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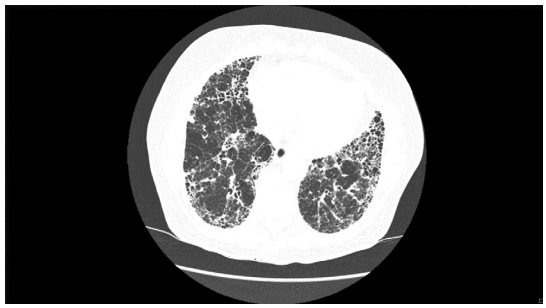

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CONTENTS

CLINICAL VIGNETTE

VIA MEDICA

ORIGINAL PAPER / GYNECOLOGY

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Modified autologous transobturator tape surgery — evaluation of short term results

Alkan Cubuk[1], Fatih Yanaral[2], Metin Savun[2], Ali Ayranci[2], Akif Erbin[2], Ozgur Yazici[2], Mehmet Fatih Akbulut[2], Omer Sarilar[2]

[1]Dr. Lutfi Kırdar Kartal Training and Research Hospital, Istanbul, Turkey
[2]Haseki Training and Research Hospital, Istanbul, Turkey

ABSTRACT

Objectives: The aim of this study is to evaluate the short-term outcomes of our modified autologous transobturator tape (aTOT) technique with rectus abdominis muscle fascial graft for the treatment of female stress urinary incontinence (SUI).

Material and methods: The data of 22 patients who underwent modified aTOT were recorded. Perioperative data regarding operative time, complications and postoperative visual analogue scores were noted. Patients were assessed 18 months after surgery. The primary endpoints of this study were the improvements in the International Consultation on Incontinence Questionnaire-Female Lower Urinary Tract Symptoms (ICIQ-FLUTS) subscores, one-hour pad test and cough stress test rates as an objective cure as well as the improvements in the PGI-I and ICIQ-FLUTS quality of life scores as a subjective cure.

Results: Mean age and the mean follow-up period were 51.7 ± 9.8 years and 20.1 ± 0.9 months, respectively. Urethral hypermobility and a positive cough stress test were detected in all the patients. Mean operative time was 43.8 ± 8.1 min. and the overall complication rate was 9%. Mean VAS scores at postoperative 24 hours were 2.6 ± 1.2. At the postoperative eighteenth month, no patient had a positive cough test and mean PGI-I score was 2 while two patients had moderate urinary incontinence according to the pad test. Pad test results, ICIQ subscores of voiding QoL, incontinence, incontinence QoL, total score and total QoL score at baseline and eighteen months after surgery were 76.9 ± 19.9, 9.6 ± 4.1, 15.5 ± 4.0, 39.5 ± 7.9, 27.9 ± 6.6, 68.4 ± 13.8 and 7.1 ± 2, 10.1 ± 2.4, 6.6 ± 2.1, 13.4 ± 4.5, 20.4 ± 4.8, 39.7 ± 9.2 respectively ($p = 0.001$, $p = 0.004$, $p = 0.001$, $p = 0.001$, $p = 0.001$, and $p = 0.001$, respectively)

Conclusions: Modified aTOT is an effective and safe method with low morbidity for SUI treatment in short term.

Key words: stress urinary incontinence; mid-urethral sling surgery; mesh; complication

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INTRODUCTION

Mid-urethral sling surgeries (MUSS): transobturator-tape (TOT) and retro-pubic tape (RT) with a non-absorbable synthetic material are the most common surgical procedures for female stress urinary incontinence (SUI) [1]. The advantages of these procedures include a reduced operative time, a favorable outpatient technique and promising long-term outcomes [2]. Nevertheless, a number of unique mesh-related complications such as erosion, migration and mesh site infection have been reported in up to 2% of the cases undergoing MUSS and these complications require surgical intervention to revise or remove the mesh [3, 4].

The United States Food and Drug Administration (FDA) released public health notifications about mesh usage in transvaginal surgeries. FDA classified meshes as class 3 devices (highest risk devices) for pelvic organ prolapse (POP) surgery and class 2 for SUI surgery [5]. FDA also noted that MUSS are less morbid surgeries, have similar cure rates with non-mesh surgeries and cause unique complications that are not present in non-mesh surgeries. Although these reports did not limit the use of mesh for SUI, MUSS has been increasingly questioned by patients, surgeons and legal communities after the emergence of these reports [6]. Moreover, television advertisements and litigation related to mesh complications have increased since the FDA reports. Although the complication rates remain stable after MUSS, the frequency of symptoms reported by patients has increased recently [1].

Corresponding author:
Alkan Cubuk
Dr. Lutfi Kırdar Kartal Training and Research Hospital, Semsi Denizer Street E-5 Highway Cevizli 34890 Kartal, 34718 Istanbul, Turkey
e-mail: alkancubuk@hotmail.com

Current guidelines still recommend MUSS for SUI treatment [7] However, numerous non-mesh techniques have been described for SUI surgery over the last decade after FDA warnings. Accordingly, traditional pubovaginal slings (PVS) using autologous rectus muscle fascia have been re-popularized [8, 9]. Moreover, Burch colposuspension surgery (BC) has been shown as a viable option for recurrent and primary SUI and urethral bulking agents have re-emerged as popular techniques [10, 11]. A number of new techniques using autologous tissues based on the surgical characteristics of MUSS have been described to avoid mesh-related complications [1, 12–13]. However, there is no consensus on an optimal surgical technique for SUI surgery in patients who are unwilling to undergo mesh surgery.

Objectives

MUSS with autologous tissue appears to be a feasible option although there is a need for further documentation of the benefits of this technique as well as its short- and long-term outcomes. The present study aimed to evaluate the outcomes of our modified autologous transobturator tape (aTOT) technique in patients with SUI.

MATERIAL AND METHODS

Study population

After obtaining an approval from the Institutional Review Board, the study evaluated a total of 22 female patients that underwent modified aTOT for SUI between December 2017 and February 2018. All the patients met the criteria for uncomplicated SUI and the exclusion criteria included POP greater than grade 2 according to the Pelvic Organ Prolapse Quantification (POP-Q) system, pregnancy, history of pelvic radiation and SUI surgery, increased post-void residual volume (PVRV) (greater than 150 cc), poor voiding patterns on uroflowmetry and history of neurologic diseases. Patients were encouraged for lifestyle modification and pelvic floor muscle training for a minimum period of three months after the diagnosis of SUI. Indications for surgery included reluctance or dissatisfaction after conservative management. The available surgical options and the concerns about synthetic meshes were discussed with patients. Modified aTOT was performed in each patient who preferred to undergo MUSS but refused the use of synthetic meshes and accepted to participate in this study protocol.

Diagnostic workup

Patients were evaluated based on a detailed medical history, urine culture, pelvic examination including urethral hypermobility test (Q-tip test), cough stress test (CST) and POP examination and uroflowmetry with measurement of PVRV. The Q-tip test was performed in lithotomy position; a well-lubricated cotton-tipped swab was introduced into the urethra and then resting and straining angles were measured at the horizontal plane. A straining angle greater than 30° was a threshold for urethral hypermobility [14]. CST was performed in the lithotomy position with 200-400 ml urine in bladder; urine leakage from urethra after one to three strong coughs was associated with a positive result [12].

The International Consultation on Incontinence Questionnaire-Female Lower Urinary Tract Symptoms (ICIQ-FLUTS), which is a validated form used for the evaluation of lower urinary tract symptoms and quality of life (QoL) in three sections (frequency, voiding, and incontinence) was administered to each patient. The one-hour pad test, which is standardized by the International Continence Society (ICS) as the measurement of pad weight increase after a standard protocol, was used for the objective assessment of SUI. The weight gain of the pad was recorded and the degree of incontinence was classified into three groups as; mild (1–10 g), moderate (10–50 g) and severe (> 50 g) [15]. Patients diagnosed with SUI and also suffering from urinary incontinence with urgency were classified as mixed urinary incontinence (MUI).

Surgical technique

Our surgical technique was elaborated in a previous article [16]. After the induction of general anesthesia, the patient was positioned in the lithotomy position and a Foley catheter was inserted. After hydrodissection with saline, a 2 cm longitudinal vaginal incision was performed at the mid-urethral level. Bilateral periurethral dissection was performed until reaching the inferior ischiopubic ramus. A 5* 1.5 cm rectus fascia was harvested via a 3 cm suprapubic transverse incision. Two 2–0 nonabsorbable polyester stay sutures (Ethibond®, Ethicon) were placed on the corners of the fascial graft on both sides. Two separate punctures were performed on both sides over the medial aspect of the obturator foramen at the level of the clitoris and the dissection was continued to the obturator foramen blindly. A TOT needle was passed twice through the foramen and the stitches were transferred from the vaginal incision to the skin separately. A bridge was established on the obturator membrane by separate stitches on both sides. The graft was placed in the mid-urethral position without tension and sutures were tied to each other on both sides. We didn't perform intraoperative cough test. The incisions were closed separately and a vaginal packing was placed at the end of the procedure. The urethral catheter and vaginal packing were removed and the patient was discharged at the first postoperative day.

Follow-up

Perioperative data regarding operative time and complications were recorded for each patient. Complications were

Table 1. Patients' characteristics	
Age [year]*	51.7 ± 9.8
BMI [kg/m^2]*	28.8 ± 3.9
Number of births*	3.2 ± 1.2
Vaginal birth*	2.9 ± 1.6
Cesarean*	0.4 ± 0.8
Assisted vaginal birth**	**NA**
Pelvic surgery history	1 (4.5%)
Menopause	9 (40.9%)
Incontinence (pure stress/mixed)	16/6
Diabetes mellitus	2 (9.1%)

* — mean + standard deviation; **— births with vacuum and forceps devices; NA — not available; BMI — body mass index

Table 2. Operative and post-operative data	
Operation time [minutes]*	43.8 ± 8.1
VAS score (post op 8. hours)*	6.2 ± 0.8
VAS score (post op 24. hours)*	2.6 ± 1. 2
Complication	
Grade 1	2 (9%)
Grade 2	0
Grade 3	0
Duration of follow up (months)*	20.1 ± 0.9

* — mean + standard deviation

Table 3. Comparison of values at the baseline and at 18 months after surgery			
	Baseline	**18th months**	**p**
ICIQ Frequency*	8.1 ± 2.8	8.4 ± 2.8	0.557
ICIQ Frequency QoL*	19.3 ± 7.3	16.3 ± 5.7	0.156
ICIQ Voiding *	4.2 ± 2.3	5.3 ± 1.4	0.095
ICIQ Voiding QoL*	9.6 ± 4.1	10.1 ± 2.4	0.004
ICIQ Incontinence*	15.5 ± 4.0	6.6 ± 2.1	0.001
ICIQ Incontinence QoL*	39.5 ± 7.9	13.4 ± 4.5	0.001
ICIQ Total Score*	27.9 ± 6.6	20.4 ± 4.8	0.001
ICIQ Total QoL Score*	68.4 ± 13.8	39.7 ± 9.2	0.001
Ped Test [gr/hour]*	76.9 ± 29.9	7.1 ± 2	0.001
Stress Test +	22	0	0.001

* — mean + standard deviation

evaluated and classified based on the Clavien system [17]. Visual analogue score (VAS) was performed for pain assessment at postoperative hours 8 and 24. All the patients were discharged at the first postoperative day after spontaneously voiding at least two-thirds of the total bladder volume as confirmed by ultrasonography. At the first postoperative week, patients were invited for a clinical evaluation of surgical wounds and the assessment of surgery-related problems.

During the follow-up, patients were evaluated at 1st, 3rd, 6th and 18th months after surgery. At the postoperative eighteenth months, patients were evaluated with stress test, the one-hour pad test, ICIQ-FLUTS and the Patient Global Impression of Improvement (PGI-I) scale. For each patient the necessity of further surgery due to complications or failure was noted.

The primary endpoints of this study were the improvements in the ICIQ-FLUTS subscores, one-hour pad test and cough stress test rates as an objective cure as well as the improvements in the PGI-I and ICIQ-FLUTS quality of life scores as a subjective cure.

Statistical analysis

Data were analyzed using Statistical Package for Social Sciences (SPSS) for Windows version 20.0 (Armonk, NY: IBM Corp.). Categorical variables were presented as frequencies (n) and percentages (%). Continuous variables were presented as mean ± standard deviation (SD) and were compared using a paired Student's *t*-test. A two-tailed p value of < 0.05 was considered significant.

RESULTS

The 22 patients with a mean age of 51.7 ± 9.8 years enrolled in this study. Preoperatively, 16 (72.7%) patients had pure SUI and 6 (27.3%) patients had stress-dominant MUI (Tab. 1). Mean follow-up period was 20.1 ± 0.9 months.

Urethral hypermobility and a positive cough stress test were detected in all the patients. Mean pad weight gain was 76.9 ± 19.9 g in the one-hour pad test and the test also showed moderate and severe urinary incontinence in 6 (27.3%) and 16 (72.7%) patients, respectively. Mean operative time was 43.8 ± 8.1 min and the overall complication rate was 9% (2/22) (Clavien Grade 1). One patient had wound infection on suprapubic incision and one had vaginal exposure of fascial graft smaller than 1 cm. Both patients were treated conservatively without any further surgical intervention. Mean VAS scores at postoperative hours 8 and 24 were 6.2 ± 0.8 and 2.6 ± 1.2, respectively (Tab. 2). No patient was diagnosed with urinary retention and urogenital tract infection during the follow up period.

Table 3 presents a comparison of pre- and post-operative findings. In the postoperative eighteenth month, no patient had a positive cough test. Mean pad weight gain was 76.9 vs 7.1 gr in the pad test at baseline and postoperative eighteenth month, respectively ($p = 0.001$). Two patients had moderate urinary incontinence at postoperative eighteenth month according to pad test. The mean PGI-I score was 2 postoperatively. ICIQ subscores of voiding QoL, incontinence, incontinence QoL, total score and total QoL

score at baseline and eighteen months after surgery were 9.6 ± 4.1, 15.5 ± 4.0, 39.5 ± 7.9, 27.9 ± 6.6, 68.4 ± 13.8, and 10.1 ± 2.4, 6.6 ± 2.1, 13.4 ± 4.5, 20.4 ± 4.8, 39.7 ± 9.2 respectively ($p = 0.004$, $p = 0.001$, $p = 0.001$, $p = 0.001$, and $p = 0.001$, respectively). At postoperative eighteenth month patients had not any complaints about pain.

DISCUSSION

The subjective cure and postoperative satisfaction rates of MUSS, PVS and BC vary from 62 to 98% in the literature. This range was associated with the diversity of the definitions of incontinence and also with the tools for measuring patient satisfaction [18]. Ford et al. [19] reported that the average subjective cure rates (improvement in any type of incontinence) for both TOT and RT at the postoperative first and fifth years were 83% and 84%, respectively. Brubaker et al. [20] further analyzed the findings of their previously published SISTer study and reported that the patients' satisfaction rates after PVS and BC decreased slightly between the second and fifth postoperative years, with a decrease from 79% to 73% for BC and from 87% to 83% for PVS. In the present study, the subjective cure rate was 100% according to the PGI-I scores and the improvements in QoL scores. Our findings are comparable with the findings of studies with a follow-up of up to two years; however, longer term findings are needed for a comparison with the findings of studies with longer follow-up periods.

Albo et al. evaluated objective cure rates after SUI surgeries and suggested that despite strict definitions of objective cure such as; negative cough stress test, negative values on one hour or 24 hours pad test and no record of incontinence on three days voiding diaries and urodynamic investigations, it is impossible to compare studies due to variation of these definitions [20, 21]. Ford et al. reported the objective cure rates at the first and fifth postoperative years as 85% and 82% for TOT and as 87% and 85% for RT, respectively [19]. Palos et al. reported that the objective cure rates of TOT and RT were 100% and 92% at postoperative month 12, respectively [22]. In SISTer trial, Albo et al. [21] reported the objective cure rates for PVS and BC at the second year as 66% and 49%, respectively. In another study, Maggiori et al [23] reported lower objective cure rates in the fifth year, with 30% for PVS and 24% for BC and reported that the majority of the study population probably consisted of the incontinent participants of the previous study. In the present study, objective cure rate was calculated as 100% based on the one-hour pad test and cough stress test results. This finding implicates that the usage of autologous graft in mid-urethral sling surgery does not reduce the short-term effects of the surgery (up to two years) compared to those of TOT and RT and thus our technique can be considered to provide better outcomes compared to those of BC and PVS.

The analysis of postoperative outcomes indicated that two patients had moderate urinary incontinence on the one-hour pad test although they had a negative stress test result and a score of < 4 on PGI-I. Abdelfettah et al. [24] calculated a correlation with 96% sensitivity and 93% specificity between self-assessment questionnaires and the one hour pad test. However, Constantini et al [25] suggested that one hour pad test has a poor predictive value in diagnosis of female SUI. At the present study, there was discordance between pad test and the other diagnostic tools. This discordance can also be noted among the guidelines; while EAU guidelines recommend the use of pad test, NICE guidelines do not [26, 27].

For the assessment of SUI, detecting urethral hypermobility had an important role in previous literature. Q-type test and voiding cystourethrogram can be used to measure urethral hypermobility [14]. Walsh at al. [14] concluded that although traditionally lower degree of urethral hypermobility indicates intrinsic sphincter deficiency and PVS is a better option for these patients, nowadays it has been a controversial issue due to the lack of a standardized definition and measurement techniques. Proper positioning of swab into urethra, rigidity of foley catheter and concomitant POP are the factors affecting measurements. Nowadays although current AUA/SUFU and NICE guidelines don't recommend to routinely use urethral hypermobility measurements at the present study it was used not only to detect hypermobility but also to detect fixed urethra which is indicated as an important issue to determine type of incontinence surgery type by Walsh at al [7, 14].

Fusco et al. [28] conducted a meta-analysis and reported that incontinence surgery resulted in a significant improvement in the QoL measurements of the patients regardless of the surgical technique. Palos et al. [29] suggested that the improvements in QoL measurements are correlated with the objective and subjective cure rates. In the present study, significant improvements were also observed in the QoL scores for the incontinence subsection and the total QoL score of ICIQ-FLUTS for all patients and it was also correlated with the continence status of the patients.

Literature indicates that PVS, BC and MUSS have similar complication rates [29–32]. For instance, perioperative bleeding requiring blood transfusion is a serious problem associated with all of these procedures and may occur in up to 2% of the cases [29–32]. In the present study, however, no patient had significant blood loss. Another feared complication of these three techniques is bowel, bladder or urethral injury which has been reported in up to 9% of the cases [29–32]. Higher rates were reported after RT procedures for bladder, vascular and bowel injuries [18]. In contrast, TOT provides technical advantages in terms of avoiding perioperative organ injury and has been reported to cause bladder or urethra injury in only a limited number

of cases [19]. In our study, no perioperative organ injury was observed in any patient.

Blavias et al. [30] reported the wound complications rate as 3% after PVS. In our study, only one patient (4%) was diagnosed with wound infection and was treated with non-surgical interventions. A biological graft material is needed to avoid the use of synthetic mesh and a Cochrane review by Rehman et al. [33] suggested that rectus muscle fascia is the most appropriate and most commonly preferred material for PVS. Mahdy et al. [31] suggested the use of fascia lata when it is impossible to harvest rectus fascia. In our study, no material other than rectus fascia was required in any patient. In our opinion, it is easy to harvest this fascia and usually patients have an incision secondary to previous cesarean or other surgical interventions; therefore, it can be performed via this incision to avoid a new incision and scar on patients. Blavias et al. [25] reported chronic pelvic pain in 0.6% of the patients. Pelvic pain rates were 0.8% and 2.9% while groin pain rates were 6.4% and 0.6% for TOT and RT, respectively [18]. The decrease in VAS scores of our patients indicates that this pelvic pain disappeared at postoperative first day. This result is comparable with literature; however we have no data about groin pain.

Erosion of mesh into the vagina, bladder, or urethra is a complication of MUSS, which has been reported in 0.7–2% of the cases [2]. No differences were reported among the TOT and RT procedures [18]. The etiological factors of this complication include inadequate vaginal closure, wound infection, early sexual intercourse and excessive tension of the sling. In contrast, PVS do not cause mesh erosions due to its autologous structure [8, 28]. In our study, no erosion was observed, however only one patient had a minimal vaginal exposure of fascial graft that was smaller than 1 cm, which was successfully treated with topical estradiol. Based on these findings, we consider that the usage of autologous graft with proper tension is of critical importance for obtaining favorable outcomes.

Abraham et al. [34] suggested that the symptoms of de novo urgency are as bothersome for the patients as the symptoms of preoperative stress urinary incontinence. Mahdy et al. [31] reported the incidences of de novo urgency and urge incontinence after PVS as 15–20% and 7.2%, respectively. On the other hand, a similar incidence of de novo urgency has been reported for BC and MUSS (10%), more common after RT than TOT [18, 30]. Gomez et al. suggested that bladder outlet obstruction, bladder perforation and infection are the major causes of de novo urgency [35]. In our study, no significant change was observed between pre- and post-operative scores of the frequency subsection of ICIQ-FLUTS. We consider that although MUSS are thought to be tension-free procedures, fibrosis secondary to mesh placement can cause urethral obstruction in the long term; thereby leading to de novo urgency [19, 35]. Accordingly, we suggest that autologous graft positioned in the mid-urethral region without tension will not cause de novo urgency. It can be explained by lower possibility of urethral obstruction owing to the very low fibrosis potential of autologous graft around the urethra when compared to synthetic meshes and by the lack of bladder neck obstruction secondary to the mid-urethral positioning of fascial graft when compared to PVS.

Voiding dysfunction and urinary retention requiring urethral catheterization are two well-known complications reported after SUI surgery and have been shown to be associated with urinary bladder detrusor dysfunction and iatrogenic urethral obstruction [30–33]. The incidence of urinary retention after PVS, BC and MUSS has been reported to be 20%, 8%, and 3%, respectively [19, 31–32]. In our study, no patient had urinary retention and there was no significant difference between pre- and post-operative scores of the voiding subsection of ICIQ-FLUTS. These findings could be attributed to two factors: the adequate preoperative detrusor contractility of all the patients assessed by uroflowmetry (patients with intermittent flow patterns and high residual urine volumes were not included in the study) and the tension-free nature of our technique.

Veit-Rubin et al. [10] detected POP in 25% of the patients that underwent BC. In contrast, PVS, MUSS and also the method used in the present study have no risk of POP formation as they do not require pelvic dissection which distorts urethral support during surgery, as in BC [28, 29].

To our knowledge, the use of autologous tissue in MUSS has been investigated in a small patient series with short-term results [1, 12–13]. El-Gamal et al. used a hybrid mesh for TOT in 44 patients, which was an elongated rectus fascia with synthetic non-absorbable mesh on both edges [12]. The cure rates were remarkably high (92%) and the complication rates were comparable with MUSS however their method could not be considered as a non-mesh surgery. Linder et al. developed an autologous transobturator sling technique [1]. They reported retreatment-free survival rate as 75% in the postoperative 18 months. The authors used an absorbable suture to elongate the rectus fascia and in our opinion after breaking down of these sutures, autologous tissue lost its tension and position [1]. This problem might be a cause of long-term treatment failure. Osman et al. described a novel technique called 'sling on a string', in which rectus fascia is positioned as a classic RT mesh. The authors published their results from 106 patients with a follow-up of 9 months and reported that their results were comparable to those of MUSS although their technique resulted in longer hospital stays (5.6 days) [13].

The present study contributes to the literature in terms of surgical modifications. However, it had some limitations

such as short follow-up period, small number of patients and the absence of cost analysis.

CONCLUSIONS

Modified aTOT is an effective and safe method with low morbidity for SUI treatment in short term.

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Efficacy and prognostic factors of concurrent chemoradiotherapy in patients with stage Ib3 and IIa2 cervical cancer

Tingting Liu[1], Weimin Kong[1], Yao Liu[2], Dan Song[1]

[1]Beijing Obstetrics and Gynecology Hospital, Capital Medical University, Beijing, China
[2]Liaocheng People's Hospital, China

ABSTRACT

Objectives: We investigated the efficacy, side effects, and prognostic factors of concurrent chemoradiotherapy for patients with stage Ib3-IIa2 cervical cancer.

Material and methods: We conducted a retrospective analysis of clinicopathologic data from 73 patients with stage Ib3-IIa2 cervical cancer who received concurrent chemoradiotherapy from January 2008 to December 2013 in our hospital. Overall response and disease control rates were used to evaluate short-term outcomes; the 3-year and 5-year disease-free survival and overall survival were used to evaluate long-term efficacy. Toxicity reactions and prognostic factors were recorded.

Results: With concurrent chemoradiotherapy, overall response and disease control rates were 91.78% and 97.26%, respectively. The 3-year disease-free and overall survival were 80.82% and 83.56%; the 5-year disease-free and overall survival were 75.34% and 79.45%, respectively. All side effects were tolerated and potentially alleviated by symptomatic treatment. Tumor pathological type, differentiated degree, primary tumor size and squamous cell carcinoma antigen levels before and after treatment were closely related to survival (univariate analysis; $p < 0.05$). Pathological type, primary tumor size and squamous cell carcinoma antigen levels one month after treatment were independent prognostic factors for long-term outcome (multivariate analysis).

Conclusions: Short- and long-term efficacy of concurrent chemoradiotherapy for stage Ib3-IIa2 cervical cancer is well-determined and tolerable. Patients with adenocarcinomas, tumor diameter ≥ 5 cm and squamous cell carcinoma antigen levels ≥ 1.5 ng/mL (one month after treatment) had poor prognosis and should be assessed further.

Key words: concurrent chemoradiotherapy; efficacy; locally advanced cervical cancer; prognostic; retrospective

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INTRODUCTION

Patients with stage Ib3 and IIa2 cervical cancer have a poorer prognosis because of the larger tumour volume and difficult control of the local lesions. The 5-year survival rate of patients was reported to be approximately 50%–60% [1, 2]. At present, there is no uniform standard therapy mentioned in the NCCN guidelines (2019). The options include pelvic external irradiation + cisplatin (concurrent chemotherapy) + vaginal brachytherapy (level 1 evidence); extensive hysterectomy + pelvic lymphadenectomy ± para-abdominal aortic lymph node sampling (level 2B evidence); and post-radiotherapy + assisted hysterectomy (level 3 evidence) [3]. However, the best treatment is controversial. We reviewed the clinical data of 73 patients with stage Ib3 and IIa2 cervical cancer treated with concurrent chemoradiotherapy at our hospital and evaluated the short-term and long-term efficacies and influencing factors associated with chemoradiotherapy in order to provide evidence for guiding clinical treatment.

Objectives

To explore the efficacy and adverse reactions of concurrent chemoradiotherapy for stage Ib3 and IIa2 cervical cancer and to discuss the related factors affecting prognosis, so as to provide reference for the follow-up clinical treatment.

MATERIAL AND METHODS

General information

The clinical and pathological data of 73 patients with stage Ib3 and IIa2 cervical cancer who received concurrent

Corresponding author:
Weimin Kong
Beijing Obstetrics and Gynecology Hospital, Capital Medical University, No. 17 Qihelou Street, Dongcheng District, Beijing 100006, China
e-mail: kwm1967@163.com

chemoradiotherapy in the Gynecological Oncology Department of our hospital (Beijing Obstetrics and Gynecology Hospital, Capital Medical University, Beijing, China.) from January 2008 to December 2013 were collected. The entry criteria consisted of the following: 1. Cervical squamous cell carcinoma or adenocarcinoma confirmed by pathology; 2. 2018 International Federation of Gynaecology and Obstetrics (FIGO) stage Ib3 or IIa2 confirmed by at least two doctors at a level of deputy director of gynaecological oncology or above; 3.patients initially treated with concurrent chemoradiotherapy;4. no serious heart, liver, kidney, brain or hematopoietic system diseases; no history of immune-related diseases; and no other tumours. 5. The clinical data are complete. Exclusion criteria: 1. Complicated with other tumours; 2. Cervical cancer of other pathological types, such as adenosquamous carcinoma, clear cell carcinoma; 3. History of previous radiotherapy or chemotherapy; 4. Refusal to participate in the study. General information for the patients is shown in Table 1.

Therapy

All patients were treated with concurrent chemoradiotherapy. Radiotherapy consisted of external beam radiotherapy and intracavitary radiotherapy. The external beam radiotherapy was performed with a Cobalt-60 machine. The prescription of external beam radiotherapy for whole pelvic was 50 Gy/2.0 Gy/25 f. When the external radiation dose reaches 20–30 Gy, the intracavitary radiotherapy started. Intracavitary radiotherapy was performed with a 192-Iridium (Ir) post-installed machine, 6–7 times at point A, for a total of 36–42 Gy. Concurrent chemotherapy was given during the radiotherapy period. The chemotherapy regimen was either a single cisplatin intravenous infusion (40 mg/m^2) once a week for five–six cycles or 5-fluorouracil (5-FU; 3–4 g/m^2, 96-hour continuous intravenous pump infusion) + cisplatin (20 mg/m^2, 1–4 days), once every four weeks for two–three cycles.

Table 1. Univariate analysis of prognostic factos

Factors	N [%]	5-year survival rate	p value
Age [year]			
≤ 40	21 (28.77)	76.3%	0.709
> 40	52 (71.23)	80.8%	
Pathological Type			
Squamous	63 (86.30)	82.5%	0.034
Adenocarcinoma	10 (13.70)	60.0%	
Stages			
Ib3	50 (68.49)	80.0%	0.137
IIa2	23 (31.51)	78.3%	
Differentiation			
G1	6 (8.22)	83.3%	0.046
G2	53 (72.60)	81.1%	
G3	14 (19.18)	71.4%	
Diameter			
< 5 cm	61 (83.56)	83.6%	0.032
≥ 5 cm	12 (16.44)	58.3%	
SCCA* before treatment			
≥ 1.5 ng/mL	49 (67.12)	77.6%	0.038
< 1.5 ng/mL	24 (32.88)	83.3%	
SCCA after treatment (1 month)			
≥ 1.5 ng/mL	13 (17.81)	53.8%	0.012
< 1.5 ng/mL	60 (82.19)	85.0%	

SCCA — squamous cell carcinoma antigen

Efficacy and adverse reactions

All patients underwent gynaecological examinations, pelvic and abdominal computed tomography (CT) scans or magnetic resonance imaging (MRI), and chest X-ray imaging before and after treatment. The curative effect of treatment was evaluated accordingly. The adverse reactions of all patients were recorded during chemoradiotherapy and during the follow up period, including gastrointestinal reactions, nephrotoxicity and urinary system reactions, and bone marrow suppression. These adverse reactions were assessed by World Health Organization (WHO) criteria for acute and subacute toxicities [4].

Follow-up began at the end of treatment and continued until December 31, 2018. Patients were followed every 3 months for 2 years and every 6 months thereafter. Follow-up assessments included a gynecological examination, a ThinPrep cytologic test (TCT), blood squamous cell carcinoma antigen (SCC-Ag) levels, basin abdominal computed tomography (CT) or magnetic resonance imaging (MRI), and chest X-ray imaging. If no abnormality was observed, TCT was checked once a year, and CT/MRI and X-ray images were checked every six months.

During the follow-up period patients were evaluated according to the Response Evaluation Criteria in Solid Tumors (RECIST) criteria. The RECIST criteria comprises four categories: complete remission (CR), partial remission (PR), disease progression (PD), and disease stability (SD).

Short-term efficacy was evaluated by CR + PR and disease control rate (CR + PR + SD) three months after treatment and long-term efficacy was evaluated by the 3-year and 5-year disease-free survival (DFS) and overall survival (OS) rates.

Criteria

We defined the survival time as the period from the beginning of treatment to the last follow-up or death. Tumor-free survival time was defined as the time of recur-

rence, metastasis, or last follow-up from the beginning of treatment of any site.

Statistical analysis

The experimental data are presented as mean ± standard deviation (SD). Kaplan-Meier method was used for survival analysis. The chi-square test was used for univariate analysis and logistic regression was used for multivariate analysis. p-values < 0.05 were considered statistically significant. Calculations were carried out using the Statistical Package for the Social Sciences (SPSS for Windows, version 19.0, SPSS Inc., Chicago, IL, USA).

RESULTS

Short-term and long-term efficacies

The average follow-up time was 68.9 months. The 3-year follow-up rate was 98.63%, and the 5-year follow-up rate was 97.26%. During the follow-up period, 18 of 73 patients relapsed (24.66%); 15 died (20.54%) after relapse, and 3 survived with tumours (4.11%). Three months after the end of treatment there were 60 cases of CR, 7 cases of PR, 4 cases of SD, and 2 cases with PD. The effective rate (CR + PR) was 91.78%, and the disease control rate (CR + PR + SD) was 97.26%. The 3-year DFS rate was 80.82%, and the total survival rate was 83.56%. The 5-year DFS rate was 75.34% and the total survival rate was 79.45%.

Adverse effects

The incidence of chemotherapy-related gastrointestinal reactions, bone marrow suppression, and nephrotoxicity were 56.16% (41/73), 58.90% (43/73), and 5.48% (4/73), respectively, all of which were grades I–II. The incidence of radiation-related proctitis and cystitis was 21.92% (16/73) and 19.18% (14/73), respectively. All adverse reactions were tolerated and remitted after symptomatic treatment. The therapy was completed as planned.

Prognostic factors

Multivariate analysis showed that pathological type, primary tumor size and SCC-Ag levels one month after treatment were independent factors affecting long-term efficacy ($p < 0.05$; Tab. 2). The respective survival curves are shown in Figure 1–3.

Table 2. Multivariate analysis of prognostic factos

Factors	β	p	OR	95% CI
Pathological type	0.191	0.023	1.958	1.473–3.166
Diameter	0.096	0.040	1.716	1.304–2.316
SCCA after treatment (1 month)	0.087	0.030	1.804	1.286–2.805

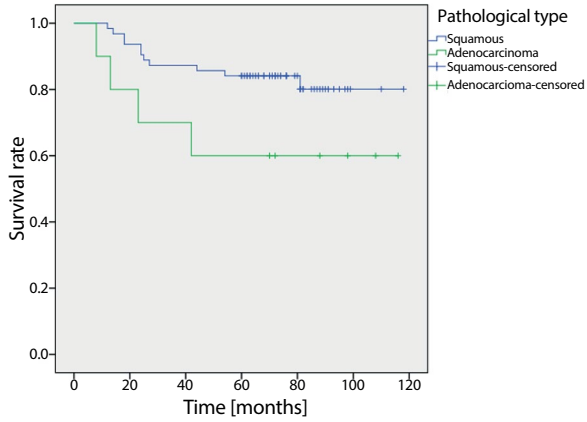

Figure 1. Survival curves of different pathological types of cervical cancer

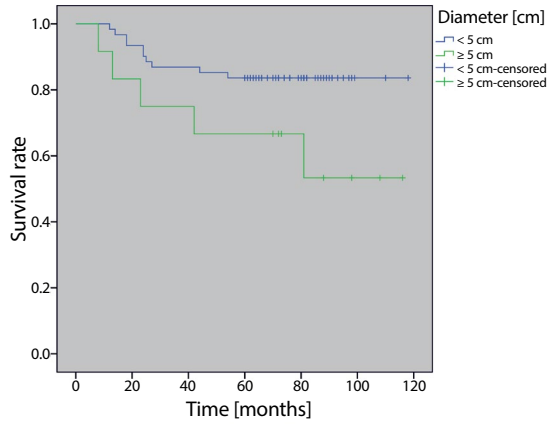

Figure 2. Survival curves of different tumor diameters

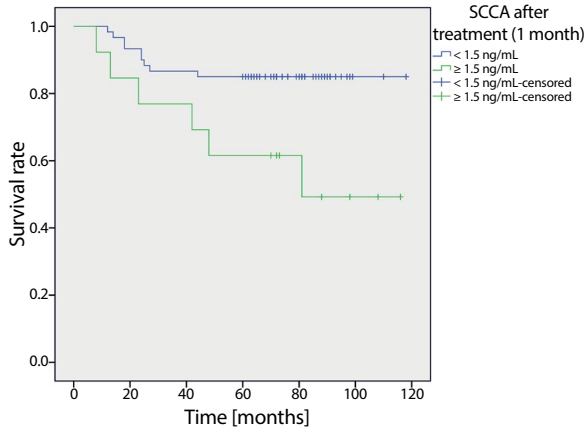

Figure 3. Survival Curves of Different SCCA Values after treatment (1 month)

DISCUSSION

According to the FIGO classification, locally advanced cervical cancer broadly refers to Ib3-IVa tumors and more

specifically to Ib3 and IIa2 tumors. Locally advanced cervical cancers have a tumor diameter larger than 4 cm. Surgery is often difficult in patients with locally advanced cervical cancer, and there are many pathological high-risk factors after surgery that can increase the risk for recurrence and metastasis [5]. At present, commonly used treatment methods are neoadjuvant chemotherapy plus surgery, post-radiotherapy supplementary surgery, and concurrent chemoradiotherapy [6].

Previous studies have shown that concurrent chemoradiotherapy can enhance the sensitivity of patients to radiotherapy [7], improve the 5-year survival rate, and increase the local control rate of tumors [8]. The mechanism may be as follows: 1. Chemotherapy is a systemic therapy, which can kill distant metastasis and local tumor cells, weaken the invasiveness of tumor; 2. Chemotherapy prevents the cell damage and repair caused by radiotherapy; 3. Chemotherapy and radiotherapy act on different phases of cell cycle and complement each other, but do not prolong the overall treatment time; 4. Chemotherapy can reduce the proportion of hypoxic cells and increase the effect of tumor cells on radiotherapy Sensitivity. Five randomized clinical trials of concurrent chemoradiotherapy for stage Ib–IVa cervical cancer reported in the United States in 1999 showed that current chemoradiotherapy reduced the risk of death by 30–50% compared with radiotherapy alone. Datta et al. [9] analyzed the curative effect of radical concurrent chemoradiotherapy, radical concurrent radiotherapy, and postoperative concurrent radiotherapy and chemotherapy in the treatment of Ib2 and IIa2 cervical cancer, and found that the curative effect of concurrent chemoradiotherapy was better than the other two groups. Currently, the National Cancer Institute recommends platinum-based concurrent chemoradiotherapy as the standard treatment for locally advanced cervical cancer [10]. Cisplatin is one of the most sensitive chemotherapeutic drugs [11]. The NCCN Guidelines® for cervical cancer in the United States in 2019 also recommend that the treatment of stage Ib3 and IIa2 cervical cancer should be the combination of pelvic radiotherapy, brachytherapy, and cisplatin-containing concurrent chemotherapy, which is the level-1 evidence.

The current study results showed that the effective rate of radical concurrent radiotherapy and chemotherapy was 91.78%. The 3-year survival rate was 83.56%, and the 5-year survival rate was 79.45%, which was similar to previous studies. Our results indicated that concurrent chemoradiotherapy was effective in the treatment of stage Ib3 and stage IIa2 cervical cancer.

Although chemoradiotherapy acts on tumor cells and coordinates and improves the therapeutic effect, it is not without adverse effects. The main reported adverse effects were radiation enteritis, radiation cystitis, digestive tract reactions, bone marrow suppression, and damage to liver and kidney functions [12]. Compared with concurrent radiotherapy and chemotherapy, neoadjuvant chemotherapy plus surgery and post-operative supplementary radiotherapy have different complications. Fabri [13] has reported no difference in adverse reactions between neoadjuvant chemotherapy and concurrent chemoradiotherapy. Dang et al. [14] compared the complications of concurrent radiotherapy and chemotherapy with that of radiotherapy alone and found that concurrent radiotherapy and cisplatin-based chemotherapy could increase the therapeutic effect in cervical cancer patients and significantly improve the therapeutic benefit without increasing adverse reactions.

Like the above studies, the current study showed that the adverse events related to chemotherapy were all grades I–II. The incidences of radiation-related proctitis and cystitis were 21.92% and 19.18%, respectively, which were tolerable.

However, concurrent chemoradiotherapy still face many problems: 1. The lymph node metastasis rate of local advanced cervical cancer is high, concurrent chemoradiotherapy can not accurately evaluate whether the lymph node metastasis or the location of metastasis, so it's difficult to determine the radiotherapy field; 2. For young patients, they are faced with the problem of ovarian function loss; 3. In addition to radiation cystitis, radiation enteritis and other radiotherapy specific adverse reactions, there are also literature reports that the long-term adverse reaction rate of concurrent chemoradiotherapy is higher than that of radiotherapy alone, especially myelosuppression and digestive tract reaction, which seriously affects the quality of life of patients [15]; 4. In some developing countries, radiotherapy equipment and afterloading equipment are insufficient; 5. The survival rate of concurrent chemoradiotherapy for local advanced cervical cancer is still not ideal. All above these questions require further observation and research.

At present, there are few reports on the prognostic factors of Ib3 and IIa2 cervical cancer treated with radical concurrent chemoradiotherapy. Kim [16] analyzed the clinical data of 174 patients with stage Ib1-IVa cervical cancer who received radical concurrent chemoradiotherapy. Stage, size, and clinical response had significant effects on OS. PFS was also affected by the level of SCC-Ag after treatment. Patients with normal SCC-Ag levels had a longer DFS after treatment. Chen [7] performed a multivariate analysis of 125 patients with stage Ib2-III cervical cancer who received intensity-modulated radiation therapy combined with concurrent chemotherapy. Chen showed that cervical adenocarcinoma and lymph node metastasis were independent adverse prognostic factors for locally advanced cervical cancer. Endo [17] found that tumor diameter > 6 cm, lymph node enlargement, and distant metastasis were significantly and independently associated with adverse outcomes in

patients undergoing radical concurrent chemoradiotherapy. Queiroz [18] showed that in stage Ib and IIa cervical cancer, there was a poor prognosis for patients with lymph node metastasis and SCC-Ag levels that did not decrease to 1.5 mg/L one month after treatment.

Our study results supported findings of previous studies in terms of the relationship of survival rate to pathological type, differentiation degree, primary tumor size and SCC-Ag value of blood before and after treatment. Limitations of our study include the retrospective design and small number of cases. Prospective studies that include larger patient cohorts are needed for further research.

CONCLUSIONS

In conclusion, we analyzed the efficacy and adverse reactions of concurrent chemoradiotherapy for Ib3 and IIa2 cervical cancer and discussed the related factors affecting prognosis. Our findings indicate that concurrent chemoradiotherapy is an effective and tolerable treatment for this cancer. We should pay more attention to patients with adenocarcinoma, tumor diameter ≥ 5 cm and blood SCC-Ag levels ≥ 1.5 ng/mL one month after treatment and explore a more adequate treatment plan in order to improve the survival rate. A multi-center, large-sample prospective study is required to further confirm the validity of our conclusions.

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TT Liu: Conception and design, Analysis and Interpretation of data, Drafting of the manuscript

WM Kong: Critical revision of the manuscript for important intellectual content

Y Liu: Acquisition of data

D Song: Statistical analysis

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The effect of lymph node metastasis on overall survival and disease-free survival in vulvar cancer patients

Volkan Karataşlı[1], Selçuk Erkılınç[1], İlker Çakır[1], Behzat Can[1], Tuğba Karadeniz[2], Mehmet Gökçü[1], Muzaffer Sancı[1]

[1]Department of Gynecologic Oncology, University of Health Sciences Tepecik Education and Research Hospital, İzmir, Turkey
[2]Department of Pathology, University of Health Sciences Tepecik Education and Research Hospital, İzmir, Turkey

ABSTRACT

Objectives: To examine the effect of lymphadenectomy on survival in patients with squamous cell vulvar carcinoma.

Material and methods: Patients with squamous cell vulvar cancer who underwent surgery were retrospectively analyzed. All procedures were performed according to current recommendations/standard of treatment. The clinical and pathological features were examined. Sixty-eight patients were studied. The mean age was 64.7 ± 10.9 years. Twenty-three (33.8%) patients had nodal metastasis. Most patients (60.3%) were in stage IB. Adjuvant radiotherapy and chemo-radiotherapy were administered to 33.8% and 25% of the patients, respectively. The median follow-up time was 28.5 (4–183) months. Recurrence occurred in 18 (26.5%) cases.

Results: There was no significant difference between node-positive and node-negative patients in terms of age, number of dissected lymph nodes and recurrence. Tumor diameter was significantly higher in the metastatic group. Age and surgical margin positivity were independent prognostic factors for overall survival (OS). Surgical margin positivity and lymph node metastasis had no effect on disease-free survival (DFS).

Conclusions: Our results showed that age and surgical margin positivity were independent prognostic factors for OS. Although surgical margin positivity increased the risk of recurrence in univariate analysis, it was not a significant factor affecting DFS. OS was significantly lower in patients with lymph node metastasis.

Key words: lymph node metastasis; prognostic factors; recurrence; squamous cell carcinoma; survival; vulvar cancer

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INTRODUCTION

The incidence of vulvar cancer was reported to be 1.1 per 100.000 women in Poland [1]. Surgery is the mainstay treatment for early stage vulvar cancer [2–4]. However, definitive radiotherapy (RT) and chemo-radiotherapy (CRT) should be selected in patients with distant metastasis, locally advanced disease and older patients with medical comorbidities that are not fit for surgery [4]. Adjuvant treatment was found to increase disease-free survival (DFS) and overall survival (OS) in node-positive patients, but the information on the role of RT and CRT in node-negative patients is lacking [5].

The prognostic factors for vulvar cancer have been investigated in several studies [6–8]. Tumor invasion deeper than 2 mm was found to be a risk factor for local recurrence [9]. Lymphovascular space involvement (LVSI) was also an independent risk factor for local recurrence [10]. Additionally, HPV-positive patients had less local recurrence than HPV-negative patients [11]. Conflicting data is present on the role of lymph node metastasis on recurrence in the literature [9, 12, 13]. Some authors reported that lymph node positivity was related with increased disease recurrence [12]. On the other hand, several studies have reported that lymph node metastasis had no effect on recurrence [9, 13]. Surgical margin distance was also studied in several reports, and there is conflicting data on the role of the margin distance on recurrence [14, 15]. There are also contradictory data on the effect of tumor size and grade on survival [6, 14].

Corresponding author:
Volkan Karataşlı
Kazım Dirik Mahallesi Sanayi Caddesi No:7 Bornova, İzmir, Turkey
e-mail: volkankaratasli@yahoo.com, phone: +905301166711

Objectives

The aim of this study was to investigate the effect of lymph node metastasis on survival in vulvar cancer patients.

MATERIAL AND METHODS

Patients with vulvar cancer who were treated between January 1995 and November 2018 were retrospectively analyzed. A total of 98 patients were encountered during the study period. Those with non-squamous histology (n = 13) and those treated with definitive RT or CRT (n = 17) were excluded. The data of the patients were obtained from patients' files and the hospital database. The collected data were tumor size, distance from midline (clitoris), association with urethra, anus and vagina, the status of inguinofemoral lymph nodes, Human Papilloma Virus (HPV) status, examination results of other parts of the lower genital tract, preoperative radiologic evaluation including posteroanterior X-ray, computed tomography, magnetic resonance imaging and positron emission tomography. All gynecologic examinations were performed by gynecologic oncologists, and all pathologic slides were evaluated by experienced gynecopatologists. The preoperative findings of the patients were discussed in a multidisciplinary tumor board. The decision on optimal treatment was made according to age, performance status, diameter of tumor, status of lymph node metastasis and stage of the disease. The criteria for inguinofemoral lymphadenectomy (superficial and deep) was tumor diameter larger than 2 cm. Sentinel lymphadenectomy was utilized to decrease the morbidity of full lymphadenectomy in unifocal tumors that were smaller than 4 cm and cases with clinically negative lymph nodes. Positive surgical margin was specified as continuity of the tumor at the surgical margin or tumor in the surgical margin below 8 mm. Surgical staging was performed according to International Federation of Gynecology and Obstetrics (FIGO) 2009 [16]. The criteria recommended in National Comprehensive Cancer Network (NCCN) 2017 vulvar cancer guidelines were used for adjuvant treatment. [4]. Performance status and risk factors for recurrence were the factors affecting adjuvant treatment decision. Adjuvant RT was administered 6 weeks after surgery. Adjuvant CRT regime was addition of 40 mg/m^2 cisplatin or 5-Fluorouracil to RT. The follow-up period was every 3 months for the first 2 years, every 6 months for the next 3 years and annual controls thereafter. Each follow-up visit included vulvovaginal and pelvic examination and imaging procedures in the suspicion of recurrence.

A total of 68 patients with vulvar squamous cell carcinoma (SCC) were enrolled in the study. The clinical and pathological features of the patients are shown in Table 1. The mean age was 64.7 ± 10.9 years. The most common (37.6%) localization of the tumor was the right side of the vulva and ≤ 2 cm from the midline. The median tumor diameter was 2.8 cm (0.1–8.5). Most tumors were smaller than 4 cm (88.2%). Tumor grade 1, 2 and 3 were found to be 50.0%, 47.1% and 2.9%, respectively. LVSI was detected in 13.2% of the cases. Information on HPV status was available only in 25 patients. Surgical margin positivity was found to be in 11.8% of the patients. Sentinel lymphadenectomy was performed in 8.8% of the patients, and all nodes were non-metastatic. Twenty-three (33.8%) patients had nodal

Table 1. Clinical data of patients

	n = 68 (%)
Age [years], mean ± SD	64.7 ± 10.9
Treatment	
Only surgery	28 (41.2)
Surgery + RT/RCT	40 (58.8)
Type of surgery	
Radical vulvectomy	55 (80.9)
Simple vulvectomy	9 (13.2)
Wide local Excision	4 (5.9)
IFN lymhadenectomy	
Ipsilateral	7 (10.3)
Bilateral	55 (80.9)
Sentinel	6 (8.8)
Dissected lymph node count, median [range]	11 [8–32]
Tumor diameter, median [range], cm	2.8 [0.1–8.5]
≤ 4 cm	60 (88.2)
> 4 cm	8 (11.8)
Surgical margin	
Positive	8 (11.8)
Negative	60 (88.2)
Grade	
1	34 (50.0)
2	32 (47.1)
3	2 (2.9)
LVSI	9 (13.2)
Stage	
I	45 (66.2)
IA	4 (5.9)
IB	41 (60.3)
II	0 (0)
III	21 (30.9)
IIIA	11 (16.2)
IIIB	3 (4.4)
IIIC	7 (10.3)
IV	2 (3.0)
IVA	1 (1.5)
IVB	1 (1.5)
Lymph node metastasis	23 (33.8)
Recurrence	18 (26.5)
Local	11 (61.1)
Groin recurrence	4 (22.2)
Distant Metastasis	3 (16.7)
Adjuvant treatment	
None	28 (41.2)
RT	23 (33.8)
CRT	17 (25)

SD — standard deviation; RT — Radiotherapy; CRT — Chemoradiotherapy; IFN — Inguinofemoral; LVSI — lymphovascular space invasion

metastasis. The most frequent (60.3%) stage was Stage IB. While 28 (41.2%) patients undergoing primary surgery did not receive adjuvant therapy, 23 (33.8%) were treated with adjuvant RT and 17 (25%) with CRT. The median follow-up time was 28.5 (4–183) months. Recurrence occurred in 18 cases (26.5%). The most common (61.1%) recurrence site was local recurrence in the surgical field. Three (16.7%) patients had distant recurrences, and the remaining (22.2%) had recurrences in inguinofemoral lymph nodes. Secondary surgery was performed in 33.3% of all recurrent patients.

The institutional ethics committee approval was received for the study. SPSS software Ver.22 (SPSS Inc. Chicago, USA) was used for statistical analysis. Independent sample t-test, Mann Whitney U-test and Chi-squared test were used to determine the differences between the groups. Log-rank test was used to compare the factors affecting survival. Kaplan-Meier method was performed to estimate the OS and DFS. Cox univariate and multivariate regression analysis were performed to detect the prognostic factors for survival. $p < 0.05$ was considered as statistically significant.

RESULTS

The 5-year OS rate was 62.2%, and the 5-year DFS rate was 59.6%. The mean OS of the group with lymph node metastasis (23 patients) was 67.0 months, while the mean OS of the non-metastatic group (45 patients) was 115.4 months ($p = 0.028$). OS was significantly higher in patients without lymph node metastasis. OS and DFS analyses for lymph node status are shown in Figures 1 and 2. The mean OS for the surgical margin-negative (60 patients) and positive (8 patients) patients were 107.9 months and 17.2 months, respectively ($p = 0.003$).

The clinicopathological features of the patients according to lymph node status are shown in Table 2. When those with and without lymph node metastasis were compared, there was no significant difference in terms of age, tumor localization, grade, number of dissected lymph nodes and recurrence. Tumor diameter was higher in the metastatic group ($p = 0.01$). LVSI and adjuvant treatment were more common in node-positive patients ($p = 0.05$, $p < 0.01$, respectively).

OS and DFS analyses of the patients are shown in Table 3. Age, surgical margin and lymph node metastasis were detected as significant prognostic factors for OS in univariate analysis ($p = 0.011$, $p = 0.001$, $p = 0.039$, respectively). In multivariate analysis, age and surgical margin positivity were important independent prognostic factors for OS [OR 1.07, 95% CI (1.01–1.12) $p = 0.015$; OR 4.76, 95 % CI (1.46–15.53) $p = 0.010$, respectively]. Tumor diameter, lymph node metastasis and adjuvant treatment had no effect on OS in the multivariate analysis. Surgical margin positivity was a significant prognostic factor for DFS in univariate analysis

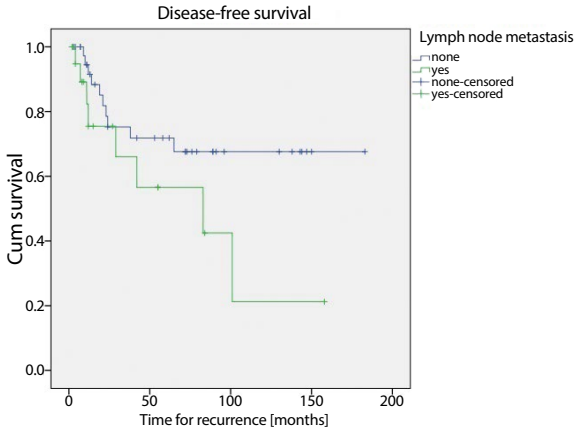

Figure 1. Disease-Free Survival for Lymph Node Status ($p = 0.079$)

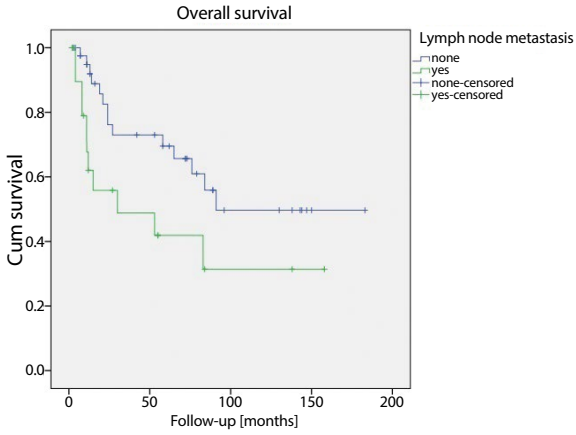

Figure 2. Overall survival for lymph node status ($p = 0.028$)

[OR 2.81, 95% CI (0.59–13.2) $p = 0.020$]. Age, tumor diameter, surgical margin, lymph node status and adjuvant treatment had no effect on DFS in multivariate analysis.

Discussion

Vulvar cancer is a rare tumor with prognostic factors described according to retrospective studies [6, 17–19]. The main limitation of these studies were heterogeneous study groups. The current study showed the experience of a tertiary center that had 20-years of experience in gynecologic oncology. The prognostic factors for OS and DFS were investigated in vulvar cancer patients with regular follow-up data. Lymph node metastasis had no effect on DFS. OS was higher in patients without lymph node metastasis. The distance to surgical margin lower than 8 mm was found to be an independent prognostic factor for OS.

Vulvar cancer is commonly seen in the elderly population. The age of diagnosis was reported to be 68 years [20]. Vulvar cancer was reported to occur in younger ages as

Table 2. Clinicopathological features of patients according to lymph node status

	LN metastasis, n = 23	No LN metastasis, n = 45	
Age, mean ± SD [years], n (%) < 65 ≥ 65	65.7 ± 9.7 13 (56.5) 10 (43.5)	64.2 ± 11.6 21 (53.3) 24 (46.7)	p = 0.60[a] p = 0.80[c]
Tumor diameter, median [range], cm ≤ 4 cm > 4 cm	3.2 [0.3–6.5] 20 (87.0) 3 (13.0)	2.6 [0.1–8.5)] 40 (88.9) 5 (11.1)	**p = 0.01[b]** p = 1.00[f]
Tumor localisation, n (%) Away from midline Midline	 3 (13.0) 20 (87.0)	 5 (11.1) 40 (88.9)	p = 1.00[f]
Grade, n (%) I II-III	 10 (43.5) 13 (56.5)	 24 (53.3) 21 (43.7)	p = 0.44[c]
LVSI, n (%)	6 (26.1)	3 (6.7)	p = 0.05[f]
Dissected lymph node count, median [range]	10 [8–30]	12 [8–32]	p = 0.48[b]
Positive surgical margin, n (%)	4 (17.4)	2 (5.1)	p = 0.43[f]
Adjuvant treatment, n (%)	22 (95.7)	18 (40.0)	**p < 0.01[c]**
Recurrence, n (%)	8 (34.8)	10 (22.2)	p = 0.27[c]

a — independent sample t-test; b — Mann-Whitney U-test; c — Chi-Square test; f — Fischer's exact test; SD — standard deviation; LVSI — lymphovascular space invasion; LN — lymph node; bold p values are < 0.05 and statistically significant

Table 3: Factors Effecting Overall and Disease-Free Survival in Vulvar Cancer Patients

	Overall survival				Disease free survival			
	Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P
Age	1.06 (1.01–1.11)	**0.011**	1.07 (1.01–1.12)	**0.015**	1.04 (0.98–1.09)	0.330	1.0 (0.99–1.11)	0.090
Tumor diameter	1.26 (1.00–1.59)	0.053	1.04 (0.75–1.44)	0.826	1.15 (0.85–1.54)	0.070	1.04 (0.70–1.53)	0.840
Surgical margin Negative Positive	Reference 5.30 (2.04 –13.76)	 **0.001**	Reference 4.76 (1.46–15.53)	 **0.010**	Reference 2.81 (0.59–13.2)	 **0.020**	Reference 1.80 (0.35–9.20)	 0.470
LN metastasis None Yes	Reference 2.31 (1.34–5.11)	 **0.039**	 2.54 (0.94–6.86)	 0.067	Reference 1.97 (0.75–5.20)	 0.460	Reference 1.54 (0.48–4.93)	 0.460
Adjuvant treatment None Yes	Reference 2.14 (0.92–4.99)	 0.077	Reference 0.83 (0.23–3.00)	 0.772	Reference 2.31 (0.81–6.60)	 0.420	Reference 1.84 (0.46–7.25)	 0.380

OR — odds ratio; CI — confidence interval, Cox regression analyses; LN — lymph node; Bold p values are < 0.05 and statistically significant

a result of an increase in HPV infection [21, 22]. In accordance with these studies, the mean age of the patients at time of diagnosis was lower in our study.

Surgery is recommended both for staging and optimal treatment in vulvar cancer patients [2]. However, elder patients with medical comorbidities who cannot undergo surgery or those with advanced disease (in whom it is thought that the tumor will not be dissected with negative surgical margins) are managed with RT or CRT [2]. The management of vulvar cancer should be individualized by multidisciplinary teamwork [3, 4]. Consistent with the recommendations, the patients in our study were discussed in a multidisciplinary tumor board, and most underwent surgery, while patients with advanced disease and medical comorbidities were treated with primarily RT or CRT. The most conservative individualized treatment was recommended to reduce morbidity and increase chance of cure [3]. Modified radical vulvectomy was performed in most patients in our study. Ipsilateral lymph node dissection was the recommended treatment of choice in patients with tumors < 4 cm in diameter and ≥ 2 cm from midline [4]. Since most of the tumors were located at < 2 cm from midline, bilateral lymphadenectomy was performed in most patients in the current study. Close surgical margins were reported to be an important risk factor for local recurrence [14]. Surgical removal of the tumors with negative margins at least 1 cm far from surgi-

cal margins was recommended. [3]. Since negative surgical margin was achieved in most patients, the recurrence rate was consistent with the literature. Most women diagnosed with vulvar cancer are detected in the early stages of the diseases, as we found [6].

Local recurrence rate was reported up to 40% in previous studies [12]. Heterogeneous study groups in the studies were reported to be possible cause of different recurrence rates [14]. Maggino et al. [23] reported a recurrence rate of 37% in surgically treated vulvar cancer patients. On the other hand, a recurrence rate as low as 19% was reported by Sznurkowski et al. [6]. Our recurrence rate was consistent with the literature. This may be due to the difference of the study designs or different age groups and adjuvant treatment regimens. Meelapkij et al. [24] examined 145 patients with vulvar SCC and detected 5-year survival rate as 50.8%. Although the study population was elder in our study, the 5-year survival rate was found to be higher. Adjuvant treatment is recommended in patients with high-risk for recurrence [3, 4]. However, the benefit of adjuvant treatment is not clear for the early stages of the disease. In the present study, lymph node positivity, margin positivity or tumor diameter greater than 4 cm were the criteria for administration of adjuvant treatment as recommended in NCCN guidelines [4]. Thus, by evaluating the patient's performance status, additional treatments were individualized, and the patients were treated with adjuvant RT or CRT by obtaining their informed contents.

Because of the rarity of vulvar cancer, the prognostic factors were evaluated by retrospective studies [6, 25]. Raspaglisei et al. [25] reported that the most significant prognostic factor was the nodal status. 5-year survival for patients with negative nodes ranged from 70% to 93%, and 5-year survival for patients with positive nodes ranged from 25% to 41% [26]. Similar with the literature, OS for patients with metastatic nodes were lower in our study. However, the effect of lymph node metastasis on recurrence is conflicting [14]. Sznurkowski et al. [9] found that recurrence was more frequent in patients with negative lymph nodes. Conversely, Grootenhuis et al. [12] reported that patients with positive lymph nodes had a higher risk for local recurrence. In our study, there was no significant difference between the node-positive and node-negative groups in terms of recurrence. This result is thought to be related to the fact that most of the metastatic patients received adjuvant therapy. In addition, it was previously reported that adjuvant radiotherapy could lead to a lower risk of recurrence, which supports this idea [14]. Gadduci et al. [13] reported higher local recurrence for node-negative patients, but 2-years overall survival rate was very low (38%), so the follow-up time was shorter for metastatic patients in their study.

In a prospective study, age was detected as a covariate associated with survival, and younger and older patients were recommended to be equally treated [27]. In our study, age was a significant prognostic factor for OS. Furthermore, tumor diameter was not an independent prognostic factor for OS [25]. Also, it was reported that tumor diameter had no effect on risk of local recurrence [14]. In convenient with the literature, tumor diameter had no effect on DFS and OS in our study. Most recurrences occur in the surgical field, so surgical margin status is an important factor in vulvar cancer [2]. The tumor is recommended to be dissected with at least 1 cm margin in NCCN and ESGO guidelines [3, 4]. In addition, previous studies have been carried out on whether close surgical margin increases risk of local recurrence or not [14, 15]. In a multicenter European study, 289 surgically treated node-negative patients were examined, and margin distance had no effect on local recurrence [15]. However, a histologic margin of 8 mm or less was detected as a risk factor for local recurrence in several studies [9, 28]. In our study, positive surgical margin was an important prognostic factor for OS, but it was not significant for DFS.

The limitation of our study was its retrospective design. However, the number of patients studied was one of the highest single-center figures in the literature reported in our country. In addition, all patients were cared for in a tertiary cancer center with regular follow-up.

CONCLUSIONS

Our results showed that age and surgical margin positivity were independent prognostic factors for OS. Lymph node metastasis increased the hazard of death; however, it was not a predictor for OS. Although surgical margin positivity increased the risk of recurrence in univariate analysis, it was not a significant factor affecting DFS. OS was significantly lower in patients with lymph node metastasis.

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Clinicopathological factors of pelvic lymph nodes involvement in advanced serous ovarian cancer

Szymon Piatek[1,2], Ksawery Golawski[3], Grzegorz Panek[4], Mariusz Bidzinski[1], Miroslaw Wielgos[2]

[1]*Department of Gynecologic Oncology, Maria Sklodowska-Curie National Research Institute of Oncology, Warsaw, Poland*
[2]*1st Department of Obstetrics and Gynecology, Medical University of Warsaw, Poland*
[3]*Gynecologic Section of Students' Oncology Research Group "Oncosphere", National Research Institute of Oncology, Warsaw, Poland*
[4]*Department of Gynecologic Oncology and Obstetrics, Centre of Postgraduate Medical Education, Warsaw, Poland*

ABSTRACT

Objectives: Retroperitoneal lymph nodes metastases occur frequently in patients with ovarian cancer. Lymphadenectomy increases risk of perioperative complications. In clinical practice to reduce rate of complications aortocaval lymphadenectomy is omitted and solely resection of pelvic lymph nodes is performed. To establish factors affecting metastases to pelvic lymph nodes in advanced ovarian cancer.

Material and methods: A retrospective study among patients with serous advanced ovarian cancer (FIGO IIIB–IVB) was conducted at the 1st Department of Obstetrics and Gynecology, Medical University of Warsaw and Department of Gynecologic Oncology, Maria Sklodowska-Curie National Research Institute of Oncology, Warsaw. All patients underwent surgical treatment including pelvic lymphadenectomy between 2014 and 2017. Data including age, body mass index (BMI), pretreatment CA125 serum level, tumor volume, grading, one-/both-sided tumor, menopausal status, ascites were analysed as possible factors influencing the pelvic lymph nodes involvement. The statistical analysis was performed with Python software.

Results: 87 consecutive patients were eligible for the study. Metastases to pelvic lymph nodes were found in 29 (33.33%) patients. Pretreatment serum CA-125 concentration (652 U/mL vs 360.9 U/mL, $p < 0.05$) and high grade histology corresponded with pelvic nodal involvement.

Conclusions: The knowledge of factors influencing metastases to pelvic lymph nodes may help clinicians in proper counselling and tailoring of therapy.

Key words: ovarian cancer; metastasis to pelvic lymph node, clinicopathological factors

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INTRODUCTION

Ovarian cancer is the fifth leading cause of death due to malignancies among women in Northern America and the European Union [1, 2]. According to FIGO 2014 Staging System resection of retroperitoneal lymph nodes remains an integral part of surgical treatment [3]. Retroperitoneal lymph nodes involvement occurs in 40–44% of all patients with ovarian cancer [4, 5]. In patients without peritoneal dissemination lymphadenectomy is used to determine stage. According to LION study systematic lymphadenectomy in advanced ovarian cancer does not improve overall survival and results in extended duration of the operation, higher median blood loss, higher transfusion rate and more frequent serious postoperative complications (re-laparotomies, re-admittance, deaths within 60 days after surgery) [6]. However Panici et al. [7] found that systematic lymphadenectomy could prolong progression free survival, which in turn improved quality of life.

In clinical practice aortocaval lymphadenectomy is omitted up to 44% of patients to reduce the rate of complications, while resection of pelvic lymph nodes is performed in almost every patient [5, 8, 9]. Factors affecting retroperitoneal lymph nodes involvement were identified in previous studies [5, 8, 9]. However, they were established for both aortocaval and pelvic regions. The aim of this study is to

Corresponding author:
Szymon Piatek
Department of Gynecologic Oncology, Maria Sklodowska-Curie National Research Institute of Oncology
5 Roentgena St, 02-781 Warsaw, Poland
e-mail: szymon.piatek@aol.com, tel: 22-546-22-95

Table 1. Patients'characteristics

Variable (median/number)		Total number of patients (n = 87)	MUW (n = 39)	MSCNRIO (n = 48)
Age [years]		62 (26–84)	63 (26–84)	61 (36–79)
Staging	IIIB	12	6	6
	IIIC	69	32	37
	IVA	0	0	0
	IVB	6	1	5
Tumor volume [cm^3]		179.59 (1.5–8704.9)	52.88 (1.5–2340)	179.59 (38–8704.9)
Number of resected lymph nodes		8 (1–28)	7 (1–14)	10.5 (2–28)
One/both sided tumor(s)		55 (63.22%) / 32 (36.78%)	28 (71.79%) / 11 (28.21%)	28 (58.33%) / 20 (41.67%)
Ascites		48 (55.17%)	23 (58.97%)	25 (52.08%)
Grading	Low	10 (11.5%)	6 (15.38%)	4 (8.3%)
	High	77 (88.5%)	33 (84.62%)	44 (91.66%)
Postmenopausal status		73 (83.91%)	37 (94.87%)	36 (75%)
Pretreatment CA-125 concentration [IU/mL]		451.9 (8.18–9418)	457.6 (53.11–7316)	446.2 (8.18–9418)
BMI		27.98 (14.91–49.25)	25.22 (16.85–49.25)	28.3 (14.91–37.35)

determine factors affecting metastases to pelvic lymph nodes in advanced ovarian cancer.

MATERIAL AND METHODS

A retrospective study was conducted at the 1st Department of Obstetrics and Gynecology, Medical University of Warsaw (MUW) and Department of Gynecologic Oncology, Maria Sklodowska Curie National Research Institute of Oncology (MSCNRIO), Warsaw between January 2013 and March 2017 among patients with serous ovarian cancer in advanced stage (FIGO IIIB–IVB). Intraperitoneal dissemination was confirmed in all patients during primary cytoreductive surgery. In each case, bilateral pelvic lymphadenectomy was conducted. Patients were divided into two groups: A — with metastases in pelvic lymph nodes, B — without pelvic lymph nodes involvement.

The exclusion criteria for primary cytoreductive surgery included: inoperable tumor *i.e.* dissemination in the porta hepatis or mesentery of the intestines, neoplastic infiltration into the aorta/inferior vena cava/pelvic main vessels estimated by computed tomography or magnetic resonance.

Potential factors affecting pelvic lymph nodes involvement were analysed. Data including age, body mass index (BMI), CA125 blood concentration, tumor volume, grading, one-/both-sided tumor, menarche, menopause, ascites were collected.

Statistical analysis was performed with Python Software. Patients' characteristics were presented as numbers of cases and percentages for categorical data, and as means with standard deviations (SD) for continuous data or — for non-continuous — medians and quartiles. The groups were compared by Chi-squared test for categorical variables. Statistical analysis was performed with t-Student test and Mann-Whitney U-test for continuous variables. The level of statistical significance was set at $p < 0.05$.

All the procedures were conducted according to the Declaration of Helsinki for Medical Research involving Human Subjects. Institutional ethics committee approval was not required — the research is an ex-post analysis of clinical experience. The clinical decisions concerning the treatment were not influenced by the purpose of this paper.

RESULTS

A total of 87 patients (39-MUW, 48-MSCNRIO) with serous ovarian cancer in advanced stage were included to the study. Pelvic lymph nodes involvement was confirmed in 29 (33.33%) patients — Group A, while in 58 women (66.67%) metastases in pelvic lymph nodes were not observed — group B. Data regarding patients' characteristics are presented in Table 1. 82 (94.25%) patients underwent primary debulking surgery. 5 patients (5.75%) received neoadjuvant chemotherapy followed by interval cytoreduction.

In group A (n = 29) number of metastatic lymph nodes were: 1 in 13 patients, 2 in 6 patients, 3 in 3 patients, 4 in 3 patients, 5 in 1 patient, 9 in 3 patients.

Patients' mean age at surgery was 61 years (26–84). 72 of 87 (82.76%) patients were after menopause. The majority of patients 72 of 87 (82.76%) were postmenopausal women. The most common histology was high-grade serous carcinoma — 77/87 (88.51%). Optimal cytoreduction (< 1 cm) was achieved in every patient. 10 (11.49%) patients underwent also aortocaval lymphadenectomy.

Pretreatment CA-125 serum concentration and grading were related to pelvic lymph nodes involvement. Patients

Table 2. Comparison of patients with metastatic pelvic lymph nodes (Group A) vs patients without metastases to pelvic lymph nodes (Group B)

Variable (median/number)		Group A (n = 29; 33.33%)	Group B (n = 58; 66.67%)	Statistics
Age [years]		62 (36–84)	63 (26–80)	p = 0.822
Tumor volume [cm^3]		179.59 (4.18– 767.15)	69.27 (1.5–8704.9)	p = 0.067
One-sided tumor		17 (58.62%)	38 (65.52%)	p = 0.12
Ascites		18 (62.07%)	28 (48.28%)	p = 0.508
Grading	Low	0	10 (15.38%)	p = 0.007
	High	29 (100%)	48 (82.76%)	
Postmenopausal status		21 (72.41%)	50 (86.21%)	p = 0.973
Pretreatment CA-125 concentration [IU/mL]		652 (54.8–5216)	360.9 (8.18–9418)	p = 0.039
BMI		24.74 (14.91–36.4)	27.98 (18.59–49.25)	p = 0.11

with pelvic lymph nodes metastases had higher pretreatment median concentration of CA-125 in serum (652 IU/mL vs 360.9 IU/mL, $p < 0.05$). All patients with pelvic nodal involvement were diagnosed with high-grade tumors (Tab. 2).

For other analysed variables, there was no statistically significant relation with pelvic lymph nodes involvement. However, patients in group A with present lymph node metastases tend to had higher median tumor volume compared to patients in group B (179.59 cm^3 vs 52.88 cm^3, $p = 0.067$).

DISCUSSION

Retroperitoneal dissemination to pelvic and aortocaval lymph nodes is commonly found in ovarian cancer. It results from lymphatic drainage pathways of the ovaries [10]. Some authors reported that lymph nodes invasion occurred more often in para-aortic than pelvic region [4, 11]. However, Bachmann et al. [12] found simultaneous metastases to both region as the most common. Other study showed that pelvic lymph nodes were more often affected by metastases than in aortocaval region [13].

Our results showed pelvic nodal involvement in 33.33% cases. Morice et al. [4] established that overall lymph nodes involvement in ovarian cancer was 44% and frequency increased with stage. Fournier et al. [14] presented similar observations, but the ratio of metastases in primary surgery was 50%. In other studies, metastases to retroperitoneal lymph nodes in early ovarian cancer were found in 13–25% [4, 15], while in advanced stage were observed in 45–75% cases [4, 7, 16, 17]. Elective pelvic and aortocaval lymphadenectomy in patients with clinical stage I and II results in final diagnosis of stage III in 20% [4]. Compared to previous studies, our outcome, showing that 1/3 of patients with advanced OC had lymph nodes involvement, is lower. This discrepancy may be caused by limitation of analysis to pelvic lymph nodes in our study. Another reason may be different number of resected lymph nodes between studies.

In our study, we analysed only serous tumors regarding it was the histologic type associated with the most common pelvic and para-aortic lymph nodes involvement. Although Roger et al. [18] found similar frequency for lymph nodes involvement in different histological types of epithelial ovarian cancer, other studies presented higher rate of lymph nodes metastases in serous tumor [8, 9, 16, 19, 20]. Zhou et al. showed higher risk (OR 2.728, 95% CI 1.072–6.945, $p = 0.035$) for nodal involvement in serous ovarian cancer [8]. Powless et al. [9] found metastases to retroperitoneal lymph nodes more frequent in serous tumor than in other types (23% vs 9%). Similar observations presented Takeshima et al., who demonstrated that the nodal involvement was the most common in serous tumors and occurs in 36.7% [21]. Nodal spread rarely occurs in mucinous tumor [4, 9].

Although in some studies tumor grading was not associated with lymph nodes involvement [5, 22], our results showed that metastases in pelvic lymph nodes were observed only in high-grade tumors. Zhou et al. [8] had similar observations to our results. They did not find metastases to retroperitoneal lymph nodes in low grade tumors, while in grade-2 and grade-3 malignancies nodal involvement was 54.8% and 45.2%, respectively. Other authors presented that the incidence of metastatic nodes was significantly higher in patients with poor-differentiated tumors [9, 20, 23]. Kleppe et al. [24] investigated patients with early stage ovarian cancer. They demonstrated that nodal involvement in low-, middle- and high-grade ovarian cancer was 4.0%, 16.5%, and 20.0%, respectively. The percentage of affected lymph nodes increases when considering an early and advanced malignancies together. Tsumura et al. [25] showed that incidence rates of lymph nodes metastases in grade I, II and III tumors were 7.1%, 31.4% and 58.3%, respectively.

In our study, we found that pretreatment CA-125 serum level was higher in patients with metastatic pelvic lymph nodes. We observed significant difference in median serum CA-125 among patients with and without nodal involvement

(652 IU/mL vs 360.9 IU/mL, p < 0.05). Zhou et al. [8] demonstrated that patients with CA-125 level of > 740 IU/mL at diagnosis had higher risk for lymph node metastasis compared to those with CA-125 level of = < 740 IU/mL (53.5% vs 22.4%, p < 0.001). Kim et al. [5] showed that the preoperative serum CA-125 level (> 535 IU/mL) was a significant predictor of lymph node metastasis. Although our results are in line with other studies, we have concerns about the importance of serum pretreatment CA-125 in predicting lymph nodes involvement, especially in patients with advanced ovarian cancers. In such cases elevated serum CA-125 level may be a result of tumor volume, peritoneal spread or distant metastasis. Nevertheless, Powless et al. [9] used the cut-off value of 35 U/mL and showed that patients with increased preoperative serum CA-125 had positive lymph nodes in 22.4%. When preoperative CA-125 level was ≤ 35 IU/mL, no metastases in lymph nodes was detected [9]. Sodolmus et al. found 72 and 123 IU/mL as a significant cut-off values for lymph nodes involvement, but the false positive ratio was 67.4% and 55%, respectively. Authors concluded that although these values may be helpful in guiding clinical management, the false positive ratios are too high to use as a screening tool for predicting lymph nodes metastases [26]. In opposition to the above studies, Ditto et al. [22] did not find any relation between lymph node metastasis and serum CA-125 level.

Although the patient's age is associated with an increased risk of ovarian cancer, it was not identified as risk factor for nodal involvement [5, 8]. Menopausal status had no effect on metastases to retroperitoneal lymph nodes as well [5, 8]. Our results were consistent with these observations. Powless et al. [9] found that ascites and bilateral adnexal masses were associated with an increased risk of retroperitoneal lymph nodes involvement. We did not observe these coincidence in our results. It may be a consequence of different characteristics of patients. Our study included patients only in advanced stage, while Powless et al. [9] analysed patients in early and advanced stage. Another explanation is a lack of aortocaval lymph nodes dissection in our study.

Our study had several limitations. First, it had a retrospective character and was not randomised, therefore, we cannot exclude bias. Patients in our study underwent predominantly pelvic lymphadenectomy without dissection of aortocaval lymph nodes. Furthermore, the median number of resected lymph nodes in our analysis was lower than in other studies so proportion of metastatic lymph nodes may be underestimated.

CONCLUSIONS

Pretreatment serum level of CA-125 and tumor grading differed significantly among both analysed groups. LION trail showed similar OS among patients with and without lymphadenectomy, but decisions about lymph node status was done by highly-skilled surgeons. In clinical practice, intraoperative lymph nodes assessment by less experienced gynecologist/surgeon may appear challenging, especially if preoperative imaging is inconclusive. In such cases high pretreatment CA-125 serum level and serous high grade histology of tumor may be helpful in lymphadenectomy extension.

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Increased osteopontin expression in endometrial carcinoma is associated with better survival outcome

Haneen Al-Maghrabi[1], Wafaey Gomaa[2,3], Jaudah Al-Maghrabi[1,2]

[1]Department of Pathology, King Faisal Specialist Hospital and Research centre, Jeddah, Saudi Arabia
[2]Department of Pathology, Faculty of Medicine, King Abdulaziz University, Jeddah, Saudi Arabia
[3]Department of Pathology, Faculty of Medicine, Minia University, Al-Minia, Egypt

ABSTRACT

Objectives: Osteopontin (OPN) is a key extracellular matrix protein that is involved in cancer progression. The aim of the current study is to investigate the relation of OPN immunostaining in endometrial carcinoma with clinicopathological parameters.

Material and methods: Archival 71 endometrial carcinomas and 30 non-neoplastic endometrial tissues were obtained from the Department of Pathology at King Abdulaziz University Jeddah, Saudi Arabia. Tissue microarrays were constructed. Tissue sections were stained using anti-human OPN monoclonal antibody. Immunostaining results were recorded and analysed.

Results: In non-neoplastic endometrial tissues, high (increased) OPN immunostaining was observed in 100%. In endometrial carcinoma, high (increased) OPN immunostaining was seen in 64.8% of cases. High (increased) OPN immunostaining was more frequent in non-neoplastic tissues than in endometrial carcinoma ($p < 0.001$). OPN immunostaining showed no association with histological type, FIGO tumour grade, tumour size, myometrial invasion, lymphovascular invasion, surgical resection margin or lymph node metastasis. On the other hand, high (increased) OPN immunostaining was associated with better overall survival [Log Rank (Mantel-Cox) = 4.385, $p = 0.003$].

Conclusions: In endometrial carcinoma, immunohistochemical staining of OPN could be a helpful tool in the prediction survival pattern. OPN immunostaining showed no association with most clinicopathological features. Further investigations both clinical and molecular are needed to explore the downstream of OPN in endometrial carcinoma.

Key words: endometrial carcinoma; tissue microarray; immunohistochemistry; osteopontin

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INTRODUCTION

Endometrial carcinoma (EC) is one of the most common malignant tumours of female genital system. While early diagnosed stages of EC can be cured by surgical resection only, advanced cases of EC can be complicated by distant organ metastasis and peritoneal involvement associated with poor patient free survival rate. Thus, understating the genetic pathophysiology pathway of EC play a crucial role in therapeutic management protocol of the disease [1]. Angiogenesis of a tumour is associated with genes expression in human endometrial endothelial cells (HEECs) which can enhance the process of angiogenesis, increase tumour permeability, rapid cell proliferation and increase metastatic rate.

Osteopontin (OPN) was first discovered as one of CD44 ligands [2]. It is a 70-KDa particle of phosphorylated N-linked glycoprotein, which was primarily discovered in bone matrix. OPN can be found in the epithelial linings of salivary glands, sweat ducts, breast, bronchi, pancreas, gall bladder, urinary bladder, and reproductive systems [3]. OPN is a glycosylated phosphoprotein of the extracellular matrix particles, which contains nine consecutive aspartic acid residues, considered a highly acidic region named N-terminal signal [4]. It can be also detected in activated defence cells like macrophages, lymphocytes and leukocytes [5]. OPN has the capacity to bind with osteocalcin, type I collagen, and fibronectin [6]. It is also involved in many precise cellular processes like cellular adhesions, tumourigenesis, angiogenesis, and tumours distant metastasis. Moreover, its overexpression can affect transduction of PI3 Kinase/AKT activation signalling pathway in various tumours which affect the cellular apoptosis [7].

Corresponding author:
Jaudah Al-Maghrabi
Department of Pathology, Faculty of Medicine, King Abdulaziz University, P.O. BOX 80205, Jeddah 21589, Kingdom of Saudi Arabia
e-mail: jalmgrabi@kau.edu.sa, tel.: 00-966-12-6401000 ext 17069, fax: 00-966-12-6408433

OPN overexpression is one of the phospho-glycoprotein (P-gp) with oncogenic potential in various body tumours [8, 9]. Many studies discussed the role of OPN in various epithelial malignancies such as breast, colon cancer, thyroid and melanoma [10–17].

However, more studies are needed to enlighten the role of OPN expression in EC. The aim of this study is to find out the relation OPN immunostaining with clinical and pathological features of EC based tissue microarray.

MATERIAL AND METHODS

Patients

The study utilised paraffin wax tumour blocks from 71 patients diagnosed with endometrial carcinoma in the period from 2003–2012. Also paraffin blocks from 30 non-neoplastic endometrial tissues in the period from 1995–1998 (20 proliferative endometrium and 10 secretory endometrium). All blocks were used from the archives of the Department of Pathology at King Abdulaziz University, Jeddah, Saudi Arabia. Some clinicopathological characteristics of patients are listed in Table 1. For statistical purpose, FIGO stages were classified into limited to uterine corpus (FIGO Stage I and II) and beyond the uterine corpus (FIGO III and IV). Also grades were reclassified as low grade (grade I) and (grades II and III). Data is shown in Table 1. The study was done following rules of the ethics committee of Faculty of Medicine, King Abdulaziz University, Saudi Arabia, and declaration of Helsinki.

Tissue Microarray

Archival paraffin-embedded endometrial carcinoma samples and neoplastic tissues were selected and the desired areas were marked on haematoxylin and eosin (H&E)-stained slides. Arrays were produced by retrieving cores (1.5 mm in diameter each) from marked areas of each 'donor' tissue block and brought into new recipient paraffin blocks. Tissue microarrays were constructed in an automated tissue microarrayer [TMA Master 1.14 SP3 (3D Histech Ltd. Budapest, Hungary)]. Placenta tissue was used for orientation [17, 18].

Immunohistochemistry

The constructed tissue microarray paraffin blocks were sliced at 4 µm. Tissues were mounted on positive-charged slides (Leica Microsystems Plus Slides). In an automated immunostained BenchMark XT, Ventana® Medical systems Inc., Tucson, AZ, USA) immunohistochemistry was performed. Slides were deparaffinised in xylene and rehydrated. Slides were incubated with pre-diluted CC1 (cell conditioning solution) for 60 minutes to perform pre-treatment. Polyclonal anti-human rabbit anti-osteopontin antibody (Spring™ Bioscience; Cat # E3284) was incubated at 37°C for 20 minutes. The detection kit was used from Ventana® I-view DAB. The slides were washed and Mayer's haematoxylin was used as a counter stain. The appropriate negative and positive control slides were used.

Interpretation of OPN Immunostaining

The immunostained slides were examined by two pathologists (HM, WG) and a semiquantitative approach was used including the percentage of OPN positive cells. The percentage of OPN positivity was scaled as follows; (1) 0–25%,

Table 1. Clinicopathological features of endometrial carcinoma (n = 71)

Parameter		Number (%)
Age	< 60 years	49 (69%)
	> 60 years	22 (31%)
Histological type	Endometrioid	66 (93%)
	Serous	5 (7%)
FIGO tumour grade	Grade 1	44 (62%)
	Grade 2	16 (22.5%)
	Grade 3	11 (15.5%)
Tumour size	≤ 2 cm	35 (49.3%)
	> 2 cm	36 (50.7%)
Myometrial invasion	< 50%	57 (80.3%)
	≥ 50%	14 (19.7%)
Lymphovascular	Absent	68 (95.8%)
	Present	3 (4.2%)
Surgical resection margin	Free	67 (94.4%)
	Involved	4 (5.6%)
Lymph node metastasis	Absent	33 (46.5%)
	Present	4 (5.6%)
	Not sampled	34 (47.9%)
FIGO Staging	I	51 (71.8%)
	II	7 (9.9%)
	III	7 (9.9%)
	IV	6 (8.5%)
Local Recurrence	Absent	60 (84.5%)
	Present	11 (15.5%)

FIGO (International Federation of Gynaecology and Obstetrics)
Stage I — tumour confined to corpus uteri
IA — tumour limited to endometrium or invades less than one-half of the myometrium
IB — tumour invades one-half or more of the myometrium
Stage II — tumour invades stromal connective tissue of the cervix but does not extend beyond uterus
Stage III — there is regional tumour spread.
IIIA — tumour involves serosa and/or adnexa (direct extension or metastasis)
IIIB — vaginal involvement (direct extension or metastasis) or parametrial involvement
IIIC — the tumour involves regional lymph nodes
IIIC1 — regional lymph node metastasis to pelvic lymph nodes
IIIC2 — Regional lymph node metastasis to para-aortic lymph nodes, with or without positive pelvic lymph nodes
Stage IV — the tumour invades contiguous organs or has metastasized to remote organ sites
IVA — tumour invades bladder mucosa and/or bowel mucosa (bullous oedema is not sufficient to classify a tumour as T4)
IVB — distant metastasis

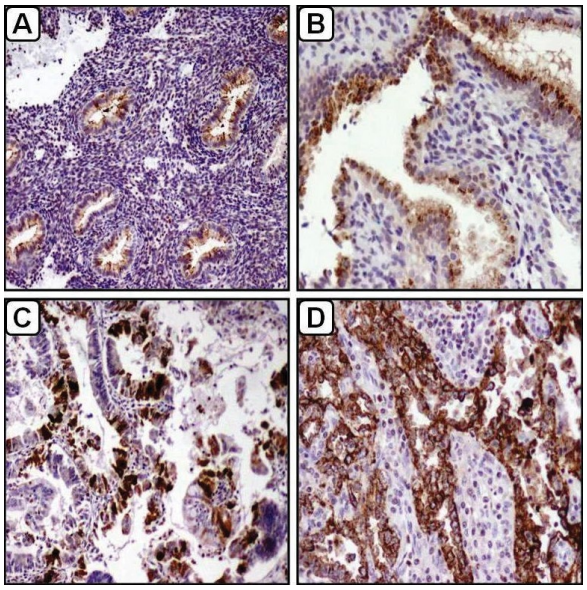

Figure 1. Immunostaining of OPN in non-neoplastic endometrium and endometrial carcinoma
OPN is shown in the cytoplasm of proliferative endometrium (A–100X), secretory endometrium (B-200X), well-differentiated endometrial carcinoma (C–200X), and in moderately differentiated endometrial carcinoma (D–200X). Immunohistochemical labelling was done using the anti-OPN antibody and diaminobenzidine used as the chromogen and haematoxylin as counterstain.

Table 2. Categories of OPN immunostaining in endometrial carcinoma and non-neoplastic endometrium

	Endometrial carcinoma (n = 71)	Non-neoplastic endometrium (n = 30)
Low (decreased) immunostaining	25 (35.2%)	0 (0%)
High (increased) immunostaining	46 (64.8%)	30 (100%)
p value	< 0.001*	< 0.001*

*One sample non-parametric chi-square test

(2) 26–50%, (3) 50–100%. For cytoplasmic immunostaining; 3 (heavy and intense brown immunostaining), 2 (brown immunostaining lighter than 3), 1 (brown immunostaining is weak), and 0 (no brown immunostaining). The result of summing percentage and intensity provided scores from 1–6. For the statistical analysis, an OPN immunostaining score of 1–3 was considered as low (decreased) immunostaining, and an OPN immunostaining score of 4–6 was considered as high (increased) immunostaining [19].

Statistical analysis

To study the variation between two groups of patients on one variable, the Mann Whitney test was used. Non-parametric chi-square was used to test variance along one variable. The survival differences and probabilities and the Log Rank test was tested by using the univariate Kaplan-Meier procedure was used. The end-point for patients was last seen or death. The model was controlled for confounding variables. Statistical procedures were performed using SPSS® Release 16.0. Statistical significance was determined at p value of ≤ 0.05 and was 2-sided.

RESULTS

Pattern of OPN immunostaining

Immunostaining of OPN was indicated by cytoplasmic brown colour in non-neoplastic and neoplastic endometrial (Fig. 1). In non-neoplastic endometrial tissues, high (increased) immunostaining was observed in all specimens (100%) while in EC was 98.5%. The incidence of increased OPN (high immunostaining) immunostaining was more frequent in non-neoplastic tissues (100%) than in endometrial carcinoma (64.9%) ($p < 0.001$). In endometrial carcinoma, high (increased) OPN immunostaining was seen in 71.8 %. The occurrence of high (increased) OPN immunostaining was statistically more than low (decreased) immunostaining ($p \leq 0.001$). Data is shown in Table 2.

Correlation of OPN immunostaining with clinicopathological features of EC

The present study revealed that there was no correlation between OPN immunostaining with most clinicopathological features (data is represented in Table 3).

Correlation of OPN immunostaining with survival outcomes

On the other hand, high (increased) OPN immunostaining in endometrial carcinoma was associated with better survival outcomes for overall survival (log-rank = 4.385, $p = 0.003$) (Fig. 2).

DISCUSSION

EC affects approximately 2–3% women worldwide [7]. The process of tumorigenesis in EC must be studied and understood in order to establish proper tumour management under convenient designed therapeutic standards. Previous reports stated the possible role of OPN in tumour progression and metastasis [20, 21].

Previously, reported that OPN is produced in higher levels in endometrial tumour cells than normal non metastatic cells. OPN particles can negatively affect the consecutive pathophysiology process of cellular adhesion, cellular migration, and invasion by αvβ3 receptors [7, 22]. Also, OPN can activate ERK1/2 and PI3K/ AKT signalling pathway leading to promotion in cellular migration, proliferation, and invasion due to increased MMP-2 expression [7]. Indeed, OPN can intercede in cell adhesion, and tumour colonies formation. The role of OPN is important to be studied as a prognostic marker in EC that might contribute to future

Table 3. Correlation between Clinicopathological features and OPN Immunostaining in tumours (n = 71)

Parameter		OPN Immunostaining (%)		P value
		Low	High	
Age	< 60 years	15 (21.1%)	34 (47.9%)	0.262*
	≥ 60 years	10 (14.1%)	12 (16.9%)	
Histological type	Endometrioid	22 (31%)	44 (62%)	0.136*
	Serous	3 (4.2%)	2 (2.8%)	
FIGO tumour grade	Low (Grade I)	13 (18.3%)	31 (43.6%)	0.184*
	High (Grade II and III)	12 (16.9%)	15 (21.1%)	
Tumour size	≤ 2 cm	14 (19.7%)	21 (26.9%)	0.488*
	> 2 cm	12 (16.9%)	25 (35.2%)	
Myometrial invasion	< 50%	18 (25.5%)	39 (54.9%)	0.168*
	≥ 50%	7 (9.8%)	7 (9.8%)	
Lymphovascular	Absent	24 (33.8%)	44 (62%)	0.908*
	Present	1 (1.4%)	2 (2.8%)	
Surgical resection margin	Free	23 (32.46%)	44 (62%)	0.380*
	Involved	2 (5.6%)	2 (2.8%)	
Lymph node metastasis	Absent	9 (12.8%)	24 (%)	0.838*
	Present	2 (2.8%)	2 (2.8%)	
	Not Sampled	34 (47.9%)		
FIGO Staging	Early (Stage I and II)	19 (26.8%)	39 (54.9%)	0.347*
	Late (Stage III and IV)	6 (8.5%)	7 (9.8%)	
Local Recurrence	Absent	22 (31%)	38 (53.5%)	0.812*
	Present	3 (4.2%)	8 (11.3%)	

*Mann Whitney test

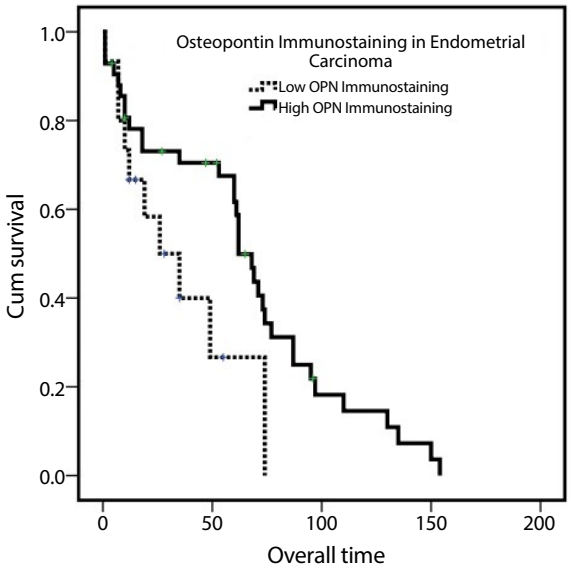

Figure 2. Overall survival curve (Kaplan Meier) according to OPN immunostaining
High (increased) OPN immunostaining is associated with better overall survival [Log Rank (Mantel-Cox) = 4.385, p = 0.003]

therapeutic management of the disease. Only a few papers in the literature correlate OPN expression and its clinicopathological significant with EC. Some results were inconclusive due to limited sample size.

In the present study, the immunostaining of OPN in normal endometrial tissue and in EC was carried on tissue microarray format to find out its correlation with clinicopathological features and possible clinical implications on the disease. In non-neoplastic endometrial tissues, high (increased) OPN immunostaining was observed in all specimens (100%). The immunolocalisation of OPN in normal endometrial tissue was reported before as strong cytoplasmic staining in both proliferative and secretory phases. This finding was attributed to the role of OPN in normal cell regulation of menstrual cycle process and maternal-foetal interface reaction during foetal placental implantation [22–25]. We found that high (increased) OPN immunostaining was found in 46 EC (64.8%), while low (decreased) OPN was reported in 25 cases (35.2%). On the other hand, these studies reported that OPN is decreased in malignant tissue, but still detected in about half of tumours [7, 23, 26–28].

In the current study, we could not establish any statistically significant association between OPN immunostaining and the clinicopathological of EC. One of the few studies of OPN in EC reported similar findings [28]. However, in our study increased OPN immunostaining was reported in

31 of low grade EC (43.6%) while in 15 high grade EC (21.1%) (p = 0.184). A previous report could not establish any relation between OPN and EC grade [28]. In a previous study, OPN immunostaining was shown to be increased with a higher tumour grade [23]. On the contrary, it was reported that high levels of OPN was associated with more differentiated tumours suggesting a protective role of OPN in EC [26].

In the present study, EC that invade less than 50% of myometrial thickness were positive in 80.3%, compared to a lower percentage (19.7%) in tumours invadeing more than 50% of myometrial thickness (p = 0.168). Although statistically not significant, however there is a trend that increased OPN immunostaining may be associated with less invading tumours. A study reported that high OPN is associated with lower stages [23]. In previous reports, silencing of OPN mRNA led to reduced invasion of EC cell lines in vitro and reduction of tumour size [1, 8, 29]. The statistical results from our study are not supporting this finding as there was no relation between OPN immunostaining and tumour stage or tumour size. In the current study, increased OPN immunostaining is significantly associated with higher overall survival probabilities. This result is in accordance with a previous report [26].

All together, our findings may support the trend that increased OPN immunostaining in EC may have good prognostic outcomes. However, the conflicting results with the few reports may be due to different sample size, technical issues, and/or different cut-off point in immunohistochemistry interpretation. Therefore, for future consideration to stratify EC using OPN as prognostic molecular marker and therapeutic target, it has to be studied in the context of its multiple functions and different isoforms. Our study has a limitation of a relatively small number of patients and, therefore, should be expanded to confirm these findings.

CONCLUSIONS

Our results showed that increased OPN immunostaining staining is considered a good predictor factor for survival outcome in EC and may have a role of future therapeutic management. The role of OPN as a molecular marker in EC is still unclear and needs to be established as it may be a possible target for future therapeutic applications in EC.

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Non-nutritional "paramedical" usage of human milk — knowledge and opinion of breastfeeding mothers in Poland

Karolina Karcz[1], Julia Makuch[2], Mateusz Walkowiak[2], Igor Olejnik[3], Barbara Krolak-Olejnik[1]

[1]*Departament of Neonatology, Wroclaw Medical University, Wroclaw, Poland*
[2]*Neonatology and Neonate Intensive Care Students Scientific Association, Wroclaw Medical University, Poland*
[3]*Department of Paediatric Bone Marrow Transplantation, Oncology and Hematology, Wroclaw Medical Uniersity, Poland*

ABSTRACT

Objectives: The objective of this study is to understand knowledge, attitudes and practices of non-nutritional breast milk use among lactating women in respect of skin diseases and other frequent ailments.

Material and methods: The study, in the form of a questionnaire, spread on social media, was targeted at breastfeeding women. The questionnaire consisted of questions regarding the knowledge of non-nutritional usage of human milk, its use in practice, subjective opinion on the observed results and inclination towards future use. Chi-square tests and c-Pearson coefficients were used for statistical calculations.

Results: A total of 1187 responses were acted upon. In the study group, 879 women claimed to have knowledge of non-nutritional use of human milk in respect of skin and most common ailments, whilst 688 of them claimed to use at least one usage. The most frequently, breast milk was used for: care of cracked nipples, care of healthy skin, treatment of diaper dermatitis and treatment of neonatal acne. A correlation between duration of breastfeeding ($p < 0.05$) and gestational age ($p < 0.05$) and practical use of non-nutritional human milk was found.

Conclusions: The study showed a great enthusiasm of mothers in respect of using breast milk for non-nutritional purposes, including the treatment of skin diseases and other common ailments. However, given the scant studies determining possible concerns surrounding these methods, there is a requirement for parental education with emphasis on the need for prompt medical examination and pertinent treatment.

Key words: breast milk; milk therapy; skin; constipation

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INTRODUCTION

For centuries, usage of home remedies has been a common practice around the world, especially in medium-intensity ailments [1]. Recently, one has been able to observe increasing popularity of alternative treatment among Polish society, primarily of those with use of easily accessible natural remedies. Moreover, self-treatment is often administered on the basis of information found in social media, without any medical consultation [2]. The rise of interest in those methods might result from a general belief in safety, efficacy and lack of side effects associated with them. Patients' practices include the non-nutritional use of human milk, which seems to be confirmed by mothers consulting in the authors' Clinic of Neonatology.

First mentions of therapeutical usage of breast milk were found thousands of years ago, and opinions of its efficacy were passed along to consecutive generations. Authentication of non-dietary use of human milk and scientific argumentation of its use as an alternative to generally approved medical remedies is still sought [1, 3]. Human milk is optimally adjusted to the needs of infants, both in nutritional components and non-nutritional bioactive compounds, which stimulate normal child development, further immunological maturing and defence against various

Corresponding author:
Karolina Karcz
Departament of Neonatology, Wroclaw Medical University, 213 Borowska St., 50–556 Wroclaw, Poland
e-mail: karolina.karcz@student.umed.wroc.pl

diseases – both infectious and autoimmunological [4, 5]. Studies concerning human milk's mechanics in aiding child development and stimulating the immune system identified various compounds, including cytokines, stem cells, oligosaccharides, growth factors, anti-inflammatory and antibacterial proteins with potential for preparation of new clinical treatments [6]. Currently, in social media and the press, one can find information regarding potential methods of human milk use as a home remedy, both in prophylactic and therapeutic purposes, yet the majority of those methods and their potential advantages are not scientifically proven.

Objectives

According to the authors' experience, non-nutritional usage of human milk is willingly practiced by breastfeeding mothers, although the scale of these practices has not been studied in Poland to date. Therefore, the objective of this study is to understand lactating women's knowledge, attitudes and practices of non-nutritional breast milk use. The survey results on the use of mothers' milk as a therapy for mucosal infections of various types in Poland has been previously reported in Part 1 [7]. The present work is a reference to practices of breast milk usage in prophylaxis and treatment of skin ailments and other common health conditions.

MATERIAL AND METHODS

The study was conducted in November/December 2018 with use of an anonymous questionnaire disseminated in electronic form through social media. The survey targeted women with an ongoing lactation period — breastfeeding or feeding with their own pumped milk (the use of a breast pump and a bottle was allowed), regardless of the duration of lactation. The questionnaire consisted of questions regarding the knowledge of non-nutritional use of human milk, its use in practice, subjective opinion on the observed results and inclination for future use. The list of non-nutritional uses of breast milk was compiled from information found on Internet forums, social media and parenting blogs — the responding mothers were well informed that little or no scientific data were currently available regarding the efficacy and dangers of implementation of those usages. The detailed description of study design and methodology was reported in Part 1 [7].

All answers were coded based on the order and date of receipt. The PQStat, version 1.6., and Microsoft Excel for Office 365 were employed to analyse the resulting data. The Chi-square test was used to investigate the statistical correlation between the categorical variables, and the measure of the relationship between nominal variables was determined using c-Pearson coefficient. The statistical significance level was set at $p < 0.05$.

Prior to the start of the study, formal permission was obtained from the local ethics committee, the Bioethical Committee at the Medical University in Wroclaw (Nr KB 703/2018, 22 November 2018).

RESULTS

A total of 1218 women replied to the questionnaire, of which 31 were excluded from the study in view of the unfulfilled basic qualifying criterium — current lactation period. A total of 1187 responses were acted on. In the study group, 890 (74.98%) women affirmed to having known about non-nutritional usage of breast milk, of those 879 (98.76%) claimed to have known of those methods in respect of skin maintenance, 47 of those answers included constipation treatment (Tab. 1). The most frequently known of usages: maintenance of damaged nipples (n = 832), healthy skin maintenance (n = 612), atopic dermatitis treatment (n = 387) and diaper dermatitis treatment (n = 360) (Fig. 1).

Seven hundred fifty-one of all surveyed mothers tried certain methods as a home remedy, of those 688 in skin ailments (Tab. 1). Three hundred forty-seven women used breast milk only in skin care and obstruction treatment, 341 used breast milk in skin care, constipation treatment and in mucous membranes care. The remaining 63 mothers

Table 1. Characteristics of women claiming to having known of ("Knowledge of") and having tried ("Tried") the non-nutritional use of human milk in skin care and constipation treatment

Demographic data	Knowledge of (n = 879; 98.76%)	Tried (n = 688; 77.3%)
Age in years (Mean ± SD)		
	30.17 ± 3.99	30.16 ± 4.05
Place of residence (n)		
Countryside	160 (18.2%)	127 (18.46%)
City < 100,000 residents	217 (24.69%)	168 (24.42%)
City > 100,000 residents	502 (57.11%)	393 (57.12%)
Education (n)		
Primary education	1 (0.11%)	0
Basic vocational education	9 (1.02%)	7 (1.02%)
General secondary education	126 (14.34%)	100 (14.53%)
Tertiary education	743 (84.53%)	581 (84.45%)
Parity (n)		
1	555 (63.14%)	437 (63.52%)
2	269 (30.6%)	209 (30.38%)
3	52 (5.92%)	40 (5.81%)
≥ 4	3 (0.34%)	2 (0.29%)
Duration of lactation in months (Mean ± SD)		
	10.59 ± 8.38	10.91 ± 8.53
Gestational age in weeks (Mean ± SD)		
	39.16 ± 2.197	39.20 ± 2.1

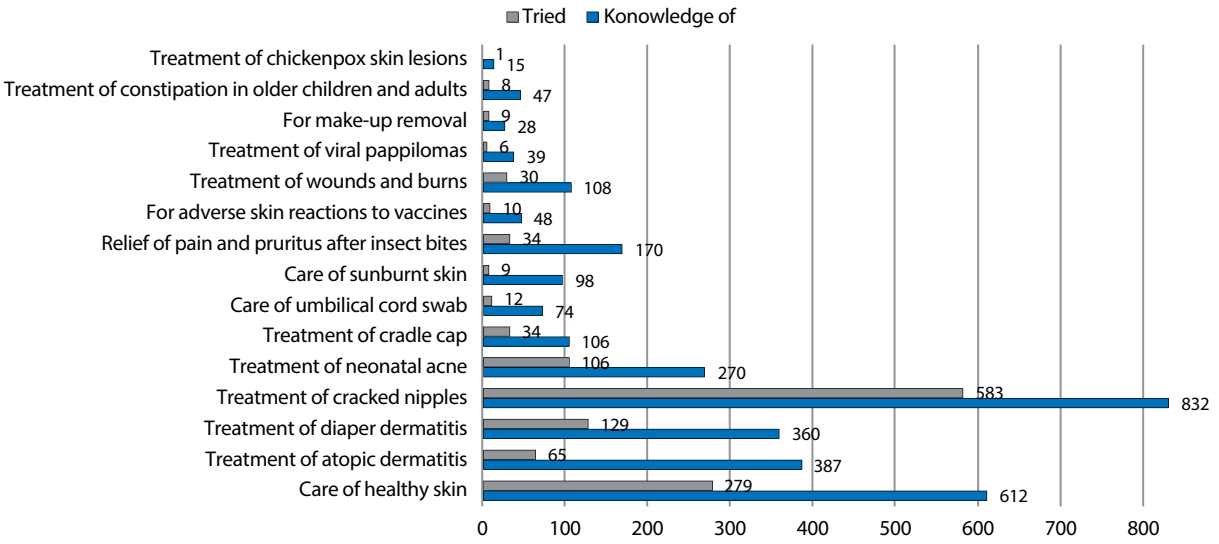

Figure 1. Comparison of the number of mothers who knew of non-nutritional use of human milk in skin care and other frequent ailments („Knowledge of") and those who tried at least one of them („Tried")

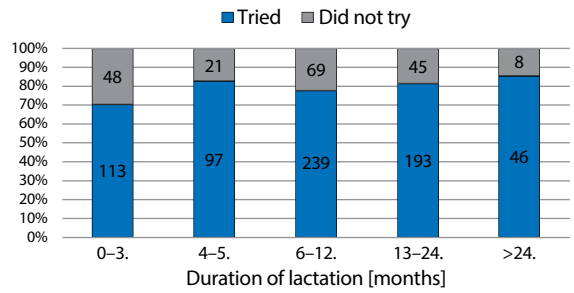

Figure 2. Duration of lactation and attempt of human milk use in prophylaxis and treatment of skin ailments ("Tried" vs "Did not try"). Numbers in graph bars represent a total number of mothers with corresponding percentage in each group

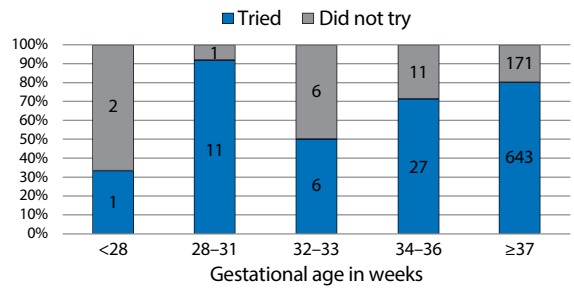

Figure 3. Weeks of gestation and attempt of human milk use in prophylaxis and treatment of skin ailments ("Tried" vs "Did not try"). Numbers in graph bars represent the total number of mothers with corresponding percentage in each group

tried non-nutritional use of human milk in prophylaxis and treatment of mucous membranes ailments. Respondents were asked to evaluate the results and commented upon

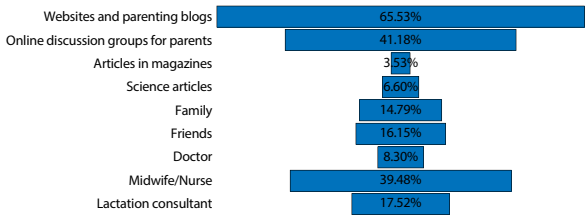

Figure 4. Source of information concerning non-nutritional use of human milk among respondents (multiple choice question)

as follows: 559 positive opinions, 55 negative opinions, and 80 opinions — difficult to assess.

Maintenance of damaged nipples (583), healthy skin care (279), diaper dermatitis (129) treatment of neonatal acne (106) were the most frequently used methods. A correlation between duration of breastfeeding (Chi-square test = 9.97; $p < 0.05$; c-Pearson adjusted coefficient = 0.15) (Fig. 2) and gestational age (Chi-square test = 11.88; $p < 0.05$; c-Pearson adjusted coefficient = 0.163) (Fig. 3) and practical use of non-nutritional human milk in skin and most frequent ailments was found.

The main source of information about non-nutritional human milk usage was constituted by websites and parenting blogs (65.53%), online discussion groups for parents (41.18%) and midwife or nurse (39.48%) (Fig. 4).

DISCUSSION

In our experience, no attempts to provide statistical data on the use of breast milk as a therapy by lactating mothers in Poland had been made prior to our study. The only identified papers provide reviews of worldwide literature

with implications to further research in this field [3, 8]. In the following part of the paper, we report on survey results in respect of management of mainly skin conditions with reference to representative studies.

Attempts at using mother's milk as a home medication are a common practice among the mothers surveyed. We noticed a great interest in information regarding possible non-nutritional uses of human milk. Owing to the use of breast milk for damaged or inflamed skin by mothers, special attention should be given to the microbiological purity of human milk. It is important due to the fact of the physiologically immature epidermal barrier in neonates and infants. Studies have proved that colostrum and human milk provide the infant's intestine with mutualistic, commensal and probiotic bacteria. This is an essential discovery, as human milk had been previously considered to be sterile. In fact, a breast-fed infant, with a daily milk supply of about 800 ml, consumes from 1×10^5 to 1×10^7 bacteria [9]. The microbiome of human milk consists mainly of genera Staphylococcus and Streptococcus. Among less frequent genera, Bacteroides, Lactobacillus, Propionibacterium, Serratia, Pseudomonas, Corynebacterium and a smaller number of Enterococcus and Bifidobacterium can be found [10]. The transient flora mainly encompasses pathogens like: HIV, HTLV-1, CMV, HBV, HCV, HSV, VZV, EBV, HHV-6, HHV-7, Toxoplasma gondii, Candida spp. and Staphylococcus aureus, Mycobacterium tuberculosis, Escherichia coli, Streptococcus B, Listeria monocytogenes, Coxiella burnetti. Furthermore, incidents of milk-borne infections have been reported [11].

To the authors' knowledge, the impact of human milk microbiome on formation of infantile epidermal flora has not been assessed to date - especially as far as the topical use of breast milk is concerned. In addition to reports of milk-borne infections via the oral route, no specific information on the risk of pathogens transmission in cases of milk applied to damaged skin is available.

The skin connects the organism with the outside environment, which affects the development of the immune system. After birth, the infantile skin microbiota depends on the type of birth and undergoes dynamic changes. Initially, it is almost identical in different parts of the body. The maturation of microbiome and initial stabilization of its structure depend on body region and takes place from the 3rd month of life. The evolution of the dermal bacterial flora can be affected not only by neonatal skin characteristics and structure, but is prone to factors such as: immune system function, antibiotic therapy and environmental exposure, such as a stay in neonatal intensive care unit. The development and maturation of skin microbiome in the neonatal period, especially in premature babies, is crucial to prevent colonization with pathogens and its subsequent progression to generalized infection [12].

Referring to the high level of interest in the non-nutritional properties of breastmilk, several attempts have been made to verify its potential applications.

The commonly known and recommended method of caring for cracked nipples is moisturizing them with women's own milk — which was reflected in the answers of the surveyed mothers. Conclusions derived from studies on this topic remain inconsistent. Regarding the rate of nipple healing and pain relief, in one piece of research, the use of breast milk together with lactation pads resulted in a better effect than using lanolin [13]. Whereas in another, care with hydrogenous lanolin was more effective than female milk application [14]. It was also found, that lanolin and breast milk are similarly effective in the prevention of pain, but they do not prevent the nipples from cracking [15]. Comparison of the effects of using human milk, hydration packs, tea wraps and drying did not confirm the usefulness of any mentioned intervention, especially in expectation of pain relief [16]. The next study proved that interventions with breast milk or hydration packs alter the pain to a lesser extent than drying the nipples, both in prophylaxis and alleviation [17]. Apart from a slight discrepancy with regard to the mentioned studies, moisturizing nipples with breast milk seems to be a quite safe method of nipple care and pain relief.

Among dermatological inflammatory ailments affecting newborns, diaper dermatitis is one of the most common. So far, the scientific research has suggested that human milk is a good and safe therapeutic agent. When locally applied to the irritated area, it alleviated inflammation and limited progression of skin lesions [18]. It was also shown, that therapeutic efficacy of breast milk was comparable to 1% hydrocortisone ointment with significant improvement in skin condition [19]. However, this study was conducted on a small group of patients. In another piece of research, traditional medicinal products showed a better effect in cases of medium and severe lesions. Better therapeutic effects were achieved with use of protective ointments [20]. Altogether, the promising results seem to support the use of breast milk as an adjunctive remedy for diaper dermatitis.

The efficacy of using human milk, comparable to the effectiveness of 1% hydrocortisone ointment, was also found in case of skin changes in the course of atopic dermatitis among infants [21, 22]. Although there was no difference in the speed of skin condition improvement, patients treated with traditional methods received a significantly lower severity scale score after intervention [21] or the score was comparable [22]. Another study, conducted only on nine patients, did not confirm the beneficial effect of breast milk on atopic eczema lesions. In milk samples used in the study, researchers identified the following bacteria: Staphylococcus aureus, coagulase-negative Staphylococcus and Alpha-Hemolytic Streptococcus. Staphylococcus aureus colonies were also detected after milk application on skin

with atopic lesions in one child, with their absence within healthy skin areas. However, no signs of infection were found. There were no cases of milk-borne infections [23]. Treatment with fresh human milk seemed easy for mothers — due to its availability and low cost, as compared to pharmaceutical agents [21–23]. The observation was confirmed by the results of our survey.

There are no studies on the possibility of using breastmilk for the treatment of seborrheic dermatitis (including cradle cap) and neonatal acne.

Undoubtedly, mother's milk has a positive impact on building the child's immunity. As mentioned above, numerous bioactive compounds are transferred via the oral route. There are, among others, specific antibodies which stimulate the immature immune system, protect against infections or shorten their duration time [5, 6] — which similarly concerns chickenpox. A case of mild and short course of VZV infection in a 41-year-old father and his 9-year-old son after use of frozen breast milk for skin eruptions was reported [24]. Based on the observation, it was hypothesized that breast milk might have shortened the duration of chickenpox . However, it requires verification on the basis of a larger research group. Moreover, it is necessary to assess the risk of superinfection of skin eruptions in relation to using fresh milk.

There is also lack of scientific reports on the usefulness of breast milk in treatment of other viral skin diseases, such as viral papillomas. Despite the proven immunomodulatory and anti-inflammatory properties of human milk [25], there are no studies on the effects of its use in pruritus, insect bites, post-vaccination reactions and care of intact, healthy skin.

As far as the care of the umbilical stump is concerned, it is an important issue in neonatal nursing. Negligence and mistakes in this respect result in impaired healing and development of bacterial infections, which affect 0.2–0.9% newborns negatively [26]. In order to reduce the infection rate, the World Health Organization recommends washing the umbilical cord stump with clean water and soap, and thorough drying afterwards [27]. The same guidelines were published by the Polish National Supervision in the Field of Neonatology in 2010. They recognize the "dry care" as a standard procedure [26]. Due to the high infant mortality rate resulting from bacterial infections in developing countries, including around 1 million cases of lethal omphalitis annually, the topic of umbilical cord care with use of breast milk as an easily available agent is undertaken [28]. In each of 10 publications found, umbilical stump separation time was reduced, and no side effects were noticed. Moreover the effectiveness of the method was greater than in the case of alcohol [29], distilled water [28] and dry care [29–33]. Furthermore, there was an observed: reduction of bacterial colonization of the umbilical stump [31], reduction of bleeding after separation [30, 31], similar frequency of infection as with other factors [30] and lower incidence of infection than in case of dry care [33]. Among the surveyed women, 12 used breast milk to care for the umbilical cord - no complications were reported. Altogether, the results of research studies suggest the breast milk might be used as beneficial means of preventing omphalitis.

On the basis of previous studies, it was observed that hard stools and constipation more often occurred in infants fed with milk formula than breast-fed [34]. This difference was partially attributed to human milk oligosaccharides (HMO) — this effect is explained by several mechanisms: 1) increase in microbial mass due to oligosaccharides fermentation may increase the content of water in stools and result in softer consistency; 2) selective fermentation and growth of Lactobacillus and Bifidobacterium spp. and production of short-chain fatty acids may increase the water content in faecal mass, but also stimulate gastrointestinal motor complex activity; 3) probably HMOs bind water, thus increase its content in faeces [34]. Scientific research has shown that long exclusive breastfeeding is a protective factor against gastrointestinal dysfunction, including constipation in children at high risk of developing autism spectrum disorder [35]. However, no attempts have been made to verify the suitability of orally administered breast milk in the immediate treatment of abnormal rhythm of bowel movements, especially in different age groups.

This work is a part of the first research in Poland, to the authors' knowledge, on the use of breast milk for non-nutritional purposes by breastfeeding mothers. This paper includes preliminary statistical data on the popularity of using their own milk by mothers during lactation. It provides an overview of patients' knowledge and experience in the application of human milk as a home remedy for skin conditions or other ailments, such as constipation. The survey involved women living in various regions of Poland, of different ages, parity rate and education level. However, the results cannot be generalised on the Polish population, as the study group encompassed breastfeeding internauts.

CONCLUSIONS

1. Polish mothers show great interest in non-nutritional applications of human milk. Websites (including parenting blogs), social networks and forums for parents are the main source of their knowledge. The information is mainly based on anecdotal evidence.
2. Increasing knowledge of human milk composition and recognizing the multitude of its immunologically active compounds creates the prospect of using breast milk as a cheap and relatively easily available therapeutic agent.
3. So far, the results of research concerning the usefulness of human milk in prevention and treatment of selected skin conditions, especially diaper dermatitis or umbilical cord stump care, prompt the updating of the current

medical standards, and legitimate breast milk as a supportive remedy.

4. Further research is needed in the field of the usefulness of human milk in treatment of gastrointestinal motility disorders, inflammatory reactions, atopic and seborrheic dermatitis.
5. It is essential to verify the risk of causing human milk microbiome induced infection in case of usage on damaged skin.

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Can coffee consumption be used to accelerate the recovery of bowel function after cesarean section? Randomized prospective trial

Sezen Bozkurt Koseoglu[1], Melike Korkmaz Toker[2], Ismail Gokbel[1], Ozgu Celikkol[1], Kemal Gungorduk[1]

[1]Mugla Sıtkı Kocman University, Training and Research Hospital, Department of Gynecology and Obstetrics, Turkey
[2]Mugla Sıtkı Kocman University, Training and Research Hospital, Department of Anesthesiology and Reanimation, Turkey

ABSTRACT:

Objectives: To evaluate whether coffee consumption accelerates the recovery of bowel function after cesarean section or not.

Material and methods: This study was designed as randomized controlled study. Patients were randomly assigned to one of two groups: Ultimately, Group 1 (n = 51) was the study group and drank three cups of coffee after cesarean, whereas group 2 (n = 52) was not given any treatment. The primary outcome measure was the time to first defecation after surgery, the secondary outcomes were time to first bowel movement, passage of flatus, time to toleration of a solid diet, additional antiemetic and analgesic requirement.

Results: There were no significant differences in demographic variables between the groups. The mean time to passage of first flatus was significantly shorter in the study group than the control group (8.6 ± 3.3 h vs 11.3 ± 7.5 h, respectively; p = 0.022). First defecation was 20.7 ± 11.5 h for the study group and at 29.1 ± 14.3 h for the control group (p = 0.001). In addition, there was a significant difference in mean time to toleration of solid food between the study and control groups (8.78 ± 2.33 h vs 12.88 ± 4.2.60 h, respectively; p < 0.001).

Conclusions: Coffee can be used in patients to enhance the recovery of gastrointestinal function after elective cesarean section.

Key words: caffeine; coffee; ileus; cesarean section

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INTRODUCTION

Cesarean section has become the most common type of obstetric surgery worldwide. As the postcesarean period coincides with breastfeeding and caring for the infant, appropriate postoperation follow-up is necessary to help not only the patient but also the baby. Postoperative ileus (POI) is a common complaint after cesarean section because gastric emptying is delayed in pregnancy, especially during labor. POI is a transient cessation of bowel function and a major contributing factor to postoperative discomfort [1]. Clinically, POI is characterized by abdominal distension, a lack of bowel sounds, nausea, vomiting, stomach cramps, and lack of flatus [2]. POI leads to prolonged hospital stays, and reduces patient satisfaction after surgery, especially after cesarean section, due to the delay in mother–baby bonding [3, 4]. Rapid recovery following cesarean section is important for both the baby and mother. Furthermore, POI is associated with costs of between $5000 and $10000 in the USA, for an annual total of $1 billion because of prolonged hospital stays and high treatment costs. Therefore, it is important to find a safe method to reduce POI. Many clinical methods have been attempted to reduce POI, including early feeding, fluid restriction, gum chewing, preoperative carbohydrate loading, and epidural analgesia [5–12]. However, none of these have been completely successful in the prevention of POI.

Coffee is a popular beverage worldwide and improves general prosperity. In addition, it has positive effects on the central nervous, cardiovascular, and reproductive systems [13]. Coffee is known to trigger the gastrointestinal motor activity

Corresponding author:
Melike Korkmaz Toker
Mugla Sıtkı Kocman University, Training and Research Hospital, Department of Anesthesiology and Reanimation, Turkey
e-mail: meltoker@gmail.com

in participants with no concomitant diseases [14, 15]. There is constrained logical proof in regards to its consequences for gastrointestinal capacity. Two reports proposed that coffee consumption after both open and laparoscopic colectomy is sheltered and is related with diminished duration to the initiation of bowel activity [16, 17]. It is also known that coffee accelerates bowel function after malignant gynecological surgery [18]. However, a methodical survey of PubMed, OvidSP, Google Scholar, and Scopus recognized just a single past examination of its impacts on gastrointestinal behaviour in patients after cesarean section [19]. Unfortunately, this study was not within Enhanced Recovery After Surgery (ERAS) Guidelines according to which early feeding is essential for patients undergoing surgery [20].

Objectives

Consequently, we carried out a randomized controlled trial to evaluate even if coffee consumption stimulates the recovery of bowel function after cesarean section in in concurrence with ERAS guidelines.

MATERIAL AND METHODS

This randomized controlled study was carried out at Mugla Sitki Kocman University Training and Research Hospital, Department of Obstetrics and Gynecology, from 30th October 2018 to 1st March 2019. After obtaining institutional research and ethics approval, 110 pregnant women with elective cesarean section were included in the study (Reference number: 2017,13/4). The study was designed in accordance with the tenets of the Declaration of Helsinki and was registered with anzctr.org.au (ACTRN12618001772235).

The inclusion criteria were women aged between 18 and 35 years, with no allergy to coffee, and undergoing spinal anesthesia. The exclusion criteria were emergency cesarean, cesarean with general anesthesia, history of previous pelvic or abdominal surgery (excluding previous cesarean section), chronic constipation, any known thyroid disease, irritable bowel syndrome, and any known hypersensitivity or allergy to caffeine. The patients were also excluded if their surgery lasted more than 60 minutes. The objectives of the trial were described to the patients, and written informed consent was received from all participants before enrollment. Blinding could not be performed due to the timing of utilization of the assigned intervention except for observers and outcome assessors.

Patients were hospitalized on the day of surgery. Patients were randomly assigned in a 1:1 ratio either group A or group B when they were admitted to our clinic. Permuted-block randomization, with concealed varying block sizes of two, four, or six, was performed centrally via an online module using a computer-generated randomization sequence. Group A served as the study group and drank three cups of coffee daily beginning from 2 hours after surgery, whereas group B was not given any treatment. As the standard clinical protocol, patients were not allowed to receive solid or liquid food 8 hours before surgery. An oral or mechanical bowel preparation was not used prior to surgery.

All patients underwent the same anesthetic protocol. Each patient received intravenous (IV) volume preloading with 15 mL/kg of 0.9% saline within 25 min before entering the operating room. After the patients arrived at the operating room, standard monitoring procedures consistent with American Society of Anesthesiologists guidelines were applied. A subarachnoid block was performed with the patients in the sitting position at the L3–4 interspaces using 2 mL (10 mg) of hyperbaric bupivacaine plus 10 µg of fentanyl with a 25-gauge Quincke spinal needle (Egemen International, Izmir, Turkey). The patients were repositioned in the supine position with a left lateral tilt and supplemental oxygen was delivered at a rate of 4 L/min via a face mask. In addition intraoperative antiemetic agents (0.05 mg/kg ondansetron and 0.1 mg/kg dexamethasone) were used prophylactically. All cesarean sections were performed by the same surgical team using the Pfannenstiel incision on the abdomen and transverse lower uterine incision. The duration of surgery was defined as the time from the onset of surgery to skin closure.

The patients in the study group drank 100 mL of caffeinated coffee without sugar or milk provided by a nurse or doctor at 2, 6, and 18 hours after surgery (Nescafe®, 2 g, 100 mg of caffeine). All women drank coffee completely. Patients were allowed to drink any measure of water without coffee, black tea, or other type of caffeinated drink. According to our post-cesarean care protocol, the patients received Ringer's lactate associated with 30 IU of oxytocin and and analgesic agent (75 mg of intramuscular diclofenac sodium, 2 x in 1 day if not contraindicated). The need for extra analgesic and other medications, including antiemetics, was recorded. No oral or rectal intestinal stimulants were used after cesarean section.

Early breastfeeding and ambulation were encouraged in both groups. All patients were mobilized after performing a sitting position for 5 minutes in bed, beginning from 6 hours after surgery, for approximately 10–15 minutes. Hemoglobin levels were checked 6 and 24 hours after surgery by a complete blood count, and the results were recorded. The weight and sex of the newborn infants were also recorded after birth.

The outlined primary outcome measure was the time to first defecation after surgery (measured from the end of surgery). The secondary outcomes were time to first bowel movement (measured from the end of surgery), first passage of flatus, time to toleration of a solid diet (measured from the end of surgery), additional antiemetic [metoclo-

pramide, 10 mg (Primperan®; Sanovi Aventis, Paris, France)] need, and additional analgesic requirement. Time to first bowel movement was defined as when the patient noticed the first bowel sound or movement.

To correctly observe the return of bowel function, participants were advised to warn nurses or researchers immediately after the first passage of flatus or a bowel movement and defecation. We examined bowel movements by auscultation eight times per day starting 24 hours postoperatively until the first bowel sounds were noted. The postoperative nutrition was regulated; a liquid diet was commenced two hours after cesarean section and advanced to a regular diet within the four hours. Postoperative ileus was described as a narrow mindedness to oral nourishment without clinical or radiological indications of obstruction, that either a) requires nasogastric tube insertion; or b) was related with two of the accompanying: nausea/vomiting, stomach distension, and the nonattendance of flatus hours on or after postoperative day two [21].

The symptoms and signs of ileus were evaluated six times daily by an investigator who was blinded to the study allocation. Discharge criteria from the hospital included tolerance of a regular diet, absence of fever or signs of surgical site infection, ambulating at baseline; and passage of flatus or stool. Consistent with our ministry of health protocol, the patients were not discharged from the hospital before 48 hours after cesarean section.

All trials reported to date that had explored coffee intake had included only patients who had undergone colonic surgery or had a gynecologic malignancy. Therefore, we ran a pilot trial with 20 patients in each group (A-coffee and B-control) before the full study. The mean time to first defecation was 23.6 ± 13.7 h in group A and 31.7 ± 6.5 h in group B. Based on these data, we calculated that, to attain a study power of 90% with an α level of 0.05, 50 patients were required in each group. Assuming a 10% dropout rate, 110 patients were required. These patients were included the study.

Statistical analyses were performed using Med Calc (version 16.4; Med Calc Software, Ostend, Belgium). Normality of the variables was examined using the Kolmogorov-Smirnov test. The chi-square and Fisher's tests were used to compare categorical variables, Student's t-test was used to compare normally distributed continuous variables, and the Mann-Whitney U test was used to compare variables that were not normally distributed. We used an intention-totreat protocol. In all analyses, $p < 0.05$ was taken to indicate statistical significance.

RESULTS

A total of 110 patients were enrolled in the study. Before randomization, two patients were excluded because they no longer fulfilled the inclusion criteria and refused to participate. Overall, 53 patients were assigned randomly to the study group and 55 were assigned to the control group. Ultimately, the conditions of 52 patients in the control group and 51 in the study group were analyzed. The reasons for exclusion after randomization are shown in Figure 1. Demographic information of the patients is presented in Table 1. There were no significant differences in demographic variables between the two groups. The indications for cesarean section in both the coffee and control groups are shown in Table 2. The most frequent cesarean indication was "previous cesarean" for both the study and control groups. The mean operation duration in the study group was 43.43 ± 7.51 min. while that in the control group was 44.25 ± 7.97 min. ($p = 0.636$).

Similar to the mean operation duration, there was no significant difference in size of incision between the study and control groups (900.98 ± 0.73 mm vs 100.0 ± 0.79 mm, respectively; $p = 0.897$).

Table 3 shows the data for return of bowel function between the two groups. There was no significant difference in time to first bowel sound between the study and control groups (5.7 ± 3.5 h vs 6.4 ± 2.6 h, respectively; $p = 0.316$), but the time to passage of first flatus was significantly shorter in the study group than in the control group (8.6 ± 3.3 h vs 11.3 ± 7.5 h, respectively; $p = 0.022$). First defecation was recorded at 20.7 ± 11.5 h for the study group and at 29.1 ± 14.3 h for the control group ($p = 0.001$). In addition, there was a significant difference in mean time to toleration of solid food between the study and control groups (8.78 ± 2.33 h vs 12.88 ± 2.60 h, respectively; $p < 0.001$).

A total of 13 patients (25.5%) in the study group and 23 (44.2%) in the control group required additional analgesics ($p = 0.046$). And also 5 patients (9.8%) in the study group and 13 patients (25%) in the control group required additional antiemetic ($p = 0.042$). There was a significant difference in antiemetic and analgesic requirement between the groups (Tab. 3). There were no symptoms of ileus in any of the patients, and all patients were discharged 48 h postoperatively with no complications.

DISCUSSION

This randomized controlled study indicates that drinking coffee early in the postoperative period after cesarean section reduced the mean times to first flatus, defecation, and toleration of solid food. The mean time to the first bowel sound was shorter in the study group than in the control group, but the difference was not significant. To our knowledge, this is the first study to evaluate the effects of early coffee consumption on the recovery of bowel function after cesarean section.

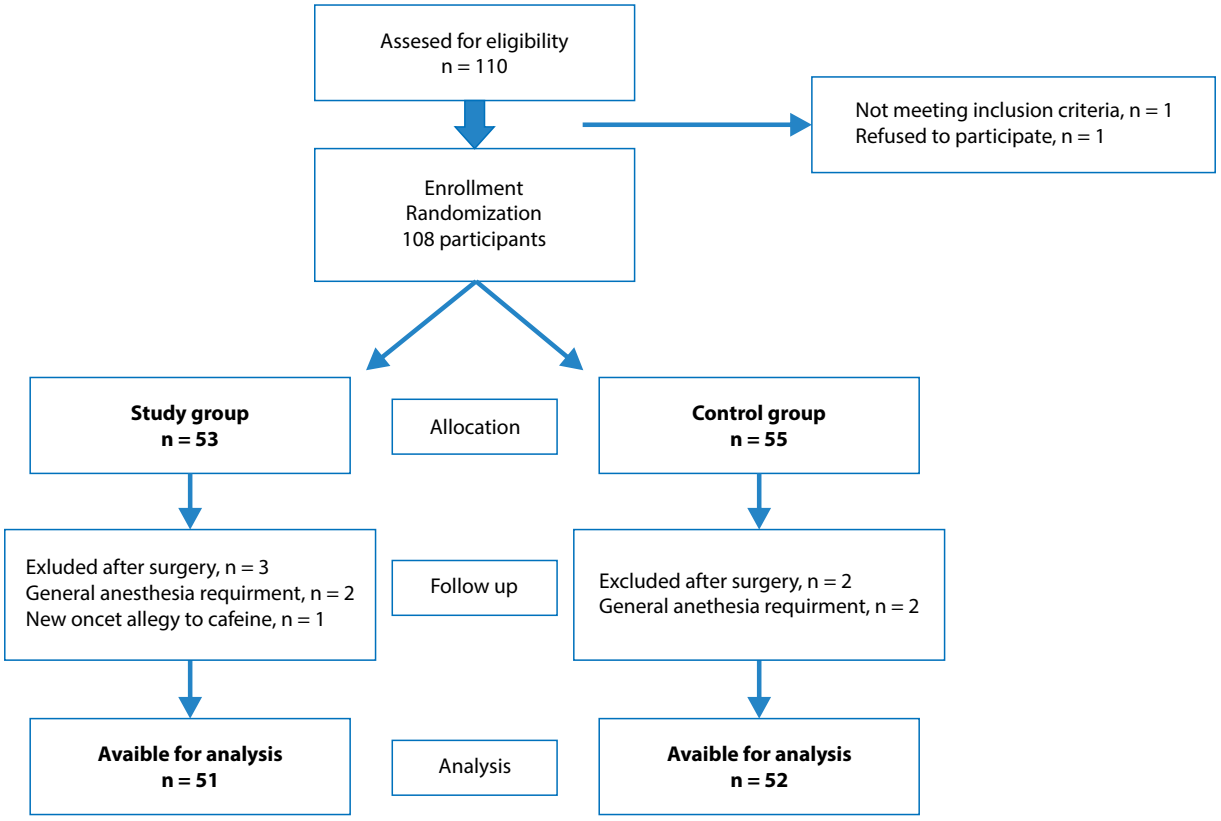

Figure 1. Flow diagram of trial recruitment and follow-up

Table 1. Baseline characteristics of the patients

	Study group (n = 51)	Control group (n = 52)	P-value
Age [years]*	28.70 ± 5.42	29.25 ± 5.74	0.622
Gravida*	2.5 ± 1.0	2.2 ± 1.0	0.283
Parity*	1.33 ± 1.01	1.23 ± 1.23	0.607
Number of prior ceserean section**			
1	38 (80.8)	39 (90.7)	
2	7 (14.8)	3 (6.9)	
3	1 (2.2)	1 (2.4)	
4	1 (2.2)	–	
Smoking**	1 (1.9)	2 (3.8)	1.0
Alcohol**	0	0	NA
Hypertension**	3 (5.8)	1 (0)	0.298
Gestational diabetes mellitus**	2 (3.9)	1 (0)	0.546

*Values are given as the mean ± standard deviation
**Values are given as the number (percentage)

Table 2. Surgical characteristics of the patients

	Study group (n = 51)	Control group (n = 52)	P-value
Indication for cesarean section			
Previous ceserean section**	47 (92.1)	43 (82.6)	
Fetal macrosomia**	2 (3.9)	2 (3.8)	
Cephalopelvic disproportion **	1 (2)	3 (5.8)	
Breech presentation**	0 (0)	4 (7.8)	0.206
Twin pregnancy**	1 (2)	0 (0)	
Operation duration [minutes]*	43.43 ± 7.51	44.25 ± 7.97	0.636
Incision size [millimeter]	900.98 ± 0.73	100.0 ± 0.79	0.897
Birth weight of fetuses [gram]*	3628.43 ± 485.00	3489 ± 492.15	0.152
Sex of fetus**			
Male	24 (47)	28 (53.8)	
Female	27 (53)	24 (46.2)	0.491
Decrease hemoglobin level [gram/deciliter]*	1.49 ± 0.41	1.45 ± 1.37	0.622

*Values are given as the mean ± standard deviation
**Values are given as the number (percentage)

The pathogenesis of ileus has not been completely elucidated, and it seems to be multifactorial in nature. Ileus may be due to an inflammatory process related to surgical manipulation of the intestine during surgery that leads to significant leukocyte infiltration of the muscular layer

Table 3. Study outcomes

	Study group (n = 51)	Control group (n = 52)	p-value
Mean time to first bowel movement [hour]	5.7 ± 3.4*	6.4 ± 2.7*	0.316
Mean time to first flatus [hour]	8.6 ± 3.3*	11.3 ± 7.5*	**0.022**
Mean time to first defecation [hour]	20.7 ± 11.5*	29.1 ± 14.3*	**0.001**
Mean time to toleration of solid food [hour]	8.78 ± 2.33 *	12.88 ± 2.60*	**< 0.001**
Postoperative ileus**	-	-	**NS**
Additional analgesic requirement**	13 (25.5)	23 (44.2)	**0.046**
Additional antiemetic requirement**	5 (9.8)	13 (25)	**0.042**

*Values are given as the mean ± standard deviation
**Values are given as the number (percentage)

of the intestine and intensive induction of inducible nitric oxide synthase [22].

There are reports in the literature with conflicting results regarding the effects of coffee on bowel function after gastrointestinal surgery. The first randomized controlled trial noted improved gastrointestinal function in patients drinking coffee without worsening of postoperative morbidity. This study was performed in 2012 by Müller et al. and included patients with malign and benign disease undergoing open or laparoscopic colectomy [16]. Müller reported shorter first bowel movement times in the coffee group, however the times to first flatus and tolerance of solid food were similar between groups. In contrast, Dulskas et al. reported diminished times to the first bowel movement and tolerance of solid food with decaffeinated coffee compared to caffeinated coffee and suggested that caffeine is not the main ingredient affecting bowel function [17]. Gungorduk et al. reported significant differences in the mean times to first flatus, first defecation, and toleration of solid food in the coffee drinking group among 114 patients undergoing surgery for gynecological malignancies [18]. In these three studies of patients following gastrointestinal or oncological surgery, coffee was given on the morning after surgery. There has been only one randomized controlled trial about the effects of coffee consumption on bowel function after cesarean section; in their study, Rabiepoor et al. started coffee consumption at 8 hours postoperatively, which is different from the present study [19]. They reported mean times to first flatus of 17.28 hours in the coffee group and 22.54 hours in the control group. This study has some limitations. Early postoperative feeding was not used in that study and oral feeding was started 24 hours after the operation. However, early feeding is recommended even in gynecological surgeries for malignant disease to decrease the hospitalization time and prevent POI risk [23]. Although cesarean section is a minor operation compared to gynecological malignancy operations, early mobilization and feeding may result in early recovery and have positive effects on breastfeeding. In addition, early time to toleration of solid food is important after cesarean section to facilitate breastfeeding. Also, in the study by Rabiepoor et al., data regarding time to toleration of solid food as well as additional analgesic and antiemetic requirements were not mentioned [19]. There was also no information regarding patient mobilization. Prolonged bedrest may enhance the risk of postoperative complications and prolong recovery [24, 25].

The main result of the present study is that the time for return of bowel function was shorter in the coffee drinking group. In previous studies, both groups of patients underwent major surgery and coffee consumption started later. In the present study, we started coffee consumption in the early postoperative period and provided early mobilization, so the mean times to first flatus, first defecation, and bowel movements were shorter than in previous reports. A number of factors, including blood loss, blood transfusion, advanced age, and increased incision size, were shown to be related to POI [26–29]. In the present study, all of these factors were similar between the two groups.

Our study has several strengths. First, it was a prospective randomized trial and the patient characteristics were similar between the two groups. Moreover, the study was performed at a single institution with the same surgical team and the same anesthetic protocol, which likely increased the validity of our results. Unfortunately, this study also has several limitations. First, blinding of the subjects postoperatively was not possible due to the nature of the study protocol. Secondly, we did not have placebo and decaffeinated control groups.

CONCLUSIONS

In conclusion, our results suggest that early coffee consumption following cesarean section contributes to the stimulation of bowel motility. Coffee is a safe, inexpensive, and welltolerated beverage, and it can be used in patients to enhance the recovery of gastrointestinal function after elective cesarean section.

Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent

Informed consent was obtained from all individual participants included in the study.

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Mode of anesthesia for cesarean delivery with pernicious placenta previa — a retrospective study

Xingxing Liu[1,2], Yuhang Zhu[2], Di Ke[3], Dexing Liu[2], Zhaoqiong Zhu[1,2]

[1]*Soochow University, Suzhou, China*
[2]*Department of Anesthesiology, Affiliated Hospital of Zunyi Medical University, Zunyi, Guizhou, China*
[3]*Department of Emergency, Affiliated Hospital of Zunyi Medical University, Zunyi, Guizhou, China*

ABSTRACT

Objectives: Anesthesia for cesarean delivery in parturients diagnosed with pernicious placenta previa remains controversial. This study aimed to review pernicious placenta previa cases to evaluate anesthetic management strategies.

Material and methods: This retrospective analysis included patients who underwent cesarean delivery (CD) for pernicious placenta previa at the Affiliated Hospital of Zunyi Medical University between December 1, 2012 and November 31, 2017. Patient demographic data, obstetric characteristics, anesthetic management, and maternal outcomes were extracted from the hospital's computerized database.

Results: In all, 61 consecutive cases of pernicious placenta previa were identified among 9512 cesarean deliveries. General anesthesia was performed on 27 of the 61 patients (44.3%). Among GA group, 16 (59.3%) had placenta accreta, 8 of whom required cesarean hysterectomy. Also, 13 of the 27 (48.1%) GA patients required transfer to the intensive care unit. The other 34 patients (55.7%) were given regional anesthesia, 9 of whom were converted to general anesthesia due to excessive bleeding and prolonged operation times. Statistical results indicated that regional anesthesia was associated with a significantly shorter operation time, less perioperative blood loss, fewer intraoperative red blood cell transfusions, and a lower incidence of complications.

Conclusions: Anesthetic management is important for parturients with pernicious placenta previa. Although regional anesthesia was our preferred method for these patients, general anesthesia is safe for patients with pernicious placenta previa who experience massive blood loss and prolonged operation times.

Key words: anesthesia; anesthetic techniques; obstetric; pernicious placenta previa; regional/general anesthesia

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INTRODUCTION

Placenta accreta is 'more common' in patients with placenta previa and a history of prior cesarean delivery (CD). Concomitant pernicious placenta previa (PPP) can lead to unmanageable, massive hemorrhaging [1, 2]. PPP was first described by Chattopadhyay et al. in 1993 [3]. It refers to the placenta previa is anterior and implanted over the prior scar, irrespective of whether there is accreta, which is a post-delivery diagnosis [4, 5].

For the past decade in China, the incidence of PPP has gradually risen because of the increased rate of CD and implementation of a more liberal two-child policy. It is a risk factor for abnormally invasive placentation, thereby increasing the number of hysterectomies performed. The reported blood loss during CD for patients with PPP is 3000–5000 mL and the rate of hysterectomy rate 55–75% [6, 7].

The number of patients with PPP admitted to our hospital is increasing every year. It is a necessary but difficult challenge for anesthesiologists to achieve good anesthesia management. The choice of anesthesia for such patients is a controversial, and the whether general anesthesia (GA) or regional anesthesia (RA) is unknown. Many anesthetists prefer GA to RA as they wish to avoid the risk of excessive bleeding and shock that may ensue with RA [8]. Thus, there has been extensive administration of GA for cesarean delivery whenever placenta previa was the indication for CD. The association of placenta previa with antepartum hemorrhage and the possibility of cesarean hysterectomy in these patients often prompts the choice of GA for CD, although

Corresponding author:
Zhaoqiong Zhu
Department of Anesthesiology, Affiliated Hospital of Zunyi Medical University, Zunyi, Guizhou, P.R. China
149#, Dalian Road, Zunyi 563000, Guizhou, China
e-mail: ganzhu_zq@sina.com

there is evidence that views may be changing. There has been an increase in the use of RA for placenta previa because of the assertion that the regional technique remains the safer option [9, 10]. There is little evidence, however, regarding the choice of anesthetic technique for CD in pregnancies complicated by PPP, especially in the presence of placenta accreta.

Because PPP is a serious, life-threatening condition resulting in significant maternal and perinatal morbidity and mortality, it is clinically relevance to evaluate mode of anesthesia utilized and whether mode of anesthesia impacts maternal outcome. We therefore performed a retrospective analysis to assess obstetric anesthesia management, including the choice of anesthesia and maternal outcomes, among parturients with PPP during a 5-year period at our university hospital.

MATERIAL AND METHODS

This study was approved by the institutional ethics committee of the Affiliated Hospital of Zunyi Medical University. Informed consent was waived owing to the retrospective nature of the study design. We performed a retrospective analysis of 61 parturients who underwent CD between December 1, 2012 and November 1, 2017 at our hospital for PPP. Inclusion criteria included (1) placenta previa, (2) at least 1 prior CD, (3) ultrasonographic evidence of placental attachment to the uterine scar. Patients for whom there were insufficient data were excluded.

The following information, extracted from the hospital's computerized database, was recorded for each patient: age, gestational age, gravidity, parity, number of prior CDs, antepartum hemorrhage, emergency vs. elective surgery, mode of anesthesia, concurrence of placenta accreta by (visual or pathological confirmation), prophylactic placement of internal iliac artery balloon catheters, intraoperative blood salvage, estimated blood loss during surgery, amount of red blood cells transfused, preoperative and postoperative hemoglobin levels, Apgar score, hysterectomy, duration of surgery, admission to the intensive care unit, intraoperative and postoperative complications, length of hospital stay.

Statistical analyses were performed using Statistical Package for Social Sciences (SPSS™), Windows version 23.0 (IBM Corp., Armonk, NY, USA). Because of the lack of agreement with normal distributions, the demographic data and obstetric characteristics are presented as medians (range) or numbers (%). The quantitative data were analyzed by the Mann-Whitney U test. Qualitative data were compared between groups using the χ^2 test. For statistical tests, a value of $p < 0.05$ was considered to indicate statistical significance.

RESULTS

Among 9512 CDs recorded during the 5-year analysis, 61 consecutive patients with PPP met the inclusion criteria and underwent CD. The incidence of PPP among all CDs was 6.4‰. Table 1 shows demographics of the population studied. The most common reason for admission was antepartum hemorrhage (n = 39). Altogether, 47 (77.05%) patients were admitted under emergency conditions.

In total, general anesthesia (GA) was utilized in 27 cases (44.26%) and regional anesthesia (RA) performed in 34 cases (55.74%). Of 34 cases under RA, 9 (14.75%) were converted to GA due to excessive bleeding, prolonged operative times, or both. Four patients required placement of internal iliac artery balloon catheters, and nine underwent intraoperative blood salvage.

Perioperative anesthesia management is outlined in Table 2. There were no differences between the two anesthesia groups regarding patient age; numbers of pregnancies, CD, or emergency cases; and baseline hemoglobin concentrations. GA was performed in 27 (44.3%) patients. More than half of these patients (16/27, 56.3%) had placenta accreta, and 8 of the 16 underwent cesarean hysterectomy. Among the 27 GA patients, 13 (48.1%) were transferred to the intensive care unit. RA was associated with higher 1-min Apgar scores and higher postoperative hemoglobin levels. Estimated blood loss was less and transfusion was required less frequently in the RA group than in the GA group.

Intraoperative and postoperative complications are summarized in Table 3. All of the women survived with no serious long-term sequelae. Two in the GA group sustained

Table 1. Principal clinical characteristics of the studies population (n = 61)

Characteristic	Outcome
Age [years], median (range)	31 (22–40)
Gestational age [weeks] , median (range)	35 (28–40)
Gravidity, n (%)	
1	0 (0)
2	8 (13.1)
3	19 (31.2)
4	21 (34.4)
4	13 (21.3)
Parity, n (%)	
1	48 (78.7)
2	11 (18.0)
3	2 (3.28)
Number of prior CDs, n (%)	
1	52 (85.2)
2	9 (14.8)
Antepartum hemorrhage, n (%)	39 (63.9)
Elective CD, n (%)	14 (23.0)
Emergency CD, n (%)	47 (77.0)

Table 2. Comparison of perioperative management with different anesthesia methods

Clinical feature	General anesthesia (n = 27)	Regional anesthesia (n = 34)
Emergency cases, n (%)	23 (85.2)	24 (70.6)
Placenta accreta, n (%)	16 (59.3)	10 (29.4)*
Duration of surgery (min), median (range)	149 (54–352)	84 (45–216)*
Estimated blood loss, mL, median (range)	3219 (300–14000)	1029 (300–3500)*
Blood product transfusion (median)		
RBC required, n (%)	27 (100)	25 (73.5)*
Red blood cells (units)	8.3 (1.5–26)	2.3 (0–6)*
Intraoperative blood salvage		
Number of cases, n (%)	7 (25.9)	2 (5.9)
The amount, mL, median (range)	607 (0–2500)	350 (0–700)
Hemoglobin concentration , median (range)		
Preoperative values [g/L]	103 (71–137)	107 (61–131)
Postoperative values[g/L]	90 (71–127)	97 (71–121)*
Apgar Score		
1 min	7 (1–10)	9 (4–10)*
5 min	9 (3–10)	10 (8–10)*
Caesarean hysterectomy, n (%)	12 (44.4)	1 (2.9)*
Admission to intensive care unit, n (%)	13 (48.1)	0 (0)*

Data are presented as: number of patients (n) and percentage (%), or median (range); *p < 0.05 for women with regional anesthesia versus general anesthesia group

Table 3. Intraoperative and postoperative complications

Complication	General anesthesia (n = 27)	Regional anesthesia (n = 34)
Intraoperative complications, n (%)		
Ureteral injury	2 (7.4%)	0 (0)
Bowel injury	0 (0)	0 (0)
Postoperative complications, n (%)		
Wound infection	1 (3.7%)	1 (2.9%)
Urinary tract infection	1 (3.7%)	0 (0)
Repeat laparotomy required, n (%)	2 (7.4%)	0 (0)
Febrile morbidity, n (%)	14 (51.9)	2 (5.9%)*
Mortality, n (%)	0 (0)	0 (0)
Days in hospital [days], median (range)	13 (4–39)	10 (5–27)

Data are presented as: number of patients (n) and percentage (%), or median (range); *p < 0.05 for women with regional anesthesia versus general anesthesia group

ureteral injuries, which were repaired without difficulty. One of these two women had a postoperative wound infection, and the other had a urinary tract infection. Among the 27 GA patients, 14 (51.9%) had a fever postoperatively.

DISCUSSION

Pernicious placenta previa (PPP) is associated with an increased risk of antepartum bleeding, postpartum hemorrhage, hysterectomy, and need for blood transfusion. Most studies report that the risk of placenta previa increases proportionately with the number of prior CDs [11–14]. The association between placenta previa and prior uterine scarring greatly increases the chance of developing placenta accreta. In the present study, the incidence of placenta accreta was 42.6%. Additionally, as the number of CD increased, the risk of the patient having PPP increased.

The optimal anesthesia technique for CD in women with PPP is controversial and clinically challenging for the anesthesiologist.

What constitutes the best anesthesia technique for CD in women with PPP is controversial, comprising a clinical dilemma for anesthetists. Kocaoglu et al.[8] advocate GA over RA for women with placenta previa to lower the incidence of bleeding. Parekh and colleagues [10] report greater use of RA compared to GA for such cases (60%) and advocate RA was associated with a significantly reduced estimated blood loss and reduced need for blood transfusion. Hong et al. [15] compared epidural anesthesia and GA in women undergoing CD for placenta previa. They found that GA resulted in lower immediate postoperative hematocrit levels. Also, the GA patients required significantly more transfusions than patients given epidural anesthesia. The authors concluded that epidural anesthesia is superior to GA for elective CD performed for placenta previa with regard to maternal hemodynamics and blood loss [15]. In a multi-institutional study, Chestnut et al. [16] found that none of the patients with continuous epidural anesthesia for elective or emergency peripartum hysterectomy required intraoperative induction of GA.

During the past 5 years at our institution, 27 parturients received GA, 16 of whom were complicated with placenta accreta, with 85% of them emergency cases. More than half of our patients (55.7%) underwent RA. Our data show that either GA or RA could be used for CD in women with PPP.

The main concerns with the use of RA for PPP by anesthetists are as follows. First, cardiovascular reflexes are impaired in all patients under extensive regional block, which may be made worse in the event of significant intraoperative hemorrhage in patients with PPP, especially those complicated with placenta accreta. Second, anesthetic management of serious bleeding in awake patients is difficult for the anesthetist and may worry the patient. These concerns can be reduced in the patients who are not actively bleeding. Well-conducted RA should improve outcomes [17].

In the retrospective analysis, mode of anesthesia was variable and likely depended on the CD indication, urgency, and the maternal volume status. Even in patients with suspicion for placenta accreta, RA use was uneventful in less urgent cases in which pre-delivery volume status was not compromised. If hemorrhaging occurs intraoperatively and the patient becomes hemodynamically unstable, conversion to GA may be necessary. Among the 61 parturients in this study, 9 required conversion from RA to GA. Those who received GA, whether primary or by conversion from RA, had greater blood loss, greater transfusion requirement, and lower postoperative anemia. We cannot distinguish between selection bias and any true association between use of GA and these higher morbidity outcomes.

For women with PPP and suspected placenta accreta, surgical management can be difficult and requires multidisciplinary efforts to minimize maternal complications. Some suggest preoperative placement of balloon catheters in the internal iliac arteries, which could potentially decrease blood loss and provide optimum exposure of the operative field [18]. Among our 61 patients, 4 (6.6%) underwent prophylactic placement of internal iliac artery balloon catheters. Our institution initiated use of the technique last year, and the current evidence is based on small retrospective studies. Large studies or randomized controlled trials are needed to demonstrate the efficacy of prophylactic placement of internal iliac artery balloon catheters.

PPP can cause serious bleeding. The largest blood loss from a single patient in our group was 14,000 mL. Intraoperative blood salvage has been used in obstetric patients. For this purpose, during CD after placental delivery, blood is suctioned from the surgical site, collected, and processed through a cell-salvage machine that yields a washed red blood cell product for transfusion. To date, no prospective randomized studies have evaluated the safety of intraoperative blood salvage in obstetrics, although the review of more than 400 case reports by Allam et al. [19] reveal no complications leading to poor maternal outcomes that were directly attributable to the use of this technique. Moreover, Goucher et al. [20] stated that cell salvage is cost-effective in patients with predictably high rates of transfusion. There were no complications in our nine patients who underwent intraoperative blood salvage.

In conclusion, we found that the incidence of PPP was 6.4‰ of all cesarean deliveries in our teaching hospital. We also found that the choice of anesthetic depends on the CD indication and urgency as well as the maternal volume status. Also, RA could be used in patients with suspected placenta accreta. Finally, significant hemorrhage is likely to require obstetric hysterectomy, and conversion to GA may be necessary.

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Unscarred uterine rupture and subsequent pregnancy outcome — a tertiary centre experience

Nurullah Peker[1], Edip Aydın[2], Mehmet Sıddık Evsen[1], Fatma Nur Hançer[2], Muhammet Hanifi Bademkıran[2], Serhat Ege[2], Bekir Kahveci[2], Talip Karaçor[3], Talip Gül[1]

[1]Department of Obstetrics and Gynecology, Dicle University, Faculty of Medicine, Diyarbakır, Turkey
[2]Department of Obstetrics and Gynecology, Health Sciences University, Gazi Yasargil Training and Research Hospital, Diyarbakir, Turkey
[3]Department of Obstetrics and Gynecology, Adıyaman University, Faculty of Medicine, Adıyaman, Turkey

ABSTRACT

Objectives: The aim of this study was to investigate the incidence, etiology and obstetric outcomes of rupture in unscarred uterine rupture and in those with a history of uterine rupture

Material and methods: The hospital records of women who had delivered between May 2005 and May 2017 at a tertiary center were examined retrospectively. Data on patients with unscarred uterine rupture in pregnancy who had undergone fertility-preserving surgery were evaluated.

Results: During the study period, 185,609 deliveries occurred. Of those, unscarred uterine rupture has occurred in 67 women. There were no ruptures reported in nulliparous women. The rupture was observed in the isthmic region in 60 (89.6%) patients and in the fundus in 7 (10.4%) patients. Thirty-eight (56.7%) patients had undergone a total or subtotal hysterectomy, and 29 (43.3%) patients had received primary repair. Ten patients had reconceived after the repair. Of these, eight patients who had a history of isthmic rupture, successfully delivered by elective C-section at 36–37 wk. of gestation, and two experienced recurrent rupture at 33 and 34 wk. of gestation, respectively. Both patients had a history of fundal rupture, and their inter-pregnancy interval was 9 and 11 mo., respectively.

Conclusions: The incidence of rupture in unscarred pregnant uteri was found to be one per 2,770 deliveries. Owing to the high morbidity, regarding more than half of the cases with rupture eventuated in hysterectomy, clinicians should be prudent in induction of labour for multiparous women since it was the main cause of rupture in this series. Short inter-pregnancy intervals and history of fundal rupture may confer a risk for rupture recurrence. Those risk factors for recurrence should be validated in another studies.

Key words: unscarred uterine rupture; recurrent uterine rupture; uterine repair; timing of delivery; pregnancy outcome

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INTRODUCTION

Unscarred uterine rupture (UUR) in pregnancy is associated with a high risk of maternal and neonatal mortality and morbidity rates [1]. Although it is a rare event, the overall rate of UUR ranges from 1/5700 to 1/20,000 pregnancies [2–5]. Rupture can be caused by traumas, including abdominal trauma and labour induction, or it can occur spontaneously and be associated with grand multiparity, malpresentation, placental invasion and prolonged labour [6, 7].

In UUR cases, the goals of surgery is to control the haemorrhage, to identify injury of other intra-abdominal organs (urinary tract, etc.) and to minimize early post-surgical morbidity. The ruptured uterus must either be removed or repaired. The decision to perform a hysterectomy is made according to a combination of factors, including the patient's desire for future fertility, the extent of the uterine injury, intra-operative haemodynamics and anaesthetic stability and the skill of the surgeon in complicated UUR cases [8, 9].

There is no consensus in the literature on the optimal timing of conception and timing of elective cesarean delivery in patients with a history of UUR who underwent uterus-preserving surgery in the past. The aim of this study was to investigate obstetric outcomes of UUR and optimal timing of elective cesarean delivery and recurrence of uterine rupture (UR) in patients with a history of UUR.

Corresponding author:
Peker Nurullah
Department of Obstetrics and Gynecology, Dicle University, Faculty of Medicine, 21070, Diyarbakir, Turkey
e-mail: dr_nurullah_peker@hotmail.com, tel.: +90 412 248 80 01, fax: +90 412 241 10 46

MATERIAL AND METHODS

The hospital records of women who had delivered between May 2005 and May 2017 at the obstetrics clinic of Diyarbakir Health Sciences University, Gazi Yasargil Training and Research Hospital were examined retrospectively. Prior to the study, approval was obtained from the local ethics committee of Dicle University School of Medicine (ethics committee approval no. 40).

UUR is defined as a full thickness separation of uterine wall and the overlying serosa. Incomplete UR cases with serosa intact, patients who had a history of previous cesarean delivery, and patients diagnosed with rupture in an external centre and referred to our clinic were excluded. UUR was diagnosed with high suspicion index including rapid fetal heart rate changes, acute or constant abdominal pain, uterine tenderness and loss of station and confirmed intraoperatively as extracted from the medical records.

Data on the age, parity number, birth weight, gestational week, cause and site of rupture, duration of surgery, length of hospital stay, amount of erythrocyte suspensions transfused, maternal and perinatal mortality and treatment modalities were noted.

In some patients, Oxytocin 1–2 mIU/min was used as the beginning dose for labour induction and augmentation. In some of these patients, it was detected that oxytocin was given more than the determined dose. As a result, hyperstimulation findings were seen in the non-stress test. This situation was defined as uncontrolled labour induction. The mismatch between the size of the fetal head and the maternal pelvis in the vaginal examination and as a result the failure to progress in labour was defined as cephalopelvic disproportion. Mothers over 35 years of age were taken as advanced maternal age.

Total or subtotal hysterectomy was performed in patients with unstable hemodynamics. Uterus-preserving surgery was performed in patients with stable hemodynamics and desire for future fertility. In uterus-preserving surgery, the rupture area was repaired primary.

Table 1. Demographic, obstetric and clinical data of the patients

Characteristics	Mean ± SD	Min–Max
Age (y)	35.28 ± 6.83	18–47
Parity	5.45 ± 2.75	1–13
Birth weight (g)	3,344 ± 953	480–4750
Gestational week	38.01 ± 4.20	21–42
Hospitalization duration (d)	4.9 ± 2.1	1–11
Duration of surgery (min)	97.8 ± 39.9	60-240
Amount of transfusion (unit)	4.1 ± 2.5	0–13

SD — standard deviation

Data on patients who had undergone fertility-preserving surgery were accessed, and their subsequent pregnancy status, the timing of delivery and occurrence of recurrent ruptures were recorded after obtaining informed patients consent.

Statistical analysis

Data were analysed using SPSS 22 for Windows (SPSS Inc., Chicago, IL, USA). The normal distribution of the data was tested using the Shapiro–Wilk test. Data are expressed as mean ± standard deviation and minimum, maximum and percentage, as appropriate.

RESULTS

Of 185,609 delivery during the study period, 67 of them culminated by UUR. Accordingly, the incidence was found to be as one in 2,770 pregnancies. Demographic, obstetric and clinical data of the patients with UUR are shown in Table 1 and 2.

Twenty (30%) pregnant women with UUR were admitted with a completely dilated cervix and taken to the delivery room for an emergency C-section. These patients had not been appropriately followed up during the antenatal period. Furthermore, they had been admitted after unsuccessful attempts at in home-deliveries with the help of a local midwife. Upon admission, there was no foetal heart beat in 16 of these 20 patients. Among these patients, three had foetuses with advanced hydrocephalus, two had a transversely located foetus with a vaginally prolapsed arm, and one had a breech presentation.

Thirty-eight (56.7%) patients had undergone a total or subtotal hysterectomy and 29 (43.3%) patients had received primary repair. Twelve patients had additional sal-

Table 2. Demographic, obstetric and clinical data of the patients

Characteristics		n
Age	< 35	31 (46.3%)
	≥ 35	36 (53.7%)
Parity	< 5	26 (38.8%)
	≥ 5	41 (61.1%)
Site of rupture	Isthmic region	60 (89.6%)
	Fundus	7 (10.4%)
Induction of labor	Yes	45 (67.2%)
	No	22 (32.8%)
Cause of rupture	Uncontrolled labour induction	32 (47.8%)
	Cephalopelvic disproportion	26 (38.8%)
	Malpresentation	9 (13.4%)
Type of surgery	Total or subtotal hysterectomy	38 (56.7%)
	Primary repair	29 (43.3%)

pingo-oophorectomy due to UR with adnexal involvement and 25 patients had required hypogastric arterial ligation. A repair procedure and bilateral tubal ligation had been performed in two patients. The adverse events were as follows: intra-operative bladder injury (n = 5); absence of a foetal heart beat (n = 21), new-born deaths (n = 2) and maternal deaths due to an uncontrolled haemorrhage (n = 2).

Ten of the 29 patients had reconceived after UR repair. Of these, eight patients who had a history of isthmic rupture delivered by an elective C-section at 36–37 wk. of gestation with no complication, and the mean inter-pregnancy interval of the remaining eight patients was 36 mo. (range: 24–48 mo.). The other two patients experienced recurrent ruptures at 33 and 34 wk of gestation, respectively. These two patients had a history of fundal rupture, and their inter-pregnancy interval was 9 and 11 mo., respectively. Figure 1 shows the conception status of the 29 patients following uterine repair.

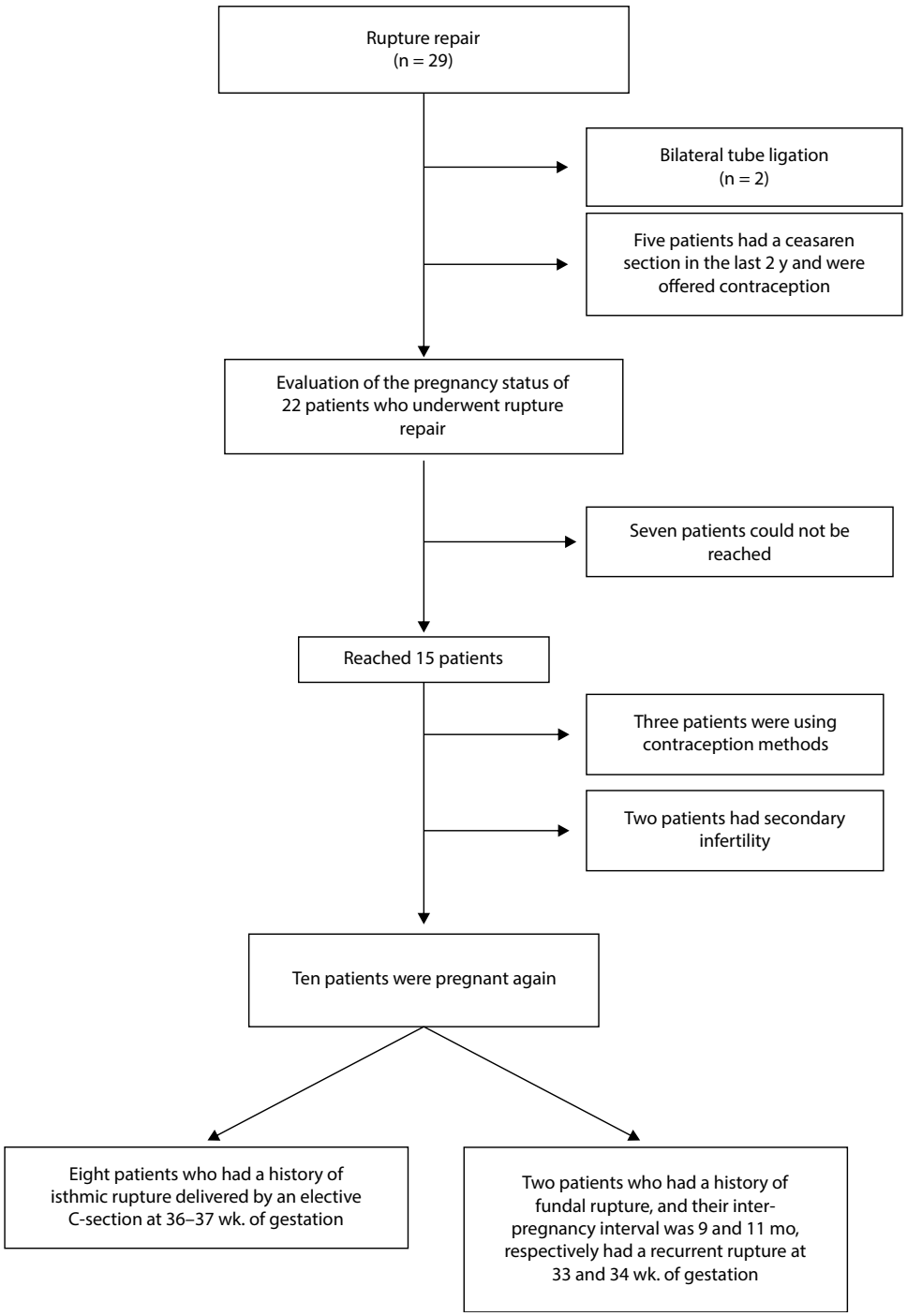

Figure 1. Conception status of the patients after uterine repair

DISCUSSION

In this study, clinical findings of UUR, and subsequent pregnancy outcomes of these patients who underwent uterine preserving surgery were examined. It was observed that in most of the patients' rupture occurred in the isthmic region and hysterectomy was performed in many of those. The patients who underwent uterus-preserving surgery with primary repair were evaluated for their next pregnancy. It was found that the patients with UUR from the isthmic region had a caesarean section without complications, and the patients with UUR from the fundus developed recurrent rupture again in the early weeks.

Previous studies reported that UUR occurred in one in every 5,700–20.000 pregnancies [2–5]. In the present study, the incidence of UR not associated with previous uterine surgery was 1/2770. This figure seems to be higher than that reported in the literature. Advanced maternal age and grand multiparity, both of which are common in southeast Turkey may have contributed to the increased incidence of UR. In addition, 20 of the patients who presented to our clinics, a referral centre for the region, with UR did so only after attempting to deliver at home, traditionally. This may have been a contributory factor to the high incidence of UR in this study.

According to the literature, the risk factors for UUR are as follows: high parity, use of uterotonic drugs, advanced maternal age, dystocia, macrosomia and possibly short inter-pregnancy intervals [1, 7, 8, 10]. In agreement with the literature, the causes of the UUR's in the present study included advanced age, grand multiparity, uncontrolled labour induction, cephalopelvic disproportion and malpresentation. In addition, in several patients, more than one risk factor was responsible for UR, as was reported in a previous study [11]. The mean gestational age was 38.01 wk. in the present study, and the patients presented to the clinic during labour or in late pregnancy. These findings are in accordance with those in the literature [12].

Previous studies reported that the isthmic region was the most common site of UR [13, 14]. Similarly, the isthmic region was the most common site of UR in the present study. This situation is attributable to the cervix becoming thinner during labour and besides, accommodating isthmic region having fewer contractile cells as compared with that of the upper uterine region [15].

UUR is reported to cause several maternal complications and sequelae, such as severe haemorrhages, bladder lacerations, hysterectomies and mortality [16–18]. Also previous studies pointed to an association between UR and foetal mortality and morbidity [16, 19]. Similarly, UR culminated in adverse maternal and neonatal outcomes in the present study. In terms of intra-operative complications, five patients experienced bladder injuries, and several patients required a blood transfusion because of a severe haemorrhage. An uncontrolled haemorrhage was responsible for mortality in two patients, both of whom were advanced aged grand multiparous patients who presented to the hospital during labour. In the present study, 21 foetuses had no heart beat at the time of maternal presentation to the clinic, and two foetuses died in the post-natal period.

A hysterectomy, whether total or subtotal, is the main surgical procedure adopted in cases of UR. Primary repair is an option for patients desiring future fertility [14]. In this study, the most frequently adopted surgical procedure was a total or subtotal hysterectomy because of the advanced maternal age, grand multiparity and accordingly a lack of desire for future pregnancy and the severity of uterine injury. Hysterectomy at full dilatation can be a challenging procedure [20]. UUR with a completely dilated cervix and subsequently underwent to emergency C-section was observed in 30% of women with UUR in the current study. On the other hand, 29 (43.3%) younger patients with a desire for future fertility underwent uterine repair. Twenty-five patients also required hypogastric arterial ligation for the management of a haemorrhage. In such cases, it should be kept in mind that hypogastric arterial ligation may help to achieve haemostasis [21].

According to the literature, the risk of recurrent UR is linked to the site of rupture as the highest risk is linked to fundal injuries [22]. Previous studies reported the risk of recurrent rupture as 22–100% in patients who reconceived after uterine repair [23, 24]. In a study on five patients with UR, Lim et al. [23] reported that all the patients delivered by a C-section, with no recurrent ruptures. However, the small size of their study population means it is not possible to draw robust conclusions. A previous study recommended an inter-pregnancy interval of at least 18 mo. for women who desired fertility following the repair of an unscarred uterus that had ruptured during pregnancy [25]. In the present study, both patients in whom UR recurred had a short inter-pregnancy period. We agree that a short inter-pregnancy interval may be a major risk factor for recurrent ruptures. Chibber et al. [24] reported that 24 of 44 rupture cases had undergone a repair procedure and that 22 of these 24 cases had reconceived. Furthermore, 20 of these 22 cases delivered by a planned C-section, with no maternal or foetal complications. The remaining two cases had no proper follow up during the antenatal period and experienced recurrent UR at 32 and 35 wk. of gestation, respectively. However, no information has been given as to where these two patients had ruptures in their previous pregnancy. In this study, there were no complications in patients with a previous history of fundal rupture in subsequent pregnancies. However, it was determined that both patients who had ruptured from the isthmic region developed recurrent rupture in early gestational weeks.

This study has some limitations, primarily that it is retrospective study, which could be open to selection bias. Likewise, it lacks data on body mass index, diabetes mellitus, and uterine pathologies (i.e., myoma uteri). In addition, that various surgeons performed the operations and might limit the real complication rate because there was no specific information regarding the surgeons' levels of experience. Finally, seven patients who could not be reached after UUR repair were seen as deficiency in our results. The strengths of the study include a very broad cohort of evaluated cases despite being a single-center study. Further, the evaluation of the next pregnancy outcomes of patients who underwent uterus-preserving surgery makes the study powerful.

There is no consensus in the literature on the optimal timing of conception and timing of elective cesarean delivery in patients with a history of UUR who underwent uterus-preserving surgery in the past. The timing of delivery of a subsequent pregnancy in UUR cases should be considered carefully, as recurrent rupture may occur early in the third trimester. Obstetricians might consider reducing the risk of recurrent ruptures by recommending a C-section and scheduling the delivery before the onset of labour. Authors postulate that a C-section at 36–37 wk. of gestation may be recommended for patients with a history of isthmic ruptures. To avoid potential early recurrent rupture, an earlier C-section at 32–33 wk. of gestation after completion of foetal lung maturation may be recommended for patients with a history of fundal ruptures and those with short inter-pregnancy intervals. These recommendations should be cautiously approached due to a current lack of data and more research is urgently needed.

CONCLUSIONS

UUR constitutes a major risk factor for fetomaternal morbidity and mortality. The incidence of rupture in unscarred pregnant uteri was found to be one per 2,770 deliveries. Owing to the high morbidity regarding more than half of the cases with rupture eventuated in hysterectomy, clinicians should be prudent in induction of labour for multiparous women since it was the main cause of rupture in this series.

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Ultrasound evaluation of a bilobed placenta with 'battledore cord insertion' — a report of an unusual case

Sylwia Dabkowska[1], Grzegorz Panek[1], Julia Bijok[1], Michal Ciebiera[2], Tomasz Roszkowski[1]

[1]*The Center of Postgraduate Medical Education, Department of Gynecologic Oncology and Obstetrics, Warsaw, Poland*

[2]*The Center of Postgraduate Medical Education, II Department of Obstetrics and Gynecology, Warsaw, Poland*

A bilobed placenta (also bipartite placenta), is a variation in placental morphology and refers to a placenta separated into two almost equal-sized lobes. The estimated incidence is approximately 4% of all pregnancies [1]. It is thought to result from localized placental atrophy as a consequence of poor decidualization or vascularization of a part of the uterus (dynamic placentation theory) and may be sonographically visualized as two separate placental discs of nearly equal size [2, 3]. The cord is usually attached to a thin connecting rim of chorionic tissue which bridges the two lobes. Less commonly, the cord may insert into one of the lobes. In such a situation, the cord insertion site is too close to the placental margin (usually defined as < 2 cm, although some references define it as < 1 cm). A marginal cord insertion, also known as a *battledore placenta,* may confer a slight increase in the risk for adverse pregnancy outcomes like placental abruption, placenta previa, preterm labor, fetal distress and intrauterine growth restriction [2–4]. A bilobed placenta with abnormal cord insertion is even less common. This condition may be detected as early as in the first trimester, especially during standard first-trimester screening, as in most centers this test is mandatory. Antenatal ultrasound is considered to have variable sensitivity (approx. 69–100%) but a high specificity (even up to 99–100%) to reveal abnormal placental cord insertion sites. The technique is extremely important and Color Doppler is known as a great aid in the identification. As the condition is associated with an increased incidence of various severe obstetric complications, like those presented above, as well as postpartum hemorrhage due to retained placental tissue [2, 3], a cesarean section is often considered to avoid the risk.

In this clinical vignette we present a rare case of 'battledore cord insertion' in a woman with bilobed placenta.

A 32-year-old secundipara (1 uncomplicated pregnancy, delivered by cesarean section due to the risk of acute fetal asphyxia during labor) woman was referred to our perinatal center at 15 weeks for a detailed ultrasound because of a band-like structure crossing the gestational sac. During the 11^{+0} to 13^{+6} ultrasound exam this band was apparently dividing the sac with an area of fluid laterally and appeared to communicate with the fetus. It was suspected that the fetus is attached to this band-like structure in its neck area (Fig. 1). A transabdominal and transvaginal consulting sonography was performed with the use of new generation high resolution sonographic systems. A 15-week-size fetus was identified with appropriate growth and normal-appearing anatomy. Fetal parts moved freely around the band. A thick chorionic band, which communicated with the placenta, was described. The placenta was visible on the posterior wall of the uterus. Color Doppler showed the blood flow within the band. The patient returned 6 weeks later for additional scanning. Subsequent ultrasound exam revealed two separate almost equal-sized placental lobes on the anterior and posterior uterine wall, with placental cord insertion at the margin of the posterior lobe. Fetal biometry proved consistent with dates at 21-week size. A thorough fetal anatomy survey revealed no structural anomalies. Later during this pregnancy we performed a control ultrasound examination once a month to exclude intrauterine growth restriction, a progress to velamentous cord insertion or vasa previa occurrence. The patient delivered a healthy female neonate at 38 weeks of pregnancy via elective cesarean due to abnormal placenta formation and the increased risk of fetal complications (*e.g.* risk of vascular rupture and fetal hemorrhage during labor). During the post-surgical examination a bilobed placenta with marginal cord insertion and vessels branching over the fetal surface of the placenta was confirmed (Fig. 1).

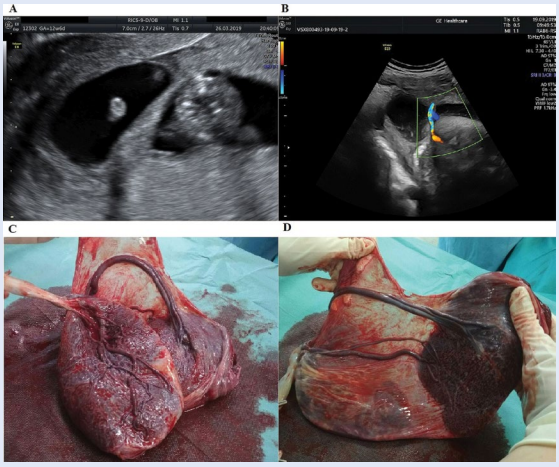

Figure 1. A. 12 weeks of gestation, transvaginal scan,. Anterior and posterior placental lobes with visible band/septum. Fetus on the right (neck area); B. 38 weeks of gestation, transabdominal scan. Anterior and posterior placental lobes with visible vessels in Doppler imaging; C. 38 weeks of gestation, bilobed placenta with atypical cord insertion (large caliber vessels) after cesarean section; D. 38 weeks of gestation, bilobed placenta with atypical cord insertion (large caliber vessels) after cesarean section — different perspective

The placenta plays a crucial role in the maternal-fetal environment throughout the pregnancy. However, it is often overlooked during a routine antenatal imaging evaluation. Seemingly, several features should be particularly noted during scanning. According to Ebbing et al. (2013) [5] the prevalence of velamentous and marginal insertions of the umbilical cord was associated with an increased risk of adverse perinatal outcomes including fetal hemorrhage, especially with velamentous insertion. Furthermore, marginal cord insertion below 0.5 cm from the placental edge may progress to velamentous cord insertion later in pregnancy [3].

To conclude, when a bilobed placenta with the accessory lobe in the lower part of the uterus is visualized via ultrasound scanning, careful ultrasound evaluation for vasa previa and velamentous cord insertion should be performed to reduce the risk of adverse perinatal outcome. In those cases a planned cesarean section should be considered to reduce the risk of fetal hemorrhage during labor.

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Corresponding author:
Michal Ciebiera
The Center of Postgraduate Medical Education, II Department of Obstetrics and Gynecology
80 Cegłowska St, 01–809 Warsaw, Poland
e-mail: michal.ciebiera@gmail.com

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Unusually high plasma values of many tumour markers in a patient with idiopathic pulmonary fibrosis

Leszek Gottwald[1,2], Mateusz Pajdzinski[2], Wojciech J. Piotrowski[3], Sebastian Majewski[3], Piotr Sieroszewski[4], Jacek Fijuth[1,2]

[1]Department of Radiotherapy, Chair of Oncology, Medical University of Lodz, Poland
[2]Department of Teleradiotherapy, Regional Cancer Centre, Copernicus Memorial Hospital of Lodz, Poland
[3]Department of Pneumology and Allergy, I Chair of Internal Medicine, Medical University of Lodz, Poland
[4]Department of Fetal Medicine and Gynaecology, I Chair of Obstetrics and Gynaecology, Medical University of Lodz, Poland

A 72-year-old patient suffering from idiopathic pulmonary fibrosis (IPF) diagnosed in 2009, presented in October 2018 at the Gynaecologic Cancer Outpatient Clinic. The patient was diagnosed due to unusually high plasma values of CA 125 (254 U/mL), HE4 (184 pmol/L), CA 15.3 (69.5 U/mL), CA 19.9 (63 U/mL) and CYFRA 21.1 (3.8 ng/mL). The plasma levels of CEA (2.51 ng/mL) and SCCAg (1.3 ng/mL) were not elevated. The patient presented with no abnormal symptoms from genital organs. A computed tomography of abdominal cavity and the pelvis did not reveal any presence of malignant neoplasm. The chest CT showed progression of the IPF with a presence of reticulation„honeycombing" (Fig. 1) and traction bronchiectasis of distribution typical for usual interstitial pneumonia consistent with the diagnosis of IPF. The progression of lung fibrosis was also documented by lung function tests which showed loss of forced vital capacity of 310 mL (11% drop of predicted value) in the period of 12 months. CT scans did not reveal any radiological symptoms of malignancy. After a four-week and three month follow-up, plasma levels of previously elevated markers were tested again and the results were similar to the previous ones: CA125 (253 U/mL and 258 U/mL), HE4 (208 pmol/L and 206 pmol/L), CA15.3 (67.2 U/mL and 69.5 U/mL), CA 19.9 (54.1 U/mL and 66.5 U/mL), CYFRA 21.1 (3.8 ng/mL and 4.3 ng/mL), CEA (2.37 ng/mL and 2.83 ng/mL) and SCCAg (1.4 ng/mL and 1.8 ng/mL). After a one year follow-up, further progression of IPF without symptoms of neoplastic disease is observed.

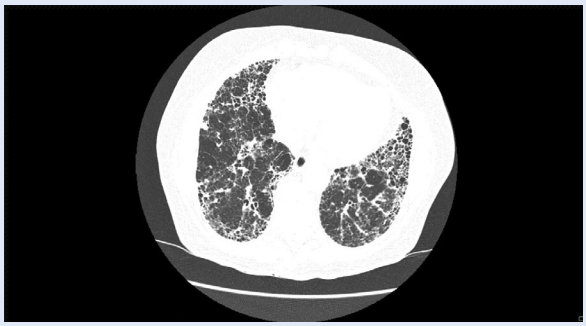

Figure 1. High-resolution computed tomography scan of the IPF

The IPF is defined as a disease of unknown origin which springs from interstitial pneumonia. It leads to a chronic, irreversible fibrosing of the lungs. The process of fibrosis does not occur in other tissues and is limited to the lungs. High resolution computed tomography is the recommended imaging technique to make the diagnosis. Clinical symptoms are nonspecific and unusually high plasma values of some tumor markers e.g. CA125 can be seen, which can lead to suspicion of adnexal cancer [1, 2].

Gynaecologic patients presenting elevated plasma levels of CA125 and HE4 only if adnexal cancer is excluded other reasons for high levels of these markers can be considered. The role of modern imaging techniques in patients with IPF, especially computed tomography in the differentiation between progression of pulmonary fibrosis and adnexal cancer, is crucial and the value of serum tumour markers assessment is limited. If no adnexal tumour is diagnosed careful follow-up is required.

In our patient the progression of IPF, an extremely rare condition in gynaecologic practice, was the reason for the elevated plasma levels of the CA125, HE4, CA19.9, CA15.3 and CYFRA 21.1. It is known, that the tumour markers CA125, CA19.9, CA15.3 and CYFRA 21.1 can accurately characterize severity of the IPF [3–5]. A review of the English literature in Medline base by searching the items idiopathic pulmonary fibrosis and HE4 showed no one items. Our case is the first report describing the relationship between the IPF and HE4.

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Corresponding author:
Leszek Gottwald
Department of Radiotherapy, Chair of Oncology, Medical University of Lodz, Poland; Department of Teleradiotherapy, Regional Cancer Centre, Copernicus Memorial Hospital of Lodz
4 Paderewskiego St, 93–509 Lodz, Poland; e-mail: leszek.gottwald@umed.lodz.pl

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