosed with USG, the diagnosis changed and in 46 percent, changes in management occurred (14, 28, 29).
Neuroectodermal elements forming the brain paranchyme are derived from the germinal matrix that surrounds the ventricle as a thick layer. Neuronal cells migrate from the germinal matrix to the cortex between weeks 6-24, forming the temporary cerebral laminar organization. This organization is completed at the twenty-eighth week. From week 16 to week 20 the cerebral surface is observed to be smooth with the exception of the minimal Sylvian fissure. We observe an increase in the sulcus formation with maturation. Observing specific sulci with magnetic resonance imaging can determine an estimated fetal age. The observed sulcus formation is observed with a delay of 2-3 weeks later than the anatomic specimens. An extra two week delay occurs in fetuses with a central nervous system malformation. In short, the relationship between sulcus formation and gestational week is very important.
Myelin formation starts in the peripheral nervous system at week 16, in the central nervous system at week 20 and progresses with a specific sequence. Myelin formation is seen with fetal MRI in the posterior brain stem at week 20, the internal capsule posterior leg at week 33 and the subcortical area at week 35. We must look at the compliance of myelin formation with the gestational week when evaluating the fetal MRI results. The corpus callosum starts to develop at week 20. The ventricles are observed larger with MRI compared to USG between weeks 20-24 (physiological hydrocephaly). The ventricle dimensions decrease between weeks 24-28. The ventricles seem narrower than normal between weeks 34-36 (30). Between weeks 23-36, cerebellar folds become evident and the middle cerebellar peduncle develops. This is why evaluation with MRI is best after week 24.

Neuronal migration anomalies

Magnetic resonance imaging plays a major role in prenatal diagnosis of cortical development anomalies. MRI findings of cortical malformations are usually similar to postnatal imaging (31). Migration anomalies can be isolated or may be accompanied by other brain anomalies.
Polymicrogria is an organization disorder occurring as a result of an injury of the cortex after neuronal migration. The cortex's six-layer structure has been corrupted. This can be due to genetic and ischemic causes and infections with cytomegalovirus. The most common cause of injury is ischemia (32).
Schizencephaly is an anomaly characterized by a cleavage in the gray matter stretching from the ventricle to the cortex. The amount of cortex area determines the prognosis (33). Lissencephaly, meaning smooth brain, is having no gyrus or a very small number of gyrus-sulcus. Heterotopy is the stopping of radial migration during brain development and the abnormal localization of gray matter nerve cells. Eighty percent of lissencephaly, 73 percent of polymicrogria, 100 percent of schizencephaly and 54 percent of heterotopy were diagnosed with fetal MRI in the third trimester (34).

Ventriculomegaly

It is the most commonly observed CNS anomaly in prenatal period and is also the most common fetal MRI indication. Ventriculomegaly is diagnosed with the transatrial width being greater than 10mm (35). The causes of ventriculomegaly and the accompanying anomalies can also be detected with fetal MRI. Eighty-four percent of fetuses with a ventriculomegaly diagnosis may have accompanying CNS anomalies, additive organ anomalies and chromosomal anomalies (36). In 40-50 percent of cases, associated anomalies can be shown with magnetic resonance imaging (37-39). When the ventricular width increases, the risk of additional anomalies also increases. Although fetuses with the diagnosis of mild ventriculomegaly (10-15 mm in transatrial width) are mostly healthy and normal at birth, they have a small amount of risk of intrauterine

growth retardation (IUGR). The prognosis is much better when ventriculomegaly is isolated (40). Congenital or acquired (after infection, hemorrhage) aquaductal stenosis can be diagnosed with MRI by detecting a normal sized 4th ventricle, expanded 3rd ventricle and lateral ventricles (41). Ventriculomegaly can be observed with cerebral atrophy after ischemia or infection. In ventriculomegaly occurring due to ischemia or infection of the brain tissue, irregularity in ventricle walls and cortical loss can be observed (42). Thus, we can understand if ventriculomegaly is developmental, destructive or obstructive with MRI. We observe ventricular dilatation in the third and both lateral ventricles of the fetus in Figure 1.

Anomalies of the corpus callosum

Abnormalities of the corpus callosum can be identified easily with magnetic resonance imaging. The distinction of total or partial agenesis, hypoplasia of the corpus callosum can be made. CNS anomalies and non-CNS anomalies accompany corpus callosum agenesis with a rate of 85 percent and 62 percent, respectively (43). Twenty percent of the cases thought to have corpus callosum agenesis with ultrasonography were found to be normal with MRI. The diagnosis of partial agenesis is very difficult with USG. An arachnoid cyst located on the upper wall of the third ventricle can mistakenly be diagnosed as collasal agenesis. Magnetic resonance imaging technique may change the diagnosis by showing the cyst wall and the corpus callosum (44).

Holoprozencephaly

It is a congenital anomaly existing because of a cleavage defect of the prozencephalon known as the front brain. It is diagnosed by a single ventricle, fusion of the thalamus, absence of the cavum septum pellisidum and falx cerebri. The diagnosis of severe forms like semilobar and alobar holoprozencephaly can be easily recognized by observing a single ventricle and fusion of the cerebral hemispheres. However, MRI is very useful in the diagnosis of lobar form and the distinction of lobar holoprozencephaly, another cause of ventriculomegaly (45).

Neural tube defects

(Anencephaly, encephalocele, inencephaly, craniorachitism, meningocele, meningomyelocele, spina bifida occulta)

The diagnosis of neural tube defects (NTD) can be done to a large extent with sonography but USG can be insufficient in detecting mild forms of NTD or accompanying anomalies. In the study of Wang and colleagues, results showed that an abnormal vertebral body sequence was detected with USG in all of the cases with spinal malformations, but only the cases with a suspicion of meningocele and myelomeningocele could be diagnosed. He found that syringomyelia, diastematomyelia, hemivertebrae, spinal cord arachnoid cysts and tethered cord were missed. It was reported that only the diagnosis of hemivertebra could not be made with magnetic resonance imaging because of the fetal vertebra bodies being too small in size (46). An encephalocele case is seen in Figure 1 (a, b, c, d). An 11 mm diameter defect has been observed in the left occipital bone and a 2.5 cm diameter cephalocele sac was observed from this defect. Brain tissue and the herniation of the posterior of the left lateral ventricle inside the cephalocele sac are noteworthy.

Posterior fossa defects

USG does not give sufficient information about posterior fossa anomalies, especially in the third trimester. The diagnosis of these pathologies can easily be made with magnetic resonance imaging. The sisterna magna measurements larger than 10 mm may suggest Dandy-Walker malformation, Dandy-Walker variant (partial wermian agenesis), mega sisterna magna, cerebellar hypoplasia or arachnoid cyst (47, 48). In the Dandy-Walker malformation there are vermis agenesis, dilatation of the fourth ventricle and elongating of the posterior fossa below the tentorium. Sixty-eight percent of supratentorial malformations are accompanied by Dandy-Walker malformation. MRI also provides the differentiation of posterior fossa arachnoid cysts from vermian development anomalies (44).

Tuberous sclerosis

It is an autosomal dominant disorder proceeding with mental retardation and seizures that can also have involvement of the brain, heart, skin, kidney and other organs. MRI is highly effective in demonstrating cardiac rhabdomyomas and subependymal tubers before week 21. The differentiation of tubers from hamartomas and subcortical heterotopic brain tissue can be made (49).

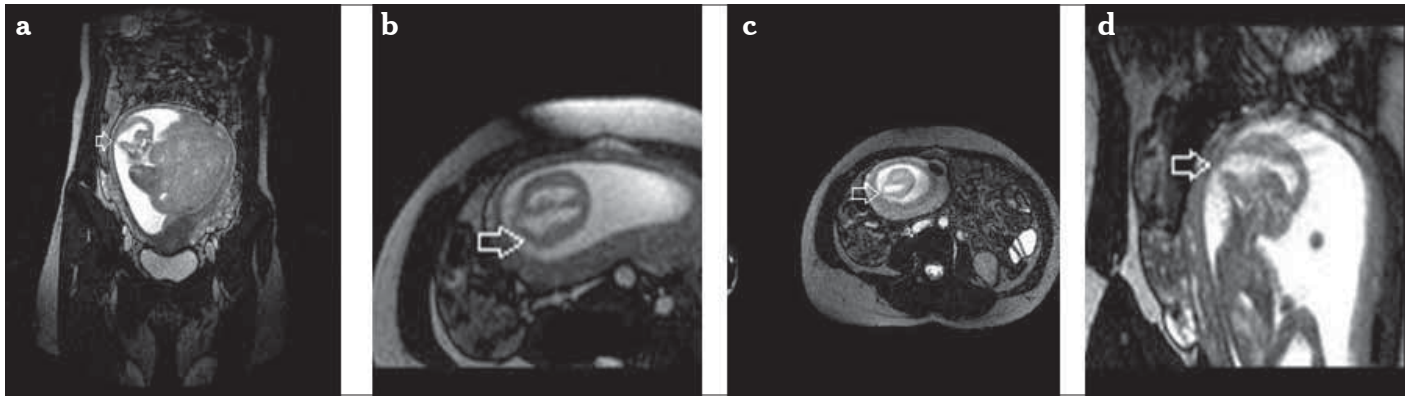

Figure 1. A case with ventriculomegaly and encephalocele

Sacrococcygeal teratoma

It is a cystic or solid tumor located at the coccyx that is classified according to its extra or intrapelvic component. Type 1 is an external presacral component, Type 2 is a small presacral component accompanying the external component, Type 3 is a small extrapelvic component with an intrapelvic and intraabdominal elongation, Type 4 frequently elongates towards the whole pelvis and abdomen. It is often accompanied by polyhydramnios. Hydrops may be seen due to compression of the fetal aorta and inferior vena cava and increased fetal cardiac output. Vascularity increases with an increase in the solid component. Magnetic resonance imaging shows the tumor's intrapelvic and intraspinal elongation. It gives a better discrimination between sacral myelomeningocele and cystic sacrococcygeal tumors (50). In Figure 2 (a, b), a 14x11x11 cm sized sacrococcygeal teratoma filling the whole fetal pelvis showing exophytic extensions to the pelvic and anal regions is seen.

Intracranial bleeding and destructive lesions

The frequency of intrauterine ischemia is unknown, but a study reported that 14 percent of perinatal mortalities occurred due to ischemic changes. Ischemic injury may result in very different appearances, such as ventriculomegaly, microcephaly, hydrocephalus, porencephaly, encephalomalacia, capsular ischemia and cerebral atrophy. Morphology depends on the affected area, and the time between the damage and imaging. Magnetic resonance imaging is superior to USG in diagnosing these lesions (23, 44, 51).

Fetal Neck Anomalies

Although fetal neck masses are not common, they are important because they can cause airway obstruction at birth. Among the neck masses cystic hygroma, goiter and teratomas are the most frequent. Teratomas are midline lesions that can be solid or cystic. Cystic hygroma may be accompanied by Down syndrome, Trisomy 18, Turner syndrome, and hydrops fetalis. Magnetic resonance imaging has an important role in characterizing the lesion and describing the relationship between large vascular structures and the airway (52).

Obstruction of the trachea and larynx causes the lungs to overinflate, a flattening of the diaphragm, and a decrease in the venous return to the heart, resulting in fetal hydrops and ascites. Bilateral hyperechoic enlarged lungs, flattening or eversion of the diaphragm, fluid leveling in the airways under the obstruction, fetal hydrops and ascites can be shown with ultrasonography. All these findings can also be described with MRI (53).

Fetal Thoracic Anomalies

Management of fetal abnormalities in the fetal thorax is very important in terms of prognosis. Especially the localization of a thoracic mass and its relationship with other organs provides us with important information. Sometimes, bronchial atresia, tracheal atresia, or pulmonary atresia can be diagnosed as cystic adenoid malformation with USG. Fetal MRI is very useful in these cases. In a study conducted by Hubberd and colleagues, the USG diagnosis of fetal thoracic anomalies changed in 50 percent of cases after performing a MRI (54).

Fetal lung maturation is very important in terms of fetal prognosis and can be detected with signal changes in T1-T2-weighted sequences with fetal MRI (55). Congenital cystic adenoid malformation, bronchopulmonary sequestration, fetal hydrothorax and congenital diaphragmatic hernia are commonly seen thoracic masses.

Congenital cystic adenomatoid malformation

They are multicystic masses associated with the normal bronchial system of the lung which are formed by bronchioles showing abnormal proliferation. Its feeding artery is from the

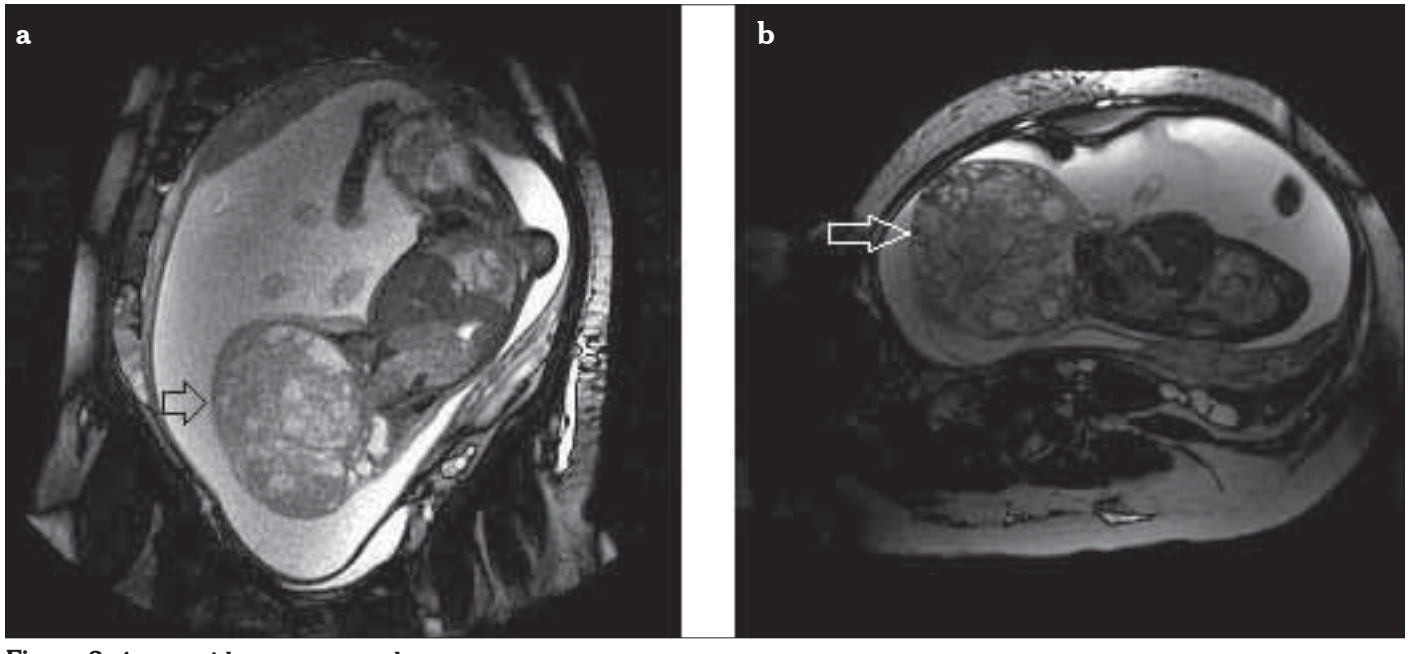

Figure 2. A case with sacrococcygeal teratoma

aorta and its venous drainage is to the pulmonary vein. It can originate from one lobe and segment or multiple lobes. Type 1 is macrocystic, Type 2 is a small macrocystic form. Type 3 includes solid and microcystic areas and has a poor prognosis. Typing can be done with magnetic resonance imaging as well as showing a better lung tissue compression when compared with USG (44).

Bronchopulmonary sequestration

It is a structure occurring from a nonfunctional lung tissue that is not related to the tracheobronchial system. It can be intralobar or extralobar. The extralobar one has its own pleura and feeding artery from the systemic circulation. Bronchopulmonary sequestration (BPS) has a relatively good prognosis. These vascular structures can be observed better with Doppler USG. Bronchopulmonary sequestration can be confused with adrenal tumors when it is located at the upper abdomen and MRI could be used for their differentiation (56).

Congenital diaphragmatic hernia

It mostly (90 percent) originates from the left posteriolateral region of the diaphragm. Only 10 percent originate from the right diaphragm. In two percent of the cases it can be bilateral. Fetal survival varies between 40 percent and 90 percent (57). The degree of pulmonary hypoplasia associated with the congenital diaphragmatic hernia, liver herniation and size of hernia sac is very important in determining the prognosis (58). The organs herniated into the thoracic cavity can easily be selected with magnetic resonance imaging. More frequently, the stomach, small intestine and colon, also liver, gallbladder and spleen are the organs that can be herniated. Comments can be made in terms of prognosis by determining the existing fetal lung volume.

Fetal Abdominal Organ Anomalies

The liver tissue can be evaluated very well with MRI. During fetal development the liver shows signal changes. By looking at the measurement changes of the T2-weighted series of the fetal liver after maternal oxygenation, evaluation of abnormalities such as placental insufficiency and IUGR can be carried out (59). Hemangioendothelioma, hepatoblastoma, and hamartomas are rare liver masses seen in the fetus. These lesions have specific magnetic resonance images.

Meconium can be seen in the rectum as early as the fourteenth week with fetal MRI. If mecomium is not visible in the middle-distal intestines we could suspect atresia or perforation. Cystic abdominal masses can be differentiated from intestinal atresia with fetal MRI,and it can also show the location of the intestinal atresia (60). MRI can be helpful in verifying anterior abdominal wall defects.

As renal anomalies are frequently associated with oligohydramnios, detection of anomalies with USG is often difficult. In complex urinary system anomalies like primary megaureter, horse shoe kidney, renal agenesis, bladder extrophy and cloacal anomaly, MRI is very helpful in the diagnosis of imperforate hymen and hydrocolpos.

Skeletal Anomalies

In general, an idea about the development of the skeleton and the size of the thorax can be obtained with MRI. It can also provide information about the details of the development of the pineal gland (61).

Monozygotic Twin Pregnancy Complications

Specific complications such as twin to twin transfusion syndrome, acardiac twins, conjoined twins and embolization syndrome create an indication for fetal surgery intervention in monochorionic twins (62). Some of these complications are associated with the neurological damage caused by thrombotic ischemia (63). Parenchymal destruction can be detected with MRI (23). The best indicator of ischemic injury is the cavitary lesions that can be visualized on MRI two weeks after ischemic injury. In the future, diffusion MRI technique may allow earlier identification of ischemic damaging.

Placental Invasion

Placental invasion anomalies are frequently associated with uterine surgery, uterine infections and placenta previa. Magnetic resonance imaging is a complementary method for ultrasound in patients who have a placental invasion risk. The USG findings of placental invasion are subplacental hypoechoic zone loss, accompanying placenta previa in most cases, detection of a large number of large intervillous ponds inside which blood flow can be observed, with large vessels expanding into the myometrium.

The magnetic resonance imaging findings in T2-weighted sequences can be seen as myometrial loss, placental tissue signal exceeding the uterine border, and loss of the fat tissue between the uterine and pelvic organs. Lax and colleagues described placental invasion with MRI with the findings of heterogeneous signal intensity inside the placenta, hypointense intraplacental band in T2 weighted sequences, and swelling of the lower uterine (64). Using godolinium in magnetic resonance imaging can help in providing discrimination of the placenta and myometrium, but because of its placental transmission the profit-loss rate must be taken into consideration. Diffusion weighted MRI based on the specific diffusion of water molecules in the tissue provides a characteristic image for the tissue. The normal endometrium has high signal intensity because of its dense cells and abundant cytoplasm. On the basis of this hypothesis, the investigation of the diagnosis of placental invasion with diffusion MRI can become easier (65). In conditions such as posterior located placenta and a previous caesarean section where imaging especially with MRI is difficult, evaluating the placenta with USG must be considered.

Volumetric Measurements

Whole fetus volume or single organ volume measurements can be made easily and accurately with fetal MRI (66). Lung volume is important in determining the degree of pulmonary hypoplasia and liver volume is important in diagnosing IUGR.

Conclusion

Ultrasonography still remains the first choice in prenatal diagnosis. However, with the development of prenatal treatment methods, the importance of prenatal diagnosis is gradually increasing. The superiorities of magnetic resonance imaging to USG are; giving good tissue contrast, the large study area thus demonstrating the lesion and its relationship between the neighboring structures, being operator independent, not being affected by maternal obesity and severe oligohydromnios. However, MRI is insufficient in the evaluation of fetal limbs and the detection of fetal cardiac anomalies according to USG. Fetal MRI has a complementary role for USG and can affect diagnosis accuracy, prenatal treatment, the prenatal approach and birth planning by providing important information in prenatal diagnosis.

Conflict of interest

None declared.

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B-Lynch suture technique to control postpartum hemorrhage in a patient with mullerian anomaly

Uterin anomali olgusunda postpartum kanama kontrolünde B-Lynch sütür tekniği

İbrahim Hakan Boyar[1], Fazilet Kübra Boynukalın[1], Nuray Boyar[1], Mehmet Vural[2]

[1]Department of Obstetrics and Gynecology, Şanlıurfa Maternity Hospital, Şanlıurfa, Turkey

[2]Department of Obstetrics and Gynecology, Medical Faculty, Harran University, Şanlıurfa, Turkey

Abstract

Congenital anomalies of the uterus may cause gynecologic, obstetric and fertility problems. Obstetrical complications are reported to occur more commonly with mullerian duct anomalies, such as postpartum hemorrhage (PPH). Uterine compression sutures may be effective in controlling PPH in these conditions as an alternative to hysterectomy, especially if the patient has a desire to conceive. As the shape of the uterus is changed in congenital malformation, the usage of compression sutures such as B-Lynch can be more difficult. In this study we report a case of PPH accompanying a large septae, treated with B-Lynch suture. A 24 year old, multigravid and nulliparous patient (G:3) was admitted to our clinic with vaginal bleeding and abdominal pain at 31 weeks of gestation. Emergency cesarean section was performed for abruptio placenta and PPH occurred subsequently. A deep uterine septum was revealed during operation. Intermittent fundal massage and intravenous uterotonics were used to improve uterine tonicity without any improvement. After the B-Lynch suture was performed, the bleeding diminished dramatically. As the shape of the uterus is changed in congenital malformation, the application of secondary interventions in postpartum hemorrhage can be more difficult. There can be slippage or overlapping of the suture while using a B-Lynch suture. Because the uterine shape is not completely distorted, patients with septate uterus can be candidates for a B-Lynch suture. There is no such reported case from the literature regarding efficacy of B-Lynch suture in mullerian anomalies. his case illustrates the potential benefits of B-Lynch compression suture in an uterus with mullerian anomalies.

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Key words: Uterine anomaly, postpartum hemorrage, B-Lynch suture

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Özet

Uterin konjenital anomalileri jinekolojik ve obstetrik sorunlara yol açabilir ve infertilite ile bulgu verebilir. Postpartum kanama (PPK) ve erken doğum gibi obstetrik komplikasyonlar uterin anomalili olgularda daha sık karşımıza çıkar. Özellikle fertilite arzusu olan olgularda uterin kompresyon sütürleri postpartum kanamanın kontrolünde faydalı olabilir. Uterin anomalide uterusun şeklinin değişmiş olması etkin sütür konulmasını zorlaştırabilir. Bu çalışmada derin uterin septumu olan bir olguda B-Lynch sütürü ile PPK'nın etkin şekilde kontrolü değerlendirilmiştir. 24 yaşında G3P0A2 hasta 31 haftalık gebe iken hastanemize vajinal kanama şikayeti ile başvurdu. Hasta plasenta dekolmanı tanısıyla acil sezeryana alındı sezeryan sonrası PPK gelişti. İntraoperatif olarak derin uterin septum izlendi. Fundus masajı ve uterotonik ajanlara başvuruldu ancak yanıt alınamadı. B-Lynch sütürü konulduktan sonra kanama kontrol altına alındı. Uterusun şeklinin değişmiş olması nedeniyle kanamayı durdurmak amacıyla kullanılan ikinci basamak yöntemler zorlaşır. Uterusun şeklinin tamamen değişmemiş olduğu septat uterusta B-Lynch sütürü faydalı olabilir. Litaratürde uterin anomalili olgularda B-Lynch sütürünün etkinliğinin değerlendirildiği başka bir olgu sunumu bulunmamaltadır bu olgu sunumu ile uterin anomalili olgularda B-Lynch sütürü kullanılmasının etkin olabileceği gösterilmiştir.

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Anahtar kelimeler: Uterin anomali, postpartum kanama, b-lynch sütürü

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Introduction

Congenital anomalies of the uterus are frequently asymptomatic and unrecognized. Mullerian duct anomalies can contribute to gynecologic, obstetric and fertility problems. The true incidence of mullerian duct anomalies is difficult to determine, because of the wide variation in presentation. They occur in approximately 3-4% of fertile and infertile women, 5-10 % of women with recurrent early pregnancy loss, and up to 25% of women with late first or second-trimester pregnancy loss or preterm delivery (1-4). Obstetrical complications reported to occur more commonly with mullerian duct anomalies include increased risks of miscarriage, preterm delivery, intrauterine growth restriction, cervical incompetence, abnormal fetal presentation, pregnancy-associated hypertension, cesarean delivery, antepartum and postpartum hemorrhage (2, 5-8).

The most common cause of antepartum hemorrhage in the third trimester is placental abruption. Placental abruption is

Address for Correspondence / Yazışma Adresi: *Uzm. Dr. Fazilet Kübra Boynukalın, Şanlıurfa Kadın Hastalıkları ve Doğum Hastanesi, Şanlıurfa, Turkey*
Mobile: +90 533 429 35 71 e.mail: drkubraboynukalin@yahoo.com.tr
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defined as decidual hemorrhage leading to the premature separation of the placenta prior to delivery of the fetus. Abruption of the placenta can lead to serious maternal and infant morbidity, as well as perinatal or maternal death. Management of women with severe placental abruption is surgical delivery (9). Also placental abruption can be complicated, with disseminated intravascular coagulopathy or postpartum hemorrhage due to uterine atony. Postpartum hemorrhage (PPH) is an obstetrical emergency that can follow vaginal or cesarean delivery. PPH is most commonly defined as having greater than 500 ml estimated blood loss for vaginal delivery and 1000 for cesarean section. It is a major cause of maternal morbidity, and one of the top five causes of maternal mortality (10). The incidence of PPH varies 1 to 5 percent of deliveries (10, 11). If the initial management of controlling hemorrhage (fundal massage, uterotonic drugs) is not effective, secondary interventions (uterine tamponade procedures, compression sutures such as B-Lynch suture, uterine artery ligation, hypogastric artery ligation, x-ray guided artery embolisation and hysterectomy) should be considered.
If the patient has a desire to conceive, B-Lynch suture should be considered as an alternative to hysterectomy.

Case

A 24 year old, multigravid and nulliparous patient (G: 3) was admitted to our clinic with vaginal bleeding and abdominal pain at 31 weeks of gestation. She had had two previous miscarriages in the past. On examination the woman was conscious, oriented but pale. Her vital signs were normal except mild tachycardia (blood pressure: 100/60 mmHg, heart rate: 96/min, body temp: 36.6 C, respiratory rate: 22 /min). On abdominal examination her uterus was contracted and tender. Abdominal ultrasonography evaluation revealed a bradycardic fetus and a retroplacental hemorrhage. Fetal biometry was concordant with 31 weeks with normal amniotic fluid index. The fetus was in transverse situs. After diagnosis of ablatio placenta she was immediately transferred to the operating room. Cesarean section was performed with low segment transverse incision. A female, 1000 gr. infant was delivered (Apgar scores were 4 and 5 in first and fifth minutes respectively). Amniotic fluid was bloody and approximately 500 cc fibrinated and defibrinated blood was drained from retro placental place. A deep uterine septum is revealed in the operation. Uterus was atonic and bleeding diffusely. Intermittent fundal massage and intravenous uterotonics used to improve uterine tonicity without any improvement. Because of worsening in homeostasis the compression suture technique of B-Lynch was performed with no 2 vicryl suture while uterine incision is open. Afterwards uterine incision was closed with continued locked sutures (Figure 1). After the practice, the patient's blood loss diminished to acceptable amounts. Intra-operative 2 units of red blood cells were given for replacement. Then the operation was finished. The patient was followed in intensive care unit postoperatively. After 12 hours her vital signs were normal and she was discharged in three days. Also postoperative weekly control was uneventful.

Figure 1. Performed B-Lynch suture in a septate uterus

Discussion

Postpartum hemorrhage is a common obstetric emergency which can lead to maternal morbidity and mortality. Surgical methods of controlling uterine bleeding by inserting compression sutures have been developed to reduce the incidence of emergency hysterectomy and to preserve fertility in these patients. B-Lynch suture is an alternative operative method for stopping postpartum hemorrhage especially in uterine atony. The chance for success of this procedure does not depend on surgical skill. With B-Lynch suture severe pressure can be achieved at the same time to both sides of uterine body. The suture provides enough compression without disturbing the anatomy. The B-Lynch suture compresses the uterus, similar to the result achieved with manual uterine compression. In case reports and small series it has successful in controlling postpartum hemorrhage caused by atony when other methods have failed. The advantage of this technique is simple to learn, safe and preserves future reproductive potential.
In a 7 year review of all uterine compression sutures for postpartum hemorrhage at one tertiary obstetric hospital, 27 B-Lynch sutures were performed. 10 patients needed additional compression suture techniques. All were done at the time of cesarean delivery. Hysterectomy was avoided in 23 of 27 women. 15 of these women were primiparous at the time of compression suture (12). In another study, Bhal and colloquies showed that, B-Lynch sutures were able to avoid hysterectomy 10 of 11 cases (13). In literature after uterine compression sutures, many successful pregnancies reported (14-16).
One fourth of women with late first or second trimester pregnancy lost or preterm delivery were associated with uterine malformations. The most common form of these malformations is septate uterus. As the shape of the uterus is changed in congenital malformation, the usage of secondary interventions in postpartum hemorrhage can be more difficult. There can be slippage or overlapping of the suture while using a B-Lynch suture. Halder A, reported a new uterine suture technique to control postpartum hemorrhage during cesarean section in congenitally malformed uterus. In his eight cases of series, hys-

terectomy was avoided in 7 patients. Long term adverse effects have not been reported in these cases (17).

Our case was the most common form of uterine malformation which is septate uterus. Because the uterine shape is not completely distorted these patients can be a candidate for a B-Lynch suture. Although we had not any technical difficulty while placing B-Lynch suture to the uterus, worried about the failure of compression suture because of two reasons. Uterine surface was too large in width, compared to a normal postpartum uterus due to fusion defect and presence of a large septum could form a handicap for compressing the anterior and posterior walls each other. After applying procedure, the bleeding was diminished dramatically. There's no such reported case from the literature regarding efficacy of B-Lynch suture in mullerian anomalies. We can assert that B-Lynch suture can be an alternative for postpartum hemorrhage even in septate uterus avoiding hysterectomy.

Conflict of interest

None declared.

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Primary melanoma of the vagina. A clinical case

Vajinanın primer melanomu. Bir klinik vaka

Judit Albareda[1], Clara Olier[2], Isabel Alemany[3]

[1]Department of Obstetrics and Gynaecology, Hospital Universitario Fundacion Alcorcon, Madrid, Spain

[2]Department of Medical Oncology, Hospital Universitario Fundacion Alcorcon, Madrid, Spain

[3]Department of Pathology, Hospital Universitario Fundacion Alcorcon, Madrid, Spain

Abstract

Primary melanoma of the vagina is a rare neoplasm that appears in the 6th and 7th decades of life. It has a poor prognosis, for which there is no consensus regarding treatment; indeed, the literature describes a number of therapeutic options. This paper describes a patient with vaginal melanoma treated by local excision and immunotherapy.

(J Turkish-German Gynecol Assoc 2011; 12: 50-2)

Key words: Vaginal neoplasms, melanoma, treatment, prognosis

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Özet

Vajinanın primer melanomu, yaşamın 6. ve 7. dekatında ortaya çıkan nadir bir neoplazmadır. Prognozu kötü nadir bir durum olup bu nedenle tedavisi hakkında bir fikir birliği yoktur; aslında literatürde birçok tedavi seçeneği tarif edilmektedir. Bu makalede lokal eksizyon ve immünoterapi ile tedavi edilen vajinal melanomlu bir hasta anlatılmaktadır. (J Turkish-German Gynecol Assoc 2011; 12: 50-2)

Anahtar kelimeler: Vaginal neoplazma, melanoma, tedavi, prognoz

Geliş Tarihi: 27 Mayıs 2010 **Kabul Tarihi:** 27 Haziran 2010

Introduction

Vaginal melanoma is an uncommon form of melanoma, affecting an area not exposed to ultraviolet radiation (1). About 1.6% of melanomas appear on the genitals (1), and some 0.3-0.8% on the vagina (2, 3). Although melanoma is the second most common neoplasm of the vagina, it represents less than 3% of all neoplasms involving this area (3, 4). It mainly affects postmenopausal women in their 6th and 7th decade of life (5) and usually has no accompanying symptoms. However, some vaginal melanomas can lead to vaginal bleeding and an increase in discharge, and on some occasions a palpable mass can be felt (6). Amelanocytic melanomas are an uncommon form, making up about 2% of all vaginal melanomas (7).

Vaginal melanomas are usually localised in the lower third of the vagina and appear as multicentric, somewhat elevated lesions. They are very aggressive tumours and overall survival rates are very low. Independent of the treatment given, overall survival of five years is 5-25% (4). This type of tumour carries a high risk of long distance metastases and local recurrence shortly after surgery; disease-free time is therefore usually short (8). The rarity of this condition means treatment is not well defined. Local excision, radical surgery, radiotherapy, chemotherapy and immunotherapy, or some combination of these, have been described by different authors (6).

The present work describes a patient with vaginal melanoma, the treatment provided, and a review of the pertinent literature in PubMed (Medline).

Clinical case

A 63 year-old patient with a background of adenocarcinoma of the endometrium (FIGO 1A G2), treated surgically for this condition at our centre in 2004, attended a routine follow-up appointment in March 2009, during which a hyperpigmented, multifocal, slightly ulcerated lesion affecting the lower third of the vagina (posterior wall) was detected. This lesion was under 3 cm in diameter and in contact with the external edge of the vagina (Fig. 1). The remainder of the vagina was free of disease. No palpable inguinal lymphatic ganglia were detected, and a pelvic examination was normal. The patient was asymptomatic and showed no skin lesions suspicious of melanoma. A biopsy of the affected area returned a result of squamous mucosa with melanoma and the presence of round cells. Immunohistochemical analysis returned positive results for HMB-45 and Melan-A (Table 1). A thoracic-abdominal-pelvic CT scan was normal.

The patient was treated surgically, involving complete excision of the affected vagina with a safety margin of 2 cm. Bilateral inguinal lymphadenectomy was also performed.

Histological analysis returned a result of vaginal melanoma in the vertical growth phase, with three nodular lesions measuring 1.3, 0.5 and 1.5 cm along their longest axes. The maximum thickness of the lesion was 9 mm. Extensive perineural invasion was noted with a mitotic index of four mitoses per 10 high power field (Fig. 2, 3). The resection margins were histologically free of neoplastic involvement. The inguinal lymphatic glands were negative. The TNM stage was T4a N0 M0 (stage IIB).

Given the risk of local recurrence and distant metastatic disease, surgery was followed by high dose interferon alpha-2b treatment according to Kirkwood (9) (20 mUI/m^2 i.v. once per day for 4 weeks, followed by a maintenance dose of 10mUi/m^2 s.c. three times a week until week 48 after surgery) with the aim of lengthening the period of disease-free survival.

In a PET CT scan performed seven months after surgery, the patient showed submillimetric pulmonary lesions compatible

Address for Correspondence / Yazışma Adresi: *Uzm. Dr. Judit Albareda, Budapest 1 St 28922 Alcorcon, Spain*
Phone: +34916219599 e.mail: jalbareda@fhalcorcon.es
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Table 1. Immunohistochemical analysis

Vimentin	positive
EMA	focally positive
S-100	positive
HMB-45	positive
Melan-A	positive
CD3	negative
CD20	negative
CD45	negative
CD79 alpha	negative
CD 34	negative
CD68	negative
CD10	negative
Chromogranin	negative
Synaptophysin	negative
Desmin	negative
Actin HHF-35	negative
Oestrogen receptor	negative
Progesterone receptor	negative
CMA 5-2	negative
CKAE1-AE3	negative

with metastases; this was confirmed histologically following radioguided punction. Palliative chemotherapy was provided. At one year post diagnosis the patient is alive but with disease.

Discussion

Primary melanoma of the vagina is a rare neoplasm that usually affects adult women. The literature only describes some 250 cases (10), which explains the lack of consensus regarding its treatment (11). The condition normally affects the lower third of the vagina (10); lesions are usually multifocal and in 2% of cases, amelanocytic (7).

Studies have shown that vaginal melanoma usually appears in the 6th and 7th decades of life (10). At the time of diagnosis the present patient was 63 years old. These tumours commonly have no accompanying symptoms (11) and are usually found by chance, as in the present case. The most common symptoms, when they occur, are vaginal bleeding and an increase in vaginal discharge; in some cases a palpable mass can be detected (2).

The prognosis of patients with melanoma is poor. The literature describes the five year survival as around 25% (2). In a meta-analysis performed by Buchanan et al., the overall five year survival was 13-19%. Only two patients survived 10 years and both suffered recurrences that required various treatments (11). A number of factors have been associated with a poorer prognosis, the most important of which appears to be tumour size (10). Tumours <3 cm in diameter localised in the lower third of the vagina seem to be associated with better overall survival (mean 41 months),

Figure 1. Macroscopic appearance of vaginal melanoma lesion

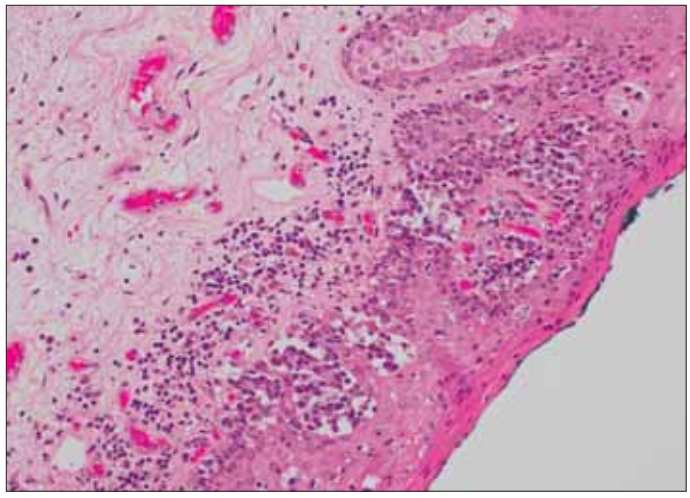

Figure 2. Staining with haematoxylin-eosin (100x). Note the nests of atypical melanocytic cells at the junction between the epithelium and the subepithelial connective tissue, reflecting neoplastic activity

probably because of the possibility of surgical removal with tumour-free margins. In tumours ≥3 cm, achieving tumour-free margins is more difficult, and survival is about 12 months (11).

The thickness of the tumour does not appear to affect overall survival. Tumours showing ≥6 mm invasion are associated with a mean survival of 16 months, while those showing <6 mm invasion are associated with a mean survival of 23 months ($p<0.288$) (11). Certainly, cell type, number of mitotic cells, ulceration, vascular involvement and amelanosis all appear to affect survival (12).

The FIGO staging system is probably not the optimum for use with vaginal cancers since it does not contemplate tumour size (which is important in vaginal melanoma) or the study of the lymph glands (13). Some authors suggest that the Breslow

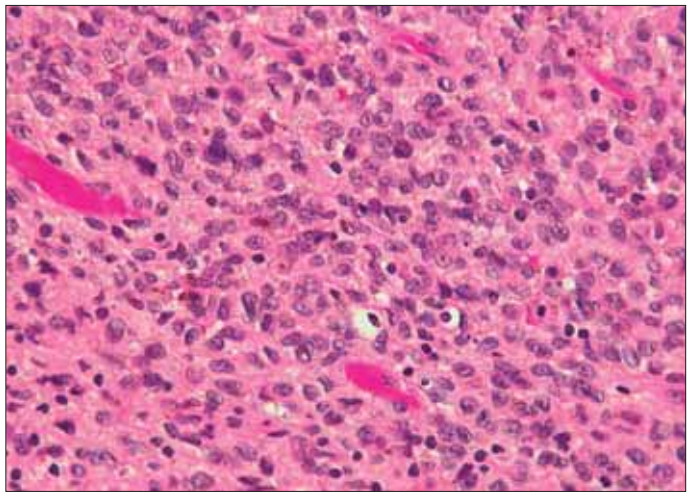

Figure 3. Staining with haematoxylin-eosin (400x). Note atypical cells of variable size and nuclear morphology, with coarse chromatin and occasional prominent nucleoli. Note the intracytoplasmic granular pigment (melanin)

method, which is valid for cutaneous melanomas, could be used in the early stages of vaginal melanomas. Clark levels, however, do not seem applicable given the absence of dermal and subcutaneous papillary and reticular structures (4, 10). Thus, the staging of vaginal melanomas can be difficult, with the microstaging method of Breslow (14) perhaps being the best available (10).

Treatment options include local excision (8), radical excision with inguinofemoral and/or pelvic lymphadenectomy (6), radiotherapy (15), chemotherapy, and immunotherapy (5, 9, 16). Most authors suggest surgical treatment (1, 3, 10, 17), although the benefit of radical surgery over conservative surgery has not been demonstrated (always supposing the margins are tumour-free) (10, 11). Non-tumour-free resection margins favour local recurrence and are associated with a poorer prognosis (11). No difference has been demonstrated between radical and conservative surgery either in terms of overall survival or disease-free survival.

Adjuvant pelvic radiotherapy and brachytherapy may help in the locoregional control of the disease (10). Exenteration and/or radiotherapy may be useful when dealing with large tumours. Radiotherapy and chemotherapy are indicated when a tumour is nonresectable (10), although the role of chemotherapy in patients with distant metastases has not been established. Although lymphadenectomy is controversial (17), some authors advise pelvic lymphadenectomy for tumours affecting the mid and upper thirds of the vagina, and inguinal lymphadenectomy for those affecting the lower third (4). However, the pelvic ganglia are not usually involved. Examination of the sentinel node, normally a matter of course for melanoma in other locations, should provide the information necessary to identify which patients require complete lymphadenectomy (1). The sentinel node illustrates the status of the regional ganglia, obviating the need to perform exhaustive lymphadenectomy and thus avoiding the morbidity this entails. In addition, it allows the presence of micrometastases to be diagnosed. If the surgical team has sufficient experience, sentinel node examination before lymphadenectomy could therefore be of benefit; unfortunately no such experience was available in the context of vaginal melanoma at our centre when the present patient underwent surgery.

In conclusion, vaginal melanomas are uncommon, highly aggressive tumours that are associated with poor overall survival. The chance of local recurrence following surgical treatment is around 80%; the risk of distant metastases is also very high. There is no consensus regarding treatment, but the combination of different therapies, plus local excision of the lesion and investigation of the sentinel node, if possible, would appear to be a reasonable option.

This work is dedicated to the memory of Dr. Antonio López Salvà, 1951-2010.

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Conflict of interest

No conflict of interest is declared by authors.

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Successful outcome in preeclamptic rudimentary horn pregnancy

Preeklamptik rudimenter boynuz gebeliğinde başarılı sonuç

Ruchi Sinha, Shikha Sachan, Anuradha Khanna

Department of Obstetrics and Gynecology, Institute of Medical Sciences, Bhu, India

Abstract

Unicornuate uterus with rudimentary horn is an uncommon type of mullerian duct malformation associated with various gynecological and obstetrical complications. Rudimentary horn pregnancy is a rare entity and the majority have rupture of gravid horn leading to maternal and fetal morbidity and mortality. A case of rudimentary horn pregnancy at 32 weeks and 6days with pregnancy induced hypertension is reported where proper management results in successful pregnancy outcome. (J Turkish-German Gynecol Assoc 2011; 12: 53-5)

Key words: Rudimentary horn, unicornuate uterus, pregnancy, preeclampsia

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Özet

Rudimenter boynuzlu unikornuat uterus, çeşitli jinekolojik ve obstetrik komplikasyonlarla ilişkili olan nadir bir müller kanal malformasyonudur. Rudimenter boynuz gebeliği nadir bir durumdur ve çoğunluğunda gebe boynuz rüptüre olarak maternal ve fetal morbidite ve mortaliteye neden olmaktadır. Uygun tedavinin gebeliğin başarılı şekilde sonuçlanmasını sağladığı 32 hafta ve 6 günlük rudimenter boynuz gebeliği ile gebeliğin neden olduğu hipertansiyonu olan bir olgu bildirilmektedir. (J Turkish-German Gynecol Assoc 2011; 12: 53-5)

Anahtar kelimeler: Rudimenter boynuz, Unikornuat uterus, Gebelik, Preeklampsi

Geliş Tarihi: 05 Nisan 2010 **Kabul Tarihi:** 07 Haziran 2010

Introduction

Unicornuate uterus with rudimentary horn is an uncommon type of mullerian duct malformation. It is associated with various gynecological and obstetrical complications.

Rudimentary horn pregnancy is a rare entity, the incidence being 1 in 76,000 (1, 2). Very rarely, live births in rudimentary horn pregnancy is reported in the literature as the majority have rupture of the gravid horn, leading to extensive intraperitoneal hemorrhage and maternal and fetal morbidity and mortality. We present a case of rudimentary horn pregnancy with preeclampsia where proper management results in successful pregnancy outcome.

Case Report

A 21-year-old primigravida at 32 weeks and 6 days of gestation with preeclampsia was referred to the department of obstetrics and gynecology, BHU for decreased fetal movements for 1 day. She had had bilateral pedal edema for the previous 2 months. She was diagnosed as a case of preeclampsia and was on 500 mg of methyl-dopa three times daily for the previous 15 days. There was no history of dysmenorrhoea and her menstrual cycles were regular. She had received 2 doses of betamethasone. On examination, the patient's vital signs were stable. Her blood pressure was 160/100 mmHg.

Obstetrical examination revealed a fundal height corresponding to 32 weeks of gestation and deviation of the uterus to the right. The fetus was cephalic and fetal heart rate was 114 bpm. Cardiotocography was carried out and was nonreactive. Her hemoglobin was 12.5 gm/dl, urine albumin 2+, uric acid 7.2 mg/dl, creatinine 1.0 mg/dl and random blood sugar 69.0 mg/dl. Her liver function tests and renal function tests were normal. The ultrasonography (USG) of the second trimester done at the periphery was reported to be normal. Repeat USG with a biophysical profile (BPP) was done which revealed a 4/10 score with an amniotic fluid index of 8. The patient was moved for emergency caesarean section in view of low BPP (fetal distress). On laparotomy pregnancy was located in the right horn of uterus and the left horn was approximately 6 weeks size. The right horn was extensively fused to the left. The left and right fallopian tubes and ovaries were attached to the respective horns (Figure 1). Low transverse incision was made over the right horn and the baby was delivered. Placenta was delivered by control cord traction. Placenta and membranes were normal on gross examination. Clamps were applied and the right horn excised along with right salpingectomy (Figure 2). Both ovaries were preserved. The baby was a 1560 gm female with an Apgar score of 8/10 and 9/10 at 1 min and 5 min respectively.

The patient made an uneventful recovery and was discharged home on the tenth day. The follow up at 6 weeks was normal.

Address for Correspondence / Yazışma Adresi: *Uzm. Dr. Ruchi Sinha, Dr. Ruchi, 7 Saryoo Nagar, Kamachhavaranasi 221010 Varanasi, India*
Phone: 915422361675 e.mail: dr.ruchi_bhu@yahoo.com
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Discussion

Mullerian duct anomalies are infrequently encountered in day to day gynecological practice. The incidence of mullerian duct malformation in the general population is estimated to be 4.3% (3). The unicornuate uterus with a rudimentary horn is a rare type of mullerian duct malformation and results from the defective fusion of the malformed duct with the contra-lateral duct, the incidence being 0.4% (3). In 80-90% of the cases rudimentary horn is not connected to the uterine cavity (4).

Rudimentary horn pregnancy (RHP) is a very rare entity. Conception occurs in the rudimentary horn due to transperitoneal migration of sperm or zygote, although a corpus luteum has been observed on the contralateral side in only 10% of the cases (5). Rudimentary horn pregnancy has a very poor maternal and fetal outcome. The most common and life threatening complication of rudimentary horn pregnancy is rupture (80%). The rupture usually occurs in the first and second trimester (80%) and infrequently in the third trimester (20%) (6). Rupture leads to torrential intraperitoneal bleeding with severe maternal and fetal mortality. Here lies the importance of prerupture diagnosis but the prerupture diagnosis is extremely difficult. Literature shows a preclinical detection rate of 8% and a preoperative detection rate of 29% only (7). The diagnosis is possible only with a high index of clinical suspicion and radiological investigations (USG & MRI) (7, 8). The bimanual finding of palpable mass extending outward from the uterine angle (Baart de la faille's sign) or displacement of the fundus to the contralateral side with rotation of the uterus and elevation of the affected horn (Ruge Simon Syndrome) or deviation of the uterus to one side with an adnexal mass in pregnancy should arouse suspicion of a rudimentary horn. USG in early trimesters are helpful in diagnosing a case of RHP. Tsafrir et al. suggested the following criteria for early sonographic diagnosis of rudimentary horn pregnancy (8). (i) a pseudo pattern of an asymmetrical bicornuate uterus, (ii) absent visual continuity in tissue surrounding the gestational sac and the uterine cervix and (iii) the presence of myometrial tissue surrounding the gestational sac. Additionally, MRI can be used to confirm the diagnosis before laparatomy is undertaken. Buntugu et al have also shown that in low resource centres, placement of a Foley catheter into the uterine cavity and performing a transabdominal ultrasound scan can conclusively exclude an intact uterine pregnancy (9).

In addition to rupture, the RHP usually lead to missed abortion or intrauterine death; and rarely, fetal survival has been reported. Until 1999, only 13 neonatal survivals were reported in the English Literature (10). In an exhaustive review of 20th century literature, Nahum reported only 6% of RHP which have progressed to term, with a 13% neonatal survival (6). Goel et al. have reported a case of post dated RHP but the baby could not survive following delivery (11).

Ours is a case of RHP referred to our hospital in the third trimester with successful fetal and maternal survival. The preoperative diagnosis was not possible in our case, as the early pregnancy USG was done at a peripheral hospital where there was no expertise and it is difficult to diagnose RHP in cases of late trimester USG.

Figure 1. Unicornuate uterus and rudimentary horn

Figure 2. Excised rudimentary horn

The endometrium of the rudimentary horn has been described as thinner than usual and sometimes even non functional (12). Pathological placentation may lead to placenta accrete, as reported in various cases (13, 14). It is also possible that poor placentation in horn pregnancy may be a cause of preeclampsia and fetal distress or low BPP in our case.

The management of RHP is laparotomy and surgical excision of the rudimentary horn and tube, as was done in our case. In the literature, the laparoscopic removal of pre and post rupture RHP is reported but this is carried out in cases of early diagnosis (6, 15).

Conclusion

RHP is an extremely rare entity. The high index of suspicion is important to diagnose it early i.e. before rupture, to prevent life threatening consequences. A timely and proper management can result in a successful pregnancy outcome even in horn pregnancy.

Abbreviations

PIH: Pregnancy induced hypertension, BPP: Biophysical profile, USG: Ultrasonography, RHP: Rudimentary horn pregnancy

Consent

Written informed consent was taken from the patient for the publication of this case report and any accompanying images. A copy of the written consent is available for the review of the Editor in Chief of this journal.

Conflict of interest

No conflict of interest is declared by authors.

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Cystoscopic suture removal by Holmium-YAG laser after Burch procedure

Burch kolposuspensiyonu sonrası mesane içi sütürün Holmium-YAG lazer ile çıkarılması

Emre Kazım Karaşahin[1], Sertaç Esin[1], İbrahim Alanbay[1], Mutlu Cihangir Ercan[1], Erol Mutlu[1], İskender Başer[1], Şeref Basal[2]

[1]*Department of Obstetrics and Gynecology, Gulhane Military Medical Faculty, Ankara, Turkey*

[2]*Department of Urology, Gulhane Military Medical Faculty, Ankara, Turkey*

Abstract

Burch colposuspension remains one of the successful operations performed for stress incontinence. Accidental suturing of the bladder wall during the procedure or subsequent erosion may lead to lower urinary tract symptoms. Diagnosis and management of these sutures indicate precise evaluation for which a 70 degree cystoscope is used. In selected cases, Holmium-YAG laser may enable us to manage long-standing, encrustated neglected sutures. Here we would like to report successful removal of intravesical sutures using the Holmium-YAG laser. (J Turkish-German Gynecol Assoc 2011; 12: 56-8)

Key words: Burch colposuspension, stress incontinence, cystoscopy, Holmium-YAG laser

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Özet

Burch kolposüspansiyonu stres inkontinans tedavisinde kullanılan en başarılı tedavilerden biri olmaya devam etmektedir. İşlem esnasında sütürün yanlışlıkla mesane duvarından geçmesi yada daha sonra gelişen erozyon nedeniyle sütürün mesane içinde kalması alt üriner sistem semptomlarına yol açmaktadır. Bu sütürlerin belirlenmesi ve ortadan kaldırılmasında ayrıntılı inceleme ve bunun için daha çok 70 derecelik sistoskopun kullanılması gerekmektedir. Seçilmiş vakalarda, uzun süre içeride kalmış ve katılaşmış sütürün çıkarılmasında Holmium-YAG lazer özellikle yardımcı olabilir. Bu vakada, intravesikal sütürlerin Holmium-YAG lazer ile başarılı şekilde çıkarılması anlatılmaktadır. (J Turkish-German Gynecol Assoc 2011; 12: 56-8)

Anahtar kelimeler: Burch kolposüspansiyonu, stres inkontinans, sistoskopi, Holmium-YAG lazer

Geliş Tarihi: 10 Nisan 2010 **Kabul Tarihi:** 10 Haziran 2010

Introduction

Burch colposuspension is a widely employed surgical treatment for genuine stress incontinence. The paraurethral vaginal wall is attached to Cooper's (Iliopectineal) ligament by polypropylene sutures to correct deficient urethral closure. Inadvertent suturing of the bladder wall during the procedure or subsequent erosion may lead to a foreign body reaction, resulting in new or worsening of preexisting symptoms (1). The localization of the sutures is usually at the dome of the bladder which complicates the diagnosis and management. The Holmium-YAG laser is a solid-state pulsed laser frequently used for benign prostatic hyperplasia and urolithiasis (2). Here we would like to report endoscopic excision of intravesical propylene suture using Holmium-YAG laser.

Case

A 42-year-old woman presented to our hospital's urology department with chronic pelvic pain and recurrent urinary tract infection. She was evaluated, urinanalysis was normal and then an office cystoscopy with a rigid 30 degrees cystoscope was performed, which was reported as normal. Thereafter, the patient was referred for consultation with our department. She was a G2P2 patient and her medical history was unremarkable except for a Burch Colposuspension operation she had undergone 2 years previously in a district hospital due to stress incontinence. The operation record was not available and according to the patient's statements, 1 day after the operation, she underwent a cystoscopy which was reported verbally as "normal". Her stress incontinence disappeared but soon after, frequency, urgency, dyspareunia, pelvic pain and recurrent urinary tract infection complaints ensued. In our clinic, the vaginal examination was normal and transvaginal sonography revealed no abnormalities in the uterus and ovaries. Her urine tests were repeated and only mild hematuria was detected. Renal ultrasonography was also normal. She was reevaluated in the gynecology and urology council and the decision was to perform a repeat cystoscopy. Under general anesthesia, we performed rigid cystoscopy with a 70 degree cystoscope. In the cystoscopy, we detected polypropylene sutures at the vesical neck both on the right and left sides close to the dome of the bladder. The sutures were surrounded by edematous inflamed bladder mucosa and granulation tissue. We attempted to cut the suture using the cystoscopic scissors but this was unsuccessful due to hardening by partial encrustation. After an intraoperative urology consultation, we decided to use the Holmium-YAG laser.

Address for Correspondence / Yazışma Adresi: *Uzm. Dr. Sertaç Esin, 42. Cadde, 18/9 Çukurambar, Ankara, Turkey*
Mobile: +90 532 386 85 37 e.mail: sertacesin@gmail.com
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The VersaPulse® PowerSuite™ 100 W was used. The Holmium-YAG laser output was 1.2 J per pulse at a rate of 5 Hz. Through the channel of the cystoscope, the Holmium-YAG laser was advanced using a 365 μm tip firing fiber and intravesical portions of the polypropylene sutures were resected on both sides (Figure 1). These resected portions were removed through the cystoscope. Total operation time was 12 minutes. The postoperative course was uneventful. 3 months later, the patient was free of all her complaints but dyspareunia.

Discussion

Burch colposuspension is the most widely performed retropubic operation for stress incontinence and attempts to reestablish the anatomic position of the bladder neck by elevating the endopelvic fascia. Non-absorbable sutures have been recommended for Burch colposuspension (3). Inadvertent placing of the sutures through the bladder at the time of surgery or postoperative erosion or migration of the sutures into the bladder (4) may cause chronic inflammatory reaction in the wall of the bladder, resulting in lower urinary tract symptoms. In our case, it was not possible to ascertain the exact mechanism of suturing the bladder wall due to nonavailability of the original operative record.

Dwyer et al. (5) reported intravesical sutures in 3 (0, 32%) out of 925 cases who underwent open Burch colposuspension. No matter the suture is accidentally placed or later migrates into the bladder, intravesical sutures are an important complication of Burch colposuspension. Timely diagnosis of these injuries is associated with lower morbidity and costs, and we agree with Patel et al. (6) that routine use of cystoscopy at the time of colposuspension may enable clinicians to detect and repair the defect concurrently. Suture injuries to the urinary tract in urethral suspension procedures for stress incontinence usually occur at 1 and 11 o'clock. As can be seen in our case, after the Burch procedure, cystoscopic examination by a 30 degree cystoscope may be inadequate. This highlights the necessity of using a 70 degree cystoscope (6).

The Holmium-YAG laser is currently the workhorse laser in urology since it can be used for multiple soft- and hard-tissue applications, including benign prostate hyperplasia (7), laser lithotripsy (8), bladder tumors and strictures. Besides these, it may also be used for excision of intravesical foreign bodies such as tension-free vaginal tape or polypropylene suture (9). During cystoscopy, due to the localization of intravesical sutures (6), it may be difficult for the physician to reach and work in these localizations. In our case, cystoscopic scissors were unsuccessful in cutting the polypropylene suture. For these challenging cases, Holmium-YAG laser is an attractive option for cutting and removing these sutures. Holmium-YAG laser material fragmentation depends upon two mechanisms. In the first mechanism, absorbed laser energy at the focus point melts and breaks down the object. In the second, if the energy used is high, the atomic structure of the material is burst (10). The safety of the Holmium-YAG laser has been shown for prostate (7), urinary calculi (8) and intravesical foreign bodies (10). The wavelength of Holmium-YAG laser is very near the absorption peak of water, thus surrounding tissue damage is minimized provided that water is present (8, 10). Precise targeting is important to prevent uroepithelial injury and this is highly unlikely if the distance between the tip of the fiber and the urothelium is greater than 0, 5 mm (8). In addition, among other laser types, Holmium-YAG laser has the lowest tissue penetration depth (10).

In conclusion, after the Burch procedure, a 70 degree cystoscopic evaluation may be helpful in order to visualize inadvertent injury to the bladder, and when intravesical sutures may not be managed by conventional cystoscopic techniques, the Holmium-YAG laser is a minimally invasive solution. Given the fact that it is easy to use and safe, the Holmium-YAG laser is an attractive option for the physician.

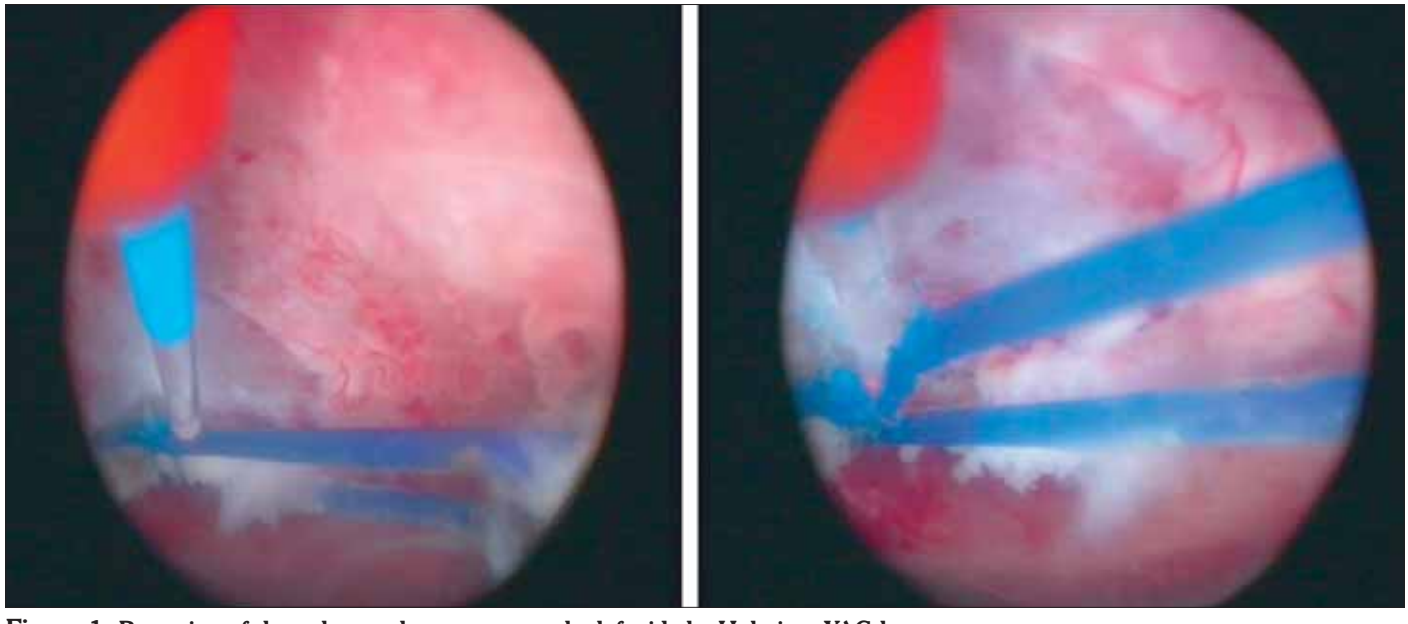

Figure 1. Resection of the polypropylene suture on the left side by Holmium-YAG laser

Conflict of interest

None declared.

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Signet-ring stromal tumor of the ovary: an extremely rare neoplasm

Overin signet-ring stromal tümörü: Çok nadir bir neoplazm

Yavuz Emre Şükür, Batuhan Özmen, Cem Somer Atabekoğlu, Murat Sönmezer, Fırat Ortaç
Department of Obstetrics and Gynecology, School of Medicine, Ankara University, Ankara, Trukey

Abstract

Signet-ring stromal tumor (SRST) of the ovary is an extremely rare neoplasm. Herein, we present a SRST of the ovary, which is the twelfth report in the literature. A 44 year-old, G4P2 patient was admitted with the complaint of polymenorrhea. She was operated on for persistent semisolid ovarian mass measuring 5 cm in diameter. The pathological examination confirmed the diagnosis of a benign ovarian SRST. In conclusion, SRST is an extremely rare benign ovarian tumor with good prognosis according to the current literature. Although the recurrence rate or malignant transformation potential of these tumors are not yet known, close follow-up in the post-operative period may be beneficial. (J Turkish-German Gynecol Assoc 2011; 12: 59-60)

Key words: Signet-ring stromal tumor, ovary
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Özet

Ovaryen signet-ring stromal tümör (SRST) çok nadir karşılaşılan bir neoplazmdır. Bu makalede, literatürdeki onikinci ovaryen SRST vakası sunulmuştur. 44 yaşında G4P2 olan hasta polimenore şikayeti ile başvurdu. Hasta 5 cm çapında persistan semisolid ovaryen kitle nedeniyle opere edildi ve patolojik inceleme ile benign ovaryen SRST tanısı koyuldu. Sonuç olarak, SRST overin çok nadir görülen ve mevcut literatüre göre iyi prognoza sahip bir tümörüdür. Ancak tekrarlama sıklığı veya malign dönüşüm potansiyeli henüz bilinmediğinden postoperatif dönemde bu hastaların yakın takip edilmesi faydalı olacaktır.
(J Turkish-German Gynecol Assoc 2011; 12: 59-60)

Anahtar kelimeler: Signet-ring stromal tümör, over
Geliş Tarihi: 26 Nisan 2010 **Kabul Tarihi:** 21 Haziran 2010

Introduction

Signet-ring stromal tumor (SRST) of the ovary, first reported by Ramzy in 1976, is an extremely rare neoplasm (1). The Ovarian SRSTs are currently classified as sex cord stromal ovarian tumors within the spectrum of thecoma-fibromas, and are non-functioning distinctive stromal tumors characterized by the proliferation of stroma and signet-ring cell appearance due to the cytoplasmic vacuoles (2, 3). Herein, we present a SRST of the ovary which is the twelfth reported case in the literature.

Case

A 44 year-old, G4 P2 patient was admitted to the out-patients clinic with the complaint of polymenorrhea for 3 months. Her medical history revealed total thyroidectomy and subsequent levo-thyroxine sodium replacement. Her bimanual gynecologic examination revealed a firm, mobile and fine contoured right adnexal mass approximately 5 cm in diameter. Transvaginal ultrasound confirmed a 48x45 mm, semisolid mass with heterogeneous echogenity in the right ovary. The basal serum levels of tumor markers including CA 125, CA 15-3, CA 19-9, CEA, βhCG, AFP, LDH, and inhibin were all within the normal ranges. Monthly follow-up was chosen by the patient after a detailed informed consent concerning the management of adnexal mass in the perimenopausal period. Operation for histological diagnosis of the mass was recommended to the patient after two months of persistence with neither a change in the diameter nor appearance. A right ovarian semisolid mass measuring about 5 cm was identified via laparotomy by Pfannenstiel incision with regard to the patient's preferred operation route (Figure 1). Except for the right ovary, all other pelvic and abdominal organs appeared to be normal. Right salphingo-oopherectomy was then performed and as the frozen-section revealed a benign ovarian neoplasm, the operation was terminated. The pathological examination of the operation specimen indicated signet ring cells with benign appearance and confirmed the diagnosis of a benign ovarian SRST. The patient was uneventfully discharged on the 3rd post-operative day.

Pathological findings

Microscopically, the tumor was composed of a diffuse growth of vacuolated cells without cellular atypia or mitotic figures. Cells with fully developed vacuoles exhibited eccentric, crescent-shaped hyperchromatic nuclei. The vacuoles of tumor cells were negative for PAS reaction. Intracytoplasmic hyaline globules were positive for PAS reaction. Mucin staining was negative in the signet-ring cells. The signet-ring cells were intensely positive for vimentin. Staining with inhibin and SMA

Address for Correspondence / Yazışma Adresi: *Asist. Yavuz Emre Şükür, Ankara Üniversitesi Tıp Fakültesi, Cebeci Hastanesi, Kadın Hastalıkları ve Doğum Anabilim Dalı, Dikimevi, 06100 Ankara, Turkey Mobile: +90 533 240 93 81 e.mail: yesukur@yahoo.com*
doi:10.5152/jtgga.2011.14

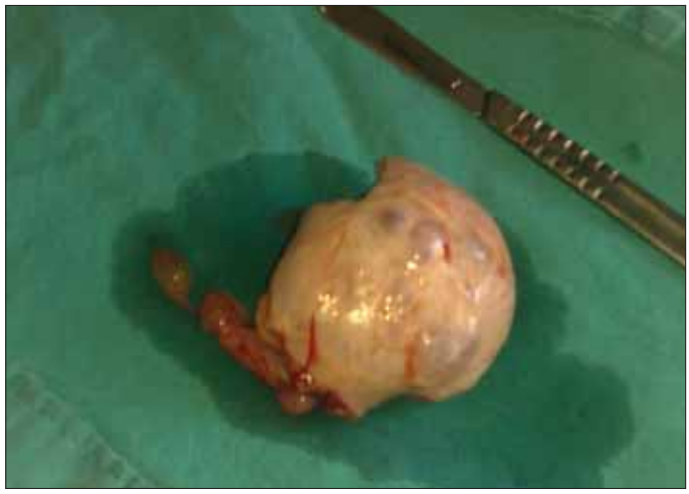

Figure 1. White-grayish, brilliant tumor and right ovary approximately 5 cm in diameter

were also focally positive. However, calretinin, CK7, CK20 and PAN cytokeratin were negative.

Discussion

There were only eleven reported cases in the literature in which unilaterality has been reported only in the present case. There is a considerable variation in the largest diameter ranging from 2.5 to 13 cm. The mean age of the patients was 52 years, ranging from 21 to 83 years (4). The most frequent symptom was abdominal pain in contrast to the present case and almost all of the tumors showed a solid appearance under ultrasonographic assessment (5).

The presence of non-lipid signet-ring cells admixed with fibromatous areas is the main microscopic feature of SRSTs, differentiating from other ovarian sex cord stromal tumors (3, 5). Hyaline globules are present in some tumors and ultrastructural examination revealed the globules to be degenerating erythrocytes, many of which had been phagocytosed by the tumor cells (ult). Stains for lipid and mucin are negative (3).

SRST of the ovary is a distinct type of stromal neoplasm that can mimic Krukenberg tumors. A negative history of carcinoma is not reliable in the distinction of SRST from Krukenberg tumor, as only a minority of patients with Krukenberg tumor have a history of carcinoma (6). Both these tumors may show multinodularity, hemorrhage, and necrosis (6). Although neither nuclear atypia nor mitotic activity is helpful in distinguishing between these tumors, there are histological differences that can be evaluated on hematoxylene-eosin sections. Furthermore, these differences are especially valuable on frozen section. The presence of glandular structures or nests supports an epithelial differentiation (Krukenberg tumor). An additional subtle difference is that the cytoplasm of the signet-ring cells in SRST is white and appears “empty” whereas the cytoplasm of the Krukenberg tumor’s signet-ring cells is characteristically pale and occasionally granular and eosinophilic (7). All the SRSTs are negative for PAS-D and mucicarmine, whereas the signet-ring cell component is positive in all the cases of Krukenberg tumor (6, 7). Pancytokeratin is a very useful marker with no expression in the SRSTs but with consistent staining of Krukenberg tumors (6, 7). Vimentin is also helpful in separating the two lesions, with positivity in SRSTs.

In the clinical perspective, management of an ovarian neoplasm highly depends on the incidence, rate of persistence, regression, recurrence, malignant transformation, as well as the metastatic potential. Thus, because of insufficient data the management of ovarian SRSTs is critically unknown and still obscure. Due to their theoretical regression potential, SRSTs may frequently be undiagnosed in asymptomatic cases or misdiagnosed as other benign ovarian masses (ie; haemorrhagic cysts) in symptomatic cases with smaller tumors (<5 cm in diameter). Although an aggressive pattern has not yet been reported, it is vitally important to determine whether SRSTs have risk of malignant transformation, recurrence or metastasis. In regard to the possible regression potential, expectant management is an acceptable approach for such tumors, especially when the size is <5 cm. However, the current management of SRSTs with a diameter 5 to 10 cm is critically controversial: extensive surgical excision is more commonly performed compared to other persistent ovarian tumors.

In conclusion, SRST is an extremely rare benign ovarian tumor with good prognosis according to the current literature, and these tumors may be misdiagnosed as Krukenberg tumors or haemorrhagic cysts. Clinical, operative and histological findings with immunohistochemical and mucin stains are useful for diagnosis. Since the recurrence rate or malignant transformation potential of SRSTs of the ovary are not yet known, close follow-up may be beneficial in the post-operative period.

Conflict of interest
None declared.

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Cornual pregnancy and interstitial pregnancy

Kornual ve interstisyal gebelik

Cemil Yaman
Department of Obstetrics and Gynecology, General Hospital of Linz, Linz, Austria

Dear editor;

Comments regarding the published case report from Günenç et al "Laparoscopic surgery of interstitial (cornual) pregnancy 2009 11-2: 102-4 in TGGA" Authors reported: "The terms cornual and interstitial pregnancy are used synonymously (page 102, line 17) to define pregnancy implanted in the interstitial part of the fallopian tube which is the proximal portion that is embodied within the muscular wall of the uterus".

Comments

In the North American literature and in a small number of European literature, the terms "interstitial pregnancy" and "cornual pregnancy" are used synonymously. However, it seems that recent studies indicate differences between these two pregnancies (1-3).

Cornual pregnancy is a pregnancy in one horn of a bircornuated uterus or, by extension, in one half of a septated or subseptated uterus. It may be that a bicornuate uterus predisposes the embryo to high implantation. Intramural pregnancies occur when the embryo implants in and is completely surrounded by myometrium clearly removed from either the uterine cavity or the interstitial portion of the tube.

The pregnancy is referred to as an Interstitial pregnancy if the implantation occurs in the interstitial part of the fallopian tube that is embodied within the muscular wall of the uterus. It is not associated with uterine anomalies.

Interstitial pregnancies often progress without symptoms until a rupture occurs later than other tubal pregnancies. The management of cornual pregnancy can be complicated because of malformations (1, 2). Due to these facts there is a need to differentiate between these pathologies. Furthermore, the occurrence of an angular pregnancy, which is distinguished from cornual and interstitial pregnancy anatomically by its position in relation to the round ligament, should be taken into the diagnostic considerations. Unlike the interstitial and cornual pregnancies, angular pregnacies may have a favorable outcome (4).

Conflict of interest
No conflict of interest is declared by authors.

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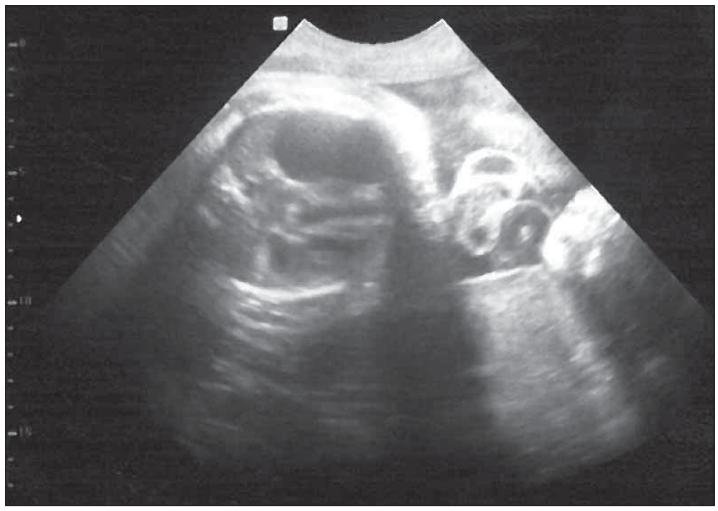
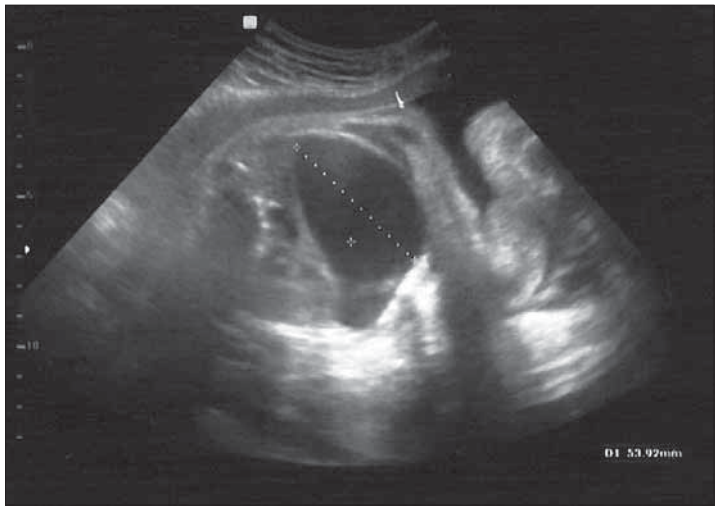
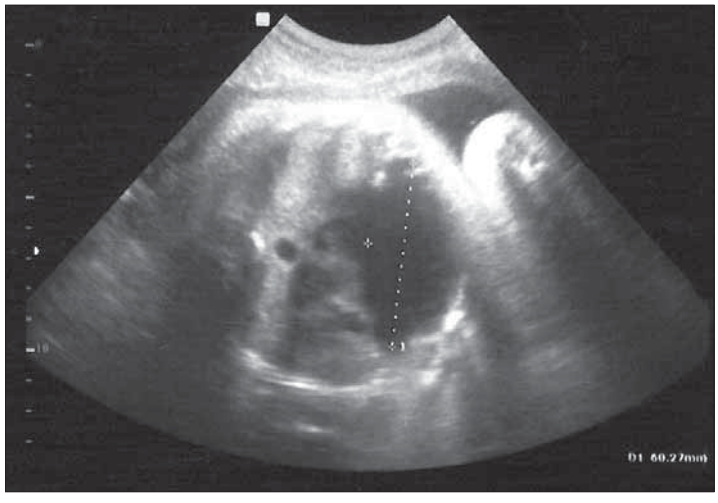
Address for Correspondence / Yazışma Adresi: *Uzm. Dr. Cemil Yaman, Krankenhausstr.9 4020 Linz, Austria*
Phone: 0436644219600 e.mail: cemil.yaman@akh.linz.at
doi:10.5152/jtgga.2011.15

What is Your Diagnosis?







Address for Correspondence / Yazışma Adresi: *Prof. Dr. Eray Çalışkan, Department of Obstetrics and Gynecology, Faculty of Medicine, Kocaeli University, IVF Center Umuttepe Kampusu, Uctepeler Kocaeli, Turkey Phone: +90 262 303 70 39 e.mail: dreraycaliskan@yahoo.com*
doi:10.5152/jtgga.2011.16

Answer

Thymus originates from the ventrolateral side of the third pharingeal arch. It has two asymmetric lobes with a fibrous capsule and an isthmus connecting them. It is located in the midline beneath the sternum and located in the anterior – superior mediastinum (1).

Thymic cysts are rare and constitute 1-2% of all masses in the anterior mediastinum (2). Although congenital cysts are seen during childhood, both congenital and acquired cysts are found later in life. Congenital cysts are thought to be the remnants of thymolaringeal channel (3). Ultrasonography plays an important role in the diagnosis of thymus originated cysts during the fetal life. These ultrasound diagnosed intrathoracic cysts might be in unilocular or multilocular morphology. Congenital cysts are unilocular and have a thin capsule with clear fluid inside them. Acquired cysts are more commonly seen in young adulthood; they are usually multilocular with thick capsule and cause pain secondary to inflammatory process. Thymic masses may cause pleurisy, fetal hydrops and polihydramnios due to pressing on blood and lymphatic vessels and shifting the vital organs. Fetal mediastinal thymic cysts should be differentiated from other more common cystic pathologies such as cystic adenoid malformations. Especially macro cystic adenoid malformation (CAM type 1) has single or multiple cysts larger than 5mm and resembles congenital thymic cysts on ultrasound. Microcystic adenoid malformations resembles solid masses and do not commonly reminds thymic cysts. In the differential diagnosis congenital diaphragmatic herniations should also be considered and ultrasound evaluation of the diaphragma with any presence of abdominal organs such as stomach, liver and intestines should be sought. Other intrathoracic pathologies that should be kept in mind in the differential diagnosis of thymic cysts include bronchopulmonary sequestration, teratomas, dilatation of the proximal pouch in case of esophageal atresia, mediastinal meningomyelocele, meningocele, bronchogenic cysts, simple lung cysts, enteric or neuroenteric cysts, neuroblastoma, laryngeal atresia, congenital left ventricular aneurysm, pericardial cysts, pleural effusions and cystic hygroma (4). Magnetic resonance imaging is important in identifying thoracic masses and their relation to other vital organs and vessels without exposing the fetus to radiation (5). The prognosis of fetal mediastinal thymic cysts is usually good if they do not cause fetal hydrops. Half of the thymic cysts will be asymptomatic if they were not diagnosed during the fetal life. Especially thymic cysts in the neck area may cause cough, wheezing, fever and frequent upper respiratory infections during the newborn and childhood periods. Thymic cysts diagnosed during the fetal life can be surgically excised for treatment and definitive diagnosis. Before surgical excision only one out of seven cases are diagnosed correctly. Surgical excision cures all the congenital cysts and recurrence is not seen. On the other hand acquired thymic cysts diagnosed during adulthood recur in 2% of the cases due to the underlying pathological process (7).

In the present case a large intrathoracic cyst is seen in figure 1 and 2. The left lung is seen behind the cyst in figure 3 with displacement of the heart to the right half of the thorax. Fetal magnetic resonance imaging raised a suspicion of thymic cyst and CAM. The cyst was excised the day after delivery and pathology confirmed thymic cyst

Emek Doğer, Eray Çalışkan,
Department of Obstetrics and Gynecology, Faculty of Medicine, Kocaeli University,

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CONGRESS CALENDAR

24-26 March 2011	**World Symposium on Endometriosis InterContinental Hotel** *Atlanta, GA, USA* http://www.endometriosisatlanta.com
2-6 March 2011	**10. Uludağ Jinekoloji ve Obstetri Kış Kongresi** *Uludağ, Bursa, Turkey* http://www.uludagkadindogum.org
6-10 April 2011	**5th International Congress On Minimally Invasive Gynecology (AAGL & JED) Swıssotel The Bosphorus,** *Istanbul* www.tsge2011.org
7-9 April 2011	**Excellence in Female Surgery (NESA Days)** *Florence, Italy* http://www.nesaflorence2011.org
13-16 April 2011	**13. Ulusal Perinatoloji Kongresi&43rd International Meeting of Gestosis Organisation,** *İstanbul, Turkey* http://www.perinatoloji2011.org/
23-25 April 2011	**7. Ulusal Üreme Sağlığı ve Aile Planlaması Kongresi** *Ankara, Turkey* www.uremesagligi2011.org
4-8 May 2011	**IX. Türk Alman Jinekoloji Kongresi** *Antalya, Turkey* http://www.tajev2011.org
17-22 May 2011	**TJOD (9th) Kongresi** *Kervansaray Hotel, Antalya* http://www.tjod.org
25-29 May 2011	**19th International Pelvic Pain Society Annual Scientific Meeting** *Istanbul, Turkey* http://www.ipps2011.org
3-6 July 2011	**27th Annual Meeting of ESHRE Stockholm,** *Sweden* http://www.eshre.eu/home
1-4 July 2012	**28th Annual Meeting of ESHRE** *Istanbul, Turkey* http://www.eshre.eu/home