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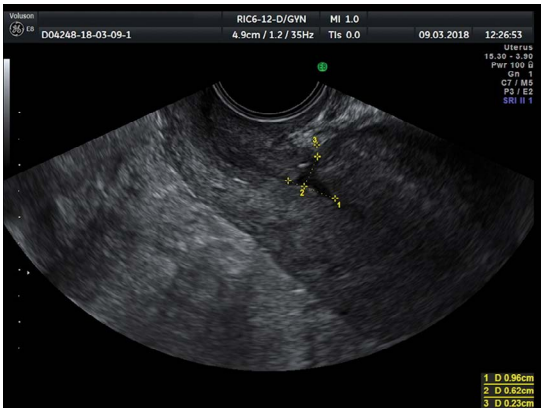

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The comparison of two methods in cervical smear screening — which method is better for smear adequacy rates?

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ABSTRACT

Objectives: In the cervical smear screening test as a sample collection method for liquid-based thin layer cytology, classically the collecting device is placed into a liquid fixative solution and vigorously swirled or rotated ten times in the solution and the collection device is removed from the solution. In this study, a plastic smear brush was used as the collection device. After the cervical cell sample was obtained, the smear brush was detached from the stick and left in the solution and given to the laboratory. Our aim in the study is to examine whether smear inadequacy rates have decreased with the method used in the study compared to the classical method.

Material and methods: While the classical technique which the collecting device is placed into a solution and mixed and removed from the solution is defined as Method 1. The technique used in the study was defined as Method 2. The cervical smear screening test results obtained by two different methods in two consecutive time periods were analyzed. The two methods were compared using chi-square test in terms of smear inadequacy.

Results: A total of 2129 test results, including 1129 smears in Method 1 and 1000 smears in Method 2 were examined. The mean ages of the patients tested in both methods were similar (36 ± 6.1 and 37 ± 6.7). Abnormal test result rate was similar for Method 1 and Method 2 (5.8% vs 4.9%, respectively). The inadequate sample rate was higher in Method 1 than Method 2 (8.3% vs 2.1%, respectively).

Conclusions: The study showed that leaving the smear brush in the solution is a better way to reduce the inadequacy sample rates. This result may guide clinicians about smear techniques.

Key words: cervical smear; inadequacy rates; liquid-based cytology; thin prep

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INTRODUCTION

Cervical cancer is the second most common cause of cancer death in women worldwide [1]. The screening test of the cervical smear (Pap smear) has led to a dramatic decrease in the incidence of cervical cancer in the past 60 years [2]. Nevertheless, according to the 2020 cancer report of the World Health Organization (WHO), more than half a million women are diagnosed with cervical cancer worldwide annually [3].

There are two main cervical smear techniques, the conventional technique and the liquid-based technique. These have been described as screening tests for cervical invasive or preinvasive lesions [4]. In the conventional Pap smear technique, the cervical swab sample taken with a brush is involved in direct transfer to the microscope slide for evaluation. This method has an inadequacy rate ranging from 5% to 25% according to studies [5–9]. Causes such as drying in the air, bad fixation, blood, inflammation, thick areas and foreign body are the causes of smear failure for conventional pap smear. The liquid-based technique was approved by the Food and Drug Administration in May 1996 as an alternative to traditional conventional smear [10]. Within the last two decades, SurePath and ThinPrep (both liquid-based cytology (LBC) tests] have replaced conven-

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tional cytology (CC) as the primary test method in cervical cancer screening programs [11]. With ThinPrep, a cervical specimen is collected using a Cervix Brush, and the brush is rinsed in a vial with a methanol based preservative fluid. Cells are released by pushing the brush to the bottom, forcing the bristles apart, and swirling the brush into the fluid. Subsequently, the brush is discarded. At the laboratory, cells are isolated from the fluid by vacuum filtration and are transferred to the slide using air pressure for adherence [11]. The main cause of smear inadequacy for this technique is the scarcity of cervical squamous cells in the smear sample. According to general recommendation for thin prep, the collecting device is placed into a liquid fixative solution and vigorously swirled or rotated ten times in the solution, then the brush is discarded [11, 12]. We identified this method as "Method 1" in our study. Instead of removing the smear brush, we left the brush in the solution in the smear box and identified this as "Method 2". Our goal was to examine whether this was effective in reducing smear inadequacy. There are many studies about cervical cytology sample collection devices [13–15]. However, we did not find a study in literature comparing leaving the brush in solution with removing the brush.

MATERIAL AND METHODS

Ethics committee approval was received for this study from the Istanbul Training and Research Hospital (number: 1880 date: 28 June 2019). In this study, two consecutive cross-sectional cohort smear results were examined. Within the last two decades, SurePath and ThinPrep have replaced conventional cytology as the primary test method in cervical cancer screening programs, so we prefer the liquid base cytology in our hospital. In our clinic, Method 1 is used as recommended in the literature. For this study, smear screening test was performed with Method 2 for a specified time period. The study was designed as prospective cross-sectional observational. Samples were obtained from patients who applied to the gynaecology outpatient clinic and required routine smear screening testing. With ThinPrep, a cervical specimen is collected using a Cervix Brush, and the brush is rinsed in a vial with a methanol-based preservative fluid (PreservCyt Solution 20 ml, Hologic Inc., Marlborough, USA). Cells are released by pushing the brush to the bottom, forcing the bristles apart, and swirling the brush into the fluid. Subsequently, the brush is discarded. At the laboratory, cells are isolated from the fluid via vacuum filtration and are transferred to the slide using air pressure for adherence with (ThinPrep 2000 Processor, Hologic Inc., Marlborough, MA, USA). Cell samples for cervical cytology were obtained during the speculum examination and a swab sample from the uterine cervix was obtained using cervical brush. Next we rotated the brush 180 degrees to obtain a sample if there was no inflamed discharge, bleeding, gross tumor. Gel lubricant on the speculum or on an examiner's hand before performing a Pap test is commonly thought to interfere with the results of cervical cytology. So no lubricants were used during sampling. A sterile medical disposable vaginal cervical cytology sampling brush was used as a product for sampling (Fig. 1). The smear brush was vigorously swirled or rotated ten times in the solution and then it was then removed (Method 1). In Method 2, once disconnected from the handles, the brush heads were deposited into the vial containing liquid preservative (not removed). The test results obtained with both methods were examined by our pahtology clinic.

Figure 1. Disposable plastic smear brush

Statistical analysis was performed using the IBM SPSS Statistics 21.0 software. Group differences were analyzed using the chi-square test. A p-value < 0.05 was considered to indicate statistical significance.

RESULTS

Initially, Method 1 was performed in gynaecology performing rooms for three months and then the second stage of the study was carried out with Method 2 in gynaecology performing rooms for three months in our hospital.

Table 1. Comparison of smear screening methods

Feature	Method 1	Method 2	P value
Number	1129	1000	
Age [years], mean ± SD; min–max	36 ± 6.1; 21–67	37 ± 6.7; 19–63	0.654
Inadequacy of smear	94 (8.3%)	21 (2.1%)	0.001
Abnormal cytological findings, n (%)	66 (5.8 %)	49 (4.9%)	0.186
ASC–US	37	24	
AG–US	1	–	
LGSIL	18	19	
HG–SIL	9	4	
ASC–H	1	2	

SD — standard deviation; ASC-US — atypical squamous cells of undetermined significance; AG-US — atypical glandular cells of undetermined significance; LGSIL — low grade squamous ıntraepithelial lesions; HGSIL — high grade squamous ıntraepithelial lesion; ASC-H — atypical squamous cell cannot exclude HSIL

A total of 2129 test results were examined. Of these, 1129 were obtained with Method 1 and 1000 with Method 2. The mean ages of the patients tested in both methods were similar (36 ± 6.1 and 37 ± 6.7) (Tab. 1). The rate of abnormal test results were 5.8% in Method 1 and 4.9 in Method 2. Details of the abnormal results are shown in Table 1.

The inadequate smear result rate was 8.3% in Method 1 and 2.1% in Method 2. The reason for the inadequacies was the scarcity of cervical squamous cells in the smear sample in all cases.

DISCUSSION

In this study, two different methods for sample collection in the liquid based cervical cancer screening test were compared in terms of smear inadequacy. As the first method, the smear brush is immersed in the solution, swirled and then removed (Method 1). Secondly, the smear brush stick is left in the solution, which is the method that was tested in this study (Method 2). The results support that Method 2 is more advantageous than Method 1 in terms of smear adequacy rates. According to the results of more than two thousand smears in this study, Method 2 was calculated to have four times lower smear inadequacy rate (8.3% vs 2.1%).

Evaluation of specimen adequacy is considered by experts to be the most important quality assurance component of the Bethesda system [16]. Satisfactory cervical cytology is defined by the number of squamous cells in the sample. According to this study, leaving the smear brush in solution and delivering it to the pathology laboratory was advantageous in terms of squamous cell number. This method may provide sufficient time for the squamous cell samples taken from the cervix to pass into the solution because the smear brush remains in the solution until the pathologist examination. In the classical method, the smear brush is immersed in solution, shaken, and then removed from the solution. Cervical cell samples must pass into the solution from the smear brush within a period of time for these procedures. Sufficient time for cervical squamous cell pass to the solution may not be given with this method.

Our limitations were that all materials could not be collected from the same obstetrician and also not examined from the same pathologist. It was a result of the large patient numbers of this study.

In conclusion, the study showed that leaving the smear brush in the solution is a better way to reduce the smear rate. These results need to be supported by randomized controlled trials. The results of this study can give clinicians an idea about the smear screening test sample collection method. Clinicians or screening test sample collectors can benefit from the results of this study on the smear screening test sample collection method. Also, when collecting smears again for cases reported as inadequate sample, the method that this study finds advantageous can be used.

Conflict of interests

The authors declare that they have no conflict of interests.

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The analysis of vaginal hysterectomy results depending on the uterine size

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ABSTRACT

Objectives: Vaginal hysterectomy is one of the oldest but still rarely used minimally invasive techniques. Although new surgical methods making use of robots in laparoscopy have been introduced recently, when compared with vaginal hysterectomy, these approaches do not offer significant benefits for the patients and the doctors operating on them.

The purpose of this study was a thorough analysis of vaginal removal of non-prolapsed uterus with benign pathology.

Material and methods: The analysis included data of 1148 women who underwent vaginal hysterectomy in the Clinic of Surgical, Endoscopic and Oncological Gynecology between 2002 and 2014. A group of patients operated on were assessed, and data from the surgeries were obtained paying attention to such aspects as the operating time, the evaluation of morphotic blood elements, the type of perioperative complications, and the length of postoperative hospital stay. Additionally, all vaginal hysterectomies were divided into groups and analyzed taking into consideration uterus weight.

Results: Vaginal hysterectomy was performed even in cases of earlier abdominal surgeries. The mean operating time was and 69.51 ± 28.32 minutes. The patients left hospital after 2.93 days on average. The mean uterus weight was 179.69 ± 113.54 g.

What is important, the enlarged uterus was not a significant obstacle during the surgery. In case of heavy uteri of more than 580g, when the fundus of the uterus reached above the navel, the attention was drawn to the need for careful preparatory procedures, which reduced the number of perioperative complications and thus had a significant influence on the length of the operation ($p = 0.0170$).

Conclusions: Vaginal hysterectomy is an operating technique which is relatively easy to perform and safe for the patients because it involves a slight decrease of morphotic blood elements and a small number of mid- and postoperative complications. Vaginal hysterectomy is not a contraindication in case of large uteri, even those of more than 1000 g; however, in such cases, a longer operating time and an increased number of perioperative complications must be taken into consideration.

Key words: vaginal hysterectomy; large uterus; reducing uterine size; minimally invasive technique

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INTRODUCTION

Hysterectomy is still one of the most frequently performed gynecologic-obstetrical operations. There is abdominal hysterectomy (AH), vaginal hysterectomy (VH) and laparoscopic hysterectomy (LH). There are also techniques that combine laparoscopic and vaginal hysterectomy (LAVH) and surgeries which make the use of robots.

As the statistical evidence worldwide and nationwide shows, despite the benefits of vaginal removal of uterus, abdominal hysterectomy has been the most frequent type of operation for the last couple of decades. This stems from the fact that a large group of gynecologists prefer traditional methods, which are often the only ones in which they gained experience in the course of their work. Abdominal hysterectomy relates to a longer hospital stay and a longer recovery time, greater pain and a higher risk of infection. On the other hand, minimally invasive techniques (VH, LH) are associated with a shorter hospital stay and a shorter recovery time [1]. A majority of elderly surgeons are not able, or perhaps willing, to change their operating habits, which often results in a lack of development and training of their younger colleagues in these minimally invasive techniques [2].

Nowadays, the crucial criteria on which the choice of the operating method is based should include the advantages

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and disadvantages of particular operating techniques, the patient's well-being after the operation, the time of the return to regular life activity, the level of satisfaction with the performed operation and the experience and skills of the operating doctor [3].

While a variety of random or patient-dependent factors affect the choice of the operating method, the size of the uterus assessed clinically during the bimanual exam and ultrasonography is one of the main decisive factors when choosing which approach to take. In patients whose uterus does not exceed the size of that at the 12th week of pregnancy, or the uterine volume is not bigger than 250–300 cm^3, vaginal hysterectomy seems to be the best solution [4]. In case of a bigger uterine size and volume, total laparoscopic hysterectomy (TLH) or a technique combining vaginal and laparoscopic hysterectomy (LAVH) are better options. Only if a laparoscopic technique was difficult or risky, should abdominal hysterectomy be considered.

Undoubtedly, with a growing experience in vaginal removal of the uterus, the size of uterus bigger than that at 12 weeks pregnant and the volume exceeding 300 cm^3 cease to be a contraindication for vaginal hysterectomy.

In case of significant uterine hypertrophy, it is necessary to use one or more techniques for reducing the size of uterus: hemisection, trachelectomy, wedging, coring, and myomectomy [5].

The most frequently used method is hemisection, which consists in cutting cervix and the body of the uterus in saggital plane. This technique facilitates access to the inside of the uterine body and allows for gradual enucleation of uterine myoma located in the closest proximity to the incision. The size as well as the location of myomas have an influence on how difficult the removal of uterus is. Using the vaginal method, it is easiest to enucleate myomas located on the posterior wall of the uterus. Myomas located on the anterior wall or near the uterine fundus are more difficult to enucleate. Intraligamentous myomas are a contraindication for transvaginal operation [3].

In a situation, when the uterus is enlarged due to adenomyosis, trachelectomy seems to be a better technique to reduce its size. This method involves separating cervix from the body of the uterus, which changes the shape of uterus from pear-shaped to apple-shaped allowing for its greater mobility. It makes it possible to turn the uterus around its own axis and as a result gain easier access to its anterior and posterior wall. This technique should be used not only in case of uterine hypertrophy but also decreased uterine mobility [5]. Another technique of uterus morcellation, also frequently used during vaginal operations, is the so-called coring which consists in circumferential intramuscular excising of the central core of tissue around the uterine cavity (preferably just under the level of the uterine isthmus) with the simultaneous pulling of the cervix. It causes progressive lengthening of the uterine body in longitudinal axis and delivering the uterus into vagina [3]. When other techniques fail, it might prove helpful to use wedge morcellation *i.e.*, excising the uterus in pieces.

The purpose of this study was the analysis of the results of vaginal removal of non-prolapsed uterus with benign pathology, depending on the size of the uterus.

MATERIAL AND METHODS

In the time period between October 2002 and June 2014, 1148 vaginal removals of non-prolapsed uteri with benign pathologies were performed in the Clinic of Surgical, Endoscopic and Oncological Gynecology of the Polish Mother's Memorial Hospital Research Institute (ICZMP) in Lodz. This paper is a thorough retrospective medical record review.

The criteria qualifying for the operation were benign pathologies of the uterus requiring surgical intervention. Patients with genital static disorders as well as those suspected of neoplastic lesions in the area of pelvis minor were excluded from the study.

Basic demographic data such as age, body mass index (BMI) and past obstetric and surgical history were collected. Additionally, the operating time, the length of postoperative hospital stay, selected parameters such as the drop of hemoglobin and hematocrit as well as the type and number of complications were analysed.

All patients were divided into three groups depending on the weight of the removed uterus in order to evaluate surgical results: Group I uterus weight below 280 g, Group II uterus weight between 280 g and 579 g, and Group III uteri heavier than 580 g.

As part of the statistical analysis basic measurements of structure description were assessed: arithmetic mean and standard deviation. Statistical significance of the differences in values obtained in the three groups was checked. The statistical significance level was set at $p \leq 0.05$. To determine differences in continuous data between the three groups regarding the weight of the removed uterus a single factor one-way analysis of variance (ANOVA) was used (for the variables having normal distribution) as well as the Kruskal-Wallis test (for non-parametric variables). Verification of the normality of distribution was conducted using The Saphiro-Wilk Test.

Statistical analysis was conducted with the use of Statistica 13 (StatSoft).

RESULTS

In the years 2002–2014, 1148 patients underwent vaginal removals of non-prolapsed uteri with benign pathologies in the Clinic of Surgical, Endoscopic and Oncological

Table 1. General characteristics of all patients who underwent vaginal hysterectomy of non-prolapsed uteri with benign pathologies in the years 2002–2014

	Number	Percentage	Average ± standard deviation	Range
Average age, years, range	1148		49.65 ± 6.92	(19–80)
Average BMI (kg/m^2), range			27.495 ± 5.51	(16.4–60.44)
Underweight (BMI < 18.5)	6	0.52%		
Normal (BMI 18.5–24.99)	426	37.11%		
Overweight (BMI 25.0–29.99)	407	35.45%		
Obese (BMI > 30)	309	26.92%		
Surgical history				
Abdominal Surgeries	284	24.74%		
Laparoscopic surgeries	47	4.09%		
Vaginal surgeries	25	2.18%		
No surgeries	793	69.08%		
Obstetric history				
Nullipara	37	3.22%		
Previous Deliveries	1111	96.78%		
Physiologic Delivery	1059	92.25%		
Forceps Delivery	11	0.96%		
Caesarean Section	127	11.06%		

BMI — body mass index

Gynecology of the Polish Mother's Memorial Hospital Research Institute (ICZMP) in Lodz (Tab. 1).

The average age of patients was 49 years and 7 months ± 7 years. The most frequently operated patients were 50 years old while the median was 49 years.

A large group of patients were women with improper body weight. The average body mass index (BMI) of operated women was 27.50 ± 5.51. The number of patients with the normal weight (BMI 18.5–24.99) was 425, which constituted 37.11%. Whereas the women who were overweight (BMI 25.0–29.99) and obese (BMI > 30) constituted 35.45% and 26.92% of all operated patients. Only six women were underweight (0.52%) with the body mass index below 18.4.

Among all the patients who underwent vaginal hysterectomy close to 1/3 of women had previous surgical history of surgeries in the abdomen and pelvis minor, out of which 24.74% were abdominal surgeries, 4.09% laparoscopic surgeries and 2.18% vaginal surgeries.

The number of patients with previous physiologic deliveries equaled 1059, which constituted 92.25% of all operated patients (Tab. 1). Instrumental and surgical deliveries (forceps or Caesarean Sections) occurred much less frequently, 0.96% and 11% respectively. Eight women gave birth both physiologically and with the use of forceps, whereas there were 76 patients who had both natural childbirth and Caesarean Section. Two patients reported that in the past they had Caesarean Section and forceps delivery.

The largest group of patients were multiparas after two deliveries, who constituted 51.66% of all operated women. Only two patients qualified for vaginal hysterectomy had as many as seven deliveries.

In case of each surgery, the size and weight of the uterus played the key role when selecting the appropriate operating method. In most cases, the volume of the removed uterus was 182.67 cm^3 ± 159.91, with the average of 141.88 cm^3. The average weight of the removed organ was 179.69 ± 113.54 g. If we assume that the average weight of a normal uterus is usually between 50 and 100 g, then the median weight of the removed uterus in this study was 150.74 g. The largest uterus removed vaginally had the volume of 1483 cm^3 and the weight of 1102.96 g and despite such considerable size the operation lasted only 75 minutes. In the analysed material, in as many as 150 patients the removed uteri weighed more than 280 g, which is equal in size to the uterus at more than 12 weeks pregnant.

Additionally, when analyzing the size and weight of the operated uterus, the patients were divided into three groups (Tab. 2). The largest group (as many as 998 patients) consisted of women whose uteri weighed up to 280 g, which was the size of uteri corresponding approximately to that at 12 weeks of pregnancy. Much larger uteri weighing more than 280 g (including 16 uteri of more than 580 g with the fundus reaching higher than the navel) were also removed using vaginal hysterectomy.

Table 2. The analysis of particular parameters depending on the size and weight of the removed uterus

	Uterus- below 280 g (n = 998)		Uterus- 280–579 g (n = 134)		Uterus- above 580 g (n = 16)		Significance factor (p)
	average	deviation	average	deviation	average	deviation	
Average operating time [min]	68.71	28.07	74.17	30.05	80.06	23.72	0.0170
Average hemoglobin decrease [g%]	1.17	0.95	1.15	1.02	1.90	2.01	0.3345
Average hematocrit decrease [%]	3.83	2.77	3.79	2.99	5.79	5.66	0.3969
Average postoperative hospital stay [days]	2.90	1.39	3.16	2.88	3.06	1.61	0.2750
Cases with complications	16 (1.60%)		4 (2.98%)		2 (12.50%)		0.0044

The performed analysis showed that the average operating time in case of uteri with a normal weight was 68.71 ± 28.07 minutes and was the shortest of all in comparison to the other two groups. The heavier the uterus, the longer the operating time. On average, the longest operation lasted 80.06 ± 23.72 minutes in the group of patients with the uteri heavier than 580 g. This correlation was statistically significant, and the significance factor was p = 0.017.

The postoperative changes in the levels of hemoglobin and hematocrit were also observed; however, these parameters were not statistically significant. The biggest drop of hemoglobin and hematocrit was registered when removing uteri heavier than 580 g; it was 1.89 ± 2.01 g% for Hb and 5.79 ± 5.66% for HCT respectively. Also, in this case, the lowest values of the evaluated parameters were observed in patients with the uteri weighing less than 280 g; they were 1.17 ± 0.95 g% for hemoglobin and 3.83 ± 2.77% for hematocrit.

The number of adverse events (n = 16) was higher in case of women with the uteri weighing less than 280 g; however, due to the numerousness of this group, it constituted the lowest percentage of complications in comparison to the other groups. The majority of complications after vaginal removal of uteri weighing less than 280 g were the occurrence of a hematoma bigger than 5 cm in the abdominal cavity in 10 patients, most of whom received outpatient antibiotic treatment and were under observation. Another complication in this group of women was heavy vaginal bleeding observed in 8 patients, who required postoperative wound revision in the first 24 hours since the operation. Additionally, out of a whole group of women with the uteri lighter than 280 g only one woman suffered from damage to urinary bladder. It was noticed and treated during the operation of vaginal removal of the uterus. In women with the uteri weighing 280–579 g, four complications were recorded, which on a scale of this group gave 2.98% of adverse events. The complications mentioned included two cases of fever above 38 Celsius degrees, one case of intraoperative damage to the urinary bladder (noticed and treated during the operation) and one case where the patient required postoperative wound revision in the first 24-hours due to heavy vaginal bleeding.

In the group of women with the uteri heavier than 580g, there were two complications recorded, which in a group that small constituted as much as 12.5% of all events. This parameter was statistically significant (p = 0.0044). In this group of patients, one complication was a hematoma bigger than 5 cm in the abdominal cavity, and the other the occurrence of rectovaginal fistula.

DISCUSSION

Modern minimally invasive techniques such as a vaginal or laparoscopic method are gradually replacing classical methods in gynecology. Most world associations, including American Association ACOG, admit that the choice of operating techniques should depend not only on autonomous factors and patient's preferences but also on the experience, skills and constant training of the operating doctor [6]. The above-mentioned association ACOG, established that it is safe to perform vaginal removal of the uterus when it is smaller than the size at 12 weeks of pregnancy or weighs less than 280 g [7, 8]. Many experienced gynecologists, including the authors of studies such as Seth and Kovac, can safely remove a much bigger uterus using the method of vaginal morcellation.

According to the data coming from our clinic, in the years 2002–2014, 150 uteri with the size corresponding to that at 12 weeks pregnant were removed vaginally, which constituted 13% of all the performed vaginal hysterectomies. In this study, the largest removed uterus had the volume of 1123.71 cm^3 and weighed 1102.96 g.

Davies et al., as well as Mazdisnian et al., analysed vaginal removal of enlarged uteri. They successfully removed a uterus the size at 12 weeks of pregnancy without increasing perioperative complications, blood loss, the operating time and the length of postoperative hospital stay [9]. Unger et al. [10], who removed uteri weighing between 200 and 700 g, achieved

similar results without increasing perioperative complications which occurred in case of abdominal hysterectomy.

In the material analysed in this study, the operating time and the percentage of adverse events were statistically significant only when removing very large uteri weighing more than 580 g. However, neither an increased hemoglobin or hematocrit loss nor the lengthening of postoperative hospital stay were observed after these procedures regardless of the uterine size.

CONCLUSIONS

Vaginal hysterectomy is a relatively safe operating technique even for patients with uterine hypertrophy. Although the size and weight of the removed uterus had a significant influence on the operating time and the increased number of perioperative complications, vaginal removal is not a contraindication even in case of large uteri of more than 1000 g. However, it should be kept in mind that a large uterus requires experience on the part of operating doctor.

Conflict of interests

The authors declare that they have no conflict of interests.

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The relation of CD3, CD4, CD8 and PD-1 expression with tumor type and prognosis in epithelial ovarian cancers

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ABSTRACT

Objectives: Ovarian cancer is a heterogeneous disease, where chronic inflammation plays a key role in carcinogenesis. In this study, it is aimed to analyze the relationship with prognosis and chemotherapy response to clinicopathological variables in epithelial ovarian cancers such as proliferation of PD-1 +, CD8 +, CD4 +, CD3 + T-lymphocytes infiltrating the tumor and tumor stroma.

Matrial and methods: Seventy-six cases diagnosed with primary epithelial ovarian tumor from biopsy or surgical resection materials were included in the study. Immunreactivity of CD3, CD4, CD8, PD1 was evaluated immunohistochemically in lymphocytes in tumor infiltrating lymphocytes and stromal lymphocytes.

Results: Seventeen (22.4%) of the cases were Type I, 59 (77.6%) of them were Type II ovarian carcinoma. PD-1 positivity was observed in stromal and intraepithelial lymphocytes in 22 (28.9%) of 76 cases. In the presence of PD-1 + T-lymphocytes that infiltrate tumor and stroma, disease-free survival are shorter ($p = 0.037$). The presence of stromal CD4 + and CD8 + T-lymphocytes was more common in late stage patients ($p = 0.012$, $p = 0.036$; respectively). The disease-free and overall survival rate was statistically significantly shorter in the presence of CD8 + T lymphocytes ($p = 0.009$, $p = 0.003$; respectively).

Conclusions: CD3, CD4 and CD8 may contribute to PD-1 mediated tumor control. Anti PD-1 therapy may be an alternative to chemotherapy in PD-1 positive patients. Identifying patients who do not respond to chemotherapy through PD-1 expression prior to immunotherapy will help develop potential personalized immunotherapy.

Key words: ovarian cancer; PD-1; CD3; CD4; stromal lymphocytes

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INTRODUCTION

Ovarian cancers are the second most common malignancy among gynecological malignancies, causing the most frequent death due to nonspecific symptomatology and the absence of effective diagnostic methods that provide early detection [1, 2]. According to global statistical data, approximately 295,414 new ovarian cancers and 184,799 deaths were reported worldwide in 2018 [3].

The immune system; it is considered to have a key role in carcinogenesis, especially the suspension of tumor development. The increased concentration of tumor infiltrating lymphocyte (TIL) is associated with good prognosis in various types of cancer [4]. Recent advances in immunotherapy, particularly immune checkpoint inhibitors (ICIs), have increased interest in the new treatment strategy and the immune status of the cancer microenvironment [5]. New treatment strategies are needed as current treatment methods are not sufficient to increase the survival rate of patients with ovarian cancer. Nowadays, there are many ongoing clinical studies on the effectiveness of ICIs in ovarian cancer [6].

The use of ICIs for cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4), programmed cell death-1 (PD-1) receptor/programmed death-ligand 1 (PD) receptors in many cancer patients, particularly malignant melanoma, lung

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cancer, and bladder cancer has been shown to increase overall survival [7]. TIL's; CD4 + and CD8 + T-cells, natural killer (NK) cells, natural killer T lymphocytes (NKT), dendritic cells, CD3 + T-lymphocytes and CD20 + B-lymphocytes are involved in the antitumor immune response. These cells directly participate in the presentation of tumor antigens and/or the attack of tumor cells [3].

PD-1, also known as CD279, is mainly expressed through activated immune cells such as regulatory T (Treg)-cells and NK-cells. Thus, it prevents excessive immune response and protects normal cells from immune attack [8, 9]. PD-1 has two ligands, PD-L1 and PD-L2. In order for PD-1 to inhibit T-lymphocyte functions, it must be combined with PD-L1 and PD-L2 ligands. The ligand commonly found in tumor cells is PD-L1. PD-L1, expressed in the micro-environment of the tumor, suppresses the immune response developing against the tumor [10]. PD-L1 is thought to play a role in the immunological escape mechanism that causes tumor cell growth, proliferation and metastasis [2]. Cancer immunotherapy is due to the emergence of T-cells through immune checkpoint blockage and its functional role to eliminate tumor cells [8]. The expression of immune checkpoint molecules carries prognostic and predictive instructions.

In this study, it is aimed to analyze the relationship with prognosis and chemotherapy response to clinicopathological variables in epithelial ovarian cancers such as proliferation of PD-1 +, CD8 +, CD4 +, CD3 + T-lymphocytes infiltrating the tumor and tumor stroma, tumor type, tumor size, lymphovascular invasion, lymph node invasion, tumor stage.

MATERIAL AND METHODS

Patients

Seventy-six cases diagnosed with epithelial ovarian tumor from biopsy or surgical resection materials at Pamukkale University Faculty of Medicine, Department of Pathology, between 2011 and 2019 were included in the study. The cases were retrospectively reviewed.

The ethics approval of this study was accepted by the Non-Interventional Clinical Research Ethics Committee of Pamukkale University at the meeting dated 19.11.2019 and numbered 60116787-020/83868.

Epithelial ovarian tumors has been reclassified as type I and II tumors according to the new carcinogenesis model. Type I tumors originate from extra-ovarian lesions that can turn into malignant lesions; 1. clear cell carcinoma, seromucinous carcinoma, endometrioid carcinoma known to be associated with endometriosis 2. low grade serous carcinomas; 3. mucinous carcinoma and malignant brenner tumors. Type II tumors developed from intraepithelial lesions in the fallopian tube and divided into three groups: 1. high grade serous carcinoma, 2. carcinosarcoma, and 3. undifferentiated carcinoma (Fig. 1) [11]. The stage of the tumor was determined according to the International Federation of Gynecology and Obstetrics (FIGO) criteria [12]. While primary epithelial ovarian tumors were included in the study; secondary malignant neoplasms (metastases) and primary nonepithelial ovarian tumors were excluded. Patient information such as age, stage, and treatment information of the cases were obtained from the gynecology

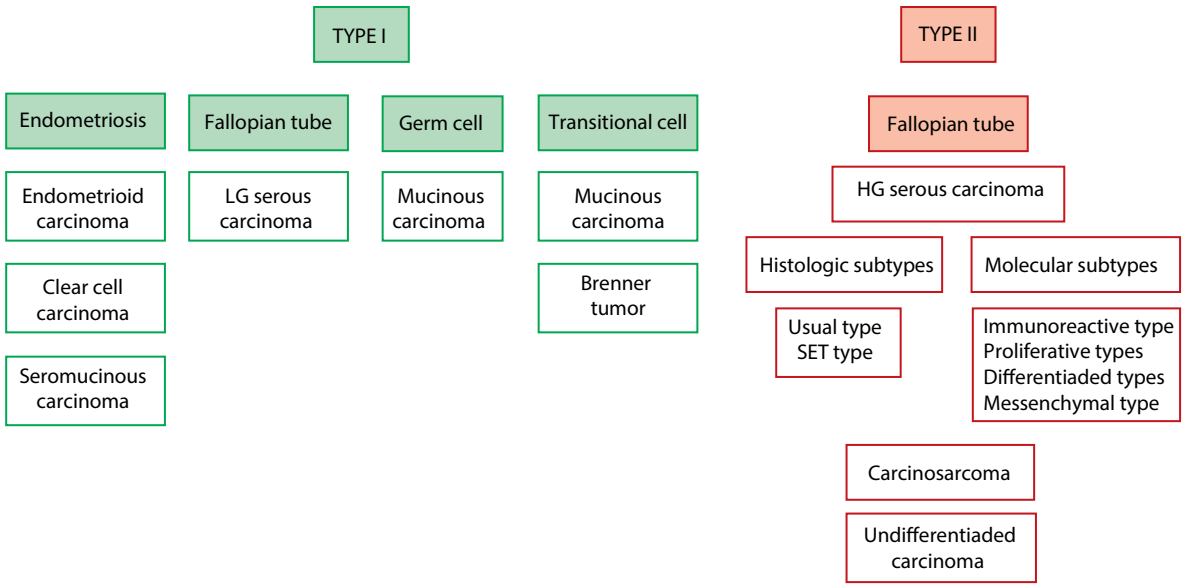

Figure 1. Expanded dualistic model of ovarian carcinogenesis. Ovarian carcinomas derive from endometrial tissue, fallopian tube tissue, germ cells, and transitional epithelium. Type I carcinomas comprise endometrioid, clear cell, LG serous, and mucinous carcinomas. Seromucinous carcinomas and malignant Brenner tumors are rare. It was recently proposed that seromucinous neoplasms be designated mixed Müllerian tumors. Type II carcinomas are largely composed of HG serous carcinoma, carcinosarcoma, and undifferentiated carcinoma. Transitional cell indicates metaplastic transitional epithelium at the tuboperitoneal junction; HG — high-grade; LG — low-grade; SET — solid pseudoendometrioid transitional [11]

department, data such as disease-free survival and overall survival were obtained from the patient files of the department of oncology.

While TAH + BSO + lymph node dissection was applied to 69 (90.8%) of the cases, 7 (9.2%) were performed biopsy. The mean age of the cases is 55 (24–81). Considered as older than 55, younger under 55. The mean tumor diameter is 0.9 cm (0.5–11.5). 42 (55.3%) of them are located bilaterally. 17 (22.4%) of the cases were Type I, 59 (77.6%) of them were Type II ovarian carcinoma. Their distribution is 59 (77.6%) high grade serous carcinoma, 8 (10.5%) borderline serous carcinoma, 4 (5.3%) clear cell carcinoma, 3 (3.9%) endometrioid carcinoma, 2 (2.6%) is in the form of mucinous carcinoma. In immunohistochemical analysis for ER 48/59 (82.7%), PR 33/52 (63.4%), C-erb 2 1/6 (16.6%), PAX8 14/15 (93.3%), WT1 39/71 (54.9%), p53 40/46 (86.9%), CEA 125 38/39 (97.4%) were positive in cases. Capsule invasion was present in 36 (47.4%) of the cases and lymphovascular invasion in 12 (15.8%). 23 (30.3%) of the intraabdominal fluid is malignant. 28 (36.8%) of the cases are early stage (I–II), 36 (47.4%) of the cases are late stage (III–IV). Recurrence was observed in 27 (35.5%) of the cases, and the disease-free survival was 29.6 ± 28.7 months. 67 (88.7%) of the cases died and the overall survival time was 34.8 ± 30.8 months.

Immunohistochemistry (IHC)

A tumor-rich paraffin block was selected for immunohistochemical examination. Ventana Benchmark XT™ fully automated staining device was used with the procedure suitable for sections of about 3–5 microns thick taken on lysine slide from selected paraffin blocks. CD3 (Dako, prediluted, ready-to-use antibody antibody; Rabbit Polyclonal Primary Antibody), CD4 (Dako, prediluted- auto-ready antibody; Mouse Monoclonal Primary Antibody, clone 4B12), CD8 (Dako, prediluted- auto-ready antibody; Mouse Monoclonal Primary Antibody, clone C8/144B), PD-1 (CD279) (Cell Marque, predilute-auto ready-to-use antibody; mouse monoclonal, clone: NAT105) antibodies were used for immunohistochemical staining. The *ultra*View Universal DAB detection kit is used for all staining. The primary antibody stage was omitted for negative control in immunohistochemical staining. For positive control, tonsil tissue for CD3, CD8, CD4 and placental chorionic villus for PD-1 were used. The slides examined were evaluated by two pathologists (FB, YAK) for the immunoreactivity of CD3, CD4, CD8, PD1, taking into account cytoplasmic and/or membranous staining in tumor infiltrating lymphocytes and stromal lymphocytes. Percentage ratio for CD3, CD4, CD8 T lymphocytes in lymphocytes infiltrating the tumor and stroma is given. Median value was taken as cutt-off. Above the median value was classified as high, below the median value was classified as low. For PD-1, it was evaluated as < 1% negative and ≥ 1% positive.

Statistical evaluation

Descriptive values of quantitative continuous variables (such as age) were examined using standard descriptive statistical methods (arithmetic mean, standard deviation, median, etc.). Categorical variables (asset frequencies) are given together with their frequencies and percentages in the total. Comparisons of categorical variables were made by Chi-square or Fischer's Exact Test, depending on the state of the case distributions. Kaplan Mayer test was performed for disease-free survival and overall survival.

RESULTS

PD-1 positivity was observed in stromal and intratumoral lymphocytes in 22 (28.9%) of 76 cases (Fig. 2A, B). PD-1 positivity in intratumoral lymphocytes was found to be higher in elderly patients than in younger patients ($p = 0.030$). Distribution of PD-1 positive cases by tumor types; 18/59 (30.5%) of our high-grade serous carcinoma cases, in 1/2 (50%) of mucinous carcinoma, 2/8 (25%) of borderline serous carcinoma, 1/4 (25%) of our clear cell carcinoma cases showed positive PD-1, in addition no PD-1 positivity was found in a patient with endometrioid carcinoma. 18/22 (81%) of PD-1 positive T-lymphocytes were seen in patients with type II ovarian carcinoma, 4/22 (19%) were seen in patients with type I ovarian carcinoma, this relationship was not statistically significant ($p = 0.500$). In PD-1 positive group, 17 (77.3%) of 22 cases were exitus ($p = 0.029$), and recurrence was detected in 6 (27.3%) ($p = 0.337$). In the presence of PD-1 + T-lymphocytes that infiltrate tumor and stroma, disease-free survival and overall survival are shorter than PD-1 negative cases ($p = 0.037$, $p = 0.063$; respectively). The relationship between the proliferation of stromal PD-1, CD8, CD4, CD3 T lymphocytes and clinicopathological variables is shown in Table 1.

High incidence of stromal CD3 + T-lymphocytes in early-stage ovarian carcinomas is associated with longer disease-free survival ($p = 0.087$). Also, high incidence of stromal CD3 + T-lymphocytes in Type I ovarian carcinomas is associated with longer disease-free survival ($p = 0.066$) (Fig. 2C, D). The presence of stromal CD3 + T-lymphocyte was found to be higher in living patients than in ex patients ($p = 0.093$). Stromal CD3+ T-lymphocytes was higher in PD-1 positive patients than PD-1 negative patients ($p = 0.012$) (Tab. 2). In the survival statistics, in the presence of PD-1 positive CD3 + T-lymphocyte, disease-free survival ($p = 0.032$), overall survival ($p = 0.063$) tends to be longer.

The disease-free and overall survival rate was statistically significantly shorter in the presence of CD8 + T-lymphocytes

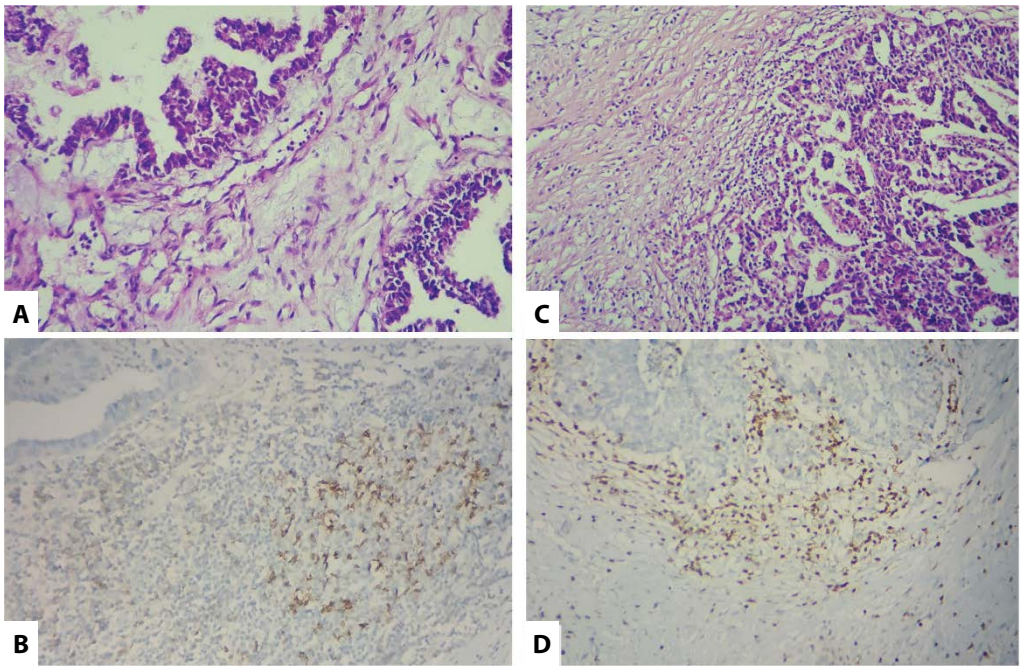

Figure 2A. Serous ovarian carcinoma, H-E, ×200; **B.** Stromal PD-1 + lymphocytes, IHK, ×200; **C, D.** High incidence of stromal CD3 + T-lymphocytes (C — H-E, ×200, D — CD 3 IHK, ×200)

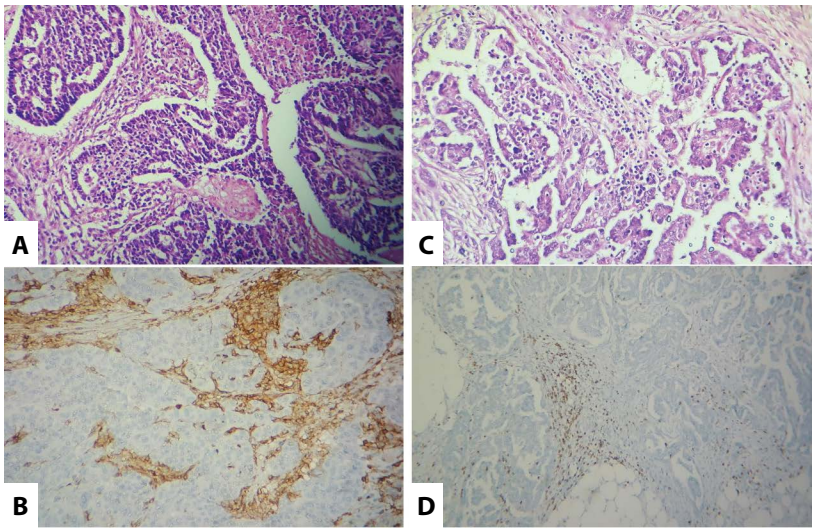

Figure 3A, B. The presence of stromal CD4 + T-lymphocyte was common in type II ovarian carcinomas (A — H-E, × 200, B. CD 4 IHK, ×200); **C, D.** The presence of stromal CD8 + T lymphocytes (C — H-E, ×200 D — CD 8 IHK, ×100)

(p = 0.009, p = 0.003; respectively). In patients receiving chemotherapy, the disease-free and overall survival rate was shorter in the presence of CD8 + T-lymphocytes (p = 0.569, p = 0.014; respectively).

The presence of stromal CD4 + T-lymphocyte above the median value was more common in type II ovarian carcinomas than in type I (p = 0.080) (Tab. 3). The presence of stromal CD4 + and CD8 + T lymphocytes was more common in late stage patients than in the early stage (p = 0.012, p = 0.036; respectively) (Fig. 3A–D). There was no statistically significant relationship between disease-free survival and overall survival in the presence of PD-1 positive CD4 + T-lymphocyte in survival statistics (p = 0.789, p = 0.863).

There was no statistically significant relationship between the proliferation of intratumoral PD-1, CD8, CD4, CD3 T-lymphocytes and clinicopathological variables.

There was no statistically significant relationship between ER, PR, C-erb 2, PAX8, WT1, p53, CEA 125 immuno-expression and CD3, CD4, CD8 and PD-1 expression.

Table 1. Relationship between proliferation of stromal PD-1, CD8, CD4, CD3 T-lymphocytes and clinicopathological variables

Stromal	CD3L	CD3H	CD4L	CD4H	CD8L	CD8H	PD-1L	PD-1H
				n/%				
Tumor diameter (n = 58)								
> 0.5 cm (n = 38)	8 (13.8)	30 (51.7)	20 (34.5)	18 (31.0)	19 (32.8)	19 (32.8)	26 (44.8)	12 (20.7)
< 0.5 cm (n = 20)	8 (13.8)	12 (20.7)	7 (12.1)	13 (22.4)	5 (8.6)	15 (25.8)	17 (29.3)	3 (5.2)
Histological grade (n = 76)								
Low (n = 17)	6 (7.9)	11 (14.5)	11 (14.5)	6 (7.9)	10 (13.2)	7 (9.2)	13 (17.1)	4 (5.3)
High (n = 59)	12 (15.8)	47 (61.8)	24 (31.6)	35 (46.0)	19 (25.0)	40 (52.6)	41 (53.9)	18 (23.7)
Stage (n = 64)								
I/II (n = 28)	8 (12.5)	20 (31.3)	19 (29.7)	9 (14.1)	15 (23.5)	13 (20.3)	20 (31.2)	8 (12.5)
III/IV (n = 36)	10 (15.6)	26 (40.6)	13 (20.3)	23 (35.9)	10 (15.6)	26 (40.6)	27 (42.2)	9 (14.1)
Lymphovascular invasion (n = 25)								
Yes (n = 12)	3 (12.0)	9 (36.0)	3 (12.0)	9 (36.0)	4 (16.0)	8 (32.0)	9 (36.0)	3 (12.0)
No (n = 13)	4 (16.0)	9 (36.0)	7 (28.0)	6 (24.0)	8 (32.0)	5 (20.0)	8 (32.0)	5 (20.0)
Capsule invasion (n = 51)								
Yes (n = 36)	9 (17.7)	27 (52.9)	15 (29.4)	21 (41.2)	16 (31.4)	20 (39.2)	28 (54.9)	8 (15.7)
No (n = 15)	6 (11.7)	9 (17.7)	8 (15.7)	7 (13.7)	6 (11.7)	9 (17.7)	11 (21.6)	4 (7.8)
Metastasis (n = 72)								
Yes (n = 45)	12 (16.7)	33 (45.8)	15 (20.8)	30 (41.7)	12 (16.7)	33 (45.8)	34 (47.2)	11 (15.3)
No (n = 27)	6 (8.3)	21 (29.2)	19 (26.4)	8 (11.1)	14 (19.4)	13 (18.1)	18 (25.0)	9 (12.5)
Intraabdominal fluid (n = 33)								
Benign (n = 10)	0 (0.0)	10 (30.3)	3 (9.1)	7 (21.2)	2 (6.1)	8 (24.2)	4 (12.1)	6 (18.2)
Malign (n = 23)	5 (15.2)	18 (54.5)	10 (30.3)	13 (39.4)	11 (33.3)	12 (36.4)	15 (45.5)	8 (24.2)
Nuks (n = 76)								
Yes (n = 27)	7 (9.2)	20 (26.3)	13 (17.1)	14 (18.4)	6 (7.9)	21 (27.6)	21 (27.6)	6 (7.9)
No (n = 49)	11 (14.5)	38 (50.0)	22 (29.0)	27 (35.5)	23 (30.3)	26 (34.2)	33 (43.4)	16 (21.1)
Ex (n = 75)								
Yes (n = 67)	18 (24.0)	49 (65.3)	32 (42.7)	35 (46.6)	26 (34.7)	41 (54.6)	50 (66.7)	17 (22.7)
No (n = 8)	0 (0.0)	8 (10.7)	3 (4.0)	5 (6.7)	3 (4.0)	5 (6.7)	3 (4.0)	5 (6.6)

Table 2. Intratumoral and stromal CD3, CD4, CD8 ratios in PD-1 positive and negative cases

		Low	High	p
CD3 intratumoral	PD-1 negative	20/54 37%	34/54 63%	0.416
	PD-1 positive	8/22 36%	14/22 64%	
CD4 intratumoral	PD-1 negative	12/54 22%	42/54 78%	0.695
	PD-1 positive	4/22 18%	18/22 82%	
CD8 intratumoral	PD-1 negative	27/54 50%	27/54 50%	0.279
	PD-1 positive	8/22 36%	14/22 64%	
CD3 stromal	PD-1 negative	17/54 31%	25/54 47%	0.012
	PD-1 positive	10/ 22 45%	12/22 55%	
CD4 stromal	PD-1 negative	29/54 53%	25/54 47%	0.947
	PD-1 positive	10/ 22 45%	12/22 55%	
CD8 stromal	PD-1 negative	27/54 50%	27/54 50%	0.468
	PD-1 positive	8/22 36%	14/22 64%	

Table 3. Intratumoral and stromal PD-1, CD3, CD4, CD8 ratios in Type 1 and Type 2 ovarian carcinomas

		Type I Ovarian Carcinoma n = 17 (22.4%)	Type II Ovarian Carcinoma n = 59 (77.6%)	p
PD-1 intratumoral	Positive negative	4 (5.3%) 13 (17.1%)	18 (23.7%) 41 (53.9%)	0.576
PD-1 stromal	Positive Negative	4 (5.3%) 13 (17.1%)	18 (23.7%) 41 (53.9%)	0.576
CD3 intratumoral	High Low	10 (13.2%) 7 (9.2%)	40 (52.6%) 19 (25%)	0.492
CD3 stromal	High Low	11 (14.5%) 6 (7.9%)	47 (61.8%) 12 (15.8%)	0.201
CD4 intratumoral	High Low	13 (17.1%) 4 (5.3%)	47 (61.8%) 12 (15.8%)	0.776
CD4 stromal	High Low	6 (7.9%) 11 (14.5%)	35 (46.1%) 24 (31.5%)	0.080
CD8 intratumoral	High Low	9 (11.8%) 8 (10.5%)	32 (42.1%) 27 (35.6%)	0.925
CD8 stromal	High Low	8 (10.5%) 9 (11.8%)	39 (51.4%) 20 (26.3%)	0.154

DISCUSSION

The presence of TILs in the intratumoral and stromal component of epithelial tumors of the ovary is an important prognostic factor. The diversity of stromal TILs with tumor cell proliferation, invasion, and matrix rearrangement that causes carcinogenesis resulting in different survival creates a tumor-specific microenvironment [13]. Tumor cells modify the tumor microenvironment, both to suppress T-cells and to stimulate tumorigenic inflammation [14]. Afterwards, PD1 becomes apparent in this process and limits T-cell activity in the tumor microenvironment [15]. In the study of Webb et al., PD-1 was positive in 22.1% of 489 ovarian cancers. PD-1 positivity was seen in 75 (38.5%) of 195 high-grade serous carcinomas, 22 (17.6%) of 125 endometrioid carcinomas, 11 (8.6%) of 128 clear cell carcinomas in this study, while 30 mucinous and 11 low-grade serous tumor was PD-1 negative [16]. In our study, PD-1 positivity was observed in 22 (28.9%) of 76 cases. PD-1 positivity was seen in 18 (30.5%) of 59 high-grade serous carcinomas, 1 (50%) of 2 mucinous carcinomas, 2 (25%) of 8 borderline serous carcinomas, 1 (25%) of 4 clear cell carcinomas, was not seen in endometrioid carcinoma in the current study.

Infiltration of PD-1 + lymphocytes is associated with distant metastasis, recurrence and poor prognosis in most tumor types [2, 17]. Wieser et al. found poor prognosis in PD-1 positivity at 170 cases of ovarian cancer series [18]. Similarly, in our study, the disease-free survival and overall survival duration were shorter at infiltration of stromal and intraepithelial PD-1 + lymphocytes.

Transformed tumor cells as a source of tumor-associated antigen or neoantigen may induce an immune response. After all, cytotoxic T-cells contribute to the elimination of tumor cells [19]. Zhang et al. (2003) reported that CD3 + T-lymphocytes show more expression in the advanced stages of serous ovarian carcinomas [20, 21]. In a recent study, higher intraepithelial CD3 and CD8 TIL scores were significantly associated with longer survival in univariate and multivariate analyzes [22]. In another study, no correlation was found in survival analysis with stromal TILs in ovarian cancer. Accordingly, the importance of evaluating TILs for each tumor type is emphasized [23]. In our study, high prevalence of stromal CD3 positive lymphocytes in Type I ovarian carcinomas and early stage patients was associated with good prognosis. Stromal CD3 positivity was higher in living patients than ex patients. CD3 positivity was higher in PD-1 positive group and was associated with good prognosis. Sato et al. [23] stated that the presence of CD8 + T-lymphocytes in ovarian tumors is associated with good prognosis. They reported that high expression of CD8 + T-lymphocytes in the tumor was observed, but not in the tumor stroma [23]. In another study, CD8 + T-lymphocyte infiltration was found to be associated with advanced stage, high tumor grade, and metastasis in the epithelial tumors of the ovary [24, 25], and therefore it was advocated to adversely affect the antitumor immune response [26]. According to the literature, there is a disagreement over the role of CD8 in the prognosis of ovarian cancer. In our study, the presence of stromal CD8 + TIL was more common in late stage patients than in the early stage. The presence of CD8 + T-lymphocytes has been associated with a worse prognosis.

Hamanishi et al. [27], showed high rates of CD4 + TILs in cases of ovarian cancer with better prognosis. These cells

can recognize cancer antigens and mature to type-1 helper cells (Th1). Although the mechanism is uncertain, it can activate M1 macrophages through interleukin-12 or interferon gamma secretion [27]. In studies conducted in different years, the presence of intraepithelial CD4 + T-lymphocytes has been associated with better survival [6, 28–30]. In our study, the presence of stromal CD4 + T-lymphocyte was more common in late stage patients than in the early stage. The presence of stromal CD4 T-lymphocyte was more prevalent in type II ovarian carcinomas than in type I. However, no significant relationship was found with the prognosis.

Cancer immunotherapy has been a controversial issue for years, but studies in this area reached a milestone in 2014. Antibodies specifically blocking PD-1 became available for melanoma in 2014 and went into use for non-small cell lung cancer (NSCLC) in the United States, the European Union and Japan, in 2015, primarily approved by the Food and Drug Administration (FDA) [31]. The FDA approved the use of anti-PD-1 antibody pembrolizumab for solid cancers with microsatellite instability (MSI)-H or mismatch repair (MMR) deficiency in May 2017 [6]. Currently, two classes of FDA-approved immunotherapy for clinical use are PD-1 / PD-L1 and CTLA-4 inhibitors [32]. New agents targeting other courses of the immune system are in the research phase [33]. Until now, single-agent PD-1 blockade has shown moderate activity in patients with ovarian carcinoma, with 15% and 8% response rates reported in nivolumab and pembrolizumab studies, respectively [19]. Phase II clinical study in ovarian cancer has shown that nivolumab, a PD-1 receptor blocker, is well tolerated and offers a 45% disease control rate [34]. A recent update to a patient cohort demonstrated the ongoing clinical benefit even after drug discontinuation. In addition, Pembrolizumab, a PD-1 blocker similar to Nivolumab, currently shows good tolerance and promising disease control on patients with ovarian cancer in early results. Therefore, it is important to identify biomarkers for immune checkpoint inhibitors in ovarian cancers. There are about 100 clinical trials testing PD-1 blockers, many of which focus on ovarian cancer [35]. PD-1 inhibition ensures proliferation of circulating tumor-specific CD8 + T-cells and reduces the functional depletion of specific T-cells [11]. To improve our current knowledge about the immunological environment of epithelial ovarian tumors, spesific immune cells need to be further investigated in different region tumors [3].

CONCLUSIONS

In our study, three important results were obtained. Firstly, PD-1 is positive in 28.9% of stromal and intraepithelial lymphocytes in our cases. CD3 positivity was higher in stromal and intraepithelial T-lymphocytes of these cases, which is associated with good prognosis. Second, infiltration of intraepithelial and stromal PD-1 + T-lymphocytes has been associated with poor prognosis. Third, stromal CD 4+ and CD 8+ T-lymphocytes are more common in late stages. In addition, the presence of CD 3 + T-lymphocytes is associated with good prognosis, while the presence of CD8 + T-lymphocytes is associated with poor prognosis. As a result, we think that CD3, CD4 and CD8 may contribute to PD-1 mediated tumor control. Anti PD-1 therapy may be an alternative to chemotherapy in PD-1 positive patients. Identifying patients who do not respond to chemotherapy through PD-1 expression prior to immunotherapy will help develop potential personalized immunotherapy and will help patients avoid unnecessary treatment.

Conflict of interest

There is no conflict of interest by the authors.

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Past physical activity and its influence on female functioning during perimenopause

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ABSTRACT

Objectives: The objective of the study was to assess correlations between practising sports at an elite level at a young age, and the current physical activity level, selected sociometric features and the severity of menopausal symptoms in women during perimenopause, which will contribute to the knowledge about undertaking sports activity.

Material and methods: The study involved a total of 334 females aged 45–65. They were purposefully assigned to both a study and control group. The study group included 148 women — former elite athletes qualified based on the presumed criteria. The control group consisted of 154 women who did not meet the criterion of practising sports activity earlier in life. In order to conduct the study, we applied the method of a diagnostic survey. The outcome measure was a survey questionnaire and contained questions concerning sociometric features, some elements of gynaecological history, and physical activity undertaken in the past. The second part used the International Physical Activity Questionnaire (IPAQ) and Blatt-Kupperman Menopausal Index.

Results: The groups were homogenous in terms of age and BMI. The former athletes most frequently used to practise athletics, team games and swimming. Both groups displayed no differences regarding the age at menarche, the onset of sexual activity, and the presence and regularity of menstruation. The former athletes had fewer children compared to the controls. They manifested a higher level of physical activity in particular areas and intensity categories. The comparison between the two groups did not show statistically significant differences in the severity of menopausal symptoms.

Conclusions: Sports training in the past differentiates selected sociometric features such as economic activity and a numerous pregnancies and births. Sports training in the past has an impact on the current level of physical activity — the females who used to train present its higher level.

Sports training in the past does not differentiate the severity of menopausal symptoms.

Key words: physical activity; sports; menopause; healthy lifestyle

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INTRODUCTION

Perimenopause is the time in a woman's life where the effects of oestrogen deficiency are mostly noticeable, ranging from vasomotor symptoms, metabolic syndrome and mood changes to urogenital disorders with the symptoms of vaginal atrophy and wasting. There are many factors that determine the age of the occurrence of menopause /the last menstrual period/ such as genetic and environmental factors, ovarian surgeries, taking stimulants, obesity and, indirectly, physical inactivity [1–4].

Physical effort regulates changes at the level of hormone metabolism and thus affects the regularity of the menstrual cycle, governed by the hypothalamic-pituitary-ovarian axis [5, 6].

As shown by research, high intensity physical effort of females during puberty may lead to an adverse syndrome referred to as the Female Athlete Triad (FAT) [7, 8]. It includes eating disorders combined with a low energy level, hormonal imbalances and the occurrence of osteopenia or osteoporosis. This phenomenon was first described more than 20 years ago by Yeager et al. [8]. The athletes could have been qualified to the triad group in the 1990s are between 40 and 50 presently, and only now is it possible to assess long-term effects of potential disorders.

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Menopause occurs later (after the age of 50) in the women who have had many children, live a healthy lifestyle and are free of addictions [9–12].

Numerous studies have attempted to evaluate the effect of physical activity on the timing and course of menopause. It has been noted that the occurrence of menopause may be delayed in those who are physically active. However, there has been no explicit research concerning the impact of high intensity physical activity or long-term observation of its effects. Moreover, many authors indicate the necessity of further investigation into this issue [13–15].

Getting familiar with long-term effects of female sports activity does not only have educational value but also potential for practical application.

Objectives

The objective of the study was to assess correlations between practising sports at the elite level at young age, and the current physical activity level, selected sociometric features and the severity of menopausal symptoms in women during perimenopause, which will contribute to the knowledge about undertaking sports activity.

MATERIAL AND METHODS

The study involved a total of 334 females aged 45––65. They were purposefully assigned to both a study and control group. The study group included 148 women — former elite athletes, according to the presumed inclusion criteria: age 45–65, female gender, consent to participate in the study, filling in the survey questionnaire, meeting the criteria of sports activity undertaken in the past (training experience of no less than five years, participation in sports competition of a championship rank on a national or international level, association with a sports club as a competitor, sports training finished at least ten years before the date of participation in the study).

The control group comprised 154 women who did not meet the presumed criteria concerning sports activity earlier in life. Thirty-two women were excluded from statistical analysis in view of failing to meet the inclusion criteria or incompletely answering the questions in the survey questionnaire.

Descriptive statistics presenting age, morphological parameters and chosen sociometric features are summarised in Tables 1, 2.

The course of sports career in the study group is characterised in Table 3. The former athletes most frequently practised athletics (n = 49; 33.11%), team games including volleyball (n = 23; 15.54%), basketball (n = 18; 12.16%) and handball (n = 14; 9.46%), as well as swimming (n = 14; 9.46%) and other disciplines (n = 30; 20.27%).

The research project obtained approval no KNW/0022/ /KB/103/14 of the Bioethics Committee of the Medical University of Silesia in Katowice, Poland.

In order to achieve the stated objective of the study, it was necessary to contact individuals from the sports environment. The respondents could receive the questionnaire in two different ways: by e-mail — as a Word document, or in person — receiving a copy of the questionnaire and an addressed envelope during a meeting. Having filled in the questionnaire the participants returned it by e-mail or by post. We collected 33% out of approximately 1000 questionnaires distributed.

In the study we applied the method of a diagnostic survey. The outcome measure was a survey questionnaire, filled in anonymously. This included our own part which contained questions concerning sociometric features (namely age, place of residence, marital status, economic activity, as well as body height and weight, based on which the body mass index (BMI) was calculated), and selected elements of gynaecological history. This part also contained questions characterising the type and character of the sports activity undertaken in the past.

The following part of the questionnaire consisted in the International Physical Activity Questionnaire (IPAQ). In accordance with the existing definition of physical activity, described as "each body movement provoked by work

Table 1. Descriptive statistics of age and morphological parameters — comparison of the study and control groups

Variable	Group	n	x	Me	Min	Max	SD	p[1]
Age (years)	Study	148	51.33	50.00	45.00	65.00	5.58	0.2173
	Controls	154	51.72	51.50	45.00	64.00	4.71	
Body mass [kg]	Study	148	68.74	68.50	50.00	98.00	9.20	0.4063
	Controls	154	70.33	69.50	49.00	108.00	11.70	
Body height [m]	Study	148	1.68	1.68	1.52	1.84	0.06	0.0000
	Controls	154	1.64	1.64	1.50	1.87	0.06	
BMI [kg/m^2]	Study	148	24.29	23.74	18.37	33.20	3.01	0.0000
	Controls	154	26.06	25.25	18.37	40.15	4.15	

[1]Analysis of variance ANOVA

Table 2. Sociometric features in the study and control groups

Variable		Study group		Control group		Chi²	p¹
		n = 148	%	n = 154	%		
Place of residence	City/town	126	85.14	121	78.57	2.18	0.1395
	Country	22	14.86	33	21.43		
Marital status	Single	23	15.54	9	5.84	8.19	0.8474
	Spouse/partner	114	7.03	133	86.37		
	Divorced/separated/widow	11	7.43	12	7.79		
Education	Primary and vocational	10	6.75	10	6.49	13.39	0.0038
	Secondary	24	16.22	53	34.42		
	University/college	114	77.03	91	59.09		
Current economic activity	Economically active	132	89.19	127	82.47	9.02	0.0110
	Inactive	16	10.81	27	17.53		
Economic activity connected with sports	Yes	78	52.70	9	5.84	80.80	0.0000
	No	70	47.30	145	94.16		

¹Chi² test

Table 3. Characteristics of the subjects' sports career — quantitative variables — descriptive statistics

Variable	X	Me	Min	Max	SD
Age when training started (years)	11.66	12.00	3.00	27.00	3.17
Age when training finished (years)	22.20	22.00	12.00	39.00	5.21
Training experience (years)	10.55	9.00	5.00	27.00	5.14
Time that has passed since the sports career ended (years)	29.05	29.00	10.00	49.00	6.63

of the skeletal muscles which requires energy expenditure exceeding the value at rest" [16], the tool allows weekly energy expenditure to be calculated and expressed in MET-minutes/week (Metabolic Equivalent of Work). This unit is the product of a MET index value ascribed to each type of physical activity, the number of days during which particular activity was performed, and duration of the activity in minutes per day (according to the instruction of the outcome calculation protocol). The value of MET-minutes/week constitutes the total capacity of the activity on a daily and weekly basis.

The application of a long IPAQ version enabled us to estimate the levels of physical activity for five areas: locomotion, economic activity, housework and cleaning, leisure time and spending time in a sitting position [17, 18].

In order to assess the severity of menopausal symptoms we used the Blatt-Kupperman Menopausal Index, which determines the severity of eleven characteristic symptoms based on a four-point scale from zero points (for the absence of symptoms) to three points (severe symptoms). The total sum of points was interpreted as follows: absence of symptoms: 0–5 points, mild degree: 6–10 points, moderate degree: 11–15 points, and severe degree > 15 points [5, 19].

Statistical analysis was performed based on the Statistica 13.3 program (by STATSOFT). In descriptive statistics for qualitative variables, the findings were presented together with the group sizes (n) and percentage values (%), considering the lack of data in some cases. The outcomes concerning quantitative variables were presented in the form of measures of location, that is, arithmetic mean (x), median (Me), and measures of variability, namely standard deviation (SD). In addition, minimum (min) and maximum (max) values were provided. In order to establish whether the variables were normally distributed regarding the group size, the Shapiro-Wilk test was applied. In the case of quantitative variables, the analysis of variance ANOVA and the Mann-Whitney U test were used for determining the level of differences between the groups, and the Pearson correlation coefficient — for checking correlations between the variables. Nonparametric statistics (Chi² test) were used for the qualitative variables. The level of statistical significance was established at $\alpha = 0.05$, providing the test probability value p.

RESULTS

The answers to chosen questions characterising the obstetric and gynaecological profiles of the women are summarised in Tables 4–7.

We have not found significant differences in the age at menarche, the onset of sexual activity, as well as presence and regularity of menstruation between the groups (Tab. 4, 6).

Moreover, the study group got divided into the individuals who had started training before the first menstruation (group 1)

Table 4. The age at menarche and the onset of sexual activity in the study and control groups — descriptive statistics

Variable	Group	n	X	Me	Min	Max	SD	p[1]
Age at menarche [years]	Study	148	13.32	13.00	10.00	18.00	1.70	0.8478
	Controls	154	13.29	13.00	10.00	17.00	1.45	
Age of sexual activity onset [years]	Study	148	20.24	20.00	14.00	26.00	2.01	0.4583
	Controls	154	20.42	20.00	16.00	28.00	2.22	

[1]Analysis of variance ANOVA

Table 5. The age at menarche in the study group: the individuals starting training before and after menarche

Variable	Group	n	x	Me	Min	Max	SD	p[1]
Age at menarche [years]	Group 1	89	13.90	14.00	10.00	18.00	1.69	0.0000
	Group 2	59	12.49	12.00	10.00	16.00	1.31	

Group 1 — the females who started training before menarche; group 2 — the females who started training after menarche; [1]Mann-Withey U test

Table 6. Presence and regularity of menstruation in the study and control groups

Menstruation		Study group		Control group		Chi2	p[1]
		n = 148	%	n = 154	%		
Presence	Yes	84	56.76	77	50.00	1.38	0.2394
	No	64	43.24	77	50.00		
Regularity	Yes	70	47.30	66	42.86	0.44	0.5067
	No	13	8.78	9	5.84		
	No data	65	43.92	79	51.30		

[1]Chi^2 test

and the ones who experienced their menarche during the sports career (group 2). A statistically significant difference has been noted between these two groups as for the age at menarche (Tab. 5).

The former athletes have had fewer children compared to the control group, and the difference was statistically significant (Tab. 7).

Comparing both the study and control groups has not revealed statistically significant differences in the severity of menopausal symptoms (Tables 8–10).

Tables 11 and 12 present the findings of the IPAQ questionnaire. The former athletes demonstrated higher levels of physical activity in particular areas and intensity categories. These differences proved statistically significant. In accordance with the suggested IPAQ methodology and considering the size of the groups, the persons with low level physical activity were joined with those with moderate level activity, forming one category. The individuals presenting high level activity constituted the other group (Table 12).

Moreover, the study group has displayed only a weak positive correlation between age and the severity of menopausal symptoms ($r = 0.236$, $p = 0.004$), and between the duration of time that has passed since the end of the sports career [in years] and the deterioration of menopausal symptoms ($r = 0.209$, $p = 0.011$). A negative correlation has also been noted between training experience [in years] and a general level of physical activity ($r = –0.188$, $p = 0.022$).

DISCUSSION

Pubertal maturation and menstrual cycle are modified by sports activity, a phenomenon confirmed in many publications [20–23]. Low proportion of adipose tissue, inappropriate diet and malnutrition relate to the delayed puberty and later menarche [24, 25]. In the present study, the age at the first menstruation was 13.3 years and in this respect, there was no statistically significant difference between the study and control groups. This age reflects the average age at menarche as determined for the European population [26]. The same value was noted in other studies of young female athletes, conducted among others by Czajkowska et al. [20] and Skierska [27]. When analysing possible causes of the lack of the difference between the groups, it is worth drawing attention to sports disciplines practised by the respondents in the past (in a vast majority of cases it was athletics, team games and swimming). Low numbers of the

Table 7. Number of pregnancies and births in the study and control groups

Variable		Study group		Control group		p[1]
		n = 148	%	n = 154	%	
Number of pregnancies	0	31	20.95	14	9.09	0.0014
	1	26	17.57	28	18.18	
	2	67	45.27	68	44.16	
	3 & more	24	16.21	44	28.57	
Number of births	0	34	22.97	15	9.74	0.0009
	1	31	20.95	30	19.48	
	2	70	47.30	82	53.25	
	3 & more	13	8.78	27	17.53	

[1]Analysis of variance ANOVA

Table 8. Descriptive statistics of the Blatt-Kupperman Menopausal Index findings

Variable	Group	n	x	Me	Min	Max	SD	p[1]
Blatt-Kupperman index	Study	148	10.45	8.00	0.00	38.00	8.19	0.6217
	Controls	154	10.93	9.00	0.00	37.00	8.75	

[1]Analysis of variance ANOVA

Table 9. Presence of menopausal symptoms based on the Blatt-Kupperman index — categories

Severity of menopausal symptoms	Study group		Control group		Chi-square	p[1]
	n = 148	%	n = 154	%		
Absence of symptoms	54	36.49	51	33.12	3.21	0.3601
Mild symptoms	30	20.27	37	24.03		
Moderate symptoms	30	20.27	22	14.29		
Severe symptoms	34	22.97	44	28.56		

[1]Chi^2 test

Table 10. Severity of menopausal symptoms in menstruating and non-menstruating women from the study group

Variable	Group	n	x	Me	Min	Max	SD	p[1]
Severity of menopausal symptoms	M	84	8.12	6.00	0.00	38.00	7.40	0.0000
	NM	64	13.52	12.50	0.00	33.00	8.24	

The division of women into 2 groups: M — menstruating; NM — non-menstruating — this refers to the women who have not had menstrual bleeding for at least 12 months;
[1]Mann-Withney U test

females training particular disciplines restricted the possibility of assessing each of them separately. According to Malina et al. [20] and Skierska et al. [21], training certain sport disciplines is related to the delay in pubertal maturation in females. This concerns for instance gymnastics, basketball, volleyball and swimming. In the remaining disciplines the menarche age corresponds to the norms for the population, or is slightly lower, which results from the high pace of pubertal maturation. It is observed in such disciplines as judo, handball or football. However, faster pubertal maturation in consequence of physical training is characteristic for males.

No publications have been found presenting the quantitative characteristics of childbirths in a population of former female athletes. Our study has demonstrated a statistically significant difference in the number of pregnancies and births between the females practising sports and the control group, which is a novelty in the light of the so far conducted research. Comparing to the control group, the former athletes more often had no offspring at all or statistically fewer children. There can be a range of explanations of this difference, starting with the above-mentioned FAT syndrome [7, 8], through the commitment to a sports career as a priority at

Table 11. Descriptive statistics of physical activity IPAQ [MET-mins/week]

Domains of physical activity	Group	x	Me	Min	Max	Q_1	Q_3	SD	p[1]
Economic activity	S	3973.5	3165	0	1377	946.5	6433	3594	0.0001
	C	2421.5	1200	0	14364	0	3976	3029.7	
Locomotion	S	1679.9	1039.5	0	6858	558	2254.5	1594	0.5163
	C	1802.3	1188	0	7758	396	2799	1676.4	
Housework, cleaning	S	2337.2	1335	0	14310	750	3135	2365.8	0.2130
	C	2715.4	1750	0	14595	670	3780	2866.5	
Leisure time	S	1659.6	1161.8	0	11118	590.3	2088	1783.1	0.0122
	C	1176.5	594	0	7128	198	1470	1586.4	
Time spent in a sitting position	S	1654.3	1470	0	5400	960	2280	958.2	0.0102
	C	2046.4	1740	0	7200	1170	2700	1286.6	
General level of physical activity	S	9650.1	8781	1650	30180	5637.7	4862.8	13519.5	0.0217
	C	8115.8	6801	498	31242	5909.2	3970.5	10668	

Groups: S — study; C — controls; [1]Analysis of variance ANOVA

Table 12. Comparing the study and control groups — persons with the low and moderate activity level vs those with the high level

Categories of physical activity		Study group		Control group		Chi-square	p[1]
		n = 148	%	n = 154	%		
Physical activity level	Low and moderate	107	72.30	127	82.47	7.87	0.0339
	High	41	27.70	27	17.53		

[1]Chi[2] test

the life stage most conducive to having a child, and finishing with concerns about changing the body image during pregnancy (where the body is sometimes considered a model), and losing certain control over it [28, 29]. Other causes also include loss of physical ability during pregnancy and thus fear of the return to full physical fitness, required in elite sports. An equally important problem is the economic situation of athletes, including maintaining grants or sponsorship irrespective of the absence [30, 31].

In the literature, there is a great deal of evidence that an active lifestyle is a factor that has beneficial effects on the process of ageing, while physical activity, which is one of its elements, brings more positive than negative consequences. This can be a starting point for considerations of the correlations between sports activity and age as well as the course of menopause. According to a publication by Serra et al. [32], the women participating in sports competition experience ageing positively, which may also be true about smoothly undergoing perimenopause. The researchers also demonstrate the benefits resulting from sports competition compared to the women presenting a sedentary lifestyle, including a higher level of maximal aerobic capacity (VO^2max), more beneficial body composition (lower proportion of adipose tissue, higher muscle mass) and a better lipid profile at an older age. To a certain extent, those observations have been confirmed by the BMI comparison performed in our study. However, no publications have been found that show direct dependencies between the age when menopause occurs and training sports before.

The former athletes presented the level of physical activity that was statistically significantly higher as well as higher physical activity in particular domains compared to the control group. Higher results in the domain physical activity connected with economic activity should be explained, among others, by the character of their professional career. More than 50% of the women had jobs connected with sports; they worked as physical education teachers. It must be assumed that this kind of work is related to a higher-than-average activity level by its definition. The fact of continuing activity in sport-related areas after finishing the career as an athlete is something that is natural and frequently observed.

CONCLUSIONS

Sports training in the past differentiates selected sociometric features such as economic activity and a numerous pregnancies and births.

Sports training in the past has an impact on the current level of physical activity — the females who used to train present its higher level.

Sports training in the past does not differentiate the severity of menopausal symptoms.

Conflict of interests

The authors declare that they have no conflict of interests.

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Morbidly adherent placenta and cesarean section methods. A retrospective comparative multicentric study on two different skin and uterine incision

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ABSTRACT

Objectives: Morbidly adherent placenta (MAP) is one of leading causes of maternal mortality, with an increasing rate because of repeated cesarean sections (CS).

The primary objective of this study is to compare two techniques of skin and uterine incisions in patients with MAP, evaluating the maternal fetal impact of the two methods.

Retrospective multicentric cohort study.

Material and methods: A total of 116 women with MAP diagnosis were enrolled and divided in two groups. Group one, comprised of 81 patients, abdominal entry was performed by Pfannenstiel skin incision plus an upper transverse lower uterine segment (LUS) incision (transverse-transverse), which was 2–3 cm above the MAP border, with the uterus in the abdomen. In group two, comprised of 35 patients, abdominal entry was performed by an infra-umbilical midline abdominal incision, by vertical-vertical technique, and the pregnant uterus was incised by a midline incision (vertical) from the fundus till the border of the MAP.

Total surgery time, blood loss, blood product consumption, total hospital stay, cosmetic outcomes, and postoperative complications were investigated.

Results: Total time of surgery was significantly shorter in group 1 ($p < 0.05$). Intraoperative blood loss was higher in group 2. Difference between preoperative and postoperative Hb and Htc levels were 3.30 ± 1.04 and 12.99 ± 5.07 respectively ($p = 0.012$; $p = 0.033$). The use of erythrocyte suspension (ES), fresh frozen plasma (FFP), and cryoprecipitate and thrombocyte suspension (TS) were found to be significantly lower in patients of group 1than vertical-vertical group ($p = 0.008$, $p = 0.009$, $p = 0.001$, $p = 0.001$, respectively). There was no difference in terms of total length of hospital stay between groups.

Conclusions: In a subgroup of patients diagnosed for MAP, the transverse-transverse incision resulted in less bleeding, less blood and blood product use, and had better cosmetic results than vertical-vertical incision. Moreover, the total time of surgery, crucial for MAP patients, seems to be shorter also in transverse-transverse incision than in vertical-vertical incision.

Key words: morbidly adherent placenta; pfannenstiel incision; uterine incision; cesarean section; complications

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INTRODUCTION

Morbidly adherent placenta (MAP) is an abnormal invasive placenta in which chorionic villi pass Nitabuch's layer [1–3]. In new obstetric nomenclature, the MAP was also called as" placenta creata spectrum" [4]. The defective or absent structure of decidua basalis and defective development of the fibrinoid layer are the possible pathological mechanisms [5].

Currently, there is an increasing number of MAP associated pregnancies in United States, with an average incidence of 1/731 cases and with 4504 estimated new annual cases, with an average 130 maternal mortalities for complications [6].

Increasing rates worldwide of cesarean section (CS) for delivery have become a major public health issue and the rates of placental insertion abnormalities have been rising accordingly. In fact, the MAP incidence is estimated on 1/533 deliveries [7]. The MAP has become a leading cause of maternal mortality, especially in hospital settings without an experienced surgical team and blood banking [8]. Most women experienced MAP because of repeated CS [9].

There are three variants of MAP that are histologically classified according to the depth of the placental invasion. Placenta accreta is defined as the attachment of chorionic villi to the myometrium, placenta increta is the invasion of the myometrium by the villi, and placenta percreta is defined as the villous invasion beyond the myometrium, reaching the uterine serosa. Anyway, the MAP terminology is accepted for practical use [10].

Such a diagnosis is crucial in the antenatal period, to manage these patients because all women with MAP must be prepared as if they need elective cesarean hysterectomy. But considering future fertility and the possibility of primary repair, a conservative approach may be selected for those whose intraoperative evaluation is appropriate [11].

While vertical skin incision may favor eventual hypogastric artery ligation in cases of massive bleeding, anyway such procedure can also be managed through Pfannenstiel incision [12, 13].

This raised a surgical question: which type of skin and uterine incision, horizontal or vertical, could be better in the management of a MAP surgery?

The aim of this study is to compare Pfannenstiel skin incision and upper transverse uterine incision (transverse-transverse) to midline vertical skin incision and vertical uterine incision (vertical-vertical) evaluating their impact on maternal, fetal and surgical outcomes.

MATERIAL AND METHODS

Authors performed a retrospective multicentric cohort study between March 2012 and December 2018. This study was approved by the ethical committee of Marmara University, School of Medicine, Turkey, with a grant number of 09.2019.253.

A total of 159 files of women who had obstetric surgery for MAP were investigated. Twenty-two patients with emergency MAP surgery were excluded from the study.

Ten women who had Pfannenstiel incisions and vertical uterine incisions and 11 women who had vertical skin incisions and upper transverse uterine incisions were also excluded from the study groups for the homogeneity of the study. The aim of the study was to investigate the impact of skin and uterine incision on maternal and fetal outcomes, total surgery time, blood loss, blood product consumption, length of hospital stay, cosmetic outcomes, and postoperative complications.

Antenatal follow-up

The pregnant women who were diagnosed, during pregnancy, for MAP were followed in the high-risk pregnancy units of the attending hospitals. All patients were scanned by ultrasound, clinical data were recorded and electively delivered at 34–35 weeks of gestation after MAP diagnosis during pregnancy.

The MAP diagnosis was performed during pregnancy surveillance, by the transabdominal ultrasound and color Doppler imaging, to verify the placental invasion and placental mapping. The diagnostic criteria for MAP were ultrasound findings of lacunar images more than three, an irregular bladder wall, increased irregular sub-placental vascularity, irregular myometrial vision, especially at the previous incision site, and loss of clear retro-placental space [14–16].

Surgical technique and preoperative preparation

All doctors involved in the investigation were skilled and performed all types of abdominal and uterine incisions. Before carrying out the CS, each patient had the diagnosis of placental localization (or placental topography), in order to decide where to incise the uterus. All patients were hospitalized at 34 weeks, and surgery for MAP was generally arranged at 34–35 weeks of gestation, under general anesthesia or spinal/epidural anesthesia, depending on patients' conditions. For all cesarean section, four units of erythrocyte suspension and four units of plasma were reserved in the blood bank before the surgery. Generally, before surgery, one course of antenatal corticosteroid was administered to the patients for fetal lung maturity.

Vertical-vertical technique (Group 1)

Bladder catheterization was performed in the operating theatre before the surgical procedure began in all patients. Following sterile cleansing and covering of the surgical field, abdominal entry was performed by an infra-um-

bilical midline abdominal incision (vertical). The pregnant uterus was incised by a midline incision (vertical) from the fundus till the border of the MAP in order to remove the fetus safely. The placenta was gently detached from the uterine wall if possible, and if it was not removed, the placenta, membranes, and the umbilical cord were left in the uterine cavity and the uterus was sutured. After that, the uterine arteries were clamped above the ureteral crossing level and a cesarean hysterectomy was performed. Then the ligamentum ovarii propria were dissected, and the cardinal ligaments were rapidly clamped and sutured. Vascular structures around the bladder were cauterized and ligated. Then the bladder was mobilized fully away from the MAP field. The uterus was removed totally in hysterectomy cases. In cases where the uterus was preserved, the MAP field was resected, the defect was sutured by a continuous locking or figure of eight No. 1 Vicryl. A Bakri balloon was inserted and inflated after the procedure if needed. Following hemostasis, the vertically incised uterus was sutured carefully. The bladder was carefully examined for any injury and filled with 200–300 mL to check for any urinary leakage in cases where bladder injury was suspected. One or two silicone drains were inserted into the pouch of Douglas, abdominal layers were sutured and closed, and the surgical operation was finished. All interventions, blood products used, complications, and the total amount of blood loss were recorded. In cases where over five to six erythrocyte suspensions and six plasma extracts were transfused, four to six units of irradiated thrombocyte transfusion were recommended. According to the fibrinogen level, cryoprecipitate or fibrinogen ampules were used. Patients were followed with hourly hematocrit and coagulation factors until they were stabilized.

Transverse-transverse technique (Group 2)

In this technique, abdominal entry was performed by a lower abdominal transverse incision, namely a Pfannenstiel incision, and the uterus remained in the abdominal cavity. The fetus was removed from the upper uterine transverse incision, which was 2–3 cm above the MAP border. All procedures**,** concerning preservation of the uterus or hysterectomy and the protocol of blood product supplementation**,** are the same as the vertical-vertical technique.

Materials removed from the field of MAP or hysterectomy were evaluated for pathological diagnosis. Type of surgery, hemodynamic changes, blood loss during surgery, total time of surgery, and incisions, transfusions of blood products, perioperative complications, maternal complications, fetal complications, Apgar scores, type of anesthesia, bladder injury, and all other parameters concerning MAP surgery were recorded and included in the database Cesarean Hysterectomy.

Statistical analysis

The data in the study were analyzed using IBM SPSS Statistics for Windows v 21.0 (IBM Corp, Armonk, NY). In the tables, the quantitative data are presented as the mean ± SD and median (minimum–maximum) values, and the categorical data as number (n) and percentage (%). Student's t test and the Mann–Whitney U test were used to compare the independent groups, and Pearson's chi-square test and Fisher's exact test to compare the categorical variables. Data were determined at the 95% confidence level, and a p value < 0.05 was accepted as statistically significant.

RESULTS

A total of 159 women who had a MAP diagnosis were evaluated. Twenty-two women with emergency cesarean section, 10 women with transverse skin and vertical uterine incision and 11 women with vertical skin and transverse uterine incision were excluded. Then, a total of 116 women were included in this study (73% of the whole investigated women). Thirty-five women (30.2%) who had surgery with vertical-vertical incisions included in Group 1, while 81 (69.8%) women who had surgery with transverse-transverse incisions were included in Group 2 for comparison. There was no difference between the groups in terms of age, gravidity, or body mass index. There was a statistically significant difference between the groups in terms of the number of previous cesarean sections ($p = 0.014$). The mean gestational weeks of the patient were 34.23 ± 2.82 and 35.46 ± 1.98 in Group 1 and Group 2, respectively ($p = 0.024$). It was found that the total time of surgery was shorter in the transverse-transverse group than in the vertical-vertical group, which was statistically significant ($p < 0.05$). However, there was no difference in terms of total length of hospital stay between groups (Tab. 1). While preoperative Hb and Htc levels were not different between the groups, postoperative Hb and Htc levels were significantly lower in vertical-vertical incision group than transverse-transverse group (7.66 ± 0.75; 8.21 ± 0.98, $p = 0.004$ for Hb; 21.76 ± 3.19; 23.15 ± 3.68 $p = 0.044$ for Htc respectively). Intraoperative blood loss was higher in vertical-vertical incision group. Difference between preoperative and postoperative Hb and Htc levels were 3.30 ± 1.04 and 12.99 ± 5.07 respectively ($p = 0.012$; $p = 0.033$) (Tab. 2). Bladder injury was found to be significantly lower in the transverse-transverse group (13 patients, 37.1% in vertical-vertical group versus 9 patients, 11.1% in transverse-transverse group ($p = 0.001$) (Tab. 3). The use of erythrocyte suspension (ES), fresh frozen plasma (FFP), and cryoprecipitate and thrombocyte suspension (TS) during surgery was found to be significantly lower in patients with transverse incisions ($p = 0.008$, $p = 0.009$, $p = 0.001$, $p = 0.001$, respectively) (Tab. 4).

Table 1. Demographic characteristics, operative time and type of anesthesia

	Group 1 (vertical – vertical) (n = 35) (Mean ± SD)	Group 2 (transverse – transverse) (n = 81) (Mean ± SD)	p value
Age [years]	32.14 ± 4.57	30.48 ± 4.48	0.071[b]
Gravida (n)	3 (2–7)	3 (2–5)	0.352[a]
Previous C/S (n)	2 (1–6)	2 (1–4)	0.014*[a]
Gestational Weeks at the time delivery [week]	34.23 ± 2.82	35.46 ± 1.98	0.024*[b]
BMI [kg/m^2]	28.94 ± 3.17	29.43 ± 2.24	0.309[b]
Total time of surgery [min]	100.44 ± 18.35	91.23 ± 16.53	0.010*[b]
Length of hospital stay [days]	5 (3–8)	4 (3–8)	0.111[a]
Type of Anesthesia General Spinal	 28 (80%) 7 (20%)	 43 (53.1%) 38 (46.9%)	 0.001*[c] 0.001*[c]

Values are stated as mean ± SD, median (minimum–maximum) and percentage (%); [a]Mann–Whitney U test; [b]Student's t test; [c]Chi-square test; *p < 0.05 indicates statistical significance; SD — standard deviation; BMI — body mass index; C/S — cesearen

Table 2. Changes in laboratory parameters

	Vertical – vertical (n = 35) (Mean ± SD)	Transverse – transverse (n = 81) (Mean ± SD)	p value
Hb [g/dL] Pre-op Post-op Difference	 10.96 ± 0.98 7.66 ± 0.75 3.30 ± 1.04	 10.98 ± 0.76 8.21 ± 0.98 2.77 ± 1.02	 0.907[b] 0.004*[b] 0.012*[b]
Htc [%] Pre-op Post-op Difference	 34.76 ± 4.46 21.76 ± 3.19 12.99 ± 5.07	 33.99 ± 4.64 23.15 ± 3.68 10.84 ± 4.43	 0.410[b] 0.044*[b] 0.033*[b]
Platelet [10^3/mL] Pre-op Post-op Difference	 250.11 ± 72.37 118.20 ± 17.98 131.91 ± 73.02	 278.54 ± 59.88 134.54 ± 28.17 144.04 ± 71.33	 0.056[b] 0.002*[b] 0.407[b]
Fibrinojen [mg/dL] Pre-op Post-op Difference	 275.57 ± 68.11 130.77 ± 37.35 140.80 ± 70.05	 289.86 ± 41.92 149.88 ± 43.81 144.98 ± 59.85	 0.207[b] 0.026*[b] 0.473[b]
INR (n) Pre-op Post-op Difference	 1.21 ± 0.10 1.70 ± 0.65 0.48 ± 0.03	 1.21 ± 10 1.31 ± 0.31 0.11 ± 0.09	 0.891[b] 0.001*[b] 0.001*[b]

Values are stated as mean ± SD; [b]Student's t test; *p < 0.05 indicates statistical significance; SD — standard deviation; Hb — hemoglobin; Htc — hematocrit; INR — international normalized ratio

Table 3. Intra-postoperative complications

	Vertical – vertical (n = 35)	Transverse – transverse (n = 81)	p value
Bladder injury (n)	13 (37.1%)	9 (11.1%)	0.001[c]
Hysterectomy (n)	29 (82.9%)	66 (81.5%)	0.860[d]
Re-bleeding (n)	2 (5.7%)	0	0.030[d]
Postpartum fever (n)	3 (8.6%)	5 (6.2%)	0.640[d]
Deep vein thrombophlebitis or pulmonary embolism (n)	2 (5.7%)	1 (1.2%)	0.163[d]
Wound infection (n)	3 (8.6%)	6 (3.7%)	0.277[d]
Sepsis (n)	0	0	N.A
Pelvic abcess (n)	0	1 (1.2%)	0.509[d]

Values are stated as percentage (%); [c]Chi-square test; [d]Fisher's exact test; *p < 0.05 indicates statistical significance; N.A — Not Applicable

Table 4. Blood product transfusion

	Vertical – vertical (n = 35)	Transverse – transverse (n = 81)	p value
Erytrocytesuspention	4 (4–10)	3 (3–10)	0.008*[a]
FFP	4 (0–8)	2 (0–8)	0.009*[a]
Cryoprecipitate	0 (0–20)	0 (0–10)	0.001*[a]
Thrombocyte	0 (0–4)	0 (0–3)	0.001*[a]

Values are stated as median (minimum–maximum); [a]Mann–Whitney U test; *p < 0.05 indicates statistical significance; FFP — fresh frozen plasma

DISCUSSION

There is no consensus on the standard type of surgery performed in MAP cases, with the increasing efforts for training surgeons, increasing number of centers, and increased success rates with reducing complications rate. Moreover, in MAP patients with anteriorly located placenta, it becomes very difficult to decide about the vertical or horizontal incisions. Incising the uterus from the lower uterine segment may be detrimental because of severe bleeding, and the surgery may have mortal outcomes.

In the MAP management, there are some important variables that may affect the selection criteria of the type of surgical procedure, including demand of continuation of potential for delivery, the experience of the surgical team, surgical skills, the degree of the health facility and the presence of blood banking, and maternal preferences [5]. Moreover, in some cases it could be difficult to remove an enlarged uterus through transverse skin incision; this could cause a delay in the removal of the baby and prolong the total

surgery time. In such a circumstance, precesarean amniotic fluid aspiration can reduce the uterine size and make ease the surgical procedure [6].

Our results showed that the transverse incisions for both skin and the uterus in case of MAP has fewer complications, reduces the time of the surgery, necessitates of less blood product and cosmetically more acceptable than vertical incisions. One of the MAP problems is the detachment of the bladder from the uterus. Surgeon, to preserve bladder vascularization, should incise rather transversally to preserve the bladder without major bleeding.

The management of MAP by using proactive peripartum multidisciplinary approach (PAMA) was effective in reducing urgent deliveries and related significant complications, without increasing rates of cesarean hysterectomy [17].

In case of emergency conditions, it should be mandatory to shorten the delivery time also by using the vertical skin and uterine incisions [18].

In a study conducted by Wylie et al., skin incisions were compared in emergency CS due to abruption, and hemorrhage due to previa, and they reported that even though transverse skin incisions prolong the surgical time by 1–2 minutes, there was no statistical difference for the surgical outcomes in the two skin incision types. Authors reported that vertical skin incisions may increase postpartum endometritis, and the neonatal outcomes were not superior in the vertical incision group, even if most of the CS were performed through suprapubic transverse skin incisions together with upper transverse uterine incisions. So, even in emergency surgery, suprapubic transverse incision may be safely selected in emergency CS [19].

Anyway, whatever technique is preferred, the most important thing is to avoid excessive maternal bleeding and eventual coagulopathy [20]. Maternal preferences and the future fertility expectation in such cases drive the surgical team to preserve the uterus by two methods. The first technique is by leaving the placenta in its place (not routinely recommended) and the second is by incising the uterus from the upper area (2–3 cm above the percreta line), partially removing the lower uterine segment and preserving the uterus [20, 21].

In a study [20], after controlled ligation of the bleeding vessels in the placental bed or segmental resection of the lower uterine segment (LUS), surgeons re-sutured the LUS to preserve uterus. In another study [21], surgeons performed hysterotomy by upper transverse incision without increase the hysterectomy rates, with no substantial difference in comparison to vertical uterine incision.

Moreover, basing on the uterine rupture rates very low after myomectomies performed by transverse uterine incisions [22], the upper transverse uterine incisions in MAP surgery rather than vertical uterine incisions should be a safe approach for uterine rupture reducing.

Our proposed uterine incision technique is similar to the Kotsuji et al. [9], method, in which it is recommend a fundal transverse incision for the fetal removal, but to do this, it is necessary a longitudinal laparotomy. On the contrary, in our transversal laparotomy, it is preferred to use a transverse incision below the fundal region and just 2–3 cm above the percreta line. That is the reason why suprapubic transverse skin incisions make it possible the fetal delivery without difficulty.

The strengths of our study are that we are first comparing both skin and uterine incisions and their surgical outcomes, performed by surgeons skilled in both incisions.

The limitations of the study were the retrospective investigation, performed only in hospital settings with a blood bank and by different surgeons. Moreover, we had difficulty in patients' homogenization.

CONCLUSIONS

As an alternative to the longitudinal skin and uterine incision, the transverse suprapubic skin incision and upper transverse uterine incision during CS can be safely performed in selected patients with MAP diagnosis, without increasing the hysterectomy rates. These transversal incisions may decrease the blood product use and total time of the surgery. Further prospective studies with large sample sizes are warranted to clarify the advantages and disadvantages of this surgical technique.

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Conflict of interest

Authors declare no conflict of interest.

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Pregnancy outcomes in different stages of systemic lupus erythematosus among Chinese women — a retrospective cohort study

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ABSTRACT

Objectives: To analyze the outcomes of pregnancies and risk factors in Chinese women with different stages of systemic lupus erythematosus (SLE).

Material and methods: A total of 55 conceptions in 52 patients with SLE between Jan 2007 and Jan 2019 were retrospected systematically from a general hospital graded 3A in China. Medical records provided us a good way to retrieve the clinical parameters and lab data of patients.

Results: Pregnant women with SLE activity had significant hyperimmunoglobulin, hypocomplement, low platelet counts, high erythrocyte sedimentation rate, C-reactive protein and 24-h urine protein. Hydroxychloroquine had been used to reduce the rates of SLE activity in pregnant women. Logistic regression analysis showed low platelet counts, hypocomplement and 24-h urine protein were significantly correlated with fetal loss. Compared to those in stable stage, the active SLE patients have more risks of hypertensive disorders of pregnancy, thrombocytopenia, lupus nephritis and placental infarction, and have worse fetal outcomes, including the higher rate of fetal loss, preterm and asphyxia neonatorum.

Conclusions: Different stages of SLE during pregnancy are closely related to maternal and fetal outcomes. It is imperative to provide SLE women with pregnancy consultation and regular multispecialty care.

Key words: systemic lupus erythematosus; clinical parameters; lab data; maternal outcome; fetal outcome

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INTRODUCTION

Systemic lupus erythematosus (SLE) is a disease involving autoimmune system, with a morbidity of 4–35 cases per 100 thousand people annually, which preponderantly affects women considerably more often than men, particularly women of reproductive age [1]. As multidisciplinary managements have increasingly involved and the treatments of SLE pregnant women have been improved, the pregnancy outcomes have significantly ameliorated for decades [2]. But such patients are still considered to have high-risk pregnancies. The general trend shows that pregnancy in patients with SLE tend to have higher maternal mortality, exacerbations of disease activity, fewer live births and more complications during pregnancy, including a higher risk of preeclampsia/eclampsia, C-section, prematurity, intrauterine growth restriction (IUGR), neonatal death and post-partum infection [3–6]. While SLE has many systemic effects, the fertility of these patients is typically unaltered from the general population [3].

Given the high popularity of SLE among women and its damage to maternal and infant health, more researches are needed to have better comprehensions about the impacts of active disease on the safety of mother and fetus as the data remain inconclusive [7]. This study aimed to evaluate factors associated with clinical outcome of active and non-active SLE in Chinese pregnant patients.

MATERIAL AND METHODS

A retrospective analysis about the medical records of 55 sequential conceptions in 52 patients with SLE in

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a general hospital graded 3A from Jan 2007 to Jan 2019 was carried out. The diagnosis of SLE is based on the revised criteria formulated by the American College of Rheumatology. Multiple gestations and elective terminations during the first trimester for personal reasons were excluded. This study was authorized from the Ethics Committee and received permission to acquire clinical parameters from the Medical Director affiliated to Lishui People's Hospital. The whole of patient information was kept confidential.

Patients' clinical characteristics were gathered with lab information from medical records. Lab data consisted of hemoglobin (HB), white blood cell (WBC), platelet (PLT), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), urine protein (PRO), 24-hour urine protein (24-h PRO), albumin (ALB), serum creatinine (CR), blood urea nitrogen (BUN), totalcholesterol (TC), triglyceride (TG), low density lipoprotein cholesterol (LDL-C), high density lipoprotein cholesterol (HDL-C) along with immunologic information including immuneglobulin A, immuneglobulin M, immuneglobulin G, complement 3 (C3), complement 4 (C4), antinuclear antibodies (ANA), anti-ds DNA antibodies (anti-dsDNA), anti-Smith antibody (anti-Sm), anti-Ro/SSA antibodies, anti-La/SSB antibodies, antiphospholipid antibodies (aPL). All laboratory tests were performed using standardised methods. The placentas were sent for pathological examination after delivery.

The disease activity of SLE was made an appropriate evaluation based on the SLE Disease Activity Index 2000 (SLEDAI-2K) [8]. Patients were categorized into two groups, according to SLEDAI score: active SLE group (≥ 5) and non-active SLE group (≤ 4).

Maternal outcomes included hypertensive disorders of pregnancy (HDP), gestational diabetes mellitus (GDM), anemia, thrombocytopenia, lupus nephritis, premature rupture of membranes (PROM), oligohydramnios, postpartum haemorrhage (PPH), placental infarction and chorioamnionitis in pathological diagnosis. Pregnancy-induced hypertension (PIH) was a state of blood pressure ≥ 140/90 mmHg on two occasions apart at least ≥ 6 hours observed after the 20th gestational week. Proteinuria > 0.3 g/L/day with hypertension was named pre-eclampsia. In this study, PIH and pre-eclampsia were both classified as HDP for a small number of cases. When hemoglobin is less than 100 g/L during pregnancy, anemia was defined. Thrombocytopenia was defined the count of platelet less than 100 × 109/L. When amniotic fluid index was less than 5cm or amniotic fluid vertical depth was less than 2cm, oligohydramnios was diagnosed. PPH was defined as the loss of blood within 24 hours after delivery, with the amount of bleeding was 500 mL or more.

Fetal outcomes included fetal loss, prematurity, IUGR and asphyxia neonatorum. Fetal loss referred to pregnancy failure due to spontaneous abortion, therapeutic abortion, stillbirth or neonatal death. Preterm birth referred to live birth between 28 weeks and less than 37 gestational weeks. IUGR was defined as a 10% lower limit for birth weight below the CI of the normal gestational weight curve. An Apgar score > 7 was considered normal, while a score ≤ 7 should be considered as asphyxia.

Statistical analysis

Statistical analysis was performed with SPSS version 19.0. The medical data were expressed as means ± SD or frequencies. The count data were compared using the $\chi 2$ test. Comparisons of measurement data were performed using the Student's t-test appropriately. Logistic regression analyses were not only used to compare multiple factors but also calculated the ORs of 95% CIs for maternal-infant outcomes. $P < 0.05$ was considered statistically significant. The missing data were processed by list deletion method and chain equation multiple interpolation method.

RESULTS

Patient characteristics

There was a total of 52 patients with 55 gestations in our study, including 26 cases with active SLE and 29 cases with non-active SLE. The average age at diagnosis of SLE was 22.71 ± 3.81 years (range, 14 to 31 years). The exhibitions of the general characteristics were displayed in Table 1. Mean ages, body mass index (BMI) and living area were not significantly different between the two cohorts as the same as the mean duration of SLE and the incidence of caesarean section. There were no significant differences in comorbid conditions including diabetes and/or hypertension diagnosed pre-pregnancy between active and non-active SLE patients. The proportion of women who had a history of spontaneous abortion and nulliparity was not significantly different between the two groups.

Most of cases both from active and non-active SLE groups were treated with low-dose glucocorticoids(GC), prednisone dose ranged from 2.5 to 25 mg. There were three cases in the active phase treated with immunosuppressants, including azathioprine, tacrolimus and cyclosporine A. Compared to non-active SLE pregnancies, patients with active SLE had a significant lower proportion taking hydroxychloroquine (HCQ) with dose of 200 mg/d (42.3% vs 69.0%, $p < 0.05$). Aspirin (100 mg/d) was taken by patients with positive aPL antibodies. Only two patients with HDP in the quiescent phase of SLE used low-molecular-weight-heparin (LMWH) during their pregnancy.

Table 1. General clinical features of active and inactive systemic lupus erythematosus (SLE) patients in pregnancy

Variables	Active SLE	Non-active SLE	P
Age [yrs, mean ± SD]	28.04 ± 3.97	30.14 ± 3.94	0.054
BMI [kg/m^2 mean ± SD]	23.94 ± 3.39	23.30 ± 2.79	0.447
Nulliparity, n (%)	20 (76.9%)	14 (48.3%)	0.051
Region, n (%)			
City	12 (46.2%)	17 (58.6%)	0.423
Rural	14 (53.8%)	12 (41.4%)	
Duration of SLE [years, mean ± SD]	5.85 ± 3.66	6.72 ± 2.87	0.324
History of spontaneous abortion, n (%)			
With	15 (57.7%)	15 (51.7%)	0.657
Without	11 (42.3%)	14 (48.3%)	
Prepregnancy diabetes, n (%)	1 (3.8%)	0	0.473
Prepregnancy hypertension, n (%)	4 (15.4%)	2 (6.9%)	0.406
Cesarean section, n (%)	14 (53.8%)	20 (69.0%)	0.279
Drugs taken at the onset of pregnancy			
Prednisone, n (%)	25 (96.2%)	26 (89.7%)	0.970
Prednisone dose (mg/d)	12.88 ± 6.19	10.26 ± 4.93	0.086
HCQ, n (%)	11 (42.3%)	20 (69.0%)	0.022
Immunosuppressants, n (%)	3 (11.5%)	0	0.099
Aspirin, n (%)	7 (26.9%)	5 (17.2%)	0.238
LMWH, n (%)	0	2 (6.9%)	0.173

SLE — systemic lupus erythematosus; SD — standard deviation; BMI — body mass index; HCQ — hydroxychloroquine; LMWH — low molecular weight heparin

Comparison of laboratory indexes of SLE in different stages

In the present study, significant differences in autoantibodies were observed between the active and non-active SLE groups, including anti-ds DNA (53.8% vs 24.1%), anti-Sm (50.0% vs 24.1%), anti-Ro/SSA (84.6% vs 58.6%). Compared to non-active SLE pregnancies, patients with active SLE had significant hyperimmunoglobulin (57.7% vs 20.7%),but had hypocomplement (76.9% vs 24.1%). Low PLT, high ESR, CRP and 24-h PRO during pregnancy were significantly associated with SLE activity. No other significant differences were found in the laboratory findings between the two cohorts (Tab. 2).

Risk factors affecting fetal loss

Based on the results of single factor analyses, fetal loss was correlated with presence of taking hydroxychloroquine (HCQ), positive rate of anti-ds DNA, anti-Sm and anti-Ro/SSA, hyperimmunoglobulin, hypocomplement, low PLT, high ESR, CRP and 24h PRO. As show in Table 3, when factors related to fetal loss in univariate analysis were used as independent variables in multivariate logistic regression analysis, it was found that low PLT, hypocomplement and high 24-h PRO were significantly correlated with fetal loss.

Table 2. Comparison of laboratory indexes of systemic lupus erythematosus (SLE) patients in different states

Variables	Active SLE	Non-active SLE	P
ANA, n (%)	26 (100.0%)	28 (96.6%)	0.339
anti-dsDNA, n (%)	14 (53.8%)	7 (24.1%)	0.024
anti-Sm n (%)	13 (50.0%)	7 (24.1%)	0.047
anti-Ro/SSA, n (%)	22 (84.6%)	17 (58.6%)	0.034
anti-La/SSB, n (%)	7 (26.9%)	4 (13.8%)	0.224
aPL, n (%)	10 (38.5%)	5 (17.2%)	0.129
Hyperimmunoglobulin, n (%)	15 (57.7%)	6 (20.7%)	0.006
A, n (%)	9 (34.6%)	2 (6.9%)	0.017
M, n (%)	8 (30.8%)	2 (6.9%)	0.035
G, n (%)	11 (42.3%)	3 (10.3%)	0.012
Hypocomplement, n (%)	20 (76.9%)	7 (24.1%)	< 0.001
C3, n (%)	17 (65.4%)	6 (20.7%)	0.001
C4, n (%)	16 (61.5%)	7 (24.1%)	0.005
HB [g/L]	109.15 ± 12.66	111.17 ± 16.95	0.622
WBC [×109/L]	8.06 ± 2.79	9.32 ± 3.58	0.155
PLT [×109/L]	125.23 ± 51.20	197.59 ± 61.57	< 0.001
ESR [mm/h]	32.10 ± 13.51	20.24 ± 8.73	< 0.001
CRP [mg/L]	15.00 ± 13.76	8.69 ± 8.92	0.045
PRO, n (%)	16 (61.5%)	12 (41.4%)	0.180
24-h PRO [g/24 h]	0.92 ± 1.16	0.34 ± 0.24	< 0.001
ALB [g/L]	30.65 ± 2.88	32.81 ± 2.76	0.701
CR [umol/L]	52.62 ± 13.99	49.79 ± 10.78	0.157
BUN [mmol/L]	3.80 ± 1.10	3.54 ± 1.38	0.305
TC [mmol/L]	3.48 ± 1.12	3.04 ± 0.72	0.082
TG [mmol/L]	4.90 ± 0.97	4.43 ± 0.85	0.063
LDL-C [mmol/L]	2.55 ± 0.55	2.49 ± 1.00	0.760
HDL-C [mmol/L]	1.47 ± 0.38	1.55 ± 0.38	0.399

SLE — systemic lupus erythematosus; ANA — antinuclear antibodies; HB — hemoglobin; WBC — white blood cell; PLT — platelet; ESR — erythrocyte sedimentation rate; CRP — C-reactive protein; PRO — urine protein; 24-h PRO — 24-hour urine protein; ALB — albumin; CR — serum creatinine; BUN — blood urea nitrogen; TC — totalcholesterol; TG — triglyceride

Pregnancy outcomes

HDP was diagnosed in 50.0% of the active SLE patients. The risk of HDP (OR 4.588, 95% CI 1.084 to 19.416) remained high after adjusting for confounding factors. The incidence of thrombocytopenia and lupus nephritis in women with active SLE was significantly higher than those in the

Table 3. Multiple factor logistic regression analysis for Risk factors affecting fetal loss

Variables	B	SE	Wald	DF	p value	OR	95% CI of OR	
							Lower	Upper
24-h urine protein	-5.635	2.573	4.797	1	0.029	0.004	0.000	0.553
Platelet counts	0.029	0.014	4.082	1	0.043	1.029	1.001	1.059
Hypocomplement C3/C4	5.122	2.291	5.000	1	0.025	6.795	1.882	14.938

SE — standard error; DF — degrees of freedom; CI — confidence interval; OR — odds ratio; B — regression coefficient

Table 4. Comparison of pregnancy outcomes between active SLE and inactive SLE patients

Pregnancy outcome	Active SLE	Non-active SLE	P	OR (95%CI)
Maternal outcome				
HDP	13 (50.0%)	6 (20.7%)	0.048	4.588 (1.084–19.416)
GDM	1 (3.8%)	1 (3.4%)	0.937	1.120 (0.067–18.861)
Anemia	7 (26.9%)	7 (24.1%)	0.813	1.158 (0.344–3.899)
Thrombocytopenia	7 (26.9%)	1 (3.4%)	0.014	10.316 (1.172–90.780)
Lupus nephritis	4 (15.4%)	0	0.028	1.846 (0.718–4.997)
PROM	11 (42.3%)	9 (31.0%)	0.415	1.630 (0.539–4.927)
Oligohydramnios	6 (23.1%)	5 (17.2%)	0.739	1.440 (0.382–5.428)
PIH	3 (11.5%)	2 (6.9%)	0.550	1.761 (0.270–11.467)
Placental infarction	15 (57.7%)	8 (27.6%)	0.031	3.580 (1.161–11.040)
Chorioamnionitis	11 (42.3%)	14 (48.3%)	0.788	0.786 (0.271–2.281)
Fetal outcome				
Fetal loss	5 (19.2%)	0	0.019	1.808 (0.670–1.970)
Premature	11 (42.3%)	6 (20.7%)	0.038	3.833 (1.124–13.076)
IUGR	6 (23.1%)	4 (13.8%)	0.295	2.344 (0.571–9.621)
Asphyxia neonatorum	7 (26.9%)	2 (6.9%)	0.029	6.300 (1.158–34.262)

other cohort, and the risks of thrombocytopenia (OR 10.316, 95% CI 1.172 to 90.780) and lupus nephritis (OR 1.846, 95% CI 0.718 to 4.997) remained unchanged after adjusting for confounding factors. Placental infarction was commonly founded among active SLE patients, and the rate was 3.58-fold higher in the group of active SLE than that in non-active SLE. Significant differences in the remaining manifestations of maternal outcomes, including GDM, anemia, PROM, oligohydramnios, PPH and chorioamnionitis, were not observed between the two groups. Peripartum infection was not occurred in two groups, except one SLE patient in the quiescent phase. Maternal deaths did not occur in either groups.

Fetal loss occurred in four cases in the active SLE phase. Two cases were accompanied by lupus nephritis (one case with intrauterine fetal death and the other with neonatal death). The rest of two cases with therapeutic abortion were in relation to immunosuppressant therapy. After adjusting for confounding factors, the total fetal loss rate (OR 1.808, 95% CI 0.670–1.974) of patients with active SLE was higher than that of patients with inactive SLE. In the two cohorts, preterm births accounted for 42.3% and 20.7%, respectively. The adjusted OR remained high for outcome (OR 3.833, 95% CI 1.124 to 13.076). Furthermore, we also observed higher rate of asphyxia neonatorum for pregnant women with disease activity. The Apgar score (1 min) in active SLE group was remarkably lower than that of the other group. It was observed in 26.9% and 6.9% of pregnancies, respectively, in the two cohorts. When the confounding factors were adjusted, the risk of asphyxia neonatorum (OR 6.300, 95% CI 1.158 to 34.262 was still high. Finally, significant difference in the rate of IUGR was not observed between the two cohorts (Tab. 4).

DISCUSSION

Most of studies show the increased flare rates by 25–65% [7, 9, 10]. Other researches have evaluated different outcomes of lupus flares during pregnancy and shown a low incidence of flare (19.4–25%). In this study, 26 (47.3%) of the patients experienced SLE activity during pregnancy. Most of the disease activity observed in these patients ranged from mild to moderate, with new skin-joint changes. The active period of the disease mainly occurred after the second trimester.

In order to avoid adverse maternal and fetal outcomes during pregnancy, rational and standardized drug treatment was very important. GC, especially prednisone, had been the hallmark medication for SLE and were especially the more widely used therapy to control mild–severe flares of SLE [14]. However, during pregnancy, drug dose should be minimised as much as possible, high dose should be taken in a short time during disease flare, and drug dose must be administered during delivery [2, 15]. In general, the basis for the use of different dosages of GC in a specific clinical setting in SLE is essentially empirical. In our sample, 25 (96.2%) pregnant women with SLE in active phase and 26 (89.7%) patients in non-active phase were treated with low-dose prednisone dose, ranged from 2.5 to 25 mg.

HCQ was shown to reduce the rates of lupus fares in pregnancy and was widely applied in the treatment of SLE in recent years and has a good reputation in controlling skin complications from SLE [11, 16]. Our prevalence usage of HCQ was 42.3% in active phase and 69% in non-active phase, which was higher than that prescribed from 18% to 32.2% in Spain [17],but close to 55% in the US [18]. The possible reasons listed as follows: Firstly, our patients had the scope from Jan 2007 to Jan 2019. Although on the early years, HCQ was not used in our country extensively, case data were mainly concentrated in the past 10 years with HCQ used widely. Secondly, in China, when patients with SLE entered the stage of fertility, they were advised to accept management not only from obstetricians but also from rheumatologists, who would prescrib HCQ more frequently.

Durcan et al. [19] found the SLE patients had abnormal lipoproteins, including a decrease in HDL and an increase in LDL, and suggested that HDL and LDL can be used as one of the important parameters to evaluate the disease activity. In our study, there was no obvious difference in lipid and lipoproteins between two groups. This finding might be due to the less cases in our study. In the follow-up study, we will conduct a multicenter study and bring more cases into our groups to obtain more data.

The caesarean section surgery was accepted by 34 (61.8%) patients in our study. The absolute rate was surprisingly high in both groups, and it was much higher than that reported in most previous studies, but lower than that of another Chinese study [15, 20]. SLE was still a risk factor for maternal and fetal outcomes. Most SLE women were inclined to undergo cesarean to terminate pregnancy, which was mainly because doctors and patients preferred elective cesarean to prevent complications closely related to SLE during birth.

Multivariable analysis showed that fetal loss correlated with low PLT, hypocomplement and 24 h PRO in the present study, which was in line with the previous reports [21, 22]. It directly confirmed the adverse effect of SLE activity on fetal outcome. The results of our study confirmed that almost one third of SLE pregnant women had obvious HDP complications, diagnosed in 50.0% of the women with active SLE and 20.7% of the women with non-active SLE. The OR remained significant, even after adjusting for confounding factors. It was in line with the reported literatures [9, 23]. Previous studies demonstrated that thrombocytopenia and lupus nephritis were significantly associated with adversely maternal-infatal outcomes [23–25]. Based on our findings, it was demonstrated as important risk factors for severe obstetric outcomes.

Additionally, placental infarction occurred in nearly 42% pregnant women with SLE, and especially 3.58-fold higher in the patients with active SLE than the others. This finding was consistent with the result described in the study Magid MS et al. [26]. Some research mainly focused on the risk factors of poor fetal outcomes in different phases of SLE. Zhan et al. [27] also carried on a retrospective study of 263 pregnant patients with SLE, which showed that patients with active lupus had a 12.4-fold higher risk of fetal loss. Moreover, Ku et al. [28] discovered an association between active disease and live births. In our study, the total fetal loss rate was higher in the active SLE patients (OR 1.808, 95% CI 0.670 to 1.974 ,which was lower than the previous reports and probably due to the more use of GC and HCQ. Furthermore, in our study, a higher rate of preterm and asphyxia neonatorum was observed in the active SLE group (42.3% and 26.9% , respectively) . The adjusted OR remained high for outcomes (OR = 3.833 and OR = 6.300, respectively). The results was similar to several other studies [29, 30].

Limitations

There were several limitations to our study. Firstly, we had some data loss because it was a retrospective study. Secondly, patients were usually referred to our institution after the second trimester and lacked information at the pre and beginning of pregnancy. So, in our work, there were no cases in the early abortion, whether spontaneous or therapeutic. Thirdly, our single-center study might have had bias. Additionally, most patients with SLE during pregnancy did not have postpartum visits in our hospital. Finally, since many patients entered this study only after pregnancy, we did not have information to review the activity of the disease before conception and to define whether conception increased the risk of activity or not.

CONCLUSIONS

In conclusion, the risks of HDP, thrombocytopenia, lupus nephritis and placental infarction increase significantly in active SLE women during pregnancy. In addition, SLE in active stage leads to higher rates of fetal loss, premature delivery and asphyxia neonatorum. Therefore, we suggest

that when these patients enter the stage of fertility, particularly in active period, they are still considered to have high-risk pregnancies, should have full access to preconception counselling, and should be ideally managed under the coordinated care of obstetricians, rheumatologists and other specialists as needed.

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Conflict of interest

The authors declare that they have no competing interests.

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Development of a peer review process to reduce maternal and infant adverse events associated with midwifery

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ABSTRACT

Objectives: The aim of this study was to establish a midwifery peer review (MPR) process to continuously improve and standardize the midwifery delivery process, thereby reducing maternal and infant adverse events.

Material and methods: First, the MPR committee (MPRC) was established. The co-chairs of our MPRC were the Head of the Nursing Department and the Nursing Director of the Obstetrics Department. Peer review targets included preventing the occurrence of nursing adverse events, improving nursing quality, and optimizing nursing management. We have established a specially digitized case submission system. All cases that met the evaluation criteria formed corresponding midwifery process improvement measures after a discussion at the meeting to continuously improve the level of midwifery.

Results: Between 2014 and 2017, a total of 240 referrals were received by our committee, 211 of which met the criteria for peer review. Our analysis showed that the proportion of adverse events evaluated gradually decreased over time. The percentage of reviewed cases in 2014 was 7.543% of all deliveries (n = 63), which decreased to 6.747% in 2015 (n = 46). The rates in 2016 and 2017 were 5.310% (n = 51) and 5.280% (n = 51), respectively, and the MPRC recommendations resulted in positive practice changes. After reviewing more than 200 cases, the committee recommended the implementation of 20 new rules and regulations through summary and discussion, thus reducing or preventing many problems that are easily ignored during clinical service.

Conclusions: MPR could be an effective tool to improve obstetric quality and midwifery skills. The implementation of MPR promoted a safer environment for mothers and infants and led to a decrease in adverse events related to midwifery.

Key words: peer review; midwifery management; adverse events; professional practice; patient safety

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INTRODUCTION

Nursing peer review is an effective non-punitive reporting system for adverse events. Peer review in nursing is a widely applied and highly effective technique. Since the report titled "To err is human" was published in 1999 by the United States Institute of Medicine [1], patient safety has attracted substantial attention from both the public and medical professionals. The labor and delivery environment is uniquely vulnerable to patient safety owing to the presence of multiple health care providers from a variety of disciplines, the acuity of cases, and the unpredictable timing of clinical events [2]. Midwifery care receives the largest number of complaints from parents or their families regarding the health care process [3]. Furthermore, the high expectations for the birth of healthy infants reduce social tolerance of adverse outcomes or medical errors and decrease the quality of patient care [4, 5]. Two surveys conducted in 2011 and 2012 demonstrated that adverse events occur in up to 10% of obstetric cases and, worryingly, that as many as half of these events are preventable [6, 7]. Furthermore, a survey in the United States of America estimated that adverse events occur in 3–16% of deliveries [8]. The frequent occurrence of obstetric adverse events and the public's high regard for maternal and child safety make the establishment of a safe obstetric culture a high priority.

Safe motherhood is a primary area of focus for policy makers and health care organizations, including those in the nursing field. Achieving safe patient care has therefore be-

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come the focus for the obstetric community. In October 2015, the Chinese "one-child policy" ended abruptly after 35 years. The new "two-child policy" era brought a higher workload and unprecedented challenges for Chinese midwives. Implementing an organizational system is crucial to promote the quality of midwifery services via reporting and analysis of adverse obstetric events. A culture of safety in delivery rooms can be accomplished through the use of an MPR process. This process is based on nursing peer review, which has been widely applied in many countries and hospitals [9–11]. MPR, an effective non-punitive reporting system for adverse events as well as timely and efficient analysis of adverse events, can not only improve the quality of obstetric services, but also reduce the recurrence of adverse obstetric events.

Women's Hospital, School of Medicine, Zhejiang University, one of the major maternity hospitals in China, is located in Zhejiang and has an annual delivery capacity of up to 10,000 people. Effective reduction or prevention of adverse events related to midwifery is essential to foster a safe culture in the hospital. Since 2014, the Obstetrics Department of our hospital has responded positively to the "Perinatal maternal and child care service practice project" of the Ministry of Public Health of China. In line with the goal of "improving the quality of delivery in obstetrics, ensuring the safety of mother and baby," our institution began to develop an effective midwifery adverse event reporting system and analyze adverse outcomes from the delivery room.

By conducting an extensive literature review, we found that many deficiencies remain in the reporting system used for adverse nursing events in China [12, 13]. After analyzing research from overseas, we concluded that nursing peer review is an effective adverse event reporting and analysis system that can reduce the recurrence of adverse events [9, 10, 14, 15]. Based on the situation specific to our hospital, the leading organization experts in our hospital jointly developed an MPR process to be deployed locally.

MATERIAL AND METHODS

Midwifery peer review committee

Before implementing the MPR program, we established an MPRC. The members of the midwifery peer review committee, the purpose of the review and the criteria to be included in the review were published on the hospital website. This committee not only created an organizational foundation and gathered ideas for the implementation of the project, but also provided core support for developing and publicizing the follow-up project. The objectives of the committee were as follows:

1. To establish and improve the MPR process by conducting a literature review and research
2. To promote and supervise the implementation of peer review
3. To take responsibility for the entire peer review process
4. To summarize the results of the review by investigating and analyzing trends in referred cases
5. To improve the midwifery practice standards and process according to the results.

Team members

The co-chairs of our MPRC are the Head of the Nursing Department and the Nursing Director of the Obstetrics Department. The chairs' responsibilities include leadership and decision-making for the committee, controlling the quality of peer review, and supervising the assessment of peer review results.

Most of the committee's members are midwives. Ad hoc members include a nurse representative from both the Quality and Patient Safety Department and the Risk Management Department. In addition, two Obstetric Directors were invited to provide the midwives with the necessary consultations during the review process, but they did not have the right to vote during the review process.

All the midwives in this hospital are members of the review board since the review process aims to identify adverse events related to midwifery. According to the circumstances of each case, different midwives are designated for peer review. The chairs of the committee serve for four years, while the other committee members are appointed for one year to ensure the scientific awareness of the members and the objectivity of the peer review process [15].

The midwifery peer review process

The midwifery peer review is monitored by specialist personnel through the diagnosis of the medical record information system. Once adverse maternal and infant outcomes occur within the evaluation criteria, the peer review process will be triggered, and the midwives of relevant cases will be notified to fill in the midwifery quality control discussion form and report it.

Inclusion criteria:

- Neonatal head hematoma 7–8 cm or bilateral neonatal hematoma ≥ 5 cm
- Third-degree perineum laceration or above
- Laceration of the vaginal wall > 5 cm
- Pallor asphyxia of the newborn
- Postpartum hemorrhage > 1000 mL
- Puerperal infection
- Clavicular fracture of the newborn
- Hematoma of the birth canal ≥ 5 cm
- Cervical laceration
- Lateral episiotomy + direct fissure
- Brachial plexus nerve injury in the newborn
- Special complications of delivery

- Residual placenta after discharge
- Residual gauze.

Exclusion criteria:

- Premature delivery
- Forceps delivery
- Cesarean section
- Conditions that the chairman of the Review Committee deems unnecessary for review

The midwifery quality control discussion form was reported by mail, and the two chairmen made a preliminary assessment of the case within 48 hours. The two chairs assess the case and make decisions based on their professional knowledge and work experience to determine whether the overall practice is questionable or outside organizational standards, or whether there is a problem in the training and education system for midwives. If the co-chairs consider the case appropriate for review, they open the case and process it through the MPRC. If there is any disagreement, the two chairs consult each other before making a decision.

After it has been decided to conduct a peer review, the chairs ask a coordinator to make follow-up arrangements. The coordinator is a midwife who is responsible and respected and has worked in the delivery room for more than 10 years. The coordinator must be fully trained, familiar with the review process, and good at controlling the pace and efficiency of the review. First, the coordinator collects all the information related to the case, including patient medical records, job descriptions, organizational policies and procedures, individual interviews applicable to the case, and internal reports. Subsequently, the coordinator sorts the data and arranges for five to eight reviewers according to the case, including the midwife involved and the group leader of the delivery team. In addition, the coordinator can decide whether to invite the clinicians to participate in the review conference to provide consultation assistance according to the actual situation. After determining the reviewers, the coordinator arranges a time and place for the peer review session and informs all participants to ensure that all can attend. The preparatory work at this stage should normally be carried out within one week of receipt of the referral.

The coordinator organizes the peer review session and mediates the review process. First, the coordinator explains the purpose of peer review to all the members participating in the review conference. Since this review system is non-punitive, objectivity and impartiality must be maintained during the review process, and all relevant information must be kept strictly confidential. The midwife involved has 15 minutes to report and share the details of the entire incident and answer the reviewers' questions. Any doubts during the process of assessing data and listening to reports can be eliminated by asking the parties concerned. Then the reviewers conduct a free discussion session, which is limited to 45 minutes. At the end of the discussion, each reviewer is required to present their views and propose an improvement or strategy to prevent the adverse event occurring in the future; these proposals are recorded by the coordinator. Finally, the coordinator makes a concluding statement regarding the nature of the incident, summarizes the opinions of each reviewer, and proposes corrective measures. After a consensus conclusion is reached, each participant is asked to sign the form to formally end the review meeting. The entire review process is limited to 90 minutes. If a consensus conclusion cannot be reached, then the coordinator collects more relevant data and information relating to the contradictory points and arranges a second review meeting within one week.

After the meeting, the coordinator submits the review form to the chairs. When the chairs' reviews are completed and the committee agrees on the disposition of the case, rectification measures are issued to all midwives. Furthermore, the midwives provide feedback one week later to indicate whether the recommendations of the peer reviewers are to be implemented. If the feedback after one week raises doubts about the recommendations, then the hospital asks midwifery experts to discuss the measures and reach a final conclusion. The committee should organize a whole hospital inspection after one month and it must understand the coverage and implementation level of the rectification measures. If necessary, the president arranges a course presentation or operative training to ensure that every midwife has mastered the appropriate corrective actions and can apply them to the delivery process (Fig. 1).

RESULTS

Between 2014 and 2017, a total of 240 referrals were received by our committee, 211 of which met the criteria for peer review. Of those, the most common adverse event was postpartum hemorrhage (n = 63), which was followed by third- and fourth-degree severe perineum laceration (n = 57). The most commonly reported adverse events in neonates were neonatal pale asphyxia (n = 13) followed by neonatal cyanosis asphyxia (n = 9) (Tab. 1). Moreover, the proportion of adverse events evaluated over the past four years gradually decreased. The percentage of reviewed cases in 2014 was 7.543% of all deliveries (n = 63), which decreased to 6.747% in 2015 (n = 46). The rates in 2016 and 2017 were 5.310% (n = 51) and 5.280% (n = 51), respectively (Tab. 2). The recurrence rate of similar events also decreased significantly. The recurrence rates of uterus inversion, residual placenta after discharge, and residual gauze incidents were all 0%.

Positive practice changes have resulted from the MPRC recommendations. Action plans and practice standards have been developed at the levels of individual midwives,

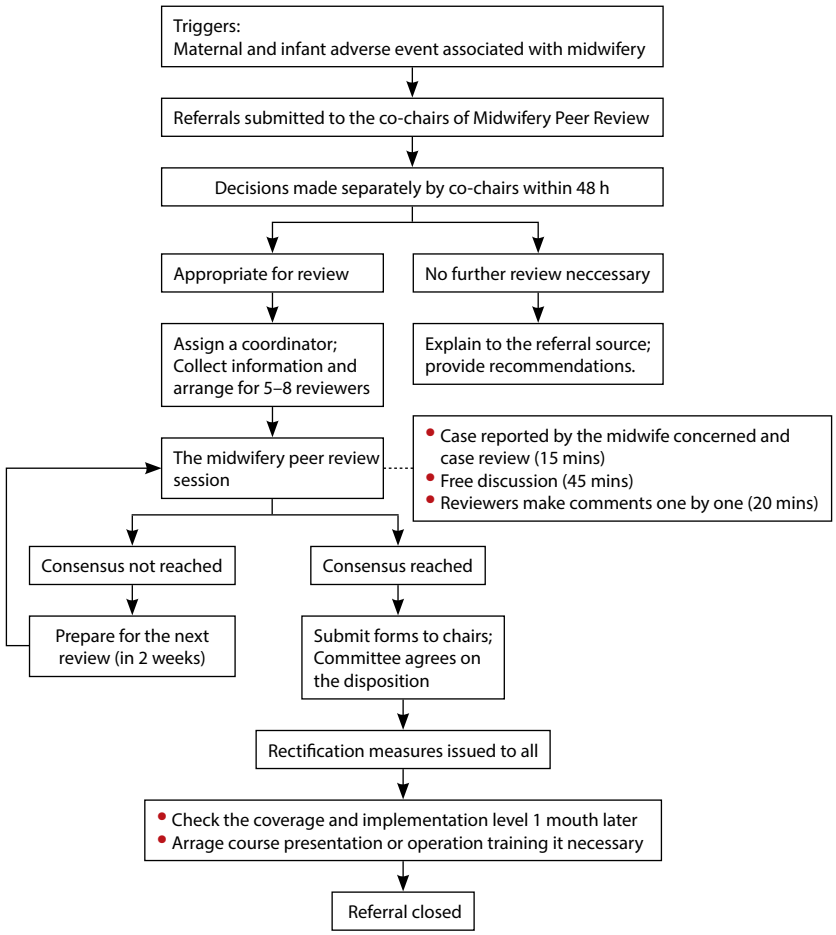

Figure 1. Midwifery peer review process

Table 1. The number of adverse events associated with midwifery over the past 4 years

Midwifery	Events
Severe postpartum hemorrhage	63
Third-degree and fourth-degree perineal laceration	57
Laceration of vaginal wall	13
Perineal lateral cutting +I	14
Laceration of cervix	9
Vaginal wall hematoma	7
Poor wound healing	11
Neonatal pale asphyxia	13
Neonatal cyanosis asphyxia	9
Shoulder dystocia and brachial plexus injury	7
Cephalohematoma neonatorum	3
Inversion of uterus	1
Residual placenta after discharge	2
Residual gauze	3

Table 2. The rates of adverse events

Years	Adverse events	Annual deliveries	Rates [%]
2014	63	8352	7.543
2015	46	6818	6.747
2016	51	9605	5.310
2017	51	9659	5.280

the birth unit, and the organization to improve midwifery practice. A total of 24 corrective actions and system/process changes have been made following the recommendations of the peer reviewers for the cases reviewed. The improved operations and standards include: maternal and infant risk assessment and registration; intrapartum uterine massage; precautions during delivery of pregnant women after hysteroscopic electrotomy; regulation of vaginal gauze compression after vaginal wall hematoma suture; shortening the observation time interval of two hours postpartum; neonatal weighing operation standard, etc. After reviewing more than 200 cases, the committee recommended the implementation of 20 new rules and regulations through summary and discussion, thus reducing or avoiding many problems that are easily ignored during clinical service.

The changes included creating a tail gauze inventory system, a safety management system for amniotic cavity injection, formulating the reporting system for critical value of fetal heart rate monitoring, and the regulations for midwives to call their superior doctors when they step over. The MPR system used to survey the midwives in Women's Hospital, School of Medicine, Zhejiang University has been well received. Below, we present some of the feedback received:

- "This has improved my recognition of my career and my sense of belonging to a group".
- "Since the implementation of peer review, it is obvious that the quality of midwifery is increasing, and everyone's work attitude is more rigorous".
- "I learned a new system of scientific evaluation and learned many new rules and regulations".
- "I think that peer review is not a disgrace, and it can make me more open-minded to accept the suggestions and comments they gave me".
- "This is an objective and efficient system".

DISCUSSION

MPR is similar to nursing peer review and comprises an organized effort in which nurses systematically monitor and assess the quality of care provided by their peers according to standards of professional practice [16]. However, since this process was applied to midwives only to reduce the maternal and infant adverse events associated with midwifery in the hospital, we made some adjustments and changes to the nursing review process according to the midwives' working practice and environment. The new process was renamed "midwifery peer review". The process involves evaluating midwives' incorrect actions during the delivery process that result in adverse outcomes for either mothers or neonates. In this study, we found that the implementation of midwifery peer review could significantly reduce the overall incidence of adverse events such as severe postpartum hemorrhage, severe perineal injury during delivery, and neonatal asphyxia. The establishment of a stable and strong midwifery peer review committee was closely related to the quality of the peer review process, the formation of corrective measures and standards, and the degree of improvement of maternal and infant-related adverse events.

Initially, the members of the peer review committee were scheduled to select the chairs and members so that the committee would remain stable until a member retired or wanted to withdraw. At that point, the committee would select new personnel. The members included some midwives, but the committee did not comprise of only midwives. However, one year after the start of the process, the midwives were very supportive and interested in the peer review system. Many applied to join the committee to be able to participate in the peer review process. On the basis of hearing the views of midwives, the committee conducted several literature reviews and found that specific terms of service should be used to ensure the scientific and objective performance of the peer review results, with a general cycle of one–two years [15, 17]. Therefore, personnel arrangements were adjusted, and the chairs were rotated every two years, whereas other members, such as coordinators and consulting doctors, were rotated every year. Another major change was the expansion of the committee membership so that all midwives in this hospital, including newly recruited midwives, could join the committee. There are currently 55 midwives in our hospital, but rather than causing staff saturation, this change has ensured that all levels of midwives are represented during the peer review process and thus encourages the enthusiasm and participation of every midwife. The implementation of peer review not only improved the midwives' self-discipline, autonomy and professional recognition, but also enhanced their sense of responsibility for maternal perinatal care, which was consistent with many foreign studies [10, 15].

Furthermore, after three years of implementation, we found that the advice provided by the junior midwives in the peer review was as valuable as that provided by senior midwives. They were better able to base their advice on clinical practice, and they provided feedback relating to their views or opinions on certain operations or processes, thus allowing them to integrate more quickly into the hospital's working environment. MPR managers can also fully understand the occurrence and distribution of midwives-related adverse maternal and infant outcomes during this process. In the review process, the problems were analyzed, and a learning and training plan was formulated based on the feedback and opinions of midwives to reduce the recurrence of similar errors. Midwives can receive monthly feedback from MPR expert groups to fully understand their comprehensive abilities and conduct more targeted learning and training. Midwifery peer review not only improved midwives' comprehensive ability, strengthened personal practical skills, but also enhanced team spirit in a non-competitive environment by encouraging managers and midwives to explore solutions together [9, 14, 18, 19]. In this study, through the review of 211 cases of adverse maternal and infant outcomes, a total of 24 rectification measures and system/process reconstruction were formed, which played a great role in standardizing clinical practice, improving personal performance and improving maternal and infant outcomes.

Another change was to invite midwives directly involved in adverse incidents to participate in the peer review conference. Initially, to comply with the principle of confidentiality and to protect the privacy of the midwives and prevent them from feeling criticized by their peers, we did not invite the midwives involved in adverse incidents to participate in the

peer review conference. However, during the process of implementation, there were a number of problems, such as the failure of committees to make appropriate judgements on time or the inability of committees to understand the process of events in detail. These problems led to delays or interruptions of meetings. After discussion, the committee decided that the midwives involved in the adverse events should participate in such meetings [18]. Furthermore, these midwives indicated that they did not feel embarrassed or nervous but instead felt comfortable talking about the adverse events with their peers. Moreover, they felt that this process helped to reduce stress. Therefore, it is extremely important for coordinators to create an inclusive and supportive atmosphere to convince midwives that this is a non-punitive process.

The advantages of this study are as follows: 1) Based on the relatively mature nursing peer review system, the midwifery peer review system which is more suitable for midwives has been innovatively established; 2) Publicize the members and inclusion criteria of the midwifery peer review committee through the website to make the system subject to public supervision and more impartial; 3) Monitoring through the diagnosis of the medical record information system and capturing cases by using the big data platform can effectively avoid missing examinations under the premise of ensuring objective and true; 4) Taking full account of the objective needs of the cases reviewed and the expertise of the members, the establishment of a midwifery peer review committee, including the responsible person of the Ministry of Nursing, the director of obstetric and gynecological care, the chief obstetric doctor, midwives, the parties and other personnel, can restore the course of the cases more comprehensively and truly. The system can evaluate and analyze cases from different perspectives such as medical treatment, midwifery, nursing and management, and put forward corresponding rectification measures, finally forming more authoritative normative standards.

However, the limitation of this study is that no special information system for midwifery peer review has been established, and the website publicity system, the medical record information system capture, and the storage of case data during the review process are all distributed on different information platforms, which cause certain inconvenience and trouble to the control and query of the progress of midwifery peer review process.

CONCLUSIONS

Although the MPR was originally developed from the nursing peer review process, it is crucial to establish a standard peer review model for midwives based on the theory and practice of midwives' work. Through its implementation, the MPR process was able to detect adverse events related to midwifery, correct the midwifery practices associated with the events, establish new and effective midwifery operation standards, and consequently reduce the incidence of adverse maternal and infant outcomes. Moreover, the review process increased the midwives' recognition of their occupation and their sense of belonging. Safe motherhood is essential for every midwife and manager, and it is the responsibility of every healthcare leader to establish effective standards to promote the reporting and analysis of adverse events related to mothers and infants. MPR can promote a safer environment for patients, mothers and infants through a commitment to conducting a timely and effective review of cases and agreement on targeted solutions that can address problems in the clinical processes associated with adverse events. Collectively, these procedures reduce the incidence of maternal and infant adverse events.

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Conflict of interest

The authors declare that there is no conflict of interest.

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Two- and three-dimensional transvaginal ultrasound in assessment of the impact of selected obstetric risk factors on cesarean scar niche formation: the case-controlled study

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ABSTRACT

Objectives: Incomplete healing of the uterine scar after cesarean section may result in formation of a niche. The aim of this study is to identify the potential risk factors for the improper uterine healing after cesarean section in women with single layer, full thickness uterine closure with the use of two- and three-dimensional transvaginal ultrasonography.

Material and methods: 204 women with a history of at least one low transverse cesarean section (CS) with a single layer uterine closure participated in the study. Residual myometrial thickness (RMT), adjacent myometrial thickness (AMT), width (W), depth (D) and volume of the niche, RMT/AMT, RMT/D, RMT/W ratio and clinical characteristics were analyzed.

Results: A niche after cesarean section was found in 153 cases. However only five patients had a RMT < 2.2 mm, and 35 had an RMT/AMT ratio ≤ 0.5. The RMT and RMT/AMT ratio among women who had undergone more than one cesarean section was lower than among women who underwent the first cesarean section. No statistically significant relationship was found between the incidence of niche, its parameters and cervical dilation, uterine contractions, cesarean section in the second stage of labor, type of uterus incision expansion and flexion, operator's experience.

Conclusion: Healing of the uterine cesarean section scar in women with single-layer continuous suture covering the entire thickness of the myometrium, excluding the decidua is not affected by the mode of caesarean section, type of uterine incision expansion and flexion, operator's experience, stage of labor at the time of caesarean section.

Key words: cesarean section; scar niche; single layer suture; 3D ultrasonography; VOCAL; risk factors

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INTRODUCTION

The consequence of each caesarean section is scar formation in the uterine muscle. In the case of incomplete healing, a niche is present within the scar. Symptoms related to the presence of uterine niches in non-pregnant women may include abnormal uterine bleeding, dysmenorrhea, chronic pelvic pain, infertility and dyspareunia [1]. According to some studies, large uterine niches eligible for surgery correction were the cause of prolonged postmenstrual spotting in 85% of patients, secondary infertility in 28% of patients and chronic pelvic pain in 14% of patients [2].

Moreover, the presence of a uterine scar niche can lead to uterine scar dehiscence/rupture in the subsequent pregnancy, as well as to caesarean scar pregnancy and to placenta accreta spectrum disorders [3, 4].

However, it needs to be stated that most small uterine niches are asymptomatic.

The aim of this study is to identify the potential risk factors for incomplete uterine healing after caesarean section in women with single layer, full thickness uterine closure with the use of two- and three-dimensional ultrasonography.

MATERIAL AND METHODS

In this case-controlled study, women who delivered by caesarean section (CS) at our institution from 2017 to 2019 were invited to undergo ultrasonographic assessment of the caesarean section scar 6–9 weeks after the caesarean section. The study protocol was accepted by the ethics committee and all participants signed the informed consent form before entering the study.

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The examinations were conducted using a Voluson V8 Expert ultrasound machine (General Electric Medical Systems) with a 4–9 MHz transvaginal 3D probe.

According to the international definition, a niche was defined as indentation of the myometrium of at least 2 mm [5].

The measurements were obtained in the sagittal transection of the uterus. The following parameters of niche were assessed according to the modified Delphi protocol [5] (Fig. 1):

— width of the anechoic triangle — W (mm)
— height of the anechoic triangle — D (mm)
— residual myometrial thickness — RMT (mm),
— adjacent myometrial thickness — AMT (mm),
— the volume of the anechoic triangle.

Additionally, the following parameters were assessed:

— the ratio of the residual myometrial thickness to adjacent myometrial thickness — RMT/AMT ratio
— the ratio of the residual myometrial thickness to the width of the anechoic triangle — the RMT/W ratio,
— the ratio of the residual myometrial thickness to the height of the anechoic triangle — RMT/D ratio.

In completely healed CS scars, when the niche was not present, only the RMT value was measured.

To create a 3D models and calculate the volume of the niche after section we used the VOCAL program (Fig. 2). The following settings were used: manual trace and rotation angle 15°. The boundaries of the anechoic niche were manually outlined on the touch screen of the Voluson V8 Expert ultrasound machine.

The ultrasound examinations were performed by a single operator experienced in caesarean scar assessment.

Clinical information regarding maternal medical history, pregnancy and caesarean section course were collected from medical records and analyzed after ultrasonographic assessment of the CS scar.

The inclusion criteria were as follows: low transverse uterine incision, single layer continuous full thickness uterine closure and uneventful postoperative course. There were the following exclusion criteria: vertical or inverted "T" uterine incision, double-layer uterine closure, congenital uterine malformations.

The obtained data was collected and systematized using the Excel spreadsheet tools. The statistical examination was performed using the Statistica 13.3 PL package. For quantitative variables, basic descriptive statistics were calculated (for all patients and taking into account the assumed division into groups), while for qualitative variables the frequency of occurrence of their individual variants were calculated (also taking into account the assumed division). The non-parametric test was used in the analysis (Mann-Whitney U test, post and hoc comparisons for the Kruskal-Wallis ANOVA test and the non-parametric Spearman rank correlation). We used the test Chi ^ 2 of Pearson, Chi ^ Yates or Chi ^ 2 NW (depending on the group size) to search the differences in the distributions of qualitative variables. The criteria for statistical significance were set at $p < 0.05$.

RESULTS

A total of 204 patients participated in this study. The study group included women with mean age of 32.25 (SD 4.156) years and gestational age 37.863 (SD 2.43) weeks. Fifty-six patients had at least one cesarean section in the past. Out of all participants, in 153 (%) of them, a uterine niche after caesarean section was detected. The presence of the uterine niche was found in 72% of women after one caesarean section, 87% of women after two and 100% of women after three cesarean sections. Detailed characteristics of the study group are presented in Table 1.

Only five patients had a residual myometrial thickness (RMT) < 2.2 mm, and 35 had an RMT / AMT ratio of 0.5 or

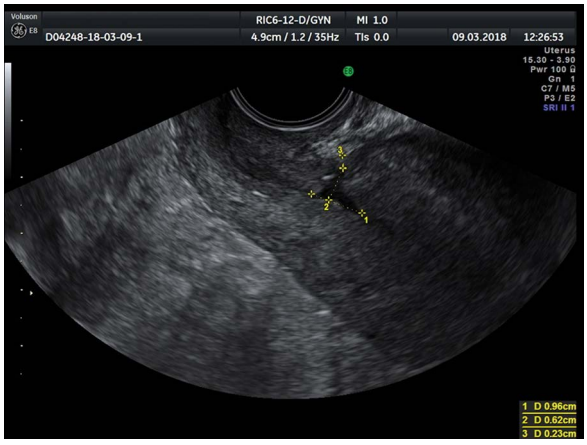

Figure 1. Measurement of the standardized cesarean section scar parameters

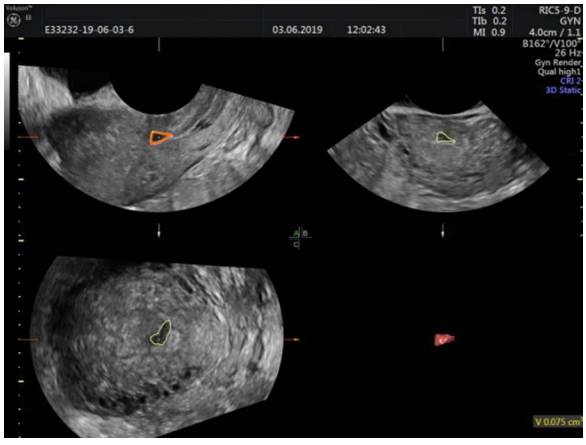

Figure 2. 3D model of cesarean scar niche

Table 1. Characteristics of the study group

Variable		Total	With niche	Without niche
Maternal age [mean (SD)]		32.25 (4,16)	32.21 (4,13)	32.27 (4,17)
Gestational age [mean (SD)]		37.83 (2,44)	37.86 (2,44)	37.87 (2,45)
Type of CS	Emergency [n (%)]	82 (40%)	63 (31%)	19 (9%)
	Planned [n (%)]	122 (60%)	92 (45%)	30 (15%)
Cervix dilatation	No [n (%)]	163 (80%)	123 (60%)	39 (11%)
	< 10 cm [n (%)]	41 (20%)	32 (16%)	9 (4%)
CS during II stage of labour	No [n (%)]	194 (95%)	147 (72%)	47 (23%)
	Yes [n (%)]	10 (5%)	8 (4%)	2 (1%)
Uterus incision expansion	Blunt [n (%)]	35 (17%)	27 (13%)	8 (4%)
	Sharp [n (%)]	169 (83%)	128 (63%)	41 (20%)
Number of previous CS	No previous CS [n (%)]	148 (73%)	106 (52%)	42 (21%)
	> 1 CS [n (%)]	56 (27%)	49 (24%)	7 (3%)
Flexion of uterus	Anteflexion [n (%)]	169 (83%)	128 (63%)	41 (20%)
	Retroflexion [n (%)]	35 (17%)	27 (13%)	8 (4%)
Operator's experience	Resident [n (%)]	101 (49%)	76 (37%)	25 (12%)
	Specialist [n (%)]	103 (51%)	79 (39%)	25 (12%)

SD — standard deviation; CS — caesarean section

less. Both parameters are considered risk factors for severe scar complications in subsequent pregnancies [6, 7].

The study did not reveal any statistically significant relationships between the parameters of the uterine caesarean scar (niche height, niche width, niche volume, residual myometrial thickness, the RMT/AMT ratio, RMT/W ratio, RMT/D ratio) and: cervical dilation, uterine contractions prior to cesarean section, caesarean section in the second stage of labor, type of uterine incision expansion (sharp vs blunt), operator's experience (resident vs specialist) or type of uterine flexion. Moreover, no statistically significant correlation was found between the occurrence of the uterine scar niche and the above-mentioned variables.

Based on the analysis, it was found that the residual myometrial thickness among women who had previously undergone at least one caesarean section was lower than among women who underwent the caesarean section for the first time [RMT = 0.69482 cm (SD = 0.37705) vs RMT = 0.88088 cm (SD = 0.30718); p = 0.000068]. Similar relationship was demonstrated for the RMT/AMT ratio. The individual results are presented in Tables 2, 3.

DISCUSSION

Due to the increasing number of caesarean sections and, consequently, the increasing number of side effects related to incomplete healing process of the uterine scar, there are worldwide efforts trying to define factors that affect uterine healing.

In this study, the evaluation of the uterine scar niche was performed using 2D and 3D unenhanced transvaginal ultrasound 6–9 weeks after caesarean section. Calculation of the niche volume and preparation of the 3D model of the niche, enabled precise evaluation of the niche. In most of previous studies the caesarean section scar was assessed only with the use of two dimensional ultrasonography [1–4, 7–12].

The aim of our study was to assess the dependence of niche parameters after caesarean section in relation to individual variables, to determine which factors can lead to the niche formation. Thus, each diagnosed niche was included in the statistical analysis, and not only those niches which can be classified as large [5] [v] or those which cause clinical symptoms [4].

In our study, as in other studies, the relationship between the number of previous caesarean sections and the risk of uterine niche formation was confirmed [1, 8–10]. The study found no correlation between the incidence of uterine scar niches and the mode of caesarean section (emergency/elective), which is supported by other studies [10, 13]. However, our study revealed that RMT, RMT/AMT ratio and RMT/W ratio are lower in women who underwent elective caesarean section versus those who underwent emergency caesarean section. Such relationship can be explained by the disproportion in size and heterogeneity of both groups.

In the search for potential factors that may affect the healing of the uterine scar after caesarean section, the influence of uterine contractions prior to caesarean section, dilation of the cervix, and thus the progress of labor, cannot

Table 2. Correlations between analyzed niche variables

Variable		Width (W) [cm]	Height (H) [cm]	RMT [cm]	AMT [cm]	RMT/AMT	RMT/W	RMT/H	Volume [cm^3]
Type of CS	Emergency	0.77	0.48	**0.89**	1.3	**0.62**	1.24	**2.08**	0.14
	Planned	0.85	0.51	**0.79**	1.26	**0.58**	1.08	**1.75**	0.16
Cervix dilatation	No	0.88	0.54	0.84	1.27	0.6	1.01	1.69	0.16
	< 10 cm	0.8	0.49	0.83	1.28	0.58	1.18	1.93	0.15
CS during II stage of labour	No	0.82	0.5	0.83	1.28	0.6	1.14	1.89	0.15
	Yes	0.73	0.44	0.83	1.19	0.62	1.17	1.74	0.09
Uterus incision expansion	Blunt	0.83	0.5	0.84	1.29	0.6	1.13	1.94	0.15
	Sharp	0.77	0.52	0.79	1.22	0.56	1.2	1.62	0.14
Number of previous CS	No previous CS	0.81	0.49	**0.88**	**1.32**	**0.62**	**1.2**	**2.01**	0.13
	> 1 CS	0.84	0.51	**0.69**	**1.17**	**0.55**	**1.02**	**1.61**	0.19
Flexion of uterus	Anteflexion	0.81	0.49	0.84	1.27	0.6	1.14	1.92	0.15
	Retroflexion	0.84	0.55	0.8	1.29	0.58	1.17	1.71	0.15
Operator's experience	Resident	0.82	0.51	0.85	1.29	0.59	1.14	1.88	0.13
	Specialist	0.82	0.49	0.81	1.26	0.6	1.15	1.88	0.16

Significant correlations at level of $p < 0.05$ are marked in bold; RMT — residual myometrial thickness; AMT — adjacent myometrial thickness; CS — cesarean section

Table 3. Correlations between incidence of uterine niche and analyzed variables

Variable	Type of CS		Contractions prior to CS		Uterus incision expansion		Operator's experience		Flexion of uterus	
	Emergency [n (%)]	Planned [n (%)]	Yes [n (%)]	No [n (%)]	Blunt [n (%)]	Sharp [n (%)]	Resident [n (%)]	Specialist [n (%)]	Anteflexion [n (%)]	Retroflexion [n (%)]
Niche	62 (40.52%)	91 (59.48%)	9 (17.65%)	121 (79.08%)	27 (17.65%)	126 (82.35%)	76 (49.67%)	77 (50.33%)	125 (82.24%)	27 (17.65%)
Non-NICHE	20 (39.22%)	31 (60.78%)	32 (20.92%)	42 (82.35%)	8 (15.69%)	43 (84.31%)	25 (49.02%)	26 (50.98%)	43 (84.31%)	8 (15.69%)
p value	p = 0.86903		p = 0.76218		p = 0.91461		p = 0.93556		p = 0.90008	

CS — cesarean section

be ignored. There are conflicting conclusions in the literature regarding the impact of these variables on the healing process of the uterus. In the study of Yazicioglu et. al. [11], it has been shown that smaller cervical dilatation at the time of caesarean section is a risk factor for incomplete uterine healing [xi]. However other studies have shown lower RMT values in women who underwent caesarean section in the second stage of labor [12]. In our study, no correlation was found between the incidence of niches after caesarean section and dilatation of cervix, contractions prior to caesarean section, performance of caesarean section during the second stage of labor. Also, no influence of the above-mentioned factors on niche parameters was found.

To the best of our knowledge this is the first study that assessed the type of uterine incision expansion (sharp vs blunt) and surgeons experience (specialist vs resident) on the healing of the caesarean section scar. In the previous studies, only the parameters related to the postoperative course were assessed. Thus, in the meta-analysis by Saad et al. [13] it was found that blunt opening of the uterus was associated with a lower decrease in hematocrit and postoperative hemoglobin level, a lower percentage of unintended openings and a shorter operation time. The analysis carried out in our study did not show a statistically significant difference between the frequency of the niche occurrence and the parameters of the niche depending on the type of uterine incision expansion and surgeons experience. This can be explained by the use of unified uterine closure technique — single layer, continuous full thickness suture, excluding the decidua.

Another issue assessed in the study was the type of flexion of the uterus. Our study found no correlation between the uterine retroflexion and the presence of the uterine scar niche, and no negative correlation between retroflexion and

residual myometrial thickness (RMT), despite the fact that such an association is reported in the literature [3, 7, 14]. Most likely, it is associated with a small group of women with uterine retroflexion in our study.

CONCLUSIONS

Healing of the uterine caesarean section scar assessed with the use of 2D/3D ultrasonography in women with single-layer continuous suture covering the entire thickness of the myometrium, excluding the decidua is not affected by the mode of caesarean section, type of uterine incision expansion, operator's experience, uterine flexion and stage of labor at the time of caesarean section.

Conflict of interest

None declared.

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COVID-19 during pregnancy one year on — what lessons did we learn?

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ABSTRACT

It is now more than a year since the first case of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) disease (COVID-19) was diagnosed in China. Current data suggest that pregnancy may not only be a risk factor for the development of severe forms of COVID-19, but that the SARS-CoV-2 infection may impact on common pregnancy complications as well. Healthy pregnant women are likely to be more susceptible to viral infection and therefore are at higher risk of developing severe COVID-19 because of adaptive changes in their immune and respiratory systems, their altered endothelial cell functions, and modified coagulation responses. However, studies show that most pregnant women diagnosed with COVID-19 developed mild-to-moderate symptoms and only a few of them have required critical care facilities. In contrast with preeclampsia, preeclampsia-like syndrome can resolve spontaneously following recovery from severe pneumonia and may not be an obstetric indication for delivery. Preeclampsia-like syndrome is one symptom of COVID-19, but its cause is different from obstetric preeclampsia and therefore not connected with placental failure. Vertical transmission of SARS-CoV-2 infection is rare but can probably occur. No evidence has been found that COVID-19 developed during pregnancy leads to unfavourable outcomes in the fetus. Most health authorities indicate that standard procedures should be used when managing pregnancy complications in asymptomatic women with confirmed SARS-CoV-2. Vaccines should not be withheld from pregnant and lactating individuals who otherwise meet the vaccination criteria.

Key words: COVID-19; pregnancy; SARS-CoV-2; vaccination

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INTRODUCTION

It is now more than a year since the first case of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) disease (COVID-19) was diagnosed in China. As of 14 March 2021 there have been over 120.3 million cases and about 2.6 million deaths reported globally since the start of the pandemic [1]. In Poland by the same date, there had been 1.9 million confirmed cases of COVID-19 and 47,178 deaths [2]. As the numbers of COVID-19 cases, hospitalizations, and deaths all continue to rise across the world, it is paramount for clinicians to be up to date with the most recent information on the course and treatment of this novel disease. By reviewing the most recent studies on maternal and fetal outcomes among COVID-19 diagnosed women from around the world, our study seeks to determine whether pregnant women are more likely to develop severe forms of COVID compared with non-pregnant women, and whether pregnant women affected by COVID during pregnancy are more likely to develop common obstetric complications, such as preterm birth, preeclampsia, caesarean section, and others. We will also make clinical recommendations based on our analysis of the literature.

SUSCEPTIBILITY TO SARS-COV-2 DURING PREGNANCY AND SYMPTOMS OF COVID-19 AMONG PREGNANT WOMEN

According to data published over the past year, healthy pregnant women are likely to be more susceptible to SARS-CoV-2 infection than non-pregnant women. This is

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most probably due to adaptive changes in the woman's immune system during pregnancy, resulting in altered immune responses to infections during pregnancy [3–5]. In addition, there are several anatomical changes that take place in the pregnant woman's respiratory system. A reduction in chest volume leads to decreased functional residual capacity, end-expiratory volumes, and residual volumes. These further result in a reduction of total lung capacity and an inability to clear secretions. These are the most significant factors that can make pregnant women more-than-otherwise susceptible to severe respiratory infections, including Coronavirus disease 2019 (COVID-19) [6]. Another important issue is the possibility of additive or synergistic risk factors for thrombosis in pregnant women affected with COVID-19. It is already established that COVID-19 is associated with high rates of thromboembolic complications [7]. Due to various changes in the coagulation response during pregnancy, which include increased thrombin production, increased intravascular inflammation and higher levels of plasminogen, pregnant women are at an increased risk of thromboembolic events [8, 9]. In light of the above, current guidelines suggest that all pregnant woman diagnosed with COVID-19 should have thromboprophylaxis postnatally until the 10th day [10].

Emerging evidence suggests that endothelial cell dysfunction plays a significant role in the onset and progression of acute respiratory distress syndrome [11], which is the main cause of mortality in COVID-19 [12–14]. Endothelial cell dysfunction is also observed in women with preeclampsia [15]. These data may suggest that this group is at a higher risk of developing severe COVID-19 [16].

IMPACT OF SARS-COV-2 ON PREGNANCY

Since January 2020, several studies have described the presentation and clinical course of COVID-19 in pregnancy. Up till now it appears that pregnant women are not at an increased risk of developing severe COVID-19 [17]. Wastnedge et al., reviewed data from 31 studies with quite reassuring results. Of more than 12,000 pregnant women with COVID-19 diagnosed, the majority developed mild to moderate symptoms, and only few women required critical care facilities. In the same review, the authors found that overall, 146 deaths had been reported. Severe complications of COVID-19 during pregnancy are rare but these can occur. Pre-existing comorbidities, advanced maternal age, and high body mass index seem to be risk factors for severe COVID-19 [18]. Based on the collected data, less than 10% of infected pregnant women required admission to an intensive care unit [19]. Most of those admitted to ICU suffered from pneumonia, acute respiratory distress syndrome (ARDS), or multiple organ dysfunction syndrome (MODS) [20–22].

COVID-19 AND HYPERTENSIVE DISORDERS IN PREGNANCY

Hypertensive disorders are the most common medical complications of pregnancy and a major cause of maternal and perinatal morbidity and death. Detecting elevated blood pressure during pregnancy is one of the cardinal aspects of optimal antenatal care. With the outbreak of novel coronavirus-19 disease important is to check all COVID-19 diagnosed pregnant women for hypertensive disorders [7].

Mendoza et al. [23], carried out an observational study in which they found some features of preeclampsia (PE) in women with COVID-19 infection. Although there is a variant pathomechanism between actual preeclampsia and preeclampsia connected with SARS-CoV-2, it can be difficult to differentiate based on clinical symptoms. Detailed laboratory assessment, including angiogenic factors can be helpful in distinguishing between the two conditions. PE-like syndrome, in contrast to preeclampsia, can resolve spontaneously after recovery from severe pneumonia and may not be an obstetric indication for delivery. PE-like syndrome is a symptom of COVID-19, and not connected with placental failure.

VERTICAL TRANSMISSION OF SARS-COV-2

Among studies that include neonatal test results for SARS-CoV-2, only a few of them report COVID-19 positive cases [7, 24, 25]. It remains unclear whether infection occurs in utero, or during labour, or at birth as the tests have mostly used polymerase chain reaction (PCR)-based methods. More evidence is required on this subject, especially in terms of routine PCR and antibody testing in neonates.

EFFECTS OF VIRAL INFECTION ON THE FETUS

In the majority of the studies reporting on neonatal outcomes, no serious adverse outcomes in the neonates born to SARS-CoV-2 positive mothers have been observed [17]. Available data comparing the neonatal outcomes in a group of symptomatic COVID-19 mothers with those of symptomatic non-COVID-19 mothers, found no significant differences in the rates of adverse neonatal outcomes [26].

MEDICAL HEALTH AUTHORITY GUIDELINES

The American College of Obstetricians and Gynaecologists (ACOG), the Royal College of Obstetricians and Gynaecologists (RCOG) and the Polish Society of Gynaecologists and Obstetricians (PTGiP) recommend testing all pregnant women admitted to hospital, and not only those with COVID-19 symptoms, due to the asymptomatic course of the disease. Treatment of typical diseases during pregnancy in asymptomatic patients with COVID-19 should be carried out using standard procedures. However, if a patient has

dyspnoea, fever, a deterioration in their general condition, they may require some or all of these additional treatments: oxygen therapy, antibiotics, steroid therapy, and thromboprophylaxis. Mode of delivery will depend on obstetric indications. COVID-19 is not an indication for caesarean section itself unless the symptoms of COVID-19 cause the woman's condition to deteriorate [27, 28].

According to most medical health authorities, including the World Health Organization (WHO), RCOG, ACOG, and the Centers for Disease Control and Prevention (CDC), COVID-19 is not a contraindication for breastfeeding, which is recommended for all women who wish to breastfeed. Up till now, there is no evidence of serious adverse events in neonates, therefore patients with confirmed SARS-CoV-2 infection should be encouraged to continue breastfeeding, while taking adequate precautions to prevent transmission of the virus to the baby [27–29]. According to the Polish Neonatal Society, and the National Perinatology Consultant in accord with the National Infectious Diseases Consultant, breastfeeding is recommended to all women who wish to breastfeed. It is only contraindicated when the general condition of the mother or the baby requires medical assistance. The decision to breastfeed is left to the mother following a documented written informed consent process has been completed prior to childbirth, where the possible risks and benefits of breastfeeding for the neonate as well as the negative impact of isolation on the mother are made clear [30].

Vaccination in pregnant women

Specific clinical trials of COVID-19 vaccines in pregnant women have not yet been carried out. Worldwide, there are numerous discrepancies between local guidelines regarding the safety of COVID-19 vaccines during pregnancy. According to the ACOG, COVID-19 vaccines should not be withheld from pregnant and lactating individuals who meet the criteria for vaccination based on the Advisory Committee on Immunization Practices (ACIP) [28]. According to the RCOG, vaccination can be discussed with pregnant and / or breastfeeding women if they are clinically in an extremely vulnerable group or if they are frontline health or social care workers, including working in a residential care facility [27, 31]. In Poland, the PTGiP emphasises that pregnant women with active COVID-19 are burdened with a higher risk of severe disease but the authority has not yet released a statement about vaccination [32]. According to the Danish Health Authority, pregnant or breastfeeding women will not be offered vaccination. However, in exceptional cases, for example in the presence of severe chronic diseases, a pregnant woman may be offered a vaccination based on an individual medical assessment [33]. According to the Health Service Executive in Ireland (HSE), pregnant and breastfeeding women should receive a COVID-19 vaccine when it is available to them; and the first dose should be given no sooner than 14 gestational weeks, and the second dose should be given before the end of 34 weeks of gestation [34]. The Swiss Bundesamt für Gesundheit (BAG) and Belgium's Superior Health Council do not recommend COVID-19 vaccination for pregnant women. Only those women with specific chronic diseases should be considered on a case-by-case basis [35, 36]. The most recent data presented by Mullins et al., based on a group of 4,005 pregnant women with either suspected or confirmed SARS-CoV-2 infection, has indicated the need for enhanced precautions to prevent SARS-CoV-2 infection in pregnancy, particularly in the context of the increased risks of preterm delivery and maternal mortality, and the need for priority vaccination of women planning pregnancy [37].

SUMMARY

Scientists are constantly expanding our understanding of COVID-19. Due to relative lack of experience with the novel disease, both pregnant women and obstetricians all around the world became anxious about the impact of SARS-CoV-2 infection on pregnancy outcomes. The above review is reassuring, showing that in most pregnant women, COVID-19 is not likely to become a severe life-threatening condition, neither for the mother nor for the neonate. The most recent treatment recommendations include the safest procedures for pregnant women, mothers, and their children immediately following delivery.

There are still many unknowns that require further study. Firstly, any mechanism of vertical transmission should be identified if such exists. In addition, it is paramount to discover whether infection during pregnancy is likely to lead to any long-term adverse effects in offspring, and whether such effects are dependent on gestational age at time of infection. Therefore, a database of all infected pregnant woman should be established and made available for further investigations and follow-up studies.

Finally, scientists should be urged to include pregnant women in the clinical trials of new treatment methods and prophylaxis in order to establish the safety of these methods for this particular group.

Conflicts of interest

The authors declare no conflict of interest.

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Management of birth, postpartum care and breastfeeding — Polish recommendations and guidelines during SARS-CoV-2 pandemic

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ABSTRACT

SARS-CoV-2 pandemic is an unusual phenomenon in the modern obstetric and midwifery history. Hospital staff from the isolation wards were trained in the safety and proper use of the hazardous materials suit and the proper managing of the biohazard materials. We were not expecting the situation, so we started to create more restrictions than facilities for mothers giving birth. In the context of infection risk for the fetus, scientists still search for vertical transmission evidence, but available data are ambiguous, and more research is needed. Concerning the infant safety and to minimalize the infection risk for medical teams, the first Polish guidelines published by the national consultants in obstetrics, midwifery, neonatology, and perinatology regarding the safest formula of birth were as the following: in the case of confirmed SARS-CoV-2 infection, the cesarean section for epidemic indications should be considered, except in an advanced or rapid labor. In the lately updated consensus (14th May), it was written that because the risk of vertical and intranatal SARS-CoV-2 transmission seemed to be low, the SARS-CoV-2 infection was not the main indication to perform cesarean section for any longer. Regardless of the birth formula, the newborns are separated from their mothers immediately after the labor in Polish obstetrician hospitals. The Polish Lactation Study Centre, consociating International Breastfeeding Certified Lactation Consultant, recommends feeding the newborn with its own mother's milk, even if she is infected with SARS-CoV-2 and isolated from her infant.

Key words: pregnancy; newborn; SARS-CoV-2; Polish guidelines

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INTRODUCTION

SARS-CoV-2 pandemic is an unusual phenomenon in the modern obstetric and midwifery history. We were not expecting the situation, so we started to create more restrictions than facilities for mothers giving birth.

In Poland, we approved the COVID-19 case definition as was proposed by the World Health Organization (WHO), adapted also by the European Centre for Disease Prevention and Control (ECDC) in which three clinical situations were distinguished: a suspected case, a probable case, and a confirmed case [1]. A suspected case is also defined as a neonate born to a mother with a history of 2019-nCoV infection between 14 days before delivery and 28 days after delivery, or the neonate directly exposed to those infected with 2019-nCoV (including family members, caregivers, medical staff, and visitors) [2].

Pregnant women do not seem to be more likely to have SARS-CoV-2 infection than the general population, and it was confirmed in a large study of 16,749 patients with COVID-19 hospitalized in the United Kingdom. The proportion of pregnant women with SARS-CoV-2 infection (6%) was comparable to the proportion in the general population. Moreover, pregnancy was not associated with increased mortality. Another noteworthy observation was made in New York, where a group of 215 women in attendance for childbirth were screened for SARS-CoV-2 infection over a two-week period (nasopharyngeal swab) and 15.4% of them were tested positive for SARS-CoV-2 infection. Of those 215 women, only four (1.9%) presented COVID-19 symptoms, while most were asymptomatic [3]. Scientists still search for vertical transmission evidence, but available data are ambiguous, and more research is needed [4].

RECOMMENDATIONS

The first public restrictions in Poland started on 13th March, when the Polish government announced the Risk of Epi-

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demic Status (Journal of Laws of the Republic of Poland, No 2019.1239) [5]. Within this act, some regulations were crucial for the health service functioning, especially:

- The duty of undergoing a health examination or applying other prophylaxis measures by the infected or suspected of being infected persons or those being in the group of high risk of infection [46 b. (4) section of act].
- The duty of quarantine [46 b. (5) section of act].
- The type and extent of patients' medical history, including personal data protection and information regarding the patients' health status (46 ba. section of act).
- A list of hospitals which had to be transformed into isolation hospitals.

On 20th March, the Polish government announced the Epidemic Status (the Ministry of Health Regulation, 20th March: Journal of Laws of the Republic of Poland, No 491) [6].

Since that time, all hospitals were obliged to modify their procedures, especially:

1. Admission to a hospital [7]
    - Triage must be held in special restricted areas. The medical staff is obligated to use the means of personal protection — certified face masks, face shields, or goggles. A temperature measurement is obligatory as well as a patient's epidemiology anamnesis.
    - Patients in the low-infection-risk group are admitted to hospital in the special areas for low-risk patients, and patients from the high-risk group (elevated body temperature, contact with infected person, the fact of quarantine) are to be directed to the special wards — dedicated for the infected patients or suspected of being infected.
    - The next step is taking a nasopharyngeal swab from patients in the high-risk group and sending the specimen to a sanitary-epidemiological station. During the time of waiting for the swab result, the medical staff is obligated to follow the safety rules (using the means of personal protection — certified face masks with FFP2/FFP3 or N95 filter, face shields, or goggles). Patients are obligated to use a certified face mask (with FFP2/FFP3 or N95 filter).

The obstetrician hospitals were obliged to modify their procedures and aforementioned areas . We split the E&A into two separate areas. In the area for the infected patients or patients from the high-risk group of infection, we can perform cardiotocography, ultrasounds, childbirth, and cesarean section. The hospital staff from the isolation wards were trained in the safety and proper use of hazardous materials suits and the proper managing of the biohazard materials (*e.g.*, blood).

2. Childbirth
    - The Polish national consultant in midwifery and obstetrics, the national consultant in neonatology, the national consultant in perinatology, the chairperson of Polish Association of Gynecologists and Obstetricians, the chairperson of Polish Association of Neonatologists, and the chairperson of Polish Association of Perinatal Medicine concerning a childbirth in the dedicated isolation ward for pregnant women in the case of the suspicion of SARS-CoV-2 infection or confirmed infection: In the case of confirmed SARS-CoV-2 infection, the cesarean section for epidemic indications should be considered, except in an advanced or rapid labour. […] The argument for the cesarean section is:
        I. The possibility of the fetus being infected in the birth canal or the general area (urinary tract, gastrointestinal tract). […] the discharges amount is reduced during the cesarean section.
        II. […] a significant risk for medical staff — obstetricians and midwives. A much longer natural childbirth (with more than one staff shift) and a reduced amount of means of personal protection and the staff' exposer time is significantly difficult and leads to a higher risk of quarantine for the medical staff, which reduces a possibility to giving care for the other infected patients. Moreover, the medical staff is not able to look after other, not-infected patients" [8].
    - In the most recently updated national obstetrics, gynecology, and perinatology consensus, issued on 14th May, it is written that because the risk of vertical and intranatal SARS-CoV-2 transmission seems to be low [9, 10], the SARS-CoV-2 infection is not the main indication to perform cesarean section currently. Under the obstetrician's consideration remains the final decision (the local wards and staff work organization and patient's clinical situation as well) [10].
    - Since 16th April, according to The Council of Ministers Regulation [11], the face and nose covering is mandatory: 2) in public places, including: b) in establishments of employment and public buildings dedicated to: […] health service centers […]". It means that even women during the childbirth should be encouraged to use a face mask.

This regulation was very controversial for pregnant women in Poland. The Childbirth with Dignity Foundation (the organization campaigning for the pregnant and delivering women rights in Poland) took a stand against this law and wrote an official statement to the Ministry of Health [12]. The reply from the Ministry of Health was equivalent in meaning. Since 28th April, a healthy woman during the first, second, or third stage of childbirth does not have to cover her face or nose under the condition of staying in an individual delivery room. Moreover, this

exception does not concern the infected patients or women under the quarantine period [13].

- Family childbirths were suspended since 13th March, when the Polish government announced the Risk of Epidemic Status in the country. The first actualization was published on 5th May [14]. The national consultant in obstetrics and gynecology and the national consultant in perinatology recommend:
  - The epidemiological questionnaire should be filled by the patient and her accompanying person.
  - The accompanying person is obligated to use a face mask all the time during his/her presence in the hospital.
  - The accompanying person should have an actual nasopharyngeal swab result for SARS-CoV-2, and the swab result is valid only for 5 days.
  - The patient and her accompanying person should stay in an individual delivery room with the separate sanitary unit.
  - The accompanying person may come into the delivery room when the childbirth starts and should leave the hospital in two hours' time after the labor.
  - The persons isolated or under the quarantine period cannot be present during the childbirth.
  - The final decision about family childbirths is made by the hospital chairman.
  - Visits in the hospital wards are suspended.

3. Postpartum period
   a) Management of infants born to mothers with the COVID-19 infection or mothers suspected to be infected.

      The procedure of separation of newborn from its mother (SARS-CoV-2 positive or suspected) immediately after the labor is practiced in Polish obstetrician hospitals, as suggested by some authors [15], but this procedure does not comply with the WHO mothers' recommendations according to which a mother can hold her newborn skin-to-skin and share room with her own baby [16]. The Centers for Diseases Control and Prevention also recommends giving a choice to the mother whether she prefers a temporary separation from her newborn in hospital. If her choice is to stay with the baby, then a two-meter distance is recommended. Additionally, some physical barriers (such as a curtain) may be indicated to minimize the risk of virus transmission. The mother should wear a face mask and wash her hands frequently [17].

      The Polish mothers report separation as an extremely soul-crushing and oppressing procedure. We strongly believe that Polish hospitals can change this policy because research results are reassuring and the newborn separation from its own mother should not be a standard practice in defiance of WHO recommendations.

   b) Breastfeeding.

      The Polish Lactation Study Centre, consociating International Breastfeeding Certified Lactation Consultant, recommends feeding the newborn with its own mother's milk, even if she is infected with SARS-CoV-2 [18]. Until now, there is no scientific evidence of virus' presence in mother's milk. Moreover, only the SARS-CoV-2 antibodies were found. The WHO states that mothers with confirmed SARS-CoV-2 infection can breastfeed their infants [16].

      The Polish guidelines for mothers are:

      a) Breastfeeding and general rules [18]:
         - Before breastfeeding and any contact with the baby, the mother should wash her hands for at least 30 seconds, using a detergent or an alcohol-based disinfectant, cover her face using a disposable face mask (utilize it only for single use) […].
         - An infant may stay in one room with the mother but the distance between them should be two meters.
         - Care of the baby should be taken by a healthy family member.
         - The above-mentioned obligations should be fulfilled for 5–7 days (an usual time of infection symptom regression).

      b) Procedure for milk expression:
         - Every single milk expression requires strict hygiene rules: washing and disinfecting hands before and after touching the milk pump and washing and disinfecting the milk pump after expressing (or using "one-day" sets). Feeding the baby from the bottle should be performed by a healthy family member.

According to the Polish Lactation Study Centre guidelines [18]:

a) If a healthy mother came back from a country where there are infection cases (in the last 14 days) or in the last 14 days she had a direct contact with a person infected with SARS-CoV-2 or a person suspected of being infected (under quarantine) or she was informed by the sanitary-epidemiological station that she had a contact with a confirmed COVID-19 case, the rules are as following:
   - Contact a sanitary-epidemiological station or a free-of-charge hotline (for Poland country area 800-190-590).

- Also contact a GP (the list of clinics: http://www.nfz.gov.pl/).
- Observe the flu-like symptoms and measure the body temperature twice a day.
- Limit personal contacts, if possible.
- Stay at home.
- Wash hands rigorously before every single contact with the infant, especially before breastfeeding or milk expressing.
- Breastfeed or feed the infant expressed milk while strictly obeying the hygiene rules.

b) Mother with confirmed COVID-19 infection, staying home [18]:
- Contact a sanitary-epidemiological station or a free-of-charge hotline (for Poland country area 800-190-590).
- Also contact a GP (the list of clinics: http://www.nfz.gov.pl/).
- Isolate from family members (separate bathroom if possible, separate towels, cutlery, dishes, handles, and worktop disinfection).
- Wash hands for at least 30 seconds, using a detergent or an alcohol-based disinfectant.
- Use a disposable face mask during breastfeeding.
- Between breastfeeding, the infant may stay in one room but the distance between them should be two meters; additionally, a curtain may be used.
- Isolation from baby may be required (depending on the mother's general condition).
- If isolation is required, the milk expressing rules described elsewhere in the guidelines should be followed [19]. Authors affirm that passing on the milk from a mother who is hospitalized or isolated in hospital to her infant staying home may be difficult. They suggest sustaining the lactation.
- Wash and disinfect hands before and after touching the milk pump, and wash and disinfect the milk pump after expressing (using "one-day" sets, if possible).
- Feeding the baby from the bottle should be performed by a healthy family member.

c) Mother with confirmed COVID-19 infection, staying in hospital (when the infant stays at home):
- Keep the lactation process by a regular milk expression.
- Take under consideration that feeding the infant its mother's milk may be impossible because of organization and safety rules.
- Feed the infant the human milk from the human milk bank or sufficient milk formula.
- After hospitalization or isolation, breastfeed according to the rules described elsewhere in the guidelines [19].

The current outbreak of COVID-19 has become the most serious public health emergency at this time. Though the majority of cases are seen in the adult population, newborns and children seem not to be exempted from the epidemic. Since there are only a few cases of SARS-CoV-2 infection in neonates, there is no equivalent-in-meaning evidence to support the possibility of vertical transmission. Clinical presentation in neonates is not specific, and the commonly observed symptoms are temperature instability, respiratory distress, poor feeding, lethargy, vomiting, and diarrhea [20].

CONCLUSIONS

The new SARS-CoV-2 pandemic has caused unprecedented and serious restrictions. Our knowledge and understanding are updated day by day, but pregnant, delivering, and breastfeeding women affected by the COVID-19 infection need our efficient and responsible response at this moment in time.

We believe that our collaborative research effort can hold safe and unharming procedures and recommendations. We want to share our experience and are looking for other countries guidelines to improve our everyday care, based on the evidence-based medicine.

Conflicts of interest

The authors declare no conflicts of interest with respect to the authorship and/or publication of this article.

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Corpus luteum in ectopic ovarian tissue miming tubal pregnancy

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ABSTRACT

We report an extraordinarily rare case of a pregnant patient with history of multiple ovarian cyst surgery. The corpus luteum developed on an ectopic ovarian tissue, miming an tubal pregnancy. One week later after the diagnostic laparoscopy an intrauterine pregnancy was visualised. Therefore, ectopic ovarian tissue with normal follicular activity may appear after multiple ovarian surgery.

Key words: corpus luteum; ectopic ovarian tissue; ectopic pregnancy; tubal pregnancy; ovarian surgery

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INTRODUCTION

Ovarian cyst surgery can lead to fragmentation of the normal ovarian tissue that has the potential of peritoneal implantation, thereafter, becoming ectopic ovarian tissue. Exceptionally this ovarian tissue can be functional and a corpus luteum may be present at this level.

CASE REPORT

A 33-year-old primipara, primigesta, with a history of multiple ovarian cysts surgery (including the last laparoscopic dermoid cysts excision five years ago), was admitted to the emergency department for severe abdominal pain and a positive pregnancy test. She was at four weeks of amenorrhoea. The human chorionic gonadotropin (HCG) serum concentration, in the emergency department, was 438 mUI/mL. The transvaginal ultrasonography revealed an adnexal right structure of 27.9 × 13.4 mm suggestive for ectopic pregnancy and liquid in the Douglas pouch (20 × 12 mm) (Fig. 1 A, B). In our case the patient required emergency laparoscopy and had no dynamic monitoring of HCG.

During diagnostic laparoscopy, both fallopian tubes and ovaries were normal without corpus luteum. An elongated cystic structure of 3 × 1.5 cm corresponding with a corpus luteum developed on the right ectopic ovarian tissue was found miming an extrauterine pregnancy (Fig. 1 C, D). Cytological analysis of intracystic liquid was realized with evidence of hemorrhagic liquid with luteinized granulosa cells. The liquid in the Douglas pouch was serocitrin.

One week later we performed a transvaginal ultrasound and a single intrauterine pregnancy was visualized and currently the patient has 14 weeks of gestation. At that time, the patient gives informed consent for publication.

DISCUSSION AND CONCLUSION

The incidence of ectopic pregnancy seems to rise especially in developing countries due to pelvic inflammatory disease, endometriosis, smoking and the assisted reproductive techniques [1, 2]. The typical symptoms are unilateral abdominal pain and vaginal bleeding between 6 and 10 weeks of gestation and the diagnosis is confirmed by measurement of serum HCG and ultrasound exam. An anechogenic ultrasonographic adnexal mass is highly suggestive for a corpus luteum and must be distinguished of an ectopic pregnancy that has an endometrium like echogenicity aspect [3].

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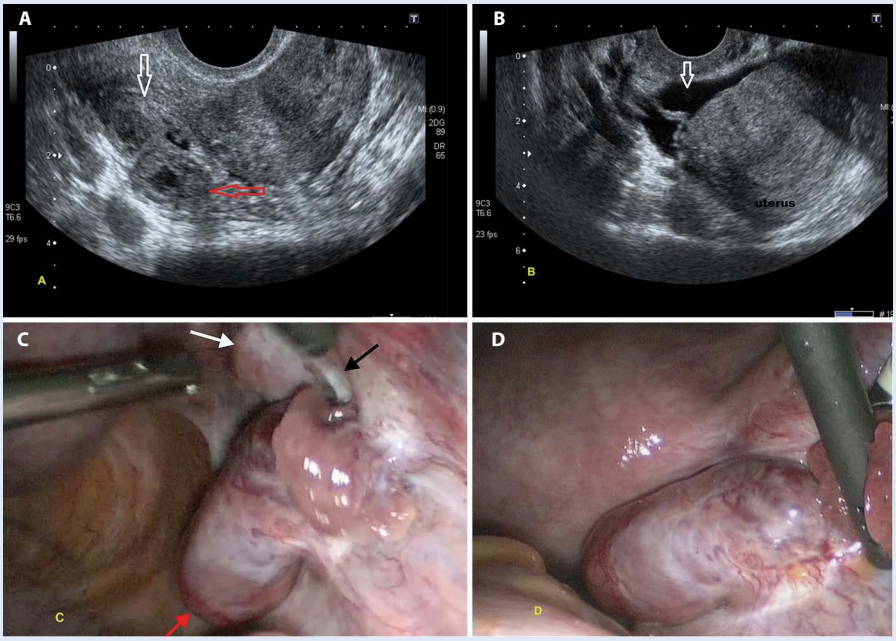

Figure 1. Transvaginal ultrasonography; **A.** The right ovary. The white arrow shows the right ovary and the red arrow shows the suspected ectopic pregnancy; **B.** The liquid in the Douglas pouch (white arrow); Laparoscopy; **C.** The corpus luteum developed on the right ectopic ovarian tissue; **D.** The red arrows shows the corpus luteum on the ectopic ovarian tissue. The black arrow shows the fallopian tube. The white arrows shows the right ovary

Differential diagnosis may be made with other adnexal masses such as functional cyst, benign pathology, borderline or malignant adnexal disease as well tubal, ovarian or synchronous intrauterine and ectopic pregnancy [4]. Ovarian or tubal torsion may be among the causes of acute pelvic pain [5].

In the case of suspected ectopic pregnancy, the surgery is proposed when the patient have severe pain or signs of complicated ectopic pregnancy. Therefore, in the surgical treatment of an ectopic pregnancy, the most important elements which define the choice of the best treatment are the severity of the disease, the clinical characteristics of the patient and her desire to preserve fertility, all in accordance with the patient desire. In our case to avoid false diagnoses ideally, we should have done a dynamic HCG evolution, but the patient presented with intense abdominal pain at the emergency room, with clinical criteria for an emergency surgical exploration.

When a history of ovarian surgery is known and in the presence of adnexal masses, we must consider the possibility of ovulation of an ectopic tissue that could mimic an ectopic pregnancy.

As far as we know there are no reported cases of corpus luteum in ectopic ovarian tissue.

Authors' contributions

All authors contributed equally to this article.

Conflict of interest

There was no potential conflict of interest was reported by the author(s).

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Recurrent cesarean scar pregnancy treated successfully with uterine artery chemoembolization

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Key words: cesarean scar pregnancy; recurrent; chemoembolization

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Cesarean scar pregnancy (CSP) is a rare but life-threatening condition representing approximately six percent of all ectopic pregnancies in women with history of cesarean delivery [1]. Treatment options vary from medical management, surgical procedures and endovascular approach and aim to prevent serious complications (massive hemorrhage, uterine rupture) and preserve fertility [2]. Superiority of any from the above-mentioned treatment modalities as well as their impact on subsequent pregnancies is a matter of an on-going debate. To date, only few reports on recurrent cesarean scar pregnancy (RCSP) are available in the literature [3, 4]. We hereby present such a case treated successfully with uterine artery chemoembolization (UAC).

A 34-year old female G6P3114 (3 cesarean deliveries, 1 miscarriage, 1 ectopic pregnancy — CSP treated with UAC and 4 living children) was admitted to the Department of Gynecology for prenatal care at eight weeks of gestation. The patient reported minor vaginal bleeding a few days prior to the examination. A physical examination disclosed no abnormalities. Laboratory tests revealed a serum β-hCG of 49.796 mIU/mL. The hemoglobin and red blood cell counts were within the reference ranges. Transvaginal ultrasound (TVUS) showed a gestational sac measuring 50 × 25 mm located in the cesarean scar (Fig. 1A, B). CRL of 0.44 cm corresponded to gestational age of six weeks and two days. Fetal heart rate was detected.

After multidisciplinary consultation and informed consent from the patient she was referred for UAC. The reason for this treatment was twofold. Firstly, the dose of methotrexate is lower compared to systemic therapy. Secondly, temporary embolization of uterine arteries reduces the blood loss during suction curettage. In all sterile conditions selective catheterization of both uterine arteries was performed (Fig. 1C, D). A total dose of 50 mg methotrexate, half of which was mixed with gelatin sponge powder, was administered bilaterally until complete obliteration of the vascular supply to the gestational sac. In control TVUS examination 24-hours after the procedure no evidence of fetal cardiac activity was noted, and suction curettage was performed. Gradual drop of serum β-hCG levels was observed in the following days. After five days the patient was discharged in good clinical condition with strict precaution to return to the emergency in case of any disturbing symptoms.

The significant increase in cesarean deliveries observed in the last half of century has led to the increase in the rate of CSP. However, cases of RCSP are extremely rare and since first reported by Hasegawa et al. [4], only a limited number of patients is available in the literature. Currently there are no guidelines for the management of neither CSP nor RCSP, but early termination is recommended. Treatment possibilities include non-surgical (intragestational/systemic MTX administration) and surgical (laparoscopic evacuation, open excision, embolization) methods. Although some authors suggest that the management of CSP might correlate with the occurrence of RCSP the evidence is scarce [5]. Therefore, all patients with history of CSP require special attention and should undergo early sonography in subsequent pregnancies in order to ensure a normal position of the pregnancy in the uterus and exclude RCSP.

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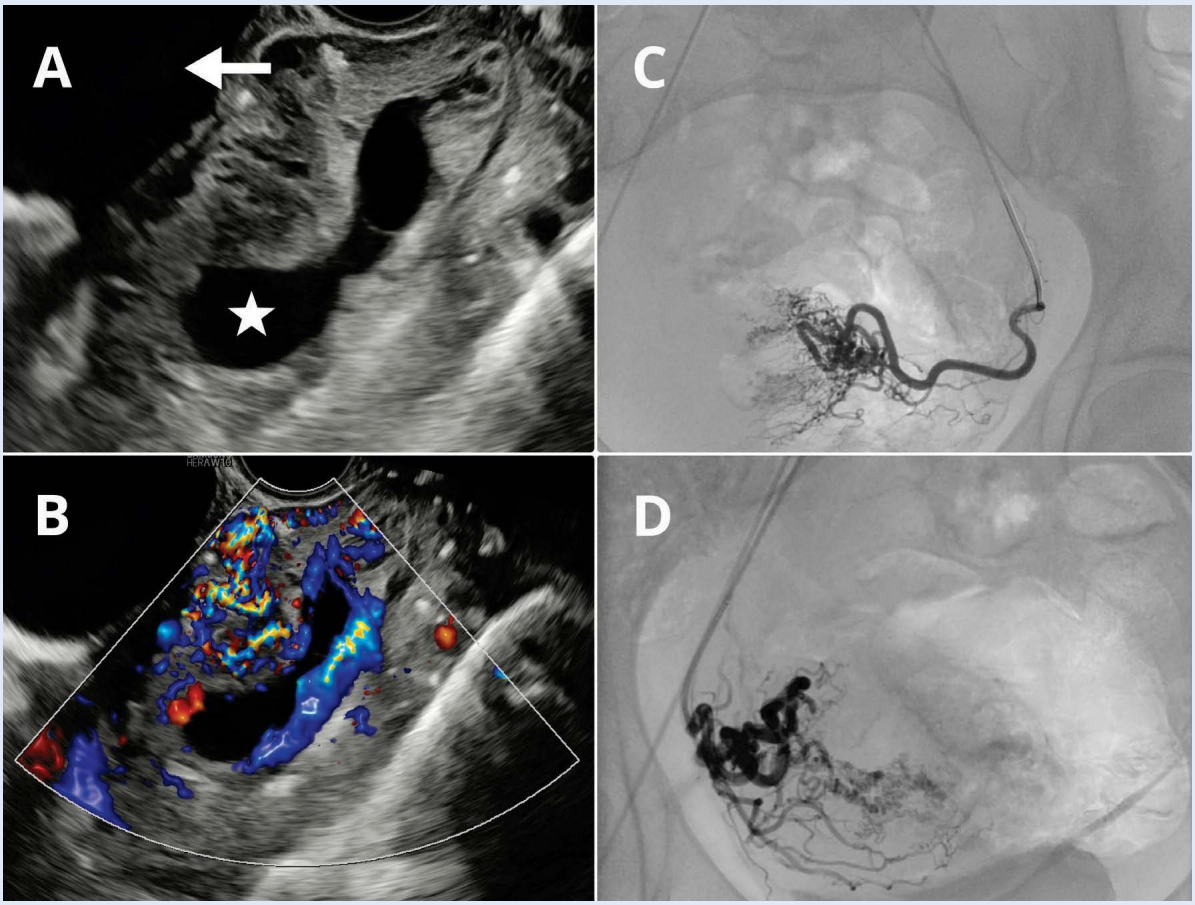

Figure 1. Transvaginal ultrasound examination showing; **A.** Gestational sac (star) with its lower part in the prior cesarean scar and urinary bladder (arrow); **B.** Numerous blood vessels. **C, D.** DSA (Digital Subtraction Angiography) showing selective angiography of uterine arteries

Conflict of interest

None.

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A case of late diagnosis and management of 46 XY complete gonadal dysgenesis in adulthood

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Key words: 46 XY complete gonadal dysgenesis; prophylactic gonadectomy; germ cell tumor; difference of sex development

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We present a case of 23-year-old woman with primary amenorrhea on hormonal replacement therapy referred for the first time to the Department of Gynecological Endocrinology. Her medical history revealed hypergonadotropic hypogonadism. On her physical examination she had tall stature, female phenotype and external genitalia, Tanner stage IV breast and pubic hair development. Vagina and normal uterus were confirmed on the gynecological exam. Pelvic ultrasound and MRI revealed remnant follicular structure (< 1 cm) localized in the right ovarian fossa, whereas there were no visible structures in the left ovarian fossa. The 46 XY karyotype was confirmed, however, molecular diagnosis was not available at the time of surgery. After she was diagnosed with 46 XY complete gonadal dysgenesis (historically named Swyer syndrome), the multidisciplinary team gathered.

Patients with differences of sex development (DSD, also known as disorders of sex development) are at risk of gonadal tumor development. The individual risk assessment is based on genetic analysis, clinical phenotyping, and biochemical analysis [1, 2]. Given the patient's age, female phenotype and gender identity, as well as no gonadal function proved on biochemical analysis, the decision for urgent removal of dysgenetic gonads was made. Due to oncological gynecologist qualification, the patient was referred to a bilateral laparoscopic adnexectomy.

During a laparoscopy ovoid shaped gonadal tissue and what seemed to be obstructed Fallopian tube were identified on the right side and streaked gonadal tissue with Fallopian tube on the left side. The uterus and rest of the pelvic cavity showed no abnormalities (Fig. 1). Histopathology of right gonad revealed dominant rete ovarii texture, hilus ovarii with presence of Leydig cells and the microcyst 0.4 cm in ovarian stroma, whereas the left side contained only connective tissue strands (Fig. 2). There was no evidence of invasive germ cell tumor. Hormonal replacement therapy has been reintroduced and patient has been well on follow-up since.

Gonadal dysgenesis is defined as an incomplete formation of the gonads, and it is caused by a disturbed process of germ cells migration into the gonadal ridge. The prevalence of females with 46 XY complete gonadal dysgenesis is estimated on 1.5 per 100,000 live born females [3]. Because of the lack of hormonal (AMH, testosterone) activity of dysgenetic gonads, affected individuals have female phenotype and Mullerian structures [4].

DSD patients have increased risk for gonadal germ cell cancer only in case of presence of the Y chromosome, particularly GBY (gonadoblastoma on the Y chromosome) region with TSPY (testis-specific protein Y) gene [5]. The risk is modulated by patient's age, location and differentiation of the gonads. It is believed to be greater in abdominal than in inguinal or scrotal gonads. Impaired differentiation relates to germ cells being blocked in an embryonic stage of development. Germ cell cancer originates from either germ cell neoplasia in situ (testicular environment) or gonadoblastoma (ovarian-like environment) [5]. Gonadoblastoma, being a preinvasive lesion in dysgenetic gonads, may differentiate into malignant tumors: dysgerminoma or less frequently into teratoma, embryonal carcinoma, yolk sac tumor, and choriocarcinoma [6].

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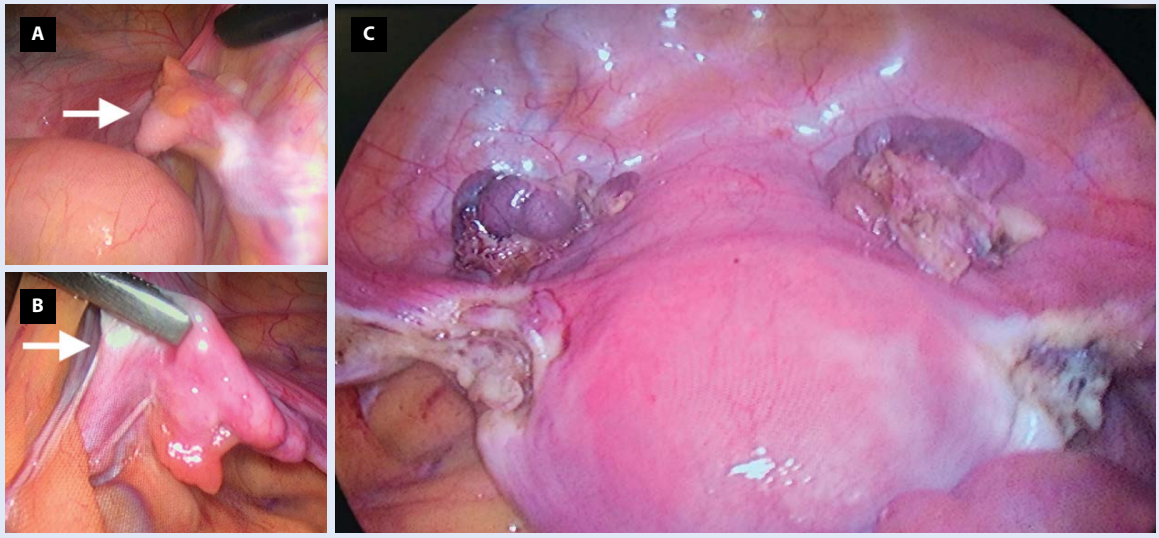

Figure 1. Laparoscopic findings. A — remnant ovoid shape gonadal tissue (marked with arrow) and obstructed distal opening of the Fallopian tube on the right side; B — Streaked gonadal tissue (grasped, marked with arrow) and Fallopian tube on the left side; C — After bilateral adnexectomy - uterus and the rest of pelvic cavity showed no abnormalities

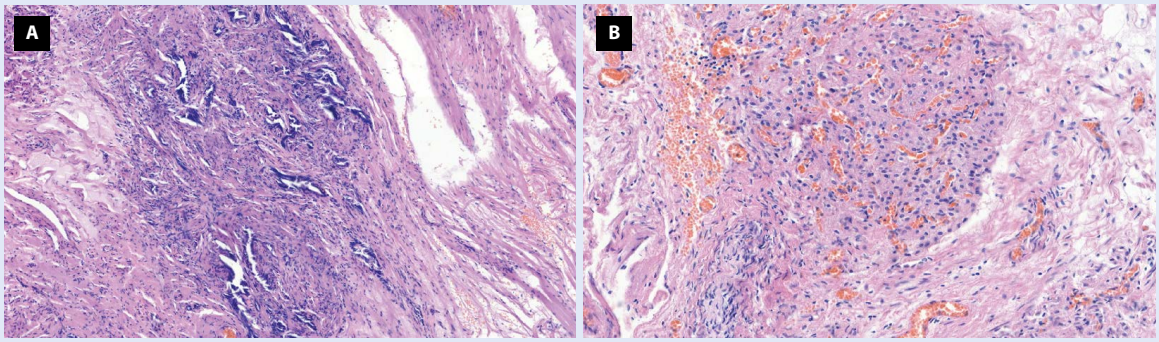

Figure 2. Postoperative histologic examination. A — The structure of rete ovarii in right gonad, hematoxylin and eosin (HE) staining, 10x; B — Leydig cells in the hilum of ovary, right gonad, HE, 20x

Lifetime risk of germ cell tumors in 46 XY DSD individuals varies according to exact diagnosis, however, in patients with complete gonadal dysgenesis is considered the highest and estimated on 12–40% [6, 7]. They are frequently found at a very young age, even in the first year of life [8, 9]. Therefore, in girls with 46 XY complete gonadal dysgenesis, female phenotype and no signs of virilization, early prophylactic gonadectomy before puberty is recommended [8].

Conflict of interests

The authors declare that they have no conflict of interests.

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