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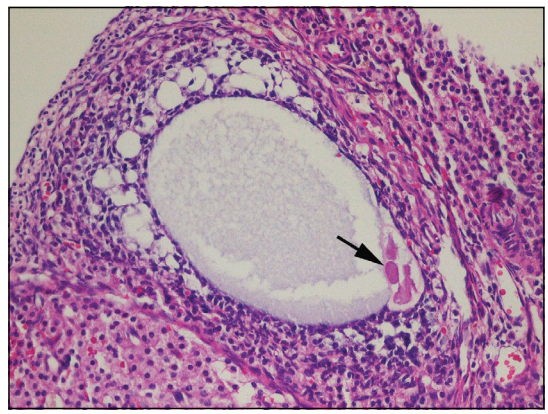

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Prognostic role of PET/CT in endometrial cancer

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ABSTRACT

Objectives: The present study evaluates the prognostic value of metabolic parameters related to the primary tumor identified in preoperative fluorodeoxyglucose (FDG) positron emission tomography (PET)/computed tomography (CT) scans in patients with endometrial cancer (EC).

Material and methods: This study included 120 patients with EC who underwent PET/CT in the preoperative period. The patients' age, maximum standardized uptake value (SUVmax), SUVmean, metabolic tumor volume (MTV) and the total lesion glycolysis (TLG) value of the primary tumor on PET/CT; as well as the stage, histological subtype, grade and size of the primary EC; the degree of myometrial invasion (MI) cervical invasion (CI), lymphovascular invasion (LVI), lymph node metastasis (LNM) and distant metastasis (DM) were all recorded. The relationship of these factors with progression-free survival (PFS) and overall survival (OS) was evaluated.

Results: The study included 120 patients with EC with a mean age of 62.3 ± 0.02 years. Of the total, 32 patients died around the time of the analysis and 38 patients showed disease progression. The mean OS was 32.7 ± 1.6 months and the mean PFS was 30.5 ± 2.8 months. No significant relationship was identified between the SUVmax, SUVmean, MTV, TLG values, patient age, tumor size, histology, grade and MI degree, and OS or PFS. Disease stage, LVI, CI, LNM and DM were identified as prognostic factors for OS and PFS.

Conclusions: The present study found no significant relationship between preoperative PET parameters in EC and OS and PFS, although prospective studies involving a larger number of patients are required.

Key words: endometrial cancer; survival; FDG PET/CT; SUVmax; MTV; TLG

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INTRODUCTION

Endometrial cancer (EC) is the most common gynecological malignancy in developed countries [1]. The majority of patients are diagnosed in the early stage [2], and early-stage EC has a good prognosis with 5-year survival reaching 90% [3, 4]. That said, the rate of recurrence and the risk of death are high in advanced-stage EC [5] with the 5-year survival in the range of 20–26% in stage 4 EC [6]. Aside from disease stage, various other prognostic factors have also been described for EC, including histological type, grade, tumor size, myometrial invasion (MI) and lymph node metastasis (LNM) [7]. These prognostic factors can only be determined after extensive surgery [8], and so preoperative prognostic factors that are particulary important for patients who have comorbidities or for young patients who wish to preserve their fertility are sought. Also, some patients may survive even when faced with the same risk factors as those who do not survive, and additive prognostic factors are sought. F-18 fluorodeoxyglucose (FDG) positron emission tomography (PET)/computed tomography (CT) is a widely used imaging method in patients diagnosed with malignancy. PET parameters have been suggested to have a prognostic value in various cancer types such as lung cancer [9], esophageal cancer [10] and lymphoma [11–13]. There are, however, only a limited number of studies assessing the value of PET in determining the prognosis of EC.

The present study investigates the relationship between the metabolic parameters of the primary tumor on preoperative PET/CT in patients with EC and overall survival (OS) and progression-free survival (PFS). The study also investigates the prognostic value of certain clinicopathological factors in our patient population.

MATERIAL AND METHODS

Patients and follow-up

This retrospective study included 120 patients with a confirmed histopathological diagnosis of EC between April

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2010 and May 2014 who underwent preoperative F-18 FDG PET/CT in our department. None of the patients underwent therapy prior to PET/CT, and after PET/CT they underwent a total hysterectomy, bilateral salpingo-oophorectomy and pelvic (± paraaortic) lymphadenectomy. Patients received adjuvant therapy involving chemotherapy and/or radiotherapy according to the histological subtype, grade and stages noted by the International Federation of Gynecology and Obstetrics (FIGO) 2009. Progression-free patients were followed up every 3 months for the first two years, every 6 months for 2–5 years and once a year thereafter. As a matter of routine during the follow-up visits, medical histories were obtained, gynecological examinations were made, ultrasonographic data was recorded and serum cancer antigen 125 (CA125) levels were tested. Patients with suspected findings for recurrence underwent a pap smear, CT, MRI and/or PET/CT.

F-18 FDG PET/CT

Images were taken from the base of the skull to the upper thigh by a PHILIPS GEMINI TF 16 Slice PET/CT device. After at least 6 hours of fasting, 0.15 mCi/kg F-18 FDG was injected into patients with a blood glucose level of less than 200 mg/dl. The patients were allowed to rest in a quiet room for one hour after the injection, after which the images were acquired. PET images were acquired in 9–10 bed positions, for 1.8 min per bed position. The CT images were used for attenuation correction.

The 3D region of interest (ROI) was drawn for the primary tumor, and the maximum standardized uptake value (SUVmax) pertaining to the primary tumor in the region of interest was measured. SUVmean and metabolic tumor volume (MTV) were calculated, considering the recommended [14] 41% SUVmax as the threshold. The total lesion glycolysis (TLG) was calculated by multiplying the MTV by the SUVmean.

Survival data and statistical analysis

OS was defined as the time from the date of diagnosis to the date of death from EC, or the time of last observation. PFS was defined as the time from the date of diagnosis to the date of progression or death. Survival curves were created for the patients using the Kaplan-Meier method. SUVmax, SUVmean, MTV, TLG values and patient age were considered as a continuous variable. The relationship between patient age, PET parameters related to the primary tumor (SUVmax, SUVmean, MTV, TLG) and OS and PFS was evaluated using the Cox proportional hazard model. The difference in OS and PFS between the groups classified according to the FIGO stage, the histological subtype, grade, size, MI, cervical invasion (CI), lymphovascular invasion (LVI) and distant metastasis was evaluated using the log-rank test. A value of $p < 0.05$ was considered statistically significant in the analyses.

RESULTS

Patient characteristics

The study included 120 patients with a mean age of 62.3 ± 0.02 years (range 42–85 years) who had been diagnosed histopathologically with EC. According to the FIGO classification, 61 patients had stage 1, 26 had stage 2, five patients had stage 3 and 28 patients had stage 4 disease. Furthermore, 67 patients had an endometrioid histology and the remaining 53 patients had a non-endometrioid histology (mixed = 27, undifferentiated = 9, serous = 7, mucinous = 5, squamous = 4, clear cell = 1). Non-endometrioid subtypes were accepted as high-grade carcinoma. Eighteen of the patients with endometrioid carcinoma were grade 1, 35 were grade 2, and 14 were grade 3. The tumor size was ≥ 4 cm in 78 patients, MI was ≥ 50% in 69 patients, CI was positive in 29 patients, LVI was positive in 80 patients, pelvic or paraaortic LNM was positive in 13 patients and DM was positive in 17 patients.

Survival

Of the total sample, 32 died around the time of the analysis and 38 patients showed disease progression. The OS and PFS were 32.7 ± 1.6 months and 30.5 ± 2.8 months, respectively. When all patients are evaluated together in terms of the PET parameters of the primary tumor, the mean SUVmax was 17.3 ± 0.07, the mean SUVmean was 8.6 ± 0.2, the mean MTV was 30.8 ± 0.01 mL and the mean TLG was 295.2 ± 0.002 g. No significant relationship was identified between SUVmax, SUVmean, MTV, TLG values, patient age and OS and PFS ($p > 0.05$) (Tab. 1). Figures 1 and 2 present the PET parameters and survival data of the sample cases. There were no significant differences in terms of OS and PFS between the patients grouped according to tumor size (< 4 cm vs ≥ 4 cm), histology (endometrioid vs non-endometrioid), grade (grade1-2 vs grade 3) and MI degree (< 50% vs ≥ 50%) ($p > 0.05$). OS and PFS were lower in patients with advanced stage than in patients with early stage, in LVİ (+) patients than in LVI (-) patients, in CI (+) patients than in CI (-) patients, in LNM (+) patients than in LNM (-) patients, and in DM (+) patients than in DM (-) patients (Tab. 2).

Table 1. Survival analysis results of PET parameters and age

	Overall survival		Progression free survival	
	p	HR	p	HR
SUVmax	0.800	1.018	0.544	1.045
SUVmean	0.916	0.978	0.667	0.914
MTV	0.865	0.997	0.098	1.016
TLG	0.615	1.001	0.644	0.999
Age	0.820	1.007	0.414	1.022

SUVmax — maximum standardized uptake value; MTV — metabolic tumor volume; TLG — total lesion glycolysis

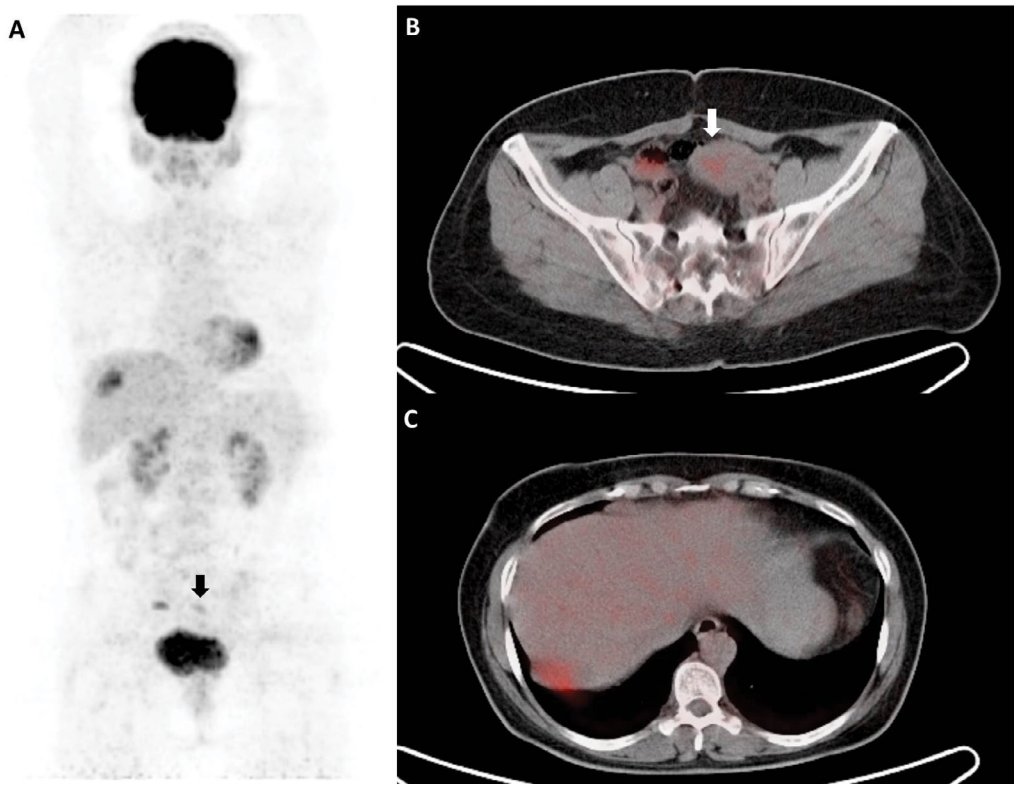

Figure 1. The MIP (A) and selected axial PET/CT (B, C) images of a 56-year-old patient with stage 4B undifferentiated endometrial cancer and a capsular implant in the liver are presented. Among the PET parameters of the primary tumor of the patient (A,B; arrows), SUVmax, SUVmean, MTV and TLG were found to be 3.8, 3, 1.2 mL and 3.6 g, respectively. The progression-free survival and overall survival of this patient were 6 months and 17 months, respectively

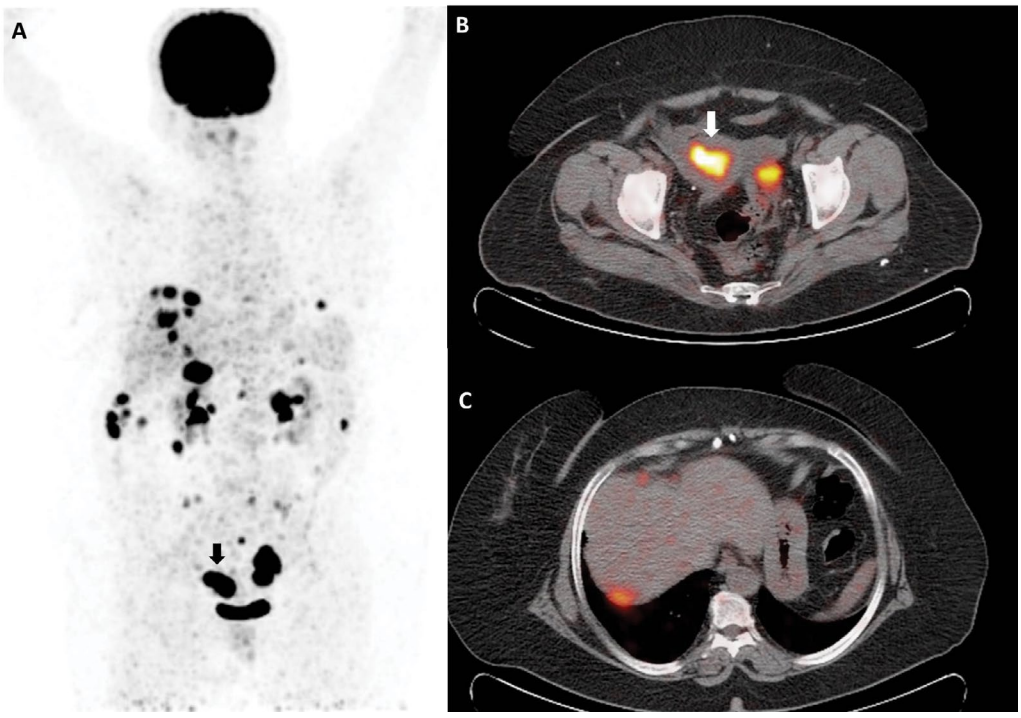

Figure 2. The MIP (A) and fusion (B, C) images of a 61-year-old patient with stage 4B mix endometrial cancer and a capsular implant in the liver are presented. The PET parameters of the primary tumor of the patient (A, B; arrows) were calculated as follows: SUVmax: 24.4, SUVmean: 8.5, MTV: 17.8 mL, and TLG: 151.3 g. The progression-free survival and overall survival of this patient were 8 months and 16 months, respectively

Table 2. Comparison of overall survival and progression free survival between the groups

	n	OS (mean ± SE, months)	p	PFS (mean ± SE, months)	p
Stage 1–2	87	43.7 ± 1.3	< 0.001*	42.7 ± 1.5	< 0.001*
Stage 3–4	33	21.9 ± 4.5		13.9 ± 4.1	
Tumor size < 4 cm	42	38.3 ± 3.0	0.881	36.6 ± 3.8	0.733
Tumor size ≥ 4cm	78	38.8 ± 2.2		36.0 ± 2.5	
LVI (–)	40	44.3 ± 2.0	0.027*	44.3 ± 2.0	0.007*
LVI (+)	80	36.0 ± 2.6		31.9 ± 3.0	
Endometroid	67	42.1 ± 2.1	0.156	41.1 ± 2.3	0.083
Nonendometroid	53	36.3 ± 2.9		32.1 ± 3.4	
Grade1–2	53	**42.8 ± 2.1**	0.190	**41.6 ± 2.3**	0.142
Grade 3	67	**36.7 ± 2.7**		**33.0 ± 3.1**	
MI < 50%	51	42.4 ± 1.9	0.163	41.0 ± 2.3	0.106
MI ≥ 50%	69	36.2 ± 3.0		32.7 ± 3.3	
CI (–)	91	42.6 ± 1.5	< 0.001*	41.6 ± 1.8	< 0.001*
CI (+)	29	25.8 ± 4.8		17.8 ± 4.6	
LNM (–)	107	41.0 ± 1.7	0.001*	39.3 ± 1.9	< 0.001*
LNM (+)	13	17.8 ± 4.8		9.1 ± 3.7	
DM (–)	103	40.9 ± 1.7	< 0.001*	39.2 ± 2.0	< 0.001*
DM (+)	17	17.4 ± 3.7		8.0 ± 2.2	

OS — overall survival; PFS — progression free survival; LVI — lymphovascular invasion; MI — myometrial invasion; CI — cervical invasion; LNM — lymph node metastasis; DM — distant metastasis; significant values (P < 0.05) are indicated with *

DISCUSSION

Most patients with EC are diagnosed in the early stage (FIGO 1–2) [6]. Five-year survival rates are 74–91% in early stage disease, 57–66% in stage 3 and 20–26% in stage 4 [6]. Aside from the disease stage, tumor histology, grade, depth of MI, LVI, presence of LNM and the patient's age can be counted among the clinicopathological prognostic factors [15]. Tumor size and various molecular factors have also been suggested to be of prognostic value in studies, although this is still under research [15]. However, survival may be different even in patients with the same risk factors. Furthermore, a large proportion of the known risk factors rely on staging during extensive surgery, which may be unnecessary in some patients with early-stage disease, and this is the subject of ongoing researches aimed at identifying preoperative noninvasive prognostic factors. FDG PET/CT is an effective imaging method that is used for initial diagnosis, staging, re-staging and evaluating response to therapy in a wide variety of cancers [16]. In the initial staging of endometrial cancer, PET/CT is recommended to detect extrauterine disease [17]. In addition, PET/CT has been shown to be useful in identifying candidates for surgical staging [18] and in determining post-operative recurrence [19]. But, only a limited number of studies evaluated the prognostic value of PET/CT in EC, and the results to date have been conflicting. In a study of 100 patients with stage 1–4 EC, Walentowicz-Sadlecka et al. [8] identified significantly shorter OS in patients with a preoperative SUVmax ≥ 17.7 than in patients with a preoperative SUVmax of < 17.7. Another study involving 42 patients with EC (stage 3C–4) found significantly longer OS in patients with a low SUVmax of the primary tumor (< 9.5) or lymph node (< 7.3) than in patients with a higher SUVmax [5]. In a study of 84 patients with stage 1–4 EC by Shim et al. [7], preoperative MTV and TLG were identified as independent prognostic factors for PFS in EC, although no significant relationship was identified between PFS and SUVmax and SUVmean, or between OS and MTV and TLG values. In a study by Liu et al. [20] involving 15 patients with stage 4B EC, whole body MTV and whole body TLG were found to be significant prognostic factors for survival. The present study found no significant relationship between the SUVmax, SUVmean, MTV and TLG values of the primary tumor and OS and PFS. The heterogeneity of the study population in terms of such clinicopathological factors as stage, histology and grade is believed to be the cause of variety in the results. Furthermore, whole body measurements were carried out in the study by Liu et al., whereas the present study evaluated the PET parameters of the primary tumor. Such methodological differences may have also caused the differences in the results.

The present study identified FIGO stage, CI, LVI, and the presence of LNM and DM as prognostic factors for OS

and PFS, while age, tumor diameter, histology, grade, and MI were not found to be related to OS and PFS. Various risk classification systems have been developed to predict prognosis and to guide treatment of endometrial cancer. Risk factors such as FIGO stage, tumor histology, grade, MI and LVI are evaluated together in these classification systems [15]. However, in our study, we discussed the risk factors one by one. And so, the non-homogeneous distribution of other prognostic factors across the age groups and patients classified in terms of tumor histology, grade, diameter and MI degree, may have also resulted in the difference in the current findings. For example, LNM was mostly present in patients aged < 62 years. In a meta-analysis including 14 studies (672 patients), complete cytoreduction to no gross residual disease for patients with advanced or recurrent endometrial cancer was found to be associated with superior overall survival outcome [21]. However, we did not evaluate the presence of post-treatment residual tumor. Furthermore, although all patients in the present study underwent surgery, post-operative treatments were not standard. Differences in the treatment management may have contributed to current results. In addition, some micrometastases may not be detected during surgery or by PET/CT. The presence of undetectable micrometastasis may also have affected prognosis. AlHilli et al. [22] declared a relationship between tumor diameter and survival. In that study, 2 cm was utilized for the cut-off value of the tumor size [22]. But we used a threshold of 4 cm that may have caused us to find a different result.

In the present study, 5-year survival rates were not evaluated and there were limitations such as relatively short follow-up period and retrospective design.

CONCLUCIONS

No significant relationship was found between PET parameters and OS and PFS, and so prospective studies involving a larger number of patients with more homogeneous groups are needed.

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Palliative treatment of intestinal obstruction in patients with gynecologic malignancies — single center experience

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ABSTRACT

Objectives: One of the common symptoms in patients with advanced gynecologic tumors is intestinal obstruction. Palliative management may include pharmacological treatment, stenting as well as surgical removal of obstruction cause. Selection of appropriate treatment should be based on careful and individual assessment of advantages, disadvantages and possible complications. The aim of the study was to analyze the effectiveness of non-invasive treatment in patients with gynecologic malignancies suffering from intestinal obstruction.

Material and methods: It was a retrospective analysis of factors associated with primary non-invasive intestinal obstruction treatment effectiveness. Data were collected from medical records of 17 patients managed and followed-up in a single gynecologic oncology center due to endometrial cancer, fallopian tube cancer, uterine leiomyosarcoma, and ovarian cancer admitted to the ward because of symptomatic intestinal obstruction. Mean observation time lasted 40.6 months. Non-invasive treatment included fluid therapy, dexamethasone, buscolysin, mebeverine, ranitidine, simethicone, omeprazole, magnesium sulphate, semi-liquid diet, and parenteral nutrition. Characteristics including age, BMI, comorbidities, oncological treatment, histology type, stage, grade, presence of ascites, location of primary tumor and metastases were analyzed.

Results: The number of obstruction episodes varied from 1 to 5. Mean time between multiple episodes lasted 3.2 months. 5 patients required surgical treatment. For the rest of the patients primary non-invasive treatment was sufficient.

Conclusions: Most cases of bowel obstruction in patients with advanced gynecologic malignancies can be successfully managed without invasive treatment. Moreover, non-invasive obstruction management can be applied multiple times in case of recurrence.

Key words: conservative treatment; intestinal obstruction; gynecologic neoplasms; ovarian neoplasms; palliative therapy; surgical procedures, operative

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INTRODUCTION

Palliative care is an integral aspect of oncological treatment. Increasing the quality of life, soothing pain and reducing symptoms of advanced disease is crucial from both medical and ethical perspective [1, 2]. Selection of appropriate treatment should be based on careful and individual assessment of both advantages and disadvantages of available methods, together with possible complications [3–5]. Intestinal obstruction is one of the most common symptoms affecting even every second patient with advanced gynecologic tumors located in the pelvis [6]. Reported incidence of this complication among ovarian cancer patients varies between 20 and 50% [7, 8]. The etiology of intestinal obstruction in this group of patients can be multifactorial — resulting from mass excess and intestinal infiltration, or oncological therapy side effects. Palliative management may include pharmacological treatment, stenting as well as surgical removal of obstruction cause. Apart from relieving the symptoms, obstruction treatment is vital for patient's proper nutritional status as malnutrition affects over half of ovarian cancer patients and may develop into cancer cachexia syndrome, a direct cause of death during oncological treatment [9, 10]. Various studies claim that in case of appropriately selected therapy, pharmacological and surgical treatment are similarly effective [11, 12].

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Objectives

The aim of the study was to analyze which patients with advanced gynecological malignancies may benefit from primary non-invasive treatment, and which require further surgical approach.

MATERIAL AND METHODS

It was a retrospective analysis of factors associated with non-invasive intestinal obstruction treatment effectiveness. Data were collected from medical records of patients managed and followed-up in a single 14-bed gynecologic oncology center. Inclusion criteria were as follows: admission to the ward caused by symptomatic intestinal obstruction and application of primary pharmacological treatment between 2014–2016 resulting in discharge in stable general condition. In case of no improvement after 7 days of non-invasive treatment or intensification of symptoms, initially conservative treatment was considered ineffective and surgical approach was introduced. Exclusion criteria were: intestinal obstruction as a primary complaint leading to initial neoplasm diagnosis followed by the radical surgery.

The non-invasive obstruction treatment protocol included fluid therapy, dexamethasone, buscolysin, mebeverine, ranitidine, simethicone, omeprazole, magnesium sulphate and semi-liquid diet. Patients not tolerating enteral nutrition were qualified for parenteral nutrition according to the European Society for Clinical Nutrition and Metabolism (ESPEN) guidelines [13]. Patients' characteristics including past medical history, comorbidities, age at malignancy diagnosis, time from disease onset, BMI during diagnosis and each obstruction episode, body mass loss, type of applied oncological treatment, histology result, stage, grade, location of primary tumor and metastases, ascites presence, number of obstruction episodes, and type of obstruction management were analyzed. Mean observation time lasted 40.6 months (3–168 months). The FIGO (International Federation of Gynecology and Obstetrics) system was used for ovarian cancer, fallopian tube cancer, endometrial cancer and uterine sarcoma staging [14–16]. Out of 20 patients initially enrolled in the study, 17 met the criteria required for further analysis, presenting altogether 30 episodes of intestinal obstruction. All patients excluded from the study were diagnosed with serous ovarian cancer stage IIIC, grade 3 and underwent radical surgery shortly after the obstruction episode.

RESULTS

Among analyzed 17 patients 1 suffered from endometrial cancer, 2 from fallopian tube cancer, 1 from uterine leiomyosarcoma, and 13 had ovarian cancer: 10 patients serous ovarian cancer, 2 patients endometrioid ovarian cancer, 1 patient clear-cell ovarian cancer (Fig. 1). All patients suffered from

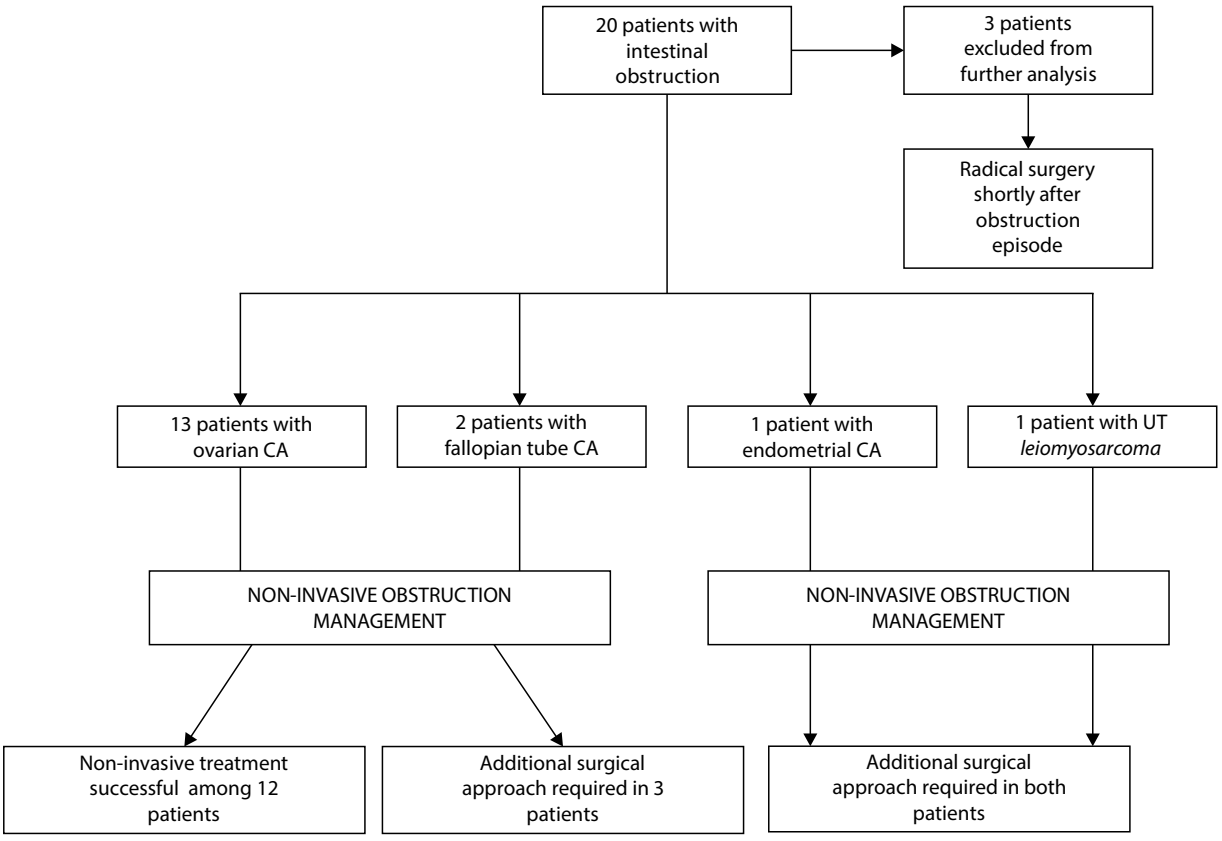

Figure 1. Intestinal obstruction in patients with gynecological malignancies — management and outcome

poorly differentiated G3 tumors at stage III–IV. The number of applied chemotherapy lines varied between 1 and 9. Because of advanced disease 3 patients were managed without radical oncological surgery. The number of obstruction episodes varied between 1 and 5. Mean time between multiple episodes lasted 3.2 months (2 weeks–22 months). In 5 (29.4%) patients non-invasive treatment was ineffective and additional surgical approach was required. Operational interventions included: 1 repeated debulking surgery, 1 colostomy, and 3 adhesion removal surgeries. The rest of patients were successfully managed non-invasively. Patient treated with colostomy developed 4 obstruction episodes following the procedure, all of them successfully treated pharmacologically. Table 1. shows a comparison of patients' characteristics depending on the needed therapy mode. Previous abdominal surgeries included Cesarean sections, appendectomies and cholecystectomies.

Table 1. Patients' characteristics depending on the needed therapy mode

Feature	Non-invasive treatment (n = 12)	Invasive treatment (n = 5)
Ovarian cancer (%)	11 (92%)	2 (40%)
Fallopian tube cancer (%)	1 (8%)	1 (20%)
Endometrial cancer (%)	0	1 (20%)
Uterine leiomyosarcoma (%)	0	1 (20%)
Mean age at cancer diagnosis (years)	63.8 (48–73)	65 (59–79)
Time of observation since cancer diagnosis (months)	40.7 (3–168)	47 (15–120)
Time of 1st obstruction episode since cancer diagnosis (months)	39.2 (8–168)	27.8 (3–84)
Mean no. of obstruction episodes during observation	1.5 (1–3)	1.8 (1–5)
Abdominal surgeries before oncological treatment (%)	2 (17%)	3 (60%)
Ascites at cancer diagnosis (%)	9 (75%)	2 (40%)
Radical surgery (%)	11 (92%)	3 (60%)
Mean no. of chemotherapy lines	3.75 (1–9)	2.6 (2–4)
Anemia during chemotherapy treated with blood transfusion (%)	7 (58%)	3 (60%)
Obesity at cancer diagnosis	6 (50%)	2 (40%)
Body mass loss over 5% (%)	8 (67%)	3 (60%)

DISCUSSION

Symptoms of over 70% of patients with stage III gynecologic malignancy analyzed in this study were successfully relieved with supportive treatment. Because of the size of the studied population it is difficult to obtain statistically significant evidence helpful in prediction of patients at risk of irresponsiveness to non-invasive management. For the same reason the power of statistical tests was decreased. Nevertheless, certain clinical observations were made.

First of all, patients with no history of radical surgical treatment were more likely to develop obstruction requiring invasive management. Similar conclusions were made by Bryan et al. [17] as in their study more surgical interventions were needed by patients who had been suboptimally debulked rather than optimally. Another aspect of past surgical history concerns abdominal interventions performed before oncological diagnosis. Patients who required operational management more frequently had undergone a C-section, cholecystectomy or appendectomy in the past. In all of these cases intestinal obstruction was associated with massive abdominal adhesions.

Another observation was made concerning the presence of ascites. In the studied group patients with recurrent ascites were more responsive to non-invasive obstruction management. This could be caused by an increased subjective feeling of obstruction and presentation of accompanying symptoms in response to relatively less advanced condition due to the presence of additional fluid excess. Whatever the reason, this finding gives hope to patients with ascites as it is known to be a risk factor for poor prognostic surgery outcomes [18]. Therefore, initially supportive management in this group of patients should be preferred.

Additional consideration of obstruction management outcome concerns the time of observation. Patients treated invasively presented the first episode of obstruction sooner after the cancer diagnosis than patients treated successfully in supportive manner. On the other hand, surgical patients were characterized by longer observation time following the first obstruction symptoms, which suggests their condition could be more acute, but at that time less oncologically advanced in comparison to the group responsive to pharmacological treatment. Of course, the etiology of indication for surgical treatment is essential in this context, as patients with adhesions are reported to present much longer interval in readmission for bowel obstruction than patients with malignant cause [19]. Similarly, in the study by Sartori et al. [20] patients who underwent surgical treatment showed better survival than conservatively treated group. However, opposite findings were presented in the study by Tran et al. as authors observed no statistically significant differences in outcome depending on the type of intervention — surgical, pharmacological or stent placement [21].

Since no official guidelines for management of intestinal obstruction in oncogynecological patients have been proposed till date, the first-line supportive treatment varies among cancer centers. In the study by Mangili et al. [7]

comparing medical and surgical approach, pharmacological treatment included different doses of octreotide. The initial management described by Bais et al. [22] consisted of nasogastric tube placement, rectal enemas and intravenous fluid administration, however it was always preceding the surgical intervention. Similar management was presented in the conservative treatment implemented by Suidan et al. [8], which included bowel rest, gastrostomy or jejunostomy tube placement and intravenous fluid administration — the surgery was performed only if the conservative treatment of obstruction symptoms was unsuccessful.

CONCLUSIONS

As this study shows, most cases of bowel obstruction in advanced gynecologic malignancies can be successfully managed without invasive treatment. Individual assessment of response to therapy should be applied each time in order to achieve symptoms relief and decide which patient requires more invasive approach.

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Stress urinary incontinence after labor and satisfaction with sex life

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ABSTRACT

Objectives: The aim of the study was to assess the incidence of stress urinary incontinence in women after labor, its determinants, and to establish its effect on women's satisfaction with their sex lives.

Material and methods: The research implemented the Gaudenz-Incontinence-Questionnaire and the Sexual Quality of Life-Female scale (SQoL-F). The principal inclusion criterion was the time of 3 to 6 months after labor.

Results: The research was carried out amongst 193 women. Thirty-two of the participants (16.6%) showed symptoms of stress urinary incontinence after labor that were statistically correlated with the number of experienced labors ($p = 0.044$) and the newborn's weight ($p = 0.016$). The participants' sex life satisfaction was on average 75.47 ± 24.68. The respondents suffering from stress urinary incontinence obtained a significantly lower ($p = 0.006$) average score for general sex life satisfaction (64.38 ± 26.15) when compared with women without symptoms of stress urinary incontinence (77.67 ± 23.86).

Conclusions: The problem of incontinence after labor affected one in six women. Occupation, number of pregnancies, damage to the perineum during labor, and the infant's birth weight significantly dependent on the incontinence occurrence after labor. The onset of incontinence symptoms in women in the reproductive age has an adverse effect on their sex life satisfaction.

Key words: parturition; stress urinary incontinence; sexuality

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INTRODUCTION

Urinary incontinence is an important, but often neglected, health problem in women. It is commonly believed that this disorder concerns mostly older people and is a consequence of aging. That is not entirely true because stress urinary incontinence occurs in young, even very young, women [1].

Papers dealing with incontinence after labor focus mostly on the epidemiology of this problem [2] and risk factors [3–5]. Much more rarely do they concern its prevention [6, 7] or the effect on sex life [8].

Many women experience a variety of problems associated with their sex life within a short period of time after giving birth. Sexual disorders are inadequately investigated, although they concern 26 to 47% of women suffering from incontinence. The etiology of the dysfunction is complex, divided into organic and psychological factors [9, 10].

The aim of the study was to assess the frequency of stress urinary incontinence in women after labor, its determinants, and to establish its effect on women's sex life satisfaction.

MATERIAL AND METHODS

The study included 193 women who checked in a women's clinical unit in one of three randomly chosen outpatient departments in Lublin. The inclusion criteria were: obtaining an informed consent to participate in the research and the time between 3 to 6 months after the last labor. The exclusion criteria were based on the information concerning patient's medical history and/or medical documentation that included:

- neurological diseases, mental disorders, congenital malformations in the urinary-reproductive system or fistulas;
- overactive bladder and mixed incontinence;

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- diagnosed inflammation of the urinary tract and/or reproductive organ.

An approval of the Ethics Committee of the Medical University of Lublin (KE-0254/194/2013) was obtained. To ensure ethical clarity, all women who participated in the study were fully informed about the nature and purpose of the study, and the voluntary nature of their participation was emphasized.

To carry out the research, a specially constructed three-part questionnaire was used. Personal information was gathered, consisting of questions regarding socio-demographic data (*i.e.* age, marital status, place of habitation, education, occupational activity before pregnancy), the number of experienced labors, the method of delivery of the last pregnancy, damage to the perineum during labor, the infant's birth mass, participation in antenatal classes, the existing chronic diseases, the problem of incontinence after labor, Kegel's exercises, and the women's height and weight before pregnancy.

The Gaudenz-Incontinence questionnaire, which is mainly used in Poland to identify the patients with the urinary incontinence, constituted the second part of the inventory. To meet the aims of the study, the following questions were particularly useful:

- Does the involuntary release of urine occur?
- How often does this happen (rarely, occasionally, every day, many times, practically all the time)?
- How much urine is involuntary released (few drops, small portions, heavy leakage)?
- Do you feel that the bladder is empty after urinating (yes, no, not always, I don't know)?
- The involuntary urine release is: not a problem, it can be disturbing, it disturbs a lot, it makes life difficult?
- In which situations does the involuntary urine release happen (when coughing, sneezing, laughing, going upstairs and downstairs, jumping, bouncing, exercising, standing, sitting or lying down)?

The third part included the Sexual Quality of Life-Female (SQoL-F) questionnaire used to assess women's sex life satisfaction within the last 4 weeks. The Polish version of the document was obtained from Mapi Research Trust. The SQoL-F scale consisted of 18 questions, each of them with 6 possible answer variants — I totally agree, I rather agree, I agree to a small degree, I rather disagree, and I totally disagree. Obtaining 0 points meant lack of satisfaction with one's sex life, while 100 points accounted for a high degree of satisfaction.

Information about weight and height was used to calculate Body Mass Index (BMI). World Health Organization (WHO) (WHO Expert Consultation, 2004) criteria were used to categorize participants as: underweight (BMI < 20), normal weight (BMI 20–25), and overweight (BMI ≥ 25.1).

The value of measurable analyzed parameters has been presented using median and standard deviation. To find differences between the groups, the χ^2 and Student's *t* tests were used. The Shapiro-Wilk test was applied to assess normality of distribution of variables within the studied groups. To examine differences between two groups, the nonparametric Mann-Whitney U test was used, and for more than two groups the Kruskal-Wallis test was applied. In this study, the level of statistical significance was set at $p < 0.05$. Database and statistical calculations were performed using Statistica 9.1 software (StatSoft, Poland).

RESULTS

The age of the study participants ranged between 17 and 41, mean 28.3 ± 4.9 years. The majority of respondents were aged 26–30 years (75; 38.9%). Women up to 25 years of age (62; 32.1%) and 31 years — old or more (56; 29.0%) constituted the second largest age group. Married women were the majority (153; 79.3%), while the rest (40; 20.7%) were single women and divorcees living in informal relationships with a child's father. An overwhelming majority of participants lived in the city (158; 81.9%) and the rest of them resided in the countryside (35; 18.1%). Moreover, 140 women had an MA or BA (72.5%). The remaining 53 (27.5%) had secondary education or lower. It was established that 148 women had worked before pregnancy (76.7%), out of which 129 (66.8%) performed intellectual work and 19 (9.9%) physical work. The study also included 45 unemployed (23.3%) women.

Additionally, 136 of the studied women had a normal body weight before pregnancy (70.5%), 40 were overweight (20.7%) and 17 were underweight (8.8%). A majority of respondents gave birth to their first child (137; 71.0%), the remaining 56 (29.0%) to the subsequent children, *i.e.* the second (49; 25.4%) or the third (7; 3.6%). Moreover, 122 of the women (63.2%) had a vaginal delivery, while 71 (36.8%) had a caesarean section. Damage to the perineum (episiotomy, rupture, or both episiotomy and rupture) during labor occurred in 86 women (44.6%), and did not occur in 107 women (55.4%). Next, 98 of the examined women (50.8%) had participated in antenatal classes, while 95 had not (49.2%). The incidence of chronic diseases (such as: diabetes, hypertension, bronchial asthma, or hypothyroidism) was confirmed by 31 (16.1%) of the examined women, while the remaining 162 (83.9%) stated having no chronic diseases. Thirty-two of the surveyed women (16.6%) reported problems with incontinence after labor. The remaining 161 (83.4%) declared no such problems. Sixty-one (31.6%) women claimed that they performed Kegel's exercises every day, 73 women (37.8%) only sometimes, while 59 — not at all (30.6%).

The dependence between the occurrence of incontinence and education level, occupation, evaluation of body

Table 1. Urinary incontinence after labor and the study characteristics

Study characteristics			Incontinence		Statistical analysis	
			No n = 161; 83.4%	Yes n = 32; 16.6%	χ^2	p-value
Education	Secondary education or lower n = 53; 27.5%	n	42	11	0.92	0.337
		%	79.3	20.7		
	College/ University n = 140; 72.5%	n	119	21		
		%	85.0	15.0		
Occupation	Intellectual work n = 129; 66.8%	n	108	21	7.35	0.023
		%	83.6	16.4		
	Physical work n = 19; 9.9%	n	12	7		
		%	63.2	36.8		
	Unemployed n = 45; 23.3%	n	41	4		
		%	91.1	8.9		
Body weight	Underweight n = 17; 8.8%	n	16	1	5.20	0.074
		%	94.1	5.9		
	Normal weight n = 136; 70.5%	n	116	20		
		%	85.3	14.7		
	Overweight n = 40; 20.7%	n	29	11		
		%	72.5	27.5		
Chronic diseases	Yes n = 31; 16.1%	n	26	5	0.04	0.849
		%	83.9	16.1		
	No n = 162; 83.9%	n	135	27		
		%	83.3	16.7		

mass, and the presence of chronic diseases are presented in Table 1, whereas the dependence between the number of experienced labors, method of delivery, damage to the perineum during labor and exercising pelvic floor muscles are shown in Table 2.

The occurrence of urinary incontinence after labor was significantly influenced by the type of occupation (p = 0.023). Women with a BMI above 25 (overweight/obese) declared incontinence symptoms more often than women of the normal body weight or those underweight. No statistically significant differences were observed, although they were close to the set level of significance (p = 0.074). No statistically significant differences was found either between incontinence occurrence after labor and education level or the occurrence of chronic diseases in the studied group (p > 0.05).

Incontinence occurrence after labor was significantly dependent on the number of experienced labors (p = 0.044) as well as with the damage to the perineum (p = 0.025). Obtained data indicate that one in four women that had given birth to two or three children complained of symptoms of incontinence, whereas after the first labor, one in ten of the examined women suffered from the involuntary release of urine. The method of delivery and Kegel's exercises proved unimportant (p = 0.189 and 0.700, respectively).

An average infant's body mass in the group was 3412.43 ± 473.51 g, with the lowest 1990 g and the highest 4830 g. The dependence between the infant's birth mass and the urinary incontinence has been presented in Table 3.

In the group of women who experienced incontinence, the average birth mass of an infant was significantly (p = 0.016) greater (3595.09 ± 581.85) than in the case of those without the symptoms (3376.12 ± 442.12).

The average sex life satisfaction in the studied group was 75.47 ± 24.68. This confirmed moderate satisfaction. However, it seems important that among the respondents who obtained the lowest possible score on the SQoL-F scale (0 points) as well as those who achieved the highest score (100 points), the variation of points within the studied group was extensive. Table 4 compiles the data on sex life satisfaction taking into account age, marital status, education, place of habitation, participation in antenatal classes, BMI, presence of chronic diseases, and incontinence occurrence.

The only variable that significantly dependent on sex life satisfaction was urinary incontinence (p = 0.006). The differences close to the significant values were noted when the age of the participants was taken into account (p = 0.081). In the case of the other variables, no statistically significant differences were found (p > 0.05).

Table 2. Urinary incontinence after labor and obstetric features

Studied characteristics			Incontinence		Statistical analysis	
			No n = 161; 83.4%	Yes n = 32; 16.6%	χ^2	p-value
Labor	First n = 137; 71.0%	n	119	18	4.04	0.044
		%	86.9	13.1		
	Second or third n = 56; 29.0%	n	42	14		
		%	75.0	25.0		
Mode of delivery	Vaginal delivery n = 122; 63.2%	n	98	24	1.73	0.189
		%	80.3	19.7		
	Caesarean section n = 71; 36.8%	n	63	8		
		%	88.7	11.3		
Perineum damaged during labor	Yes n = 86; 44.6%	n	66	20	4.99	0.025
		%	76.7	23.3		
	No n = 107; 55.4%	n	95	12		
		%	88.8	11.2		
Exercising pelvic floor muscles (Kegel's muscles)	Every day n = 61; 31.6%	n	50	11	0.71	0.690
		%	82.0	18.0		
	Does not exercise n = 59; 30.6%	n	48	11		
		%	81.4	18.6		
	Exercises occasionally n = 73; 37.8%	n	63	10		
		%	86.3	13.7		

Table 3. Infant's body mass and urinary incontinence in the studied women

Studied characteristic		Infant's body mass	Statistical analysis	
		M* ± SD**	t-Student's t — test	p-value
Incontinence	Not present n = 161; 83.4%	3376.12 ± 442.12	2.42	0.016
	Present n = 32; 16.6%	3595.09 ± 581.85		
Group total		3412.43 ± 473.51	-	

*M — average; **SD — standard deviation

DISCUSSION

Pregnancy and labor cause numerous changes to a woman's body [11]. These changes might be temporary (functional) or permanent, resulting from alterations within the tissues due to the maximum stretching of the fiber bundles of pelvic floor muscles and perineal nerve fibers in the second stage of labor [12]. A tangible dependence has been observed between vaginal delivery and postpartum incontinence [13, 14]. Some authors claim that incontinence occurs in 15–30% of women as early as in the first three months after labor [13]. In our study, incontinence affected 16.6% of the respondents, but the research was carried out later, *i.e.* between the third and sixth month after labor. We regret that we did not ask participants when they first noticed symptoms. Nevertheless, the occurrence of incontinence in such a short period after labor can be perceived as a bad prognosis, because in such cases the risk of incontinence development increases greatly [15].

The number of experienced labors proved to be a factor affecting incontinence occurrence after labor [5, 16]. In our study, one in four women who had given birth to two or more children suffered from incontinence, whereas in the case of the women who had given birth to one child, only one in ten.

Among the women with incontinence after labor, first-time mothers were more numerous than those who had already given birth at least once. During the second part of labor, weakening of the pelvic floor muscles might occur as a result of their tearing or stretching. The resulting changes in pelvic floor muscles do not cause incontinence symptoms straight away. Most commonly directly after birth, so-called subclinical symptoms, which can be diagnosed with the help of ultrasonography, occur, while clinical symptoms become apparent later [17].

Significant differences in the frequency of incontinence were observed (p = 0.025) between women with the perineum damaged during labor (episiotomy, rupture, or episiotomy and rupture) and those without any damage. Due to the unsubstantial number of examined patients, we did

Table 4. Sex life satisfaction and the study characteristics

Study characteristics		Satisfaction with sex life		
		M ± SD	Z*/ H**	p-values
Age	Up to 25 years n = 62; 32.1%	76.52 ± 24.45	5.03**	0.081
	26–30 years n = 75; 38.9%	78.90 ± 23.09		
	31 years and more n = 56; 29.0%	69.70 ± 26.37		
Marital status	Single n = 40; 20.7%	70.83 ± 28.02	0.95*	0.354
	In relationship n = 153; 69.3%	76.68 ± 23.68		
Education	Secondary education or lower n = 53; 27.5%	74.15 ± 24.60	0.29*	0.771
	College/University n = 140; 72.5%	75.97 ± 24.78		
Place of habitation	City n = 158; 81.9%	76.65 ± 24.15	1.60*	0.110
	Country side n = 35; 18.1%	70.13 ± 26.67		
Participation in antenatal classes	Yes n = 98; 50.8%	72.90 ± 24.21	1.08*	0.282
	No n = 95;49.2%	76.54 ± 24.89		
BMI	Underweight n = 17; 8.8%	72.61 ± 34.43	0.41**	0.814
	Normal weight n = 136; 70.5%	75.51 ± 24.55		
	Overweight n = 40; 20.7%	76.53 ± 20.55		
Suffers from chronic diseases	Yes n = 31; 16.1%	75.18 ± 25.11	0.23*	0.822
	No n = 162; 83.9%	76.99 ± 22.66		
Occurrence of incontinence	Not present n = 161; 83.4%	77.67 ± 23.86	2.73*	0.006
	Present n = 32; 16.6%	64.38 ± 26.15		
Group overall n = 193; 100.0%		75.47 ± 24.68	-	

*Z — Mann-Whitney U test; **H — Kruskal-Wallis test

not attempt to find differences between women who had an episiotomy and those with rupture. Rockner [18] studied 185 women after labor with episiotomy or spontaneous rupture, and observed the occurrence of incontinence symptoms in 36% of the studied group. However, there were no significant differences in the occurrence frequency between the groups. This may suggest that perineum damage during labor, irrespective of its underlying cause, increases the risk of incontinence occurrence. This assumption is further confirmed by the fact that routine episiotomy during labor, as incontinence prophylaxis, is controversial amongst various authors [10, 19–22]. Presumptions about the protective effect of surgical labor on urinary incontinence on the basis of the accumulated data have to be attempted very carefully as it is not clear whether urinary incontinence occurred during pregnancy, which ended in Caesarean section due to various causes. The probability of worsening of symptoms after labor in such cases is greater [23].

Mother's body mass and chronic disease occurrence, which are thought to predispose to postnatal incontinence occurrence, proved to be insignificant in the studied group of women ($p > 0.05$). Occupation significantly dependent on

incontinence occurrence, especially in the case of women performing physical work (p = 0.023).

It has been observed in clinical studies that the larger the fetus, the greater the probability of incontinence occurrence after labor [12, 24]. Our research has confirmed this. Alling Møller et al. [25] found no such relations.

Pelvic muscle floor dysfunction and the associated incontinence are viewed as the cause of a decrease in sex life satisfaction. [11, 26]. This has been confirmed by our research. Women who did not suffer from this ailment had a significantly higher (p = 0.006) score on the Sexual Quality of Life-Female scale (signifying greater satisfaction) than those with this ailment. In the available literature, there were no publications using SQoL-F scale that would describe the influence of muscle fundus dysfunction on the sexual life. Therefore, we searched for the authors' reports that examined this correlation with the use of other tools. Dean et al. assessed women's sexual functions and satisfaction 6 years after labor with the use of Golombok Rust Inventory of Sexual Satisfaction (GRISS). They noted an adverse impact of the urinary incontinence on women's sexual lives [8]. It is worth noting that the variables assumed by these authors [8] (similarly to our research) did not significantly dependent on women's sexual life satisfaction.

Proper contractility of particular pelvic floor muscle bundles during the sexual act causes the narrowing and elongation of the vagina, elevation of the uterus, and makes reaching orgasm easier [27]. Moreover, disordered contractility hinders sexual intercourse, and causes many women who suffer from incontinence to avoid sexual contact in fear of rejection by their partner or dyspareunia [28]. Proper Kegel's muscle exercises during pregnancy and the postpartum period increase deep perineal pouch muscle strength, enabling control of urinary-reproductive system functioning [11, 29]. Additionally, it is effective in the treatment of stress urinary incontinence (especially minor cases) and improves sex life satisfaction. Hence, Kegel's muscle exercises are recommended for all women in the reproductive period, not only as a free and effective prophylactic measure, but also as an important part of treatment [30].

At present, well-documented knowledge exists concerning the negative impact of vaginal delivery on the functioning of pelvic floor muscles and the urethra. On the basis of the selected bibliography and our own research, it can be concluded that incontinence, as a dysfunction of the deep perineal pouch, has a destructive effect on women's quality of life. Therefore, in the clinical practice, hospital's and primary healthcare medical staff (doctors, physiotherapists, midwives/nurses) should cooperate in the range of prophylactics of this problem. A midwife and a patient should work together to prepare the pelvic floor muscles for labor and delivery. The promotion of Kegel's muscle exercises after labor is crucial.

CONCLUSIONS

The problem of incontinence after labor affected one in six women. Occupation, number of pregnancies, damage to the perineum during labor, and the infant's birth weight significantly dependent on the incontinence occurrence after labor. The onset of incontinence symptoms in women in the reproductive age has an adverse effect on their sex life satisfaction.

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A comparison in an experimental rat model of the effects on adhesion formation of different hemostatic methods used in abdominopelvic surgery

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ABSTRACT

Objectives: To evaluate the effects of different hemostasis methods used in abdominal surgery on the development of abdominal adhesion.

Material and methods: A total of 48 Wistar albino female rats were separated into six groups; Group 1 — Control group, Group 2 — Hemorrhage group, Group 3 — Electrocoautery group, Group 4 — Gel Spon-P®, Group 5 — PAHACEL®, and Group 6 — Ankaferd-Blood Stopper®. Adhesions that developed were scored according to the Knightly classification and the prevalence of adhesions according to the Linsky classification. The total adhesion score was calculated as the total of the severity and prevalence scores.

Results: The lowest total adhesion values were determined in Group 1 (control) and the highest adhesion values were in Group 2 (hemorrhage) group in terms of all parameters. The adhesion values in Group 3, where the rats were administered hemostasis with electrocautery were similar to those of Group 2 (hemorrhage). When the alternative methods were evaluated, the lowest adhesion scores were in Group 6 (Ankaferd-Blood Stopper®).

Conclusions: In cases of minor pelvic or abdominal bleeding, not providing hemostasis or applying hemostasis with electrocautery can increase the development of intra-abdominal adhesions. The use of alternative hemostatic materials instead of electrocautery for hemostasis may reduce the formation of adhesions.

Key words: intra-abdominal hemorrhage; abdominal adhesion; hemostatic agents; pelvic surgery; hemostasis

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INTRODUCTION

Post operative adhesions may develop following any abdominal surgical procedure as a response to all foreign bodies in direct contact with the peritoneum, such as powder or sutures, or as an abnormal response of the organism to minor or major bleeding. Both minor and major intra-abdominal bleeding can cause significant morbidity and mortality in patients postoperatively. To avoid this, it is imperative that careful hemostasis is obtained during surgical procedures.

Various methods are used to prevent post operative bleeding, such as mechanical or thermal devices and topical hemostatic agents. Each technique has advantages and disadvantages. Minor bleeds are often seen in the post operative period, but generally can not be determined. Although this does not cause hemodynamic impairment, it does cause the collection and activation of thrombocytes in the peritoneal area and the accumulation of fibrinogen [1, 2].

Fibrinogen and thrombin interact to create fibrin monomers then polymers. When these fibrin polymers are not

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removed from the region, they combine with coagulation factors such as Factor VIII, becoming insoluble, and create a fibrin gel matrix [2, 3]. Then, as a result of fibrin polymers combining with leukocytes, erythrocytes, thrombocytes, mast cells and other cells, the development of adhesions is caused with a fibrin gel matrix between two serosal surfaces [4].

The adhesions that develop restrict intestine movements post operatively and diminish qualty of life [2–4]. Various blood-stopping methods and materials are used to prevent bleeding [5–12]. Although the effects on adhesion development of some of these agents have been evaluated in literature, to the best of our knowledge, there has been no previous study that has collectively and comprehensively compared hemostatic agents with different mechanisms in respect of the inflammatory response and the later emergence of adhesions that have formed.

Objectives

Considering that it was necessary to evaluate the potential of hemostatic material to form abdominal adhesions and to determine which material formed the least adhesions, the aim of this study was to evaluate the effects on adhesion development of blood-stopping materials frequently used during surgical procedures.

MATERIAL AND METHODS

Approval for the current study was granted by the Local EthicsCommittee (decision no: 14.03.2017/02). The study was conducted in the Experimental Animals Reproduction and Research Center of Kahramanmaraş Sütçü Imam University in conformity with the principles of the National Institutes of Health Guide for the Care and Use of Laboratory Animals.

A total of 48 female adult Wistar albino rats, each weighing 300–350 g were used in the study. The animals were acclimatised to the laboratory conditions for one week before the experiment, at a temperature of 22 ± 2°C, and fed with Standard rodent food (SPRF) (Purina®). At 12 hours before the experiment, food was withdrawn but free Access to drinking water was continued. All the surgical procedures were conducted in the morning between 08.00 and 11.00.

The rats were randomly separated into 6 groups of 8, as follows:

- Group 1: Control group (n: 8),
- Group 2: Hemorrhage group (n: 8),
- Group 3: Electrocautery group (n: 8),
- Group 4: GelSpon-P® group (n: 8),
- Group 5: PAHACEL® group (n: 8),
- Group 6: Ankaferd-Blood Stopper® group (n: 8).

In the first operation, general anaesthesia for the surgical procedure was applied to all rats with an intramuscular injection of 50 mg/kg ketamine hydrochloride (Ketalar; Eczacibasi, Istanbul, Turkey) and 10 mg/kg xylazine hydrochloride (Rompun; Bayer Türk Ilaç Ltd., Istanbul, Turkey). When a sufficient depth of anaesthesia was obtained, the abdomen of each rat was shaved and cleaned with povidone iodine. The abdomen was entered with a midline incision and the uterus was visualised (Fig. 1A).

After making the abdominal incision, the rats in Group 1 were applied with 2cc saline into the abdomen and the abdomen was left open for 1 min (Fig. 1B). All the rats in all the other groups were traumatised using a no. 15 scalpel starting from the uterus bifurcation until petechial bleeding was observed macroscopically in a 1 cm serosa segment in both horns (Fig. 1C). The following procedures were then applied to the study groups. To Group 2, no coagulation procedure was applied (Fig. 1D). To Group 3, cauterisation was applied for a maximum of 5 seconds at 10 watt power until sufficient coagulation was obtained, using a manually controlled monopolar cautery, disposable high-temperature cautery device [low-temp fine tip 2200°F (1204°C)] (5115 Ulmerton Road Clearwater, Florida 33760 USA) (Fig. 1E).

To Group 4, a 2 × 1 cm absorbable hemostatic gelatine sponge (GelSpon-P®) (Eucare Pharmaceuticals Limited, Plot No. AC-25B, SIDCO Industrial Estate, Thirumudivakkam, Chennai-600 044. India) was placed over the incision (Fig. 1F). To Group 5, a 2 × 1 cm absorbable hemostatic oxidized regenerated cellulose patch (PAHACEL®) (Altaylar Medikal

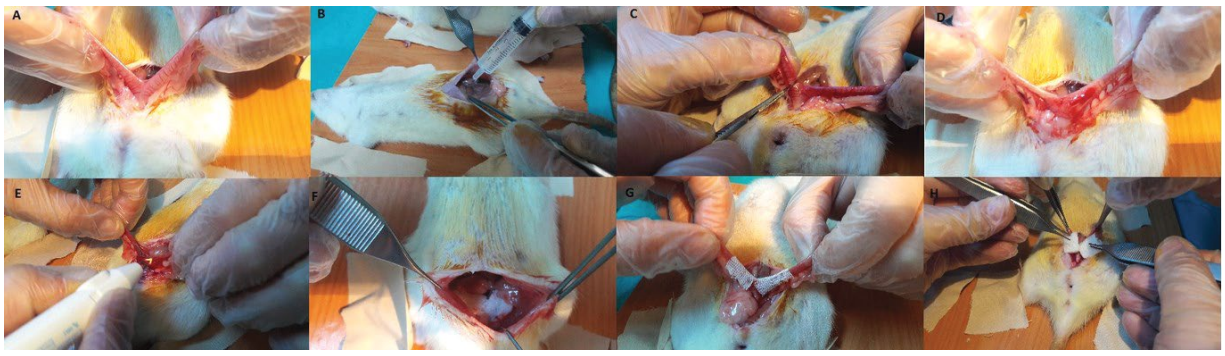

Figure 1. Operations applied to the study groups

Tıbbi Malz. İnş. Teks. Gıda İth. İhr San ve Tic. Ltd. Şti ATB İş Merk. No: 222 Yenimahalle, Ankara, Turkey) was placed over the incision (Fig. 1G). To Group 6, a 2 × 1 cm wet pad blood stoper (Ankaferd-Blood Stopper®) (İmmun Gıda İlaç Kozmetik San. Ve Tic. Ltd. Şti. Kireçburnu Cd. Raifbey Sk. No: 8/A Kireçburnu Sarıyer/Istanbul, Turkey) was placed over the incision and when hemostasis was obtained, was removed from the abdomen (Fig. 1H).

In all the rats, the abdominal wall was then closed with 3-0 silk sutures and the operations were completed. On the 14th day, decapitation was applied and the development of adhesions was examined with second-look laparotomy using the same incision. The adhesion scoring was applied according to the Knightly classification [13] for adhesion severity and according to the Linsky classification [14] for adhesion prevalence. A total adhesion score was obtained from the total of these verity and prevalence scores. The histopathological evaluation of adhesions was applied using the Zühlke microscopic adhesion classification system [15].

Data obtained in the study were analysed statistically using IBM SPSS for Windows, version 22.0 software (IBM statistics for Windows version 22, IBM Corporation, Armonk, NY, USA). Data were presented as mean ± standard deviation (SD). Variance analysis (Repeated measures ANOVA with Bonferroni correction) was applied to repeated measurements. In the comparisons of paired groups, the Tukey HSD method was used. A value of $p < 0.05$ was accepted as statistically significant.

RESULTS

The adhesion severity score was determined to be statistically significantly higher in all the study groups than in the control group ($p < 0.01$). No statistically significant difference was determined between Group 2 and Group 3 in respect of the severity score ($p = 0.994$). A statistically significant difference was determined between the severity scores of the groups where hemostatic agents were used (Group 4, Group 5, Group 6) and those of Group 1, Group 2, and Group 3 ($p < 0.01$ for all). The lowest adhesion severity score of the groups where hemostatic agents were used was determined in Group 6, but no significant difference was determined between these groups ($p > 0.05$) (Tab. 1) (Fig. 2A).

No statistically significant difference was determined between the groups where hemostatic agents were used in respect of the adhesion prevalence scores ($p > 0.05$ for all). Compared to the control group, the adhesion prevalence scores were determined to be statistically significantly higher in all the study groups ($p < 0.01$ for all). No significant difference was determined between Group 2 and Group 3 in respect of adhesion prevalence scores ($p = 0.915$). Compared to Group 2 and Group 3, the adhesion prevalence scores of the groups where hemostatic agents were used were statistically significantly higher ($p < 0.01$ for all) (Tab. 1) (Fig. 2B).

According to the Zühlke histological scoring system, the values of all the study groups were statistically significantly higher than those of the control group ($p < 0.01$ for all). In the evaluation of all the adhesion groups, no statistically significant difference was seen ($p > 0.05$). The results are shown in Table 1 and Figure 2C. The fibrosis and inflammation scores are shown in Table 1.

DISCUSSION

The results of the current study demonstrated that the lowest adhesion values were seen in Group 1, as expected. The highest adhesion values in respect of all the parameters were determined in the hemorrhage group. In the rats applied with hemostasis with electrocautery, the adhesion values were seen to be similar to those of the hemorrhage group. When the alternative methods were evaluated, the lowest adhesion values were determined in the Ankaferd Blood Stopper group.

The development of post operative adhesions starts on days 5–7 following the surgical procedure [16], and therefore, it is most appropriate for evaluation to be made after-day 7 [5]. In the current study, adhesions were evaluated on post operative day 14.

One mechanism in the formation of adhesions is the inflammatory response associated with increased leukocytes and insufficient tissue oxygenation caused by metabolites

Table 1. Comparison of the adhesion severity, adhesion prevalence, Zuhlke histology, fibrosis and inflammation scores of the groups

	Group 1 (n: 8)	Group 2 (n: 8)	Group 3 (n: 8)	Group 4 (n: 8)	Group 5 (n: 8)	Group 6 (n: 8)
Adhesions everity score	0.25 ± 0.462	3.87 ± 0.353[b]	3.75 ± 0.462[b]	2.62 ± 0.517[b-d-f]	2.75 ± 0.462[b-d-f]	2.50 ± 0.534[b-d-f]
Adhesion prevalence score	0.25 ± 0.462	3.75 ± 0.462[b]	3.50 ± 0.534[b]	2.50 ± 0.534[b-d-f]	2.75 ± 0.462[b-d-e]	2.50 ± 0.534[b-d-f]
Zuhlke Histological score	0.5 ± 0.534	2.50 ± 0.755[b]	2.37 ± 0.517[b]	1.50 ± 0.534[b-c-e]	1.62 ± 0.517[b-c]	1.37 ± 0.517[a-d-e]
Fibrosis score	0.25 ± 0.462	2.75 ± 0.707[b]	2.25 ± 0.462[b]	1.37 ± 0.517[b-d-e]	1.87 ± 0.640[b-c]	1.25 ± 0.462[b-d-f]
Inflammation score	0.37 ± 0.517	2.87 ± 0.640[b]	2.75 ± 0.886[b]	1.62 ± 0.744[b-d-e]	1.62 ± 0.517[b-d-e]	1.37 ± 0.517[a-d-e]

[a] — $p < 0.05$difference between the group and the control group; [b] — $p < 0.01$ difference between the group and the controlgroup; [c] — $p < 0.05$ difference between the group and the hemorrhage group; [d] — $p < 0.01$ difference between the group and the hemorrhage group; [e] — $p < 0.05$ difference between the group and the electrocautery group; [f] — $p < 0.01$ difference between the group and the electrocautery group

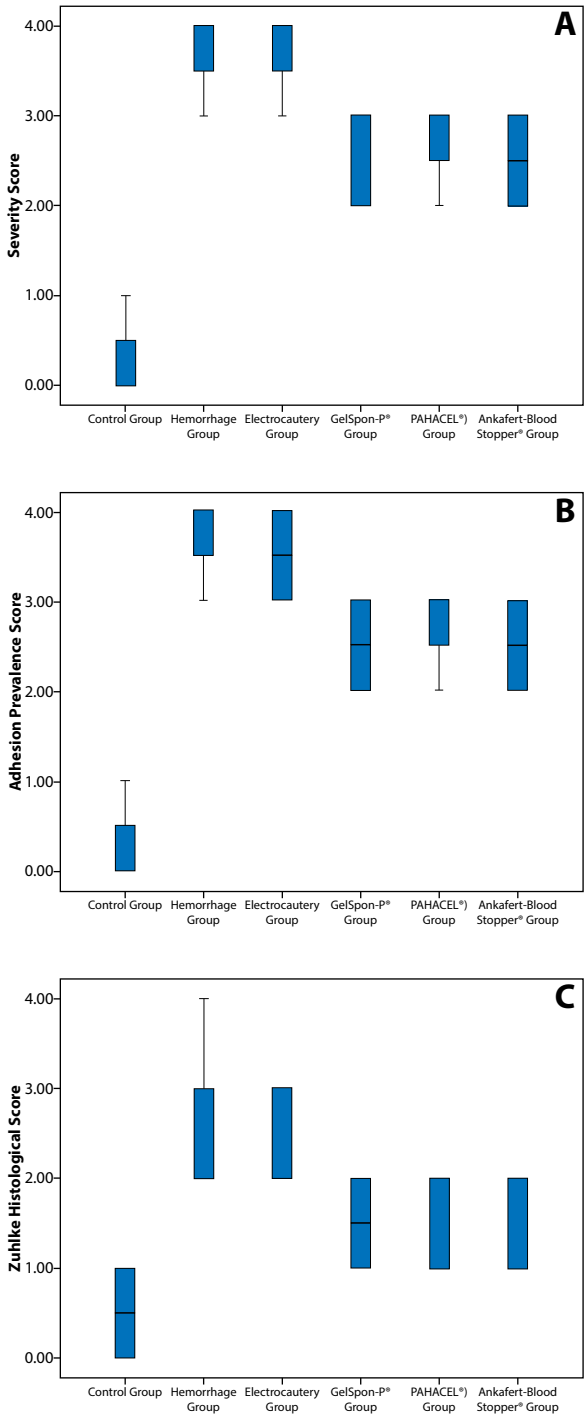

Figure 2. Comparison graph of the adhesion severity, adhesion prevalence, and Zuhlke histology scores of the group

of free oxygen radicals [6]. The high levels of free oxygen radicals that emerge cause an increase in vascular permeability, trigger the formation of exudate, and cause fibrosis. In a study by Pellicano M et al. [7], which compared sutures and electrocautery used for hemostasis, the abdominal adhesions in the subjects applied with electrocautery were seen to have formed at a statistically significantly higher level. Wallwiener CW [8] reported that deep electrocoagulation increased the development of abdominal adhesions compared to superficial electrocoagulation. Therefore, in the current study, the hemostasis method with deep electrocautery was used as a control group, as this has been shown in previous studies to be a model causing widespread abdominal adhesions.

The other control group in the current study was the hemorrhage group. The basic approach in forming this group was to evaluate the effect of bleeding on fibrosis development and to be able to more clearly evaluate the benefit of using blood stopping agents. The results of the current study showed that the most significant fibrosis values occurred in the hemorrhage group in respect of both the scoring systems and the histopathological evaluation results, and the development of fibrosis in the electrocautery group was seen to be similar to that of the hemorrhage group.

Ankaferd Blood Stopper® (ABS) is a plant-origin topical hemostatic agent, which has started to be used in recent years. It helps the formation of a fibrin gel matrix in the bleeding area. Recent studies have emphasized that ABS has antiinflammatory and antineoplastic features, decreases the development of tissue necrosis and the potential for the development of foreign body reaction is minimal [17–19]. Conflicting results have been reported in studies evaluating the effects of ABS on the development of adhesions. In an experimental rat study by Cömert et al, the effect of the abdominal application of a single-dose of ABS was evaluated, with one group applied with saline to the open abdomen, two groups were applied with ABS to uterine and peritoneal injuries, and one group was not applied with any treatment to uterine and peritoneal injuries. The adhesions in the subjects applied with ABS were reported to be at a significantly lower rate than those that were not treated [9].

In an other study that evaluated the effect of ABS and calcium alginate on the development of peritoneal adhesions, there was reported to be less development of adhesions in rats applied with ABS [10]. In a liver laceration model in rats, Akarsu et al reported that similar effects were seen from saline and ABS in respect of the histopathological effects on intra-abdominal adhesion formation [11]. In the current study, with the exception of the control group, the lowest values in respect of all the parameters were seen to be in the rats applied with ABS. When the Zühlke histological scoring results and the inflammation values were compared with those of the control group applied with saline, the results were statistically significantly different but the level of significance was seen to be weak ($p = 0.040$, $p = 0.041$, respectively).

The other alternative agent used in this study to stop intra-abdominal bleeding was a gelatine sponge (GelSpon-P®). This is made from a gelatine-based material such as colla-

gen, and is in the form of a hard, porous sponge in various sizes. It can absorb blood up to 45 times its own weight because of the porous structure. The hemostatic effect occurs by allowing thrombocytes to adhere to the smooth porous structure [20]. However, it has been reported that an inflammatory response occurs during the absorption process, and the absorption of a gelatine sponge placed in the subdural area of rabbits was reported to cause granulomatous inflammation [12].

In the current study, the rats applied with gelatine sponge were determined to have developed adhesions at a significantly high rate compared to the control group. However, the level of adhesions was significantly lower compared to Groups 2 and 3 (Tab. 1). When the alternative treatment methods were compared with each other, the adhesion values in Group 4 were higher than in Group 6, and lower than in Group 5, but no statistically significant difference was determined between these groups ($p > 0.05$).

Surgicel absorbable hemostat is a material made from oxidised regenerated cellulose, the main component of which is poly anhydro glucoronic acid. Woven in the form of threads, it is prepared to resemble gauze. As it has a pH of 3, when compared with a substance such as thrombin, it destroys that substance. By swelling when in contact with blood, it adheres to blood vesels and wound edges. Thus, the clots that form provide hemostasis within 2–3 mins [21]. In a study by Günay et al. [22], Surgicel and quercetin were used in an experimental abdominal adhesion model, and the highest inflammation and fibrosis values were determined in the Surgicel group, and were reported to be significantly lower than the results of the control group. Ateş et al. [23] compared Interceed and double layer Surgicel, and reported that compared to the control group, adhesions in the study groups were significantly reduced. In the current study, consistent with previous findings in literature, although the adhesion values of the Pahacel group were significantly lower than those of the hemorrhage group and the electrocautery group, in the comparison with the gelatine sponge and ABS groups, the highest adhesion values were determined in the Pahacel group.

That this was an experimental study conducted on rats was the most significant limitation. However, it was not possible to conduct a study of this design on humans, but as this is the first study to compare the effect on adhesion development of blood stopping agents commonly used in humans, this is a step in a positive direction.

CONCLUSIONS

In conclusion, the results of this study showed the effect of minor abdominal bleeding on adhesion development and that according to objective criteria, it is necessary to apply hemostasis in these types of bleeds. In accordance with previous findings in literature, adhesions developing as a result of hemostasis applied with electrocautery were determined to be similar to the group where no hemostasis was applied. In addition, adhesions were observed at a statistically significantly lower rate in the alternative hemostasis method groups of Gel Spon-P®, Pahacel®, Ankafert-Blood Stopper® compared to the groups where no hemostasis was applied and the group applied with hemostasis with electrocautery. Thus, it was determined that in patients requiring hemostasis, alternative treatment methods should be preferred rather than electrocautery.

In cases with minor pelvic or abdominal bleeding, not applying hemostasis or applying hemostasis with electrocautery can increase the development of intra-abdominal adhesions. The use of alternative hemostatic materials instead of electrocautery for hemostasis can reduce the formation of adhesions.

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Comparison of the protective effects of sildenafil, vardenafil and tadalafil treatments in ischemia-reperfusion injury in rat ovary

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ABSTRACT

Objectives: The aim of this study was to compare the effects of sildenafil, vardenafil and tadalafil in treatment for ischemia/reperfusion injury which is created experimentally in rat ovaries.

Material and methods: For this study, 30 female Wistar albino rats were used, and the rats were separated randomly into five groups consisting of six rats each: normal, torsion-detorsion, torsion-detorsion + sildenafil 1.4 mg/kg, torsion-detorsion + vardenafil 1.7 mg/kg and torsion-detorsion + tadalafil 5.0 mg/kg. The agents were given intraperitoneally 30 minutes before detorsion. An ovarian torsion procedure was implemented in all other groups for 3 hours with the exception of the normal group. Then, a detorsion procedure was implemented to the groups for 3 hours.

Results: The sildenafil and vardenafil treatments showed protective effect by preventing significant increase in inflammation parameters. ($p = 0.058, 0.138$). The tadalafil treatment was only protective for cellular degeneration ($p = 0.140$). The vardenafil treatment was protective for edema ($p = 0.238$), vascular congestion ($p = 0.111$), inflammation ($p = 0.138$) and cellular degeneration ($p = 0.532$). Sildenafil, vardenafil and tadalafil inhibited the increase of atretic follicle. AMH levels were statistically different between torsion and detorsion and vardenafil group ($p = 0.004, 0.004$), whereas tadalafil and sildenafil groups were similar to normal group ($p = 0.108, 0.108$).

Conclusions: PDE inhibitors were found to be effective in reducing ovarian ischemia/reperfusion injury. Sildenafil and tadalafil seem to be more effective than the vardenafil in protecting the ovarian reserve.

Key words: adnexal torsion; ischemia-reperfusion injury; sildenafil; vardenafil; tadalafil; rat model

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INTRODUCTION

Ovarian torsion refers to a complete or partial rotation of the infundibulopelvic or utero ovarian ligament, resulting in ischemic changes in the ovary. Ovarian torsion accounts for 2.7% of all the gynecologic emergencies [1]. Ovarian torsion could occur at all ages but it is more common in reproductive ages, especially early 20 s and mid 30 s [2].

Early diagnosis and treatment is essential for protecting ovarian injury and fertility [3]. In case of delayed diagnosis and intervention, it may cause to impairment or loss of fertility [4]. When ovarian damage occurs; follicular reserves decrease, infertility and early menopause risk increases [5]. Ovarian reserves can be assessed by serum markers or follicle counts [6].

This course of ovarian torsion/detorsion is called as ischemia/reperfusion (I/R) damage [7]. Reperfusion of the ischemic tissue may cause more serious damage to the tissue than ischemia-induced damage [8]. Reperfusion exacerbates ischemic injury at cellular level through reactive oxygen radicals [9]. The release of inflammatory mediators and free oxygen radicals from plasma, leukocytes and vascular cells results in response to inflammatory agents [10].

Nitric oxide (NO), a powerful vasodilator, is an important source of free radical production in I/R injury and NO levels decreases in case of endothelial dysfunction. Neutrophil and platelet adhesion, collection and activation are limited to NO. NO also inhibits lipid peroxidation chain reactions via second precursor cyclic guanosine monophosphate (cGMP) that is cleaved by the phosphodiesterase (PDE) enzyme [11, 12].

The PDE-5 enzyme regulates cGMP catabolism in vascular beds. Sildenafil has been shown to increase the effect of NO by increasing cellular cGMP levels. Increase in cGMP

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levels provides smooth muscle relaxation and an increase in tissue blood flow [13].

Due to all these effects, phosphodiesterase inhibitors have been used widely in many areas. In the literature, sildenafil, vardenafil and tadalafil have been shown to be effective in prevention of I/R damage in many different tissues. Sildenafil has protective effects on I/R damage in tissues such as heart, liver, lung, kidney, colon and testis [14–18]. Vardenafil has also been reported to be effective in the treatment of liver, brain and ovarian injuries in I/R injury [19].

There are a few recent trials published that investigated the effectiveness of PDE inhibitors in the prevention/treatment of ovarian I/R damage and these trials suggested that PDE inhibitors are effective at these kinds of injuries. However, there are no studies investigating the effects of these drugs on ovarian follicles and their effects on AMH levels. In addition, there is no research evaluating the differences between efficacy and success among these agents.

Our aim in this study is to evaluate the success of PDE inhibitors in ovarian I/R injury and to compare the differences between agents.

MATERIAL AND METHODS

This study was conducted at the Animal Testing Laboratory of Marmara University after the approval of the Ethics Committee (dated on November 5, 2018; protocol No. 102.2018.mar).

Laboratory animals and the care of animals in research

Ten-twelve weeks old, female Wistar Albino (Rattus Norvegicus species) rats weighting 200 to 250 grams were used in this study. Rats received light exposure 12 hours a day (from 08:00 to 20:00) and had access to food (standard rodent pellet) and drinking water (tap water) without restriction and kept at room temperature of 21 to 23^{0}C and a humidity of 40 to 50% and were housed 4 or 5 per cage. The number of rats was chosen in in the light of previous studies. Rats were randomly assigned to four groups of 6. Considering bowel transit time, rats were not fed within 6 hours before laparotomy to empty the gut and allow surgery, but they had access to drinking water.

Groups

For this study, 30 female Wistar albino rats were used, and the rats were separated randomly into five groups consisting of six rats each: normal, torsion-detorsion, torsion-detorsion + sildenafil 1.4 mg/kg, torsion-detorsion + vardenafil 1.7 mg/kg and torsion-detorsion + tadalafil 5.0 mg/kg.

Group 1 (normal ovary group — Group N): this group of rats underwent laparotomy once. During the laparotomy, one of the ovaries was removed and fixed in 10% formaldehyde. And at least 1 mL of blood sample was taken for AMH test.

Group 2 (torsion ovary group — Group O): Laparotomy was performed and one of the ovaries was twisted 720 degrees and untwisted 3 hours later and the surgical wound was closed without administering any medicine. A second surgery was performed 3 hours later and both ovaries were removed. And at least 1 mL of blood sample was taken for AMH test.

Group 3 (sildenafil group — Group S): At the first laparotomy one of the ovaries was twisted 720 degrees. Sildenafil 1.4 mg/kg (Degra® film tablet, Deva Ilac, Istanbul, Turkey) was administered intraperitoneally 30 minutes before detorsion. At the second laparotomy, the ovaries were detorsioned and reperfusion was maintained for 3 hours. At the third laparotomy rats were sacrificed and at least 1 mL of blood was taken for AMH testing and both ovaries were removed by laparotomy.

Group 4 (vardenafil group — Group V): At the first laparotomy one of the ovaries was twisted 720 degrees. Vardenafil 1.7 mg/kg (Levitra® film tablet, Bayer, Istanbul, Turkey) was administered intraperitoneally 30 minutes before the second laparotomy. At the second laparotomy, the ovaries were detorsioned and reperfusion was maintained for 3 hours. At the third laparotomy rats were sacrificed and at least 1 mL of blood was taken for AMH testing and both ovaries were removed by laparotomy.

Group 5 (tadalafil group — Group T): At the first laparotomy one of the ovaries was twisted 720 degrees. Tadalafil 5.0 mg/kg (Cialis® film tablet, Lilly ilac, Istanbul, Turkey) was administered intraperitoneally 30 minutes before the second laparotomy. At the second laparotomy, the ovaries were detorsioned and reperfusion was maintained for 3 hours. At the third laparotomy rats were sacrificed and at least 1 mL of blood was taken for AMH testing and both ovaries were removed by laparotomy.

Surgical procedures

Sterile, powder-free, latex gloves were used during all surgical procedures. Every rat underwent a laparotomy procedure under anesthesia using 10% ketamine hydrochloride (Ketalar; Eczacıbaşı¸ Warner Lambert, Istanbul, Turkey) at a dose of 80 mg/kg and 2% xylazine hydrochloride (Rompun; Bayer Health Care LCC, Kansas, KS) at a dose of 15 mg/kg. The procedure was performed while rats were lying in supine position. Abdominal area was shaved before the procedure and the surgical site was prepared using 10% Povidone-iodine solution (Batticon; Adeka Laboratories, Istanbul, Turkey). A 5 cm median (on the line between the xiphoid process and pubis) incision was made to enter into the abdominal cavity and the right ovary was twisted 720 degrees along

with tubo-ovarian blood vessels (Fig. 1). The twisted ovary was fixed to the abdominal muscles with 5/0 silk sutures and the abdominal wall (peritoneum, fascia and skin) was closed in two layers using running locking sutures with 2/0 polyglactin 910, following bleeding control. Each surgical procedure lasted 15 to 20 minutes to protect the drying effect of the room air and the rats were allowed to wake up.

Histopathological examinations

Surgically excised ovaries were fixed in 10% formalin. Paraffin blocks were prepared 24 hours after the oophorectomy procedure. Tissue sections of 5 micrometers were taken and follicular activity was assessed in 5 randomly selected samples from each ovary. Slides were stained with hematoxylin eosin and examined under the light microscope. The paraffin blocks were sectioned using a microtome blade (Leica, Nussloch, Germany). Every slide was blindly assessed by the same pathologist. A light microscope (Olympus Clinical Microscope, Tokyo, Japan) was used to analyze the sections.

Edema, vascular Congestion, inflammation, cellular degeneration and hemorrhage were examined as histopathological injury scores. The scores were evaluated as described by Celik et al. [13]. Pathological findings were rated. Grade 0 indicated normal alterations, no abnormal findings; Grade 1 indicated mild edema, mild vascular congestion, absence of hemorrhage or leukocyte infiltration; Grade 2 indicated moderate edema, moderate vascular congestion, absence of hemorrhage or leukocyte infiltration; Grade 3 indicated severe edema, severe vascular occlusion, minimal hemorrhage and minimal leukocyte infiltration, Grade 4 indicated severe edema, severe vascular occlusion, hemorrhage and leukocyte infiltration (Fig. 2–4).

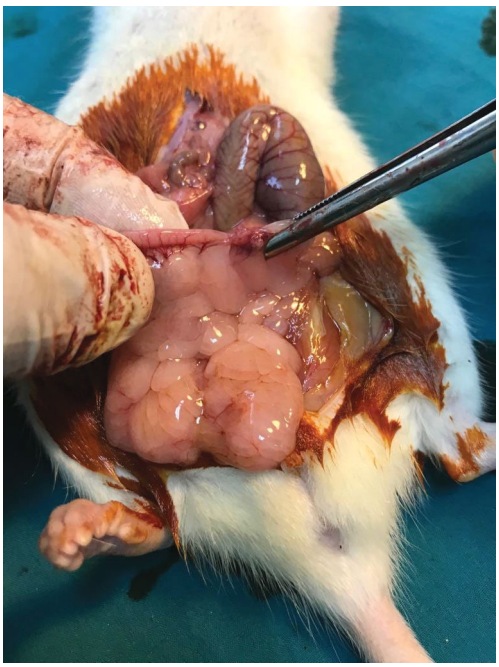

Figure 1. Torsion of ovaries

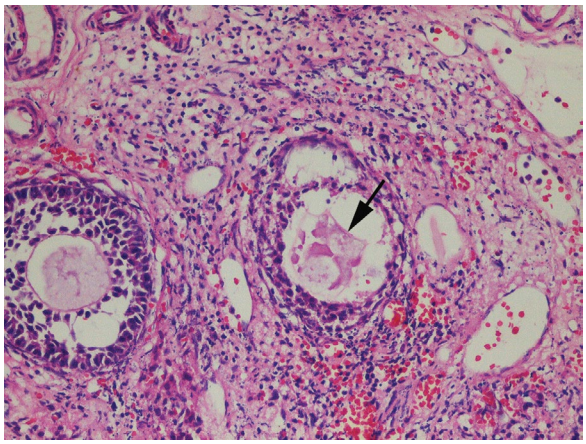

Figure 3. Degenerated secondary follicle and degenerated oocyte in the area of hemorrhage and edema (arrow); (hematoxylin eosin, ×400)

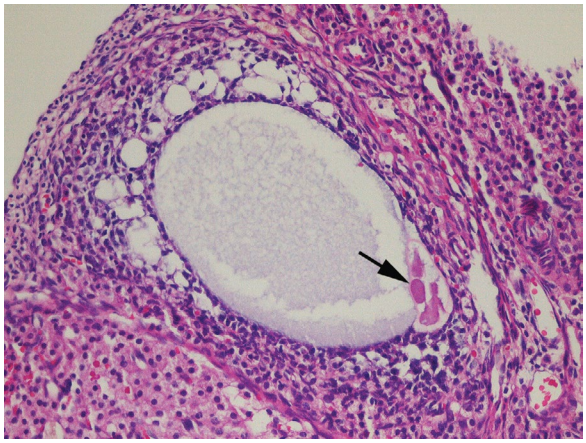

Figure 2. Degenerated oocyte (arrow) in degenerated tertiary follicle; (hematoxylin eosin, ×400)

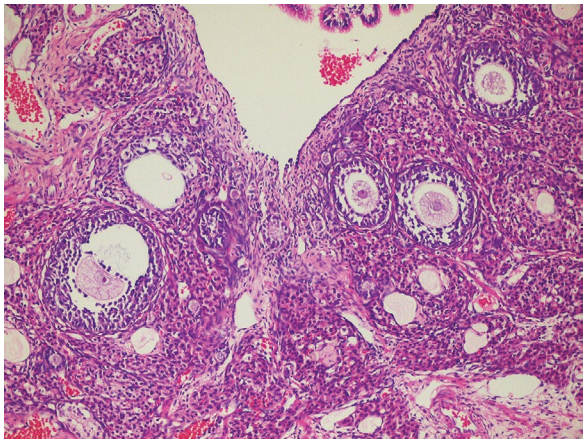

Figure 4. Multiple primordial, primary, secondary and antral follicles in the ovarian cortical region; (hematoxylin eosin, ×200)

All follicles were counted to assess ovarian reserve. Primordial, primary, secondary (pre-antral) and tertiary (antral) follicles were counted.

Follicles were evaluated as described by Parlakgumus et al. [20]. Primordial, primary, secondary (pre-antral) and tertiary (antral) follicles were counted. Primordial follicle is described as an oosit with surrounded only one layer of epithelial cell layer, primer follicle is surrounded with one or more layer of cuboidal granulosa cells. Secondary (pre-antral) follicle is surrounded with more than two cell layers and consists of antrum folliculi and zona pellucida. Tertiary (antral) follicle is defined if there are antrum, stratum granulosum and surrounding cumulus oophorus layers.

Statistical analysis

Statistical analyses were performed using the SSPS Version 15.0. The Kolmogorov-Smirnov test and histograms were used to assess the normality of the distribution of variables. The mean ± standard deviation or median (interquartile range) were used to present descriptive analyses. One-way ANOVA test was used to analyze normally distributed numerical data and the Kruskal-Wallis test was used to analyze non-normally distributed numerical data. The limit of statistical significance was set at p-values < 0.05.

RESULTS

Histopathological damage scores

According to the histopathological damage scores, minimum damage was seen in the normal group and maximum damage was seen in the torsion-detorsion group. There was an increase in all histopathological damage scores (edema, vascular congestion, inflammation, cellular degeneration, hemorrhage) in the torsion group which was not given any drug. (p scores respectively; < 0.001, < 0.001, < 0.001, 0.006, < 0.001).

Hemorrhage were statistically different between normal and torsion group (p < 0.001) and PDE inhibitors were not useful for decreasing hemorrhage (S, V, T group; p = 0.002, 0.002, 0.001).

Sildenafil and vardenafil treatments showed protective effect by preventing significant increase in inflammation parameters. (p = 0.058, 0.138) (Tab. 1). Tadalafil treatment was only protective for cellular degeneration (p = 0.140). Vardenafil treatment was protective for edema (p = 0.238), vascular congestion (p = 0.111), inflammation (p = 0.138) and cellular degeneration (p = 0.532). Vardenafil treatment were effective for 4/5 parameters in histologic examination.

Ovarian follicle counts and AMH levels

Primiordial, primary, secondary (pre-antral) and tertiary (antral) follicles counts were similar between all the groups. After three hours of ischemia and reperfusion there was not significantly decrease in the study groups than the normal group. Atresic follicle counts and AMH levels were statistically different between normal and the torsion group. Atresic follicles were significantly increased (p < 0.001) and AMH levels were significantly decreased in the torsion group (p = 0.004). The increase in atresic follicles was prevented in all groups using PDE inhibitors. In the vardenafil group the increase in the number of atresic follicles was prevented

Table 1. Comparison of histopathologic damage scores between study groups

	Normal	Detortion	p*	Detortion + Sildenafil	p**	Detortion + Vardenafil	P***	Detortion + Tadalafil	p****
Edema									
Mean SD	0.93 ± 0.69	2.25 ± 0.79	< 0.001	2.33 ± 0.52	0.003	1.50 ± 1.05	0.238	2.67 ± 0.52	0.005
Median- IQR	1.00 (0.00–1.00)	2.00 (2.00–3.00)		2.00 (2.00–3.00)		1.50 (1.00–2.00)		3.00 (2.00–3.00)	
Vascular congestion									
Mean SD	0.80 ± 0.85	2.13 ± 0.95	< 0.001	2.83 ± 0.41	0.002	1.83 ± 0.75	0.111	2.50 ± 0.84	0.028
Median	1.00 (0.00–1.00)	2.00(1.00–3.00)		3.00 (3.00–3.00)		2.00 (1.00–2.00)		3.00 (2.00–3.00)	
Inflammation									
Mean SD	0.10 ± 0.31	0.67 ± 0.56	< 0.001	0.67 ± 0.82	0.058	0.33 ± 0.52	0.138	0.67 ± 0.52	0.019
Median	0.00 (0.00–0.00)	1.00 (0.00–1.00)		0.50 (0.00–1.00)		0.00 (0.00–1.00)		1.00 (0.00–1.00)	
Cellular degeneration									
Mean SD	0.17 ± 0.38	0.75 ± 0.94	0.006	0.33 ± 0.52	0.138	0.33 ± 0.52	0.523	0.50 ± 0.84	0.140
Median	0.00 (0.00–0.00)	0.50 (0.00–1.00)		0.00 (0.00–1.00)		0.00 (0.00–1.00)		0.00 (0.00–1.00)	
Hemorrhage									
Mean SD	0.13 ± 0.35	2.46 ± 0.78	< 0.001	2.33 ± 1.03	0.002	2.17 ± 0.98	0.002	2.83 ± 0.41	0.001
Median	0.00 (0.00–0.00)	3.00 (2.00–3.00)		3.00 (1.00–3.00)		2.50 (1.00–3.00)		3.00 (3.00–3.00)	

p*; p**; p***; p**** (Mann Whitney U Test)

(p = 0.461), but the decrease in the AMH level could not be prevented (p = 0.004). Sildenafil and tadalafil groups were similar with the normal group regarding athretic follicle count (p = 0.138, 0,108 respectively) and AMH levels (p = 0.140, 0.108 respectively). They prevented the increase in atresic follicle count and the decrease in AMH levels (Tab. 2).

DISCUSSION

Histopathological examination of the ovary reveals the ischemia/reperfusion injury of the ovary. I/R is associated with edema, vascular congestion, inflammation, cellular degeneration and hemorrhage. I/R injury were studied in the literature and histologic examination score results varied between the trials.. Also several agents were used to prevent I/R injury and their efficiency varied widely in the trials leading to conflicting findings.

Sildenafil was shown to reduce histopathologic injury after two-hour torsion procedure. Sildenafil doses were compared between groups and were not significantly different when applied 0.7 mg/kg and 1.4 mg/kg. Congestion, hemorrhage and edema were reduced similar to our study. Further they have assessed oxidative stress index [total antioxidant status (TAS), total oxidant status (TOS) and oxidative stress index (OSI)] and showed that these scores were also reduced [21]. But there were no data about the differences of follicle count and AMH levels between groups.

In another study, sildenafil was found to be effective in I/R damage by providing reduction in antioxidant enzymes (superoxide dismutase, glutathione peroxidase), hemorrhage, degenerative cells and atresic follicles. In this study, AMH examinations were not tested [13].

As a result of two studies investigating the effects of vardenafil on ovarian I/R injury; edema, vascular congestion, hemorrhage and the number of atresic follicles were decreased. In these studies, oxidative stress markers were examined. Pre-antral + antral follicle's and AMH examinations were not performed [19, 22]. In our study, vardenafil showed an effective improvement in all histopathological damage scores. Pre-antral + antral follicles remained similar and the increase of atresic follicles was prevented. However, it was observed that AMH values decreased.

The results of a study investigating the protective effects of tadalafil on I/R injury resulted in a significant reduction in damage scores such as edema, vascular congestion and hemorrhage after 3 hours of ischemia 12 hours of reperfusion and in another group after 24 hours of reperfusion. However, in this study, there is no AMH examination and follicular examinations [23]. In our study, we determined that tadalafil provided similar reduction in edema, vascular congestion, inflammation and hemorrhage scores.

Although these agents are in the same drug class, their success in treatment of I/R damage is different. We think that

Table 2. Comparison of ovarian follicle counts and AMH levels between groups

	Normal	Detortion	p*	Detortion + Sildenafil	p**	Detortion + Vardenafil	p***	Detortion + Tadalafil	p****
Primordial follicle									
Mean SD	6.07 ± 5.46	3.38 ± 2.55	0.153	3.17 ± 1.47	0.403	3.00 ± 1.67	0.285	1.83 ± 0.75	0.930
Median- IQR	3.50 (2.00–11.00)	2.50 (2.00–4.00)		3.00 (2.00–3.00)		2.50 (2.00–5.00)		2.00 (1.00–2.00)	
Primer follicle									
Mean SD	10.30 ± 4.99	8.71 ± 3.18	0.451	9.67 ± 3.27	0.104	7.50 ± 2.66	0.106	8.33 ± 3.83	0.417
Median	8.00 (7.00–13.00)	8.00 (6.00–11.50)		9.00 (7.00–13.00)		7.50 (6.00–8.00)		10.00 (4.00–11.00)	
Secondary (pre-antral) follicle									
Mean SD	5.50 ± 3.18	5.29 ± 3.11	0.642	3.50 ± 0??.84	0.680	3.33 ± 1.63	0.466	5.17 ± 2.48	0.373
Median	5.00 (3.00–7.00)	4.00 (3.00–7.50)		4.00 (3.00–4.00)		3.00 (2.00–4.00)		5.50 (3.00–7.00)	
Tersier (antral) follicle									
Mean SD	4.80 ± 2.34	4.79 ± 2.08	0.923	5.17 ± 1.94	0.738	5.00 ± 2.53	0.371	4.33 ± 2.16	0.564
Median	5.00 (3.00–7.00)	5.00 (3.00–6.50)		5.00 (5.00–6.00)		4.00 (3.00–7.00)		3.50 (3.00–7.00)	
Athresic follicle									
Mean SD	0.03 ± 0.18	0.96 ± 1.12	< 0.001	0.33 ± 0.52	0.138	0.50 ± 0.84	0.461	0.50 ± 0.84	0.140
Median IQR	0.00 (0.00–0.00)	0.50 (0.00–2.00)		0.00 (0.00–1.00)		0.00 (0.00–1.00)		0.00 (0.00–1.00)	
AMH									
Mean SD	2.641 ± 0.95	1.372 ± 0.66	0.004	1.753 ± 0.79	0.108	1.090 ± 0.47	0.004	1.801 ± 0.55	0.108
Median	2.591 (1.64–3.70)	1.211 (0.95–1.66)		1.596 (1.16–2.01)		1.070 (0.64–1.60)		1.659 (1.37–2.30)	

p*; p**; p***; p**** (Mann Whitney U Test)

this can be related with the difference in ischemia/reperfusion duration, chemical success and/or half-life of agents.

Tadalafil is effective 36 hours after the dose, its half-life is 17.5 hours [24] and it is about 4.5 hours longer than sildenafil [23].

Vardenafil is more sensitive to PDE-5 than sildenafil and has similar pharmacokinetic parameters [25–27].

In a study conducted by Yeral et al. [6], it was determined that there was no significant difference in the number of pre-antral + antral and total follicles between the groups with and without albumin treatment after 3 hours of ischemia and 7 days of reperfusion.

In these cases, some questions come to mind. Is it important whether different durations are effective in changes in follicle damage? Does short-term ischemia or short-term reperfusion provide a full effect in the creation of follicular damage? As a result of this important study, 2 hours, 4 hours and 16 hours ischemia was performed. Then reperfusion for 28 days was performed. They reported that the number of follicles does not differ between the torsion ovary and contralateral ovary, but this condition cannot guarantee the survival of the ovarian follicles [28].

In our study, no significant difference was observed between the groups in the number of pre-antral + antral follicles after 3 hours of ischemia and 3 hours of reperfusion.

In another study, 3 hours of ischemia and then 7 days of reperfusion decreased ovarian follicles. Atorvastatin has been shown to help with follicular healing but not AMH. They also pointed out that they did not know whether this follicular recovery was permanent and whether the primordial follicles would turn into functional mature follicles [20].

AMH is a dimeric glycoprotein released from granulosa cells of the antral follicles. Therefore, evaluation of the ovarian reserve with AMH test after iatrogenic events such as pelvic radiotherapy, chemotherapy, uterine artery embolization or ovarian surgery may be helpful in maintaining fertility at an early stage. AMH expression begins in the primordial follicles, whereas the levels of pre-antral and small antral follicles are highest. According to the literature, AMH level is thought to be a better indicator of ovarian reserve compared to age, FSH, LH, E2 and inhibited B levels [29–31].

When follicles show signs of atresia, anti-mullerian hormone (AMH) decreases. Some cells probably show a higher AMH expression than proliferative capacity and others that reflect differences in steroidogenic activity. In our study, in the vardenafil group even though the increase in the number of atresic follicles was prevented, AMH levels remained low compared to the normal ovarian group. It is seen that the number of atresic follicles and AMH levels are not in direct relationship with ovarian damage scores and pre-antral + antral follicles [32, 33].

When the literature is examined, it is seen that there are decreases in the AMH levels after 3 or 6 hours of ovarian torsion followed by 3 hours, 24 hours or 7 days of reperfusion. It is seen that short-term or long-term I/R events affect AMH levels [20, 31, 34, 35].

As a result of our study, 4/5 of the histopathological damage scores improved with vardenafil treatment, there was no decrease in pre-antral + antral follicles, undesired increase in atresic follicles was prevented but the decrease of AMH value could not be prevented.

Sildenafil and tadalafil showed partial improvement in histopathological damage scores, no decrease in pre-antral + antral follicles, increased atresic follicles, and AMH values remained within normal ranges.

CONCLUSIONS

PDE inhibitors were found to be effective in reducing ovarian ischemia/reperfusion injury. The sildenafil and tadalafil seem to be more effective than the vardenafil in protecting the ovarian reserve.

Statement of ethics

This study was conducted at the Animal Testing Laboratory of Marmara University after the approval of the Ethics Committee (dated on November 5, 2018; protocol No. 102.2018.mar).

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Anti-androgenic therapy in young patients and its impact on intensity of hirsutism, acne, menstrual pain intensity and sexuality — a preliminary study

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ABSTRACT

Objectives: Using anti-androgenic contraception is one of the methods of birth control. It also has a significant, non-contraceptive impact on women's body. These drugs can be used in various endocrinological disorders, because of their ability to reduce the level of male hormones.

The aim of our study is to establish a correlation between taking different types of anti-androgenic drugs and intensity of hirsutism, acne, menstrual pain intensity and sexuality .

Material and methods: 570 women in childbearing age that had been using oral contraception for at least three months took part in our research. We examined women and asked them about quality of life, health, direct causes and effects of that treatment, intensity of acne and menstrual pain before and after. Our research group has been divided according to the type of gestagen contained in the contraceptive pill: dienogest, cyproterone, chlormadynone and drospirenone. Additionally, the control group consisted of women taking oral contraceptives without antiandrogenic component.

Results: The mean age of the studied group was 23 years ± 3.23. 225 of 570 women complained of hirsutism.

The mean score for acne intensity before the use of contraception was 2.7 ± 1.34. The mean score for acne intensity after 3 months of using contraception was 1.85 ± 1.02 ($p < 0.001$). 192 women reported excess hairiness in one or more area before treatment. Mean value based on Ferriman-Gallway scale before the treatment was 6.23 ± 6.21 and 5.39 ± 5.6 after the treatment ($p < 0.001$).

Conclusions: All groups of drugs effectively reduced pain and acne severity. Cyproterone and drospirenone turned out as the most effective drugs in treating hirsutism. Surprisingly, according to our research, dienogest does not have any impact on body hairiness.

Key words: anti-androgenic therapy; oral contraceptives; acne; hirsutism; menstrual pain; young patients

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INTRODUCTION

Hyperandrogenaemia is a very frequent endocrinopathy. It concerns about 7% of women in childbearing age. Its clinical symptoms can be pretty troublesome and often affect our patients' self-esteem. Oral contraceptives, many times viewed only as a method of contraception, turn out to be very useful in those conditions and offer a variety of non-contraceptive health benefits. They are becoming more and more popular in women with higher levels of androgens. Additionally, they reduce menstrual pain and the amount of blood loss during the menstruation. Moreover, taking hormonal contraceptives regulates the menstrual cycle [1].

Hyperandrogenaemia can be caused by different disease entities, for example polycystic ovary syndrome, obesity, Cushing syndrome, ovarian secreting androgens, adrenal tumors, adrenal hyperplasia, liver insufficiency. The most common symptoms connected with higher levels of androgens are hirsutism and acne. Hirsutism affects about 5–15% and acne about 6–55% of women, according to epidemiological data [1].

Physiologically, androgens are responsible for hair growth regulation, production and secretion of gonadotropins, wound healing and cutaneous barrier formation. The pathogenesis of acne and hirsutism in hyperandroge-

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naemia is connected with sebaceous glands, hair follicles and enzymatic reactions in them. Androgens are converted into the dihydrotestosterone (DHT) which has 5 to 10 times higher affinity to androgen receptor than testosterone [1].

The involvement of androgens in acne vulgaris is supported by different evidences such as lack of acne in men with androgen insensitivity or responding in reduced sebum production in women with acne using antiandrogenic drugs. It is also known, that androgens are responsible for the replacement of vellus hair, which are slight and unpigmented, by thicker and darker terminal hair. That is observed in androgen-sensitive areas and happens in hyperandrogenic entities. Therefore, it seems to be justified to use drugs that decrease the level of male hormones, to help with those complaints [2, 3].

For now, two types of oral contraceptives are known: combined and progestin-only. Combined hormonal contraceptives are very effective in skin changes, whereas progestin-only contraception may even worsen the condition of the skin [1].

One of the types of oral contraceptives are antiandrogenic oral contraceptive pills. They are combined hormonal contraceptives that consist of two components: estrogen and progestogen. The mechanism of action of those drugs concentrates on decreasing the level of androgens in four ways. Firstly, inhibition of secretion of gonadotropins, mostly the luteinizing hormone (LH). This mechanism is the main reason for using antiandrogenic pills in ovarian hyperandrogeneamia, especially hyperthecosis. Then, those drugs increase the liver synthesis of sex hormone binding globuline (SHBG), which ends up with a higher level of bounded androgens and reduced level of biologically active male hormones. Moreover, they decrease the adrenal androgens synthesis, and finally, reduce the activity of androgen receptors.

Antiandrogenic hormonal pills can be divided into four groups depending on the type of progestogen: drospirenone, chlormadynone, cyproterone and dienogest.

Drospirenone

Drospirenone is a derived form of 17 alfa-spironolactone and has a similar chemical structure to spironolactone. It is mostly bounded to albumin, so that the free blood amount is about 3–5%. Despite having anti-mineralocorticoid and anti-androgenic activity, which is almost 30% of the anti-androgenic activity of cyproterone acetate, drospirenone has diverse metabolic effects such as potential to reduce blood pressure and weight loss. The overall pearl index of the combined ethinylestradiol/drospirenone contraceptive is 0.64 [4, 5].

Chlormadyinone

Chlormadyinone acetate is one of derived form of progesterone. Studies have shown its high efficiency in treatment of acne, comparing to other anti-androgenic hormonal pills. This contraceptive is well tolerated and shows a reliable contraceptive effect. The overall pearl index of the combined ethinylestradiol/chlormadinone contraceptive is 0.34 [6, 7].

Cyproterone acetate (CPA)

Cyproterone acetate (CPA) is the most common anti-androgenic drug prescribed to patients with PCOS. According to researches, there are no significant differences in mechanism of action between types of those drugs, but CPA seems to play a significant role in women with high LH/FSH ratio. On the other hand, cyproterone acetate should be prescribed wisely, because of its side effects. According to different studies, CPA should not be used only as a contraceptive. It can be prescribed in specific complaints like moderate to severe acne and hirsutism in women in reproductive age, but only if alternative treatments, such as topical therapy and systemic antibiotic treatment, have failed [4, 8].

Dienogest

Dienogest is the only nortestosterone derivative with antiandrogenic potency. Its antiandrogenic activity is measured as about 30% of cyproterone acetate activity. Only 10% of dienogest is bond to SHBG or CBG so that high serum levels are achieved. Moreover, dienogest is known as a proven way to treat endometriosis, as it has tolerable profile, minimal side effects, it is safe for long-term use and lowers the risk of recurrence of endometriosis. The overall pearl index of the combined ethinylestradiol/dienogest contraceptive is 0.21 [5, 9, 10].

Despite many positive aspects of oral contraception, it should be avoided in women suffering from migraine headache, systemic lupus erythematosus, cholecystic diseases, crescent cell anemia, mitral valve prolapse and item in patients who smokes cigarettes, hyperlipidemiae, arterial hypertension, who had in past gestational diabetes and mechanical jaundice during pregnancy. The contraindications to that treatment are as follows: pregnancy, breast feeding, birth canal bleeding with unknown etiology, estrogen-dependent cancers, circulatory system and hepatic diseases, migraine treated by ergotamine, significant hypercholesterolemia or hypertriglyceridemia and smoking after age of 35 years [1, 11].

Of course, the possible harmful effects of oral contraception should also be considered. Other side effects reported with hormonal contraception is breast tension, headaches, nausea, irregular menses, weight growth, diminished libido and depression [12]. Therefore, prescribing oral contraceptives to the patient should always be carefully thought out.

The aim of the study was to establish the correlation between the type of active progestogen ingredient in oral antiandrogenic contraception and reducing hirsutism in specific areas, reducing intensity of pain and acnes in womens body for 3-month follow-up period.

MATERIAL AND METHODS

This prospective, observational, non-interventional study was carried out at the Department of Pregnancy Pathology, Department of Woman's Health, School of Health Sciences in Katowice, Medical University of Silesia, Poland between March 2018 and March 2019. Patients were recruited personally while waiting for their routine medical check-ups. Women above eighteen years old, in childbearing age and non-pregnant were enrolled to our study. Patients with indications for use of oral contraception, who had given permission for the beginning of hormonal therapy took part in our research. Exclusion criteria were using oral hormonal contraception or another drug with antiandrogenic component, for example finasteride and flutamide, for at least three past months and lack of patient's consent. Finally, 570 patients were included into the study. The university Ethics Committee waived the requirement for informed consent due to the anonymous and non-interventional nature of the study (KNW/0022/KB/68/19). Patients gave informed consent to the study.

The completely self-administered questionnaire was provided to the patients twice. At the first visit we asked about gynecological, endocrinological and general medical conditions, menorrhea disorders, used medicaments and intensity of menstrual pain. Information about relationship, habitation, education and quality of life were also collected. Physical examination contained weight and height measurement, evaluation of intensity of acne and hairiness in 9 androgen sensitive areas — upper lip, chin, chest, upper and lower back, upper and lower abdomen, upper arms and thighs. Based on results of examination hirsutism assessment with Ferriman-Gallwey (FG) scoring were done. Hair growth was marked in all of those areas on scale from 0 (no terminal hair) to 4 (maximal growth). The maximum score is 36. Women with a score of 8 and more were diagnosed with hirsutism [13]. During three weeks before evaluation patients were requested not to use shaving or other mode of hair removal. Patients were prescribed oral contraception. According to the type of active ingredient women were divided into five groups: control group (patients using oral contraceptives without anti-androgenic component) and four research groups, depending on active progestogen substance (Fig. 1).

After three months patients were asked to visit the outpatient clinic again in order to re-evaluate the score in the Ferriman-Gallwey scale. Rules of not shaving for three weeks before the evaluation were persistent. The intensity of acne was marked. Questions about the intensity of menstrual pain were also asked.

All data analyses were conducted using StatSoft Statistica version 13.0 PL software and P value of < 0.05 was considered as significant. Quantitative variables are presented as mean and standard deviation (SD) or a median and interquartile range (IQR). The qualitative variables are presented as an absolute value and/or percentage. Between-group differences for quantitative variables were verified using parametric (t-test or ANOVA) or non-parametric tests (Mann-Whitney U or Kruskal-Wallis), with previous verification of their distribution by the Shapiro-Wilk or Kolmogorov-Smirnov test. In the case of qualitative variables, the chi-square test or Fisher's exact test were used.

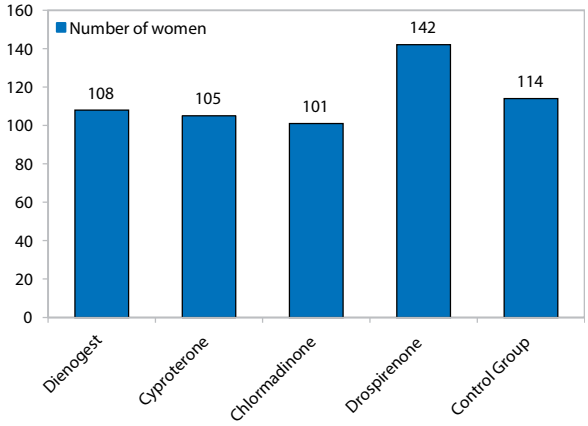

Figure 1. Patients' oral contraception intake divided by type of gestagen

Table 1. Subjects' characteristics.

	Research group	Control group	p
Age [years]	23 ± 3.04	23 ± 3.9	> 0.05
Martial status			
Married	66 (14.5%)	15 (13.15%)	> 0.05
Informal relationship	294 (64.5%)	89 (78.1%)	
Single	96 (21%)	10 (8.8%)	
Education			
University degree	171 (37.5%)	44 (38.6%)	> 0.05
High school	280 (61.4%)	68 (59.7%)	
Vocational	5 (1.1%)	2 (1.7%)	
No education	1 (0.02%)	0 (0%)	
Place of residence			
City above 200,000 residents	222 (48.7%)	67 (58.8%)	> 0.05
City 50,000–200,000 residents	77 (16.9%)	24 (21.1%)	
Town below 50,000 residents	59 (12.9%)	11 (9.7%)	
Village	98 (21.5%)	12 (10.5%)	
Living conditions			
Very good	199 (43.6%)	53 (46.5%)	> 0.05
Good	202 (44.3%)	48 (42.1%)	
Average	54 (11.8%)	13 (11.4%)	
Below the average	1 (0.2%)	0 (0%)	
Growth [cm]	167 ± 7.14	167 ± 6.01	> 0.05
Weight [kg]	62 ± 12.2	59 ± 8.54	> 0.05

Data are presented as number (%) or mean SD

RESULTS

The mean age of the patients was 23 years ± 3.23. Their average age in both of groups was similar. Table 1 presents general characteristics of the studied group (Tab. 1).

Pain and acne

The mean score for acne intensity before the use of contraception was 2.7 ± 1.34. The mean score for acne intensity after 3 months of using contraception was 1.85 ± 1.02 ($p < 0.001$). The intensity of acne before and after the use of contraception in each group is presented in Figure 2. The reduction of acne intensity was statistically important in all five groups ($p < 0.001$).

The mean score of menstruation pain intensity before the use of contraception was 6.15 ± 2.55. The mean score of pain intensity after 3 months of using contraception was 2.96 ± 1.92 ($p < 0.001$). The intensity of pain before and after the use of contraception in each group is presented in Figure 3. All of anti-androgenic groups and control group reduce the intensity of menstrual pain in three months period ($p < 0.001$).

Hirsutism

The mean score based on Ferriman-Gallway scale in the studied group was 2.1 ± 4.65 before the treatment and 1.83 ± 4. 12 after the treatment ($p < 0.001$).

378 women (66.32%) did not report excess hairiness in any part of the body before the treatment (0 points). 386 patients (67.72%) didn't report excess hairiness after the treatment (0 points).

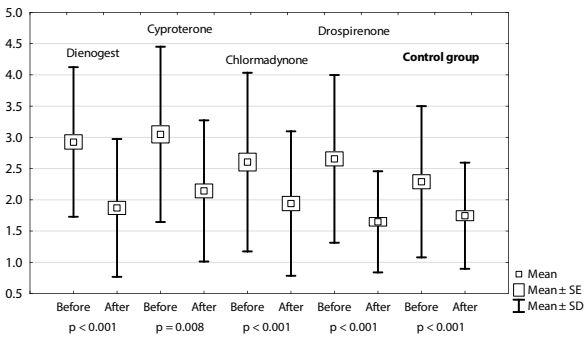

Figure 2. The intensification of acne before and after treatment

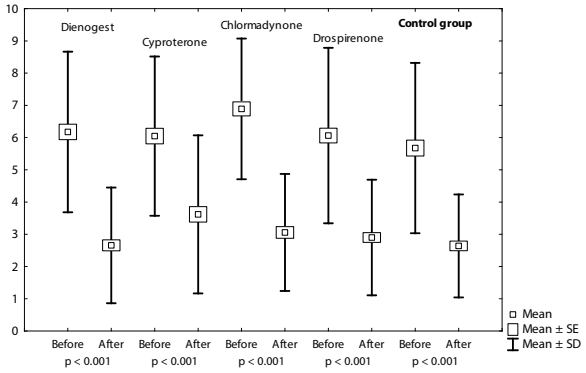

Figure 3. The intensification of the menstrual pain before and after treatment

Table 2. Mean value of excessive hairiness in the group of 192 women who reported excessive hairiness in one or more parts of the body before the treatment

	Before	After	p
Dienogest	2.43 ± 5.38	2.06 ± 4.88	< 0.001
Cyproterone	3.71 ± 5.5	3.48 ± 4.88	< 0.001
Chlormadynone	1.96 ± 4.93	1.73 ± 4.55	< 0.001
Drospirenone	1.7 ± 4.25	1.35 ± 3.34	< 0.001
Control group	0.91 ± 2.36	0.79 ± 2.19	< 0.001

Data are presented as mean ± SD

192 women reported excess hairiness in one or more area before treatment. Mean value based on Ferriman-Gallway scale before the treatment was 6.23 ± 6.21 and 5.39 ± 5.6 after the treatment ($p < 0.001$). In this group, 59 of women had a score of 8 or more, in a scale Ferriman-Gallway this result is regarded as hirsutism.

Table 2 presents the intensity of excessive hairiness in the group of 192 women who reported excessive hairiness in one or more parts of the body before the treatment, depending on the type of contraception.

Effects of the treatment on hirsutism in different parts of the body are shown in Table 3. Cyproterone reduces hairiness on chin ($p = 0.04$), thighs ($p = 0.05$) and buttocks ($p = 0.04$). Drospirenone has the effect of reducing excessive hair on upper lip ($p = 0.01$), thighs ($p = 0.04$) and buttocks ($p = 0.04$). Chlormadinone has statistically important impact on underbelly and thighs ($p = 0.01$) hirsutism. After three months of using control group the p value is important for upper lip ($p = 0.04$). On the other hand, dienogest does not contribute to decrease body hairiness in any of the chosen areas ($p > 0.05$ for each part of the body).

DISCUSSION

Hyperandrogenism is a complex condition that can manifest in different clinical symptoms such as hirsutism, acne and others, which often result in lower self-esteem. For now, we know that oral antiandrogenic pills are helpful, but are prescribed rather randomly because the main differences between ways and places of action are still not known [14].

Although it is unclear how the biochemical markers of hyperandrogenism affect the quality of patients' life, study shows that the clinical manifestations play the main role in worsening it. That is probably because the severity of symptoms in hyperandrogenism correlate poorly with the androgen excess and some of the patients with clinical symptoms of hyperandrogenism have androgen levels in normal ranges. That is why it is important to choose the treatment that can help with patients' complaint, not only the biochemical markers [15].

Table 3. The intensification of the hirsutism before and after treatment

Part of the body	Dienogest			Cyproterone			Chlormadynone			Drospirenone			Control group		
	Before	After	p-value	Before	After	p-value	Before	After	p-value	Before	After	p-value	Before	After	p-value
Upper lip	2.22	1.815	> 0.05	1.571	1.375	> 0.05	1.773	1.55	> 0.05	1.931	1.625	**0.01**	1.444	1.125	0.04
Chin	1.294	1.200	> 0.05	1.667	1.571	**0.04**	2.286	2.444	> 0.05	1.182	1.182	> 0.05	1.143	1.00	> 0.05
Chest	2.200	1.667	> 0.05	1.000	1.00	> 0.05	1.000	0	> 0.05	1.500	1.556	> 0.05	1.250	1.00	> 0.05
Stomach	1.529	1.467	> 0.05	1.500	1.667	> 0.05	1.733	1.600	> 0.05	1.563	1.375	> 0.05	1.222	1.300	> 0.05
Underbelly	2.083	2.000	> 0.05	1.667	1.556	> 0.05	2.316	1.895	**0.01**	1.778	1.444	> 0.05	1.389	1.400	> 0.05
Arms	1.833	2.000	> 0.05	1.667	1.667	> 0.05	2.571	2.571	> 0.05	1.667	1.400	> 0.05	1.667	1.667	> 0.05
Thighs	1.857	1.650	> 0.05	2.500	2.167	**0.05**	2.235	1.765	**0.01**	2.214	1.857	**0.04**	1.875	1.625	> 0.05
Back	2.000	2.000	> 0.05	1.500	1.500	> 0.05	0	0	0	1.400	1.000	> 0.05	1.000	1.000	> 0.05
Buttocks	3.182	2.818	> 0.05	2.400	2.500	**0.04**	2.800	2.800	> 0.05	2.667	2.429	**0.04**	2.333	1.750	>0.05

Data are presented as mean ± SD

Polycystic ovarian syndrome (PCOS) is a common gynecologycal problem that affects about 5–9 % of women in reproductive age. Rotterdam criteria ESHRE/ASRM are used to define that condition. They include clinical or biochemical hyperandrogenism, infrequent or absence of ovulation and polycystic ovaries on ultrasound [17]. It is necessary to exclude other disorders with androgen excess. Ovaries and adrenals are responsible for increased androgen level in PCOS. The excess of testosterone (T), total, unbound and free form can be found. Also, that disorder can be related to high level of Δ4-Androstendione (Δ4-A), dehydroepiandrosterone (DHEA), and DHEAsulfate (DHEAS). It turned out that testosterone is a superior marker of hyperadnogenemia. Free testosterone and Δ4-Androstendione are also important, but less than testosterone. Many women who are suffering from PCOS had increased level of testosterone and normal free testoserone and Δ4-Androstendione. Increased Δ4-A level can be associated with more severe phenotype of PCOS [16–19].

One of the studies, examined the effects of different physical training protocols on the sexual function of women with PCOS. This research revealed that continuous aerobic training as well as intermittent aerobic training increased the quality of sexual life and reduced the anxiety and depression of women with polycystic ovary syndrome [20]. According to that study, women suffering from hyperandrogenism and its clinical symptoms are less satisfied with their sexual life. It turned out that choosing oral antiandrogenic contraception containing chlormadinone acetate cause the change in sexual behavior during the treatment. Patients found themselves to be more sexually attractive and as well their partners found them more sexually attractive than before. That is probably because of the aesthetic improvement obtained by the pill intake. More researches are needed to be done to find out if other groups of antiandrogenic pills have similar impact on women's sexual behavior [21, 22].

One of the studies analyzed the influence of genotype and hyperandrogenism on sexual function, gender identification, and partner preference in women with congenital adrenal hyperplasia (CAH) who present symptoms of hyperandrogenism [23]. This study is pointing to importance of early beginning of antiandrogenic treatment in women with congenital adrenal hyperplasia [23].

This study is only a prototype for comparison between the four groups of antiandrogenic drugs. It is focused on searching the differences between place of action in hirsutism. That means the treatment probably can be matched to specific problems more precisely, limiting the side effects to the minimum for every woman's case.

According to our research the most effective in hirsutism are drospirenone and cyproterone so that they would be the best for patients with polycystic ovary syndrome. A systematic review is pointing to similar effectiveness of these two drugs [24]. They reduce hairiness mostly on thighs, buttock and accordingly on upper lip and chin. Additionally, dienogest statistically does not have any impact on body hairiness. Other study confirms that dienogest is worse in reducing hirsutism than cyproterone [25]. That can suggest withdrawal of prescribing it to women with those complaints. Chlormadinone has impact only on underbelly and thighs excessive hair. According to study these antiandrogenic drug is effective in hirsutism, but less than drospirenone [1].

It is important to remember that the most common symptom of polycystic ovary syndrome is moderate and severe acne. There, gyneacologist should always take into consideration all of the symptoms that patient complaints of and try to find a solution to all of them. However, this research did not indicate any important differences in reducing intensity of menstrual pain and acne. All of the antiandrogenic groups and control group seem to have similar impact on those complaints. That is why matching

the specific group of drug to specific hirsutism area probably can be independent of other popular factors, excluding the side effects [16].

Polycystic ovary-related hyperandrogenic symptoms can by effectively treated by cyproterone acetate and ethinylestradiol (CPA/EE). Besides all the over obvious effects such as improvement in hirsutism, acne, seborrhea, alopecia, irregular bleeding and decrease in hyperandrogenemia and hyperinsulinemia, this treatment may result in reduction in risk of ovarian, colon and endometrial cancer. There are also researches, which indicate that short-term pre-treatment CPA/EE could potentially increase fertility in female patients and improve pregnancy outcomes, however more studies are needed [26].

Considering lipid and glucose metabolism cyproterone acetate and ethinylestradiol seems to be better choice for patient with polycystic ovary syndrome, because this condition is associated with multitude of metabolic disorders. Androgenic progestogens such as levonorgestrel may have negative influence on metabolism parameters [26, 27].

The side effects or hormonal contraception should be always taken into consideration, prudent usage of medicaments with cyproterone is justified and the balance between profits and side effects needs to be kept [12, 28].

CONCLUSIONS

The main finding from this study was different impact on reducing hirsutism in specific areas depending on used drug: dienogest, cyproterone, chlormadinone or drospirenone. It means that the treatment can be precisely matched to specific woman's problem. The biggest impact on chin hair had cyproterone. To reduce hirsute intensity on upper lip prime choice could be drospirenone and oral contraception without antiandrogen component. If thigh area is the most problematic for the patient, she should take cyproterone, drospirenone or chlormadinone. The best treatment for buttocks hairiness is cyproterone or drospirenone and for lower abdomen — chlormadinone. According to this research, dienogest does not have important influence on hirsutism.

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Nutritional behavior in pregnancy

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ABSTRACT

Objectives: The aim of the study was to characterize nutritional behavior in pregnancy.

Material and methods: The survey study included 250 pregnant women. The survey concerned dietary behavior reffered to the type of diet, the number of meals per day, snacking between meals, consumption of meat, fish, dairy products, bread, fruits and vegetables.

Results: 88.8% of the respondents were not on a special diet. The most of the women ate more than three times a day. The women usually ate fruits and vegetables, yogurt and sweets as snacks between meals. The majority of respondents consumed meat and sliced meats twice or once a day with the preference of poultry. Only 17.6% of them ate fish with the recommended frequency and as much as 21.2% chose not-recommended species. Almost 29.6% of patients consumed 3 to 4 servings of milk or milk products a day and 16.8% of them excluded milk. Half of the respondents declared eating wheat bread and 24% of them chose wheat roll during pregnancy. Despite the large number of women who consumed wheat baking, a considerable amount of women chose wholemeal bread and wholemeal rolls. Nutritional behaviors were correlated with on education level and weight gain during pregnancy.

Conclusions: The frequency of meals was adequate for the most of pregnant women as well as recommended consumption of meat with poultry preference. However, the inappropriate nutrition was also observed in a low consumption of fish and dairy products, a high consumption of wheat breadstuff and sweets, as well as in a small intake of milk. Education level and weight gain during pregnancy were associated with nutritional behaviors.

Key words: nutritional behavior; proper diet; eating habits; healthy lifestyle; body mass index; weight gain

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INTRODUCTION

Proper nutrition in pregnancy is one of the public health concerning problem. The malnutrition affects more than a half of women in many low- and middle-income countries with the highest risk among the poorest [1].

Both among underweight as well as overweight women, the risk of small for gestational age fetuses (SGA) and prematurity is increased [2]. Moreover, maternal obesity can lead to many consequences such as pregnancy induced hypertension, preeclampsia, gestational diabetes, increased rate of cesarean sections and delivering large for gestational age infants (LGA) [3].

Leonard SA. et al. reported that high maternal body weight in the reproductive period increases the risk of childhood obesity. Furthermore, the high pre-pregnancy BMI influences more on the postpartum weight retention than weight gain during pregnancy [4].

According to the Academy of Nutrition and Dietetics statement, reproductive-aged women should implement a healthy lifestyle, which reduces the risk of fetal defects, inappropriate fetal development and chronic diseases of both mother and newborn. The factors affecting the perinatal outcomes include correct pre-pregnancy weight, appropriate weight gain and physical activity during gestation, consumption of a wide variety of food, vitamins and minerals supplementation, elimination of alcohol and smoking [5].

Objectives

The aim of the study was to characterize nutritional behavior in pregnant women in Poland.

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MATERIAL AND METHODS

The survey study included 250 women who gave birth in the Obstetric-Gynecological Hospital, University of Medical Sciences in Poznan. All patients signed informed consent and fulfilled a questionnaire prepared by authors (Supp. file 1). Then the women were divided into two groups- those with lower and higher education level and the nutritional behaviors were analyzed. Independently, they were divided for three groups according to pre-pregnancy BMI and gestational weight gain recommended by the Institute of Health [6]. The first group was composed of women with lower weight gain than recommended, the second group consisted of females with proper weight gain and the third group included respondents who put on weight more than recommended**.**

The questions referred to general information, such as age, pregestational and actual weight, place of residence, education, marital status, employment before and during pregnancy, the period of working during pregnancy and the type of pregnancy (singleton or multiple). Moreover, the questions also concerned diseases and complications during pregnancy. The part of dietary behaviours referred to the type of diet and the number of meals per day. It also concerned snacking between meals, consumption of meat, fish, dairy products, bread, fruits and vegetables.

The general characteristics of the study group is presented in the Table 1. The coexisting diseases and pregnancy complications are shown in the Table 2. The data are expressed as a percentage or as mean (M) and standard deviation (SD).

The calculations were performed using Microsoft Excel 2010 and Statistica StatSoft 13.1. The data in interval scale were assessed using nonparametric Mann-Whitney test and the data in nominal scale were analyzed using the Fisher's exact test. The significance level was assumed as p-value below 0.05. The data do not add up because of multiple choice questions.

RESULTS

88.8% of the respondents were not on any special diet. Only 7.2% of women were on diabetic diet and 0.8% on gluten-free diet. The same number of women were on low-salt diet and 0.4% on low-fat diet. Only 1.2% of pregnant women were vegetarians or vegans. High protein food responded 0.8% women. When assessing the frequency of meals, it was noticed that only 33.6% of women ate 5 times a day or more often. Pregnant women consumed meals 4 (36.0%) or 3 (26.0%) times a day, and up to 4.4% ate less than 3 times a day. Especially often they ate fruits and vegetables (84.8%) and yoghurt (68.8%). Almost half of them ate sweets (46.8%) between meals. According to fruits and vegetables, the most often chosen were apples, bananas, oranges, and among vegetables tomatoes, carrots, cucumber and potatoes.

Table 1. The general characteristics of survey respondents

Characteristics	Pregnant women
Age [years] (Mean ± SD)	30 ± 5
BMI [kg/m^2] (Mean ± SD)	22.8 ± 4.4
Place of residence [%]	
rural areas	33.2
urban areas	66.8
Education [%]	
lower	29.2
higher	70.8
Marital status [%]	
unmarried	16.0
married	81.2
divorced	2.8
Work activity [%]	
before pregnancy	86.4
during pregnancy	59.6
Term of gestational work activity discontinuation [weeks] (Mean ± SD)	20 ± 10
Type of pregnancy [%]	
singleton	91.2
multiple	8.8

Table 2. The diseases and pregnancy complications of survey respondents

Diseases and pregnancy complications	Number of pregnant women [%]
Chronic arterial hypertension	4.4
Pregnancy induced arterial hypertension	4.4
Gestational diabetes mellitus	9.6
Anaemia	7.6
Hypothyroidism	8.4
Hyperthyroidism	1.2
Polyhydramnion	2.0
Oligohydramnion	2.0
Premature membrane rupture	4.0
Intrauterine growth restriction	3.6
Fetal defect	2.0
Cervical insufficiency	4.8
Threatening preterm delivery	18.8
Vaginal bleeding in pregnancy	8.8
Spine pain	30.4

The majority of respondents consumed meat and sliced meats twice (38.8%) or once (34.8%) a day. As for meat, most of them consumed poultry (73.2%). Much less women consumed beef (13.2%) and pork (8.8%). Even less pregnant women ate veal (3.2%) and rabbit meat (0.4%) that are considered very healthy. Only 17.6% of women ate fish with the recommended frequency. 75.6% of them chose fish

called „fish of best choices" (salmon, cod, zander, herring, pollock, hake, blue hake, trout, sole) and even 21.2% chose not-recommended species such as mackerel, panga, and tuna. The majority of women (65.6%) consumed fish only once a week, and 12.4% did not eat fish at all. Almost 29.6% of patients consumed three to four servings of milk or milk products a day. However, 16.8% of patients excluded milk completely. Half of the respondents declared eating wheat bread and 24% of them chose wheat roll during pregnancy. Despite the large number of women who consumed wheat baking, a considerable amount of women chose wholemeal bread (49.2%) and wholemeal rolls (35.6%).

The high-educated women ate significantly more often five (34% vs 12%, p = 0.0002) or more than five (8% vs 0%, p = 0.0068) meals a day in comparison to women with lower education level. Additionally, women with lower education consumed two dishes a day statistically more often (7% vs 2%, p = 0.0491). The high-educated respondents declared eating vegetables (92% vs 74%, p = 0.0002), yoghurt (75% vs 55%, p = 0.0020), beef (18% vs 3%, p = 0.006) and „fish of best choices" (80% vs 64%, p = 0.0096) significantly more often than the rest of respondents. Taking into account the frequency of meat consumption, high-educated respondents declared eating meat and sliced meats once a day (39% vs 25%, p = 0.0206) significantly more often. Statistically the greater group of women with lower education consumed dairy products four or more times a day (15% vs 5%, p = 0.0107) but they also declared significantly more often eating dairy products occasionally (10% vs 2%, p = 0.0078) or not eating at all (4% vs 0%, p = 0.0242). The wholemeal bread (59% vs 25%, p < 0.0001) and wholemeal rolls (40% vs 26%, p = 0.0285) were eaten significantly more often by high-educated women in comparison to those with lower education, who preferred wheat bread (66% vs 44%, p = 0.0010). Considering fruits and vegetables, the respondents with higher education chose apples (78% vs 63%, p = 0.0123), raspberries (21% vs 8%, p = 0.0077), grapefruits (18% vs 5%, p = 0,0077), asparagus (14 vs 1%, p = 0,0013), tomatoes (76 vs 53%, p = 0,0004), onions (14 vs 5%, p = 0.0469) significantly more often but they also ate potatoes (35 vs 58%, p = 0.0009) and broccoli (28% vs 42%, p = 0.0175) statistically less often than those with lower education.

According to pre-pregnancy BMI and gestational weight gain the women with lower weight gain than recommended declared consumption of wheat bread (62.8% vs 45.7%, p = 0.0329), watermelon (15.3% vs 4.3%, p = 0.0250) and beef (17% vs 6.6%, p = 0.0410) significantly more often than women with proper weight gain. Moreover, the females, who put on weight too low than recommended declared significantly more often consumption of watermelon (15.3% vs 2.7%, p = 0.0448) and statistically less often eating between meals (1.2% vs 8.1%, p = 0.0462), consumption of cod (23.9% vs 43.6%, p = 0.0250) and herring (14.8% vs 33.3%, p = 0.0167) than females with higher weight gain than recommended. Furthermore, women with higher weight gain ate herring (33.3% vs 10.5%, p = 0.0027) and avoided eating meat (10% vs 0%, p = 0.0044) significantly more often than those with proper weight gain.

DISCUSSION

Proper nutritional behavior in pregnancy is important for the wellbeing of both mother and fetus, because well-balanced diet supports maternal health during gestation, delivery and breastfeeding [7–11]. Most of our respondents were not on a diet similar to the results observed by Mielnik [12]. A special type of diet was implemented mostly as a consequence of pregnancy complications, forcing them to change the diet.

The Institute of Medicine recommends eating of three meals and two or more snacks a day [13]. Siega-Riz et al. [14] observed that women, who consumed main meals and snacks less often, had a higher risk of preterm delivery. In our study, only 26% of females followed the recommendations and consumed three main meals a day. Moreover, the most of our respondents declared eating four (36%) or five (28%) meals a day. The similar results were obtained by Mielnik [12]. Furthermore, Pieszko et al. [15] observed the increasing frequency of consumed meals in comparison to the pre-pregnancy period.

In the study of Kobiołka et al. the most often eaten snacks between meals were fruits (80%). Consecutively, pregnant women as snacks chose yogurt (61%), sweets (54%) and vegetables (19%) [16], what was compatible with the results of our study.

During pregnancy, the main recommended source of animal protein should be lean meat and its products, skimmed milk and its products, as well as fish and eggs. The consumption of pork due to the high content of saturated fats should be limited [17]. The consumption of meat and its products allows to cover the increasing iron demand for the prevention of anaemia and preterm delivery [18, 19]. According to Szostak-Węgierek and Cichocka [20] study, the pregnant women should consume one portion (about 150 grams) of poultry a day in the first trimester and one and a half servings of poultry a day in the second and third trimester, interchangeably with fish two to three times a week. In our study, most women followed the recommendations and consumed meat and sliced meats twice (38.8%) or once (34.8%) a day, which was comparable with results of Mielnik. Moreover, she presented a similar number of non-eating meats women as it was found in our study (3.4%). Similarly to Mielnik's research, pregnant women preferred poultry [12].

During gestational period pregnant women should also eat fish meals. It is recommended to eat one portion of fish (about 150 grams) in the first trimester and one and a half portion of fish during the second and third trimester with the frequency of two to three times a week [20]. In accordance with the Food and Drug Administration recommendations [21], the pregnant women should consume two to three servings of fish of best choices a week or one serving of fish of good choices a week. Only about one fifth (17.6%) of our patients ate fish with the recommended frequency. Moreover, even 21.2% of the respondents chose not-recommended species of fish. Kobiołka et al. [16] noticed that the majority of pregnant women consumed fish once or twice a week (74%), three to four times a week (18%) and 8% of them declared not eating fish at all.

Furthermore, it is recommended to consume three servings of milk or milk products a day in the first trimester and four servings a day in the second and third trimester of pregnancy. One glass of milk, yogurt, kefir, 100 grams of curd cheese or 2 slices of cheese is considered as one serving [20]. Our study revealed that only less than one third of patients followed these recommendations (29.6%). This means that pregnant women eat dairy products in an insufficient amount, which may have an undesirable adverse effect on the course of pregnancy. Similar eating habits in relation to dairy products were presented by Kobiołka et al. [16]. Moreover, only about one fifth of pregnant patients consumed milk every day (23.2%). Furthermore, 16.8% of our patients did not drink milk. Similarly, in the Mielnik's study [12] as much as 33% of women did not drink milk during gestation. Contrary, Kobiołka et al. [16] revealed that only 1% of pregnant respondents declared drinking of milk.

The basic products recommended in the daily diet of pregnant women are cereal products, being the main source of carbohydrates and minerals [22, 23]. Wholemeal bread, rich in fiber, regulates the motility of the digestive tract, gives a sense of satiety, which prevent snacking between meals, and thus creates a greater opportunity to maintain proper weight. Half of our respondents declared eating wheat bread and 24% of them chose wheat roll during pregnancy. Despite the large number of women who consumed wheat baking, a considerable amount of females chose wholemeal bread (49.2%) and wholemeal rolls (35.6%). Slightly worse nutritional habits were observed by Mielnik. The most of survey respondents chose wheat bread (48.9%) and wheat roll (46.6%). The rest of pregnant respondents ate wholemeal bread (29.5%), wholemeal roll (20.5%), wheat-rye bread (19.3%), rye bread (14.8%) and toasted bread (3.4%) [12].

The positive association between consumption of fruit and vegetables and a birthweight was observed in previous studies [24–26]. Our respondents ate the most often apples, bananas and oranges, and the most often chosen vegetables were tomatoes, carrots and potatoes. The similar preferences were observed by Mielnik [12].

A lot of dietary behaviors were associated with education level. That's why education of pregnant patients regarding healthy nutrition is so important. Interestingly, only a few dietary preferences differed between patients after taking into account BMI and gestational weight gain. We assumed that differences between groups may not be statistically significant because all groups were composed of patients whose pre-pregnancy BMI was too low, normal or too high, therefore the differences of nutritional behaviors may be unnoticeable. In addition, the questionnaire referred to the consumption of food in pregnancy without specifying the consumed quantity. Dietary intake is difficult to measure but the meals quantity is one of the most important factors of the appropriate weight gain during pregnancy. The larger meal portions contribute to higher weight gain in pregnant women. The method of measurement of the food consumption should be easy and clear for all pregnant women. According to Nöthlings study [27], measuring food intake by cups, servings and grams is effective and adequate for most analyzes. Taking into account cups and servings may be much easier for most surveyed patients. In our study we decided that it would be difficult to determine because of probable differences between gestational trimesters, even within the same trimester and seasonal changes in meals composition. Anyway, the calculation of food intake should be consider in further studies.

Analyzing the dietary preferences data in pregnancy, it should be stated that many pregnant women do not follow the food recommendations. It has to be underline that there is a lot to do in this area. The principles of healthy eating based on the pyramid of healthy nutrition should be promoted among reproductive-aged women. Doctors and health professionals should be obliged to implement proper dietary behavior and inform about harmful effects of both malnutrition as well as overeating in pregnancy.

CONCLUSIONS

The study revealed that the most pregnant women consumed meals with adequate frequency. Moreover, we noticed the recommended consumption of meat with poultry preference. However, the dietary habits revealed nutritional mistakes such as low consumption of fish and dairy products, consumption of wheat breadstuff and sweets, as well as small intake of milk. The high education level was related with greater consumption of vegetables, yoghurt, beef„fish of best choices", wholemeal bread and eating five meals a day. The weight gain during pregnancy was associated with consumption of wholemeal bread, beef, herring, watermelon, eating between meals and eating meat in general. Therefore, there is still a considerable need to expand nutritional education and to develop mother awareness in the perinatal care programs.

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Supplemental file 1. The questionnaire

Part I — demographic data (please highlight the correct answers)			
Age			
Body weight before pregnancy			
Current body weight			
Height			
Place of residence			
	rural area less than 5000 people		
	small city less than 20,000 people		
	city more than 20,000 people		
Monthly household income without taxes			
	less than 1,000 PLN		
	1,100–3,000 PLN		
	3,100–6,000 PLN		
	6,100–10,000 PLN		
	more than 10,000 PLN		
Education			
	primary		vocational
	high school		higher
Marital status			
	unmarried		married
	divorced		other .....
Did you work professionally?			
	before pregnancy		
	yes		no
	during current pregnancy		
	yes		no
If yes, until which week of pregnancy did you work?			
Type of professional work (describe)			
	physical work		
	mental work		
	housewife		
	other		

In which area are you employed?			
	agriculture		food industry
	textile industry		construction
	hotel and gastronomy		transport
	finance and banking		media, publishing
	advertising		
	information technology, telecommunications		
	public administration		education
	health service		social assistance
	culture, entertainment		recreation
	other		
Type of the work (you can choose more than one answer)			
	sitting, about 4 hours per day		
	sitting, about 8 hours or more per day		
	physical, less than 4 hours per day		
	physical, about 8 hours or more per day		
	work mostly related with driving		
	student		
	unemployed		
What is the main source of the stress for you in your work ? (choose maximum 3 answers)			
	conflicts between employees		
	conflicts with management		
	problems with defining the responsibilities		
	sense of control		
	workload		
	possibility of self-realization and the use of own potential		
	conflict of values		
	health		
	physical working conditions		
What is the main source of the stress for you in your family life? (choose maximum 3 answers)			
	conflicts with your spouse/partner		
	conflicts with other family members		
	health of family members		
	financial problems		
	work		
	division of duties (cleaning, babysitting)		
	conflict of values		
	political views		
	other		
Part II — questions about general health and obstetric history (please write or highlight the correct answer)			
Obstetric history			
	labors		
	period between current and last pregnancy (years)		
	miscarriages		
Week of gestation			

Type of pregnancy	
	single
	multiple
Did you suffer from (you can choose more than one option)	
	chronic arterial hypertension
	pregnancy induced arterial hypertension
	coronary heart disease
	pregestational diabetes mellitus
	gestational diabetes mellitus
	asthma
	anaemia
	hyperthyroidism
	hypothyroidism
	viral hepatitis (typ B or C)
	renal failure
	liver diseases (which) .....
	other ....
Did you suffer from any other pregnancy complication: (several answers are possible)	
	polyhydramnion
	oligohydramnion
	premature rupture of membranes) (which week of pregnancy? .....
	intrauterine growth restriction
	complications of multiple pregnancy (twin-to-twin transfusion syndrome, selective intrauterine growth restriction)
	fetal defect .....
	genetic fetal defect .....
	cervical insufficiency, did you have cervical suture? If yes, in which week of pregnancy? .....
	threatening preterm delivery
	threatened miscarriage
	intrauterine infection
	bleeding
	abdominal pain
	abnormality of placenta or umbilical cord: placenta increta, vasa previa, umbilical cord collision
	other .....
Did you have the back pain during pregnancy?	
	yes
	no
When did the back pain occur first time? (week of gestation)	
In which part of spine did a pain occur? (multiple choice)	
	cervical
	thoracic
	lumbar
	pelvic
	all

Did a pain awake you?			
	yes		
	no		
Did you have hands oedema?			
	yes, in which week of pregnancy?		
	no		
Did you have legs oedema?			
	yes, in which week of pregnancy?		
	no		
Was there a time during the day when the back pain was stronger? (Multiple choice)			
	morning, just after awake		morning
	early afternoon		afternoon
	evening		whole day
	at night		
Part III — nutritional behaviors during pregnancy (please highlight the correct answer)			
Were you on any special diet?			
	no		
	vegetarian		
	vegan		
	other, what?		
How many meals did you have every day (without sweets)			
	one		two
	three		four
	five		more than five
What did you eat between main meals?			
	fruits, vegetables		
	yoghurt		
	sweets		
	sandwiches		
	sweet buns		
	other, what?		
	I don't eat between meals		
What kind of bread did you eat the most often (choose maximum 2 answers)			
	wheat bread		
	wholemeal bread		
	rye bread		
	wheat rolls		
	wholemeal rolls		
	crispy bread		
	I don't eat bread		
What fruits were you most likely to eat (choose maximum 3 options)			
	apples		strawberries
	grapes		plums
	raspberries		cherries
	bananas		oranges
	peaches or apricots		watermelons
	lemons		grapefruits
What vegetables were you most likely to eat (choose maximum 3 options)			
	potatoes		carrots
	parsley		broccoli
	cauliflower		asparagus
	celery		tomatoes
	cucumbers		onions
What kind of meat did you eat most often during pregnancy?			
	poultry		
	beef		
	veal		
	other, what?		
	I didn't eat meat during pregnancy		
What kind of fish did you eat most often during pregnancy?			
	salmon		
	carp		
	cod		
	zander		
	mackerel		
	herring		
	pollock		
	panga		
	hake		
	other, what?		
	I didn't eat fish during pregnancy		
How often per week did you eat fish as main meal?			
	once a week		
	twice a week		
	3 times a week		
	4 times a week		
	five or more than 5 times a week		
	I didn't eat fish at all		
How often did you eat meat and sliced meats?			
	once a day		
	twice a day		
	3 times a day		
	4 or more than 4 times a day		
	I didn't eat meat and sliced meats at all		
	occasionally		
How often did you eat dairy products?			
	once a day		
	twice a day		
	3 times a day		
	4 or more than 4 times a day		
	I didn't eat dairy products		
	occasionally		

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Donor human milk in Neonatal Intensive Care Unit — to whom, how much and how long?

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ABSTRACT

Objectives: The aim of the study was to present the variability of patients who received donor human milk (DHM) during Neonatal Intensive Care Unit (NICU) hospitalization, including time of its usage and volume of portions.

Material and methods: A retrospective analysis of data was conducted for all infants admitted to the NICU at the University Hospital during the first year of the Human Milk Bank operation. One-way analysis of variance in the intergroup scheme, Kruskal-Wallis variance analysis with the Jonckheere-Tepstra test, correlation analysis using Pearson's r and Spearmann's rho, frequency analysis using the Fisher's exact test were used to conduct analyses.

Results: 133 newborns received DHM. 3 groups of neonates were identified: < 32 0/7 weeks, 32 0/7–36 6/7 weeks and > 37 0/7 weeks of gestational age (GA). Time of DHM supplementation was similar in all groups and does not differ depending on the GA but preterm infants received the smallest total volume of DHM. However, infants > 37 weeks of GA had almost a threefold greater chance of abandoning breastfeeding than the others (odds ratio (OR) = 2.89, 95% CI: 0.69–12.20). There was a statistically significant, weak negative correlation between period of total parenteral nutrition and the volume of milk from the bank: rho = –0.194; p = 0.026.

Conclusions: The DHM supply did not have a negative impact on lactation and breastfeeding. Stimulation of lactation was necessary for 5–7 days. The time of DHM supply was the same regardless of GA. The majority of infants were breastfed or received only MOM on the day of discharge from the hospital.

Key words: human milk bank; neonatal intensive care unit; neonate; preterm infant; breastfeeding

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INTRODUCTION

Enteral feeding of newborns treated in a Neonatal Intensive Care Unit (NICU) is a challenge for medical staff. World Health Organization (WHO) [1, 2], American Academy of Pediatrics (AAP) [3] and The European Society for Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) [4] have recognized the superiority of mother's own milk (MOM) over all infant formulas. It is not always possible to get milk from biological mother just after delivery, then the second choice is the donor human milk (DHM). This is compatible with the international guidelines [1–4], which states that: "Donor human milk from a professional milk bank is the second best choice for newborns after mother's own milk."

The main recipients of DHM are premature newborns. In the last decade, the use of pasteurized DHM has become the standard of care for very low birthweight (VLBW; < 1500 g) infants when MOM is not available [5, 6]. The usage of DHM by other high-risk newborns hospitalized in NICU also increases, primarily for full-term infants with severe complications and for infants in pre- and postoperative period [7]. Human milk is an ideal food for newborns, both as a full-fledged food and as a missing link in the immune protection of the baby. The activity of Human Milk Banks creates equal opportunities for all infants to access the best nourishment.

OBJECTIVES

The aim of the study was to present the variability of patients who received DHM during hospitalization, including time of its usage and volume of portions. The study also concerned the duration time of total parenteral nutrition and the moment of hospitalization when the infants had been fed only with MOM, and the method of feeding at the time of discharging from the hospital.

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MATERIAL AND METHODS

A retrospective analysis of available data was conducted for all infants admitted to the NICU of Department of Neonatology at University Hospital, during the first year of Human Milk Bank (HMB) activity between 10/02/2017 and 31/12/2017. The study received ethical approval from the Ethics Committee (177/2015 and 242/2017). Permission to apply DHM had to be given by the infants' legal guardian.

Feeding policy

Minimal enteral feeding with MOM or DHM was introduced, usually within the first 6 hours of life. Mothers were also encouraged to obtain colostrum by initiation of lactation during the first 6 hours post-delivery. After few hours of priming the infant's intestine, feeding was increased by 15–30 mL/kg/day depending on the maturity and feeding tolerance of the infant. When enteral feeding has reached 100 mL/kg/day, parenteral nutrition was discounting.

Preparation of DHM

HMB in Department of Neonatology in the University Hospital is the seventh bank operating in Poland, associated in the European Milk Bank Association (EMBA). Donors must undergo rigorous screening before donation, concerning the health condition, blood and milk analysis. The milk is subject to Holder Pasteurization (62.5˚C for 30 minutes) and then is frozen, while awaiting for final results of microbiological cultures.

Infant formula

If after 14 days of using DHM, MOM was not in sufficient quantities to cover the nutritional needs, neonates were given infant formula according to the gestational age (GA).

Data collection

All data was collected from paper and electronic medical database. Maternal data regarding age, pregnancy, delivery and health were analyzed. Neonatal data concerning the gestational age, birth weight, clinical condition of newborns, including the need for intensive therapy, time of total parenteral nutrition (TPN) supply, DHM volume given to the child and time of breast milk supply were analyzed. The final point of the analysis was the method of feeding the child at discharge from the NICU.

Statistics

Two sets of analyzes were carried out. At first, descriptive characteristics of children and mothers participating in the study were reported. The Kołmogorow-Smirnov test was used to determine if the sample belongs to population with a normal deviation. The Mann-Whitney U test's purpose was to compare continuous data to avoid assuming a normal distribution. Descriptive statistics were used to demonstrate the mean ± standard deviation or median (min–max) for constant variables, whereas nominal variables were expressed as case number and percentages. One-way analysis of variance in the intergroup scheme, Kruskal-Wallis variance analysis with the Jonckheere-Tepstra test, correlation analysis using Pearson's r and Spearmann's rho, frequency analysis using the Fisher's exact test were used to conduct analyses. All statistical analysis were performed using IBM SPSS Statistics 23. A p value < 0.05 was considered statistically significant in all analyses.

RESULTS

There were 2 560 newborns hospitalized in the Neonatology Department, including 248 neonates admitted to NICU between 10/02/2017 and 31/12/2017. During the first year of Human Milk Bank activity 133 newborns had been receiving DHM. Each newborn had been receiving colostrum and MOM, but nutrition was supplemented with DHM to quickly terminate TPN. The characteristics of newborns and their mothers are presented in the Table 1.

Donor human milk and gestational age of the newborn infants

A hypothesis was verified concerning the relationship between milk supply from the HMB and gestational age (GA). For this purpose, a group of children included in the study was divided into three subgroups depending on GA: under 32 0/7, between 32 0/7 and 36 6/7, over 37 0/7 weeks. In such separate groups two factors were compared: volume of DHM portion (mL) and number of days when DHM was provided to newborns. There were substantial differences between the groups: $[H(2) = 17, p < 0.001, \eta 2 = 0.13]$. In addition a statistically significant trend was captured: the higher the gestational age, the higher DHM supply ($J = 2910.00$, $p = 0.002$). Results are summarized in Figure 1.

Days of using DHM was analyzed, a one-way analysis of variance was performed in 3 groups of neonates. The result was not statistically significant: $F(2; 130) = 2.58$; $p = 0.079$. The value of coefficient $\omega 2$ was 0.02. Days of supplied of DHM was similar in all groups and does not differ depending on the GA of newborn infants. The results are presented in the Table 2.

DHM and duration of total parenteral nutrition (TPN)

Duration of TPN related with the supply of DHM in terms of its quantity (mL) and period of time were analyzed. To this end, a correlation analysis was carried out with the Spearman rho coefficient comparing the above-mentioned variables with period of time of TPN (in days).

There was a statistically significant, weak negative correlation between days of TPN and the volume of milk from

Table 1. Demographics of newborns who received DHM and their mothers

Maternal characteristics (n = 103)	
Age [years] M ± SD, (min–max)	32.42 ± 5.12 (18–45)
Pregnancy complications, n (%)	
Gestational diabetes	15 (14.6)
Preeclampsia	20 (19.4)
Twin gestation	18 (17.5)
Triplet gestation	3 (2.9)
Vaginal delivery, n (%)	17 (16.5)
Cesarean section, n (%)	86 (83.5)
Infant characteristics (n = 133)	
Male n (%)	77 (58)
Female n (%)	56 (42)
Gestational Age [weeks] M ± SD, (min–max)	33.98 ± 3.4 (23–41)
Birth weight [g] M ± SD, (min–max)	2108.95 ± 737.62 (510–4090)
Apgar 1 min. Me (min–max)	8 (0–10)
Apgar 5 min. Me (min–max)	8 (4–10)
Adaptive disorders	32 (24%)
Respiratory disorders	84 (63%)
Hipotermia	3 (2.6%)
Triplets	9 (6.8%)
Congenital malformations	5 (3.8%)
Post-surgery treatment	4 (3%)
Days of Hospitalization M ± SD, (min–max)	22.84 ± 15.72 (5–90)
Weight at discharge [g] M ± SD	2513.7 ± 510.9
Donor Human Milk	
Days M ± SD, (min–max)	6.09 ± 4.98 (1–23)
Volume mL M ± SD, (min–max)	703.33 ± 974.35 (3–4726)

M — medium; Me — median; SD — standard deviation; min and max — the lowest and highest value of the distribution

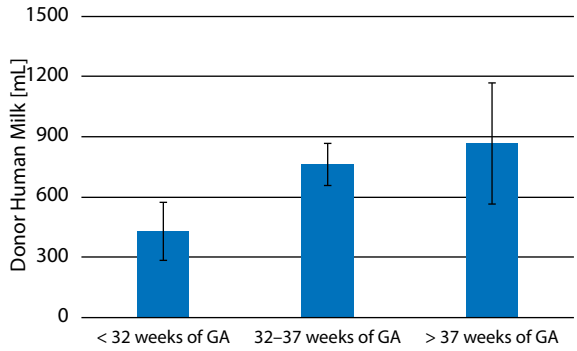

Figure 1. Volume of DHM and gestational age of infants

HMB: rho = –0.194; p = 0.026. The longer TPN period, the smaller DHM supply. However, in case of comparing the days of DHM supply and the days of TPN, the relationship did not turn out to be statistically significant: rho = –0.061; p = 0.489.

Table 2. Comparison of days of DHM supply in the groups of the newborn infants

				95% CI	
Week of GA	**n**	**M**	**SE**	**LL**	**UL**
< 32 0/7	29	5.03	0.96	3.06	7.01
32 0/7–36 6/7	87	6.78	0.54	5.70	7.86
≥ 37 0/7	17	4.35	0.81	2.63	6.08

n — number of observations; M — medium; SE — standard error; 95% CI — confidence interval for the difference between means; LL and UL — the lower and upper limits of the confidence interval of milk with BM

DHM and exclusively feeding with mother's own milk on the day of discharge from the NICU

Relative risk (RR) of non-breastfeeding for infants born > 37 weeks of GA compared with the rest of newborns were calculated. Frequency analysis using the exact Fisher test showed a statistically insignificant result: p = 0.149. The vast majority of infants received either exclusively MOM or mixed feeding at discharge, both in the group > 37 weeks of GA (82.4%) and in preterm infants (93.1%). The calculated value of the odds ratio (OR) indicates that newborn infants > 37 weeks of GA have almost a threefold greater chance of abandoning breast-feeding than the others (OR = 2.89, 95% CI: 0.69–12.20). Subsequently, the odds ratio (OR) was calculated for exclusive mother's milk feeding the neonates born < 32 weeks of GA compared with other infants. Frequency analysis using the exact Fisher test showed a statistically insignificant result: p = 0.475. The majority of infants received only MOM at discharge, both in the group < 32 weeks of GA (69.0%) and in other infants (76.0%). The calculated value of OR indicates that infants born > 32 weeks of GA have a slightly higher chance of feeding exclusively with MOM than the others (OR = 1.42, 95% CI: 0.58–3.52). On the other hand, the relative risk of exclusively breastfeeding is similar in both groups (RR = 0.91, 95% CI: 0.70–1.19). However, since the Fisher test result did not turn out to be statistically significant, and the 95% confidence interval reported for the odds ratio and relative risk contains the value 1, it should be considered that the chance of breastfeeding alone at discharge is not meaningfully greater for any group. The results are summarized in Table 3.

DISCUSSION

Numerous recommendations confirm, that MOM is always preferred, but DHM should be used for high-risk infants, when the mother's milk is not available [3, 4, 7, 8]. DHM does not replace MOM but is a supplement. Increas-

Table 3. Exclusively MOM feeding on the day of discharge

Exclusively MOM at the day of discharge		GA		
		< 32 weeks of GA	> 32 weeks of GA	
No	N	9	25	p = 0.475; OR = 1.42
	%	31.00%	24.00%	
Yes	N	20	79	
	%	69.00%	76.00%	

ingly, the multiple beneficial outcomes attributed only to MOM can be generalized to DHM [9].

There are no explicit recommendations regarding the supply of DHM in NICU. Indications for administering milk from the bank are usually: prematurity (< 28, < 34, < 36 weeks of GA), very low birth weight infant (VLBW), extremely low (ELBW) and low birth weight (LBW). Fewer beneficiaries of DHM are infants who require intensive treatment or newborns in the pre- and postoperative period. In Poland the order is based on the recommendations of the Human Milk Banking Association of North America (HMBANA) [10]. Priority should be given to provide DHM to infants < 1500 g birth weight for minimal enteral feeding, as quickly as the patient's condition allows [11].

According to the recommendations in force in Poland, the minimum enteral feeding was started from the mother's colostrum during first 6 hours after birth and if possible even in the first 2 hours of life. Newborn infants received DHM in the absence of MOM. When enteral feeding has reached 100 mL/kg/day, parenteral nutrition discounted. Children were receiving DHM until 14 days of life, especially near term infants, because longer usage caused mother's negative motivation to stimulate and maintain lactation.

Research on the clinical benefits of using DHM in NICU is underway. The influence of human milk on the health-promoting effects is best documented [9, 12, 13]. The early nutrition plays an important role on later cognition [14]. The duration of TPN in all analyzed groups was similar. It did not differ significantly. Also, the duration of feeding with DHM did not differ between three groups of infants divided according to the gestational age. Although no statistical significance was obtained, infants born between 32 0/7 and 36 6/7weeks of GA required DHM for the longest time. Mothers of these newborns required special lactation care, and the stimulation of lactation was the most difficult. At the same time, the preterm required the shortest treatment in NICU, because they had mainly respiratory distress syndrome, transient tachypnea of the newborn or adaptive disorders in the perinatal period. Infants received DHM to replenish the volume of MOM and no donor milk was used instead of mother's milk.

However, the nutritional value of DHM compared to mother's raw milk needs further research. Low weight gain, body length, and head circumference in the early postnatal period may be associated with the preparation of milk. DHM undergoes pasteurization which influences its bioactive properties. However, donor milk maintains documented advantages compared to formula [9, 15].

Donor human milk usually comes from women after stabilization of lactation, when the protein content in breast milk is reduced. The premature milk composition differs significantly from the mature milk [16, 17]. The system of DHM energy content categorization and distribution would improve energy intake from human milk [18].

Fewer data are available regarding the use of DHM in other high-risk infants, including infants with abdominal wall defects, such as gastroschisis or omphalocele, and other conditions, such as perinatal asphyxia [11]. Nonetheless, some infants with these conditions or other neonatal disorders may benefit from DHM either, because of a direct effect on intestinal growth or improved feeding tolerance [19]. Our retrospective observations have shown that children always received colostrum and raw mother's milk, and DHM was used to rapidly increase enteral nutrition, supplementing but not replacing MOM.

Patients in the NICU in University Hospital were not only premature neonates and newborns with symptoms of respiratory failure, but also infants treated with hypothermia after perinatal asphyxia, infants after surgical intervention due to esophagus atresia, intestinal obstruction, overgrown anus/rectus or gastroschisis. Newborns received DHM during the initial stages of maternal lactation when the volume of milk was insufficient, while it was possible to increase the volume of enteral nutrition and rapid withdrawal of TPN. Among our patients, no complications related to the rapid increase of enteral nutrition were observed, no necrotizing enterocolitis cases were also recognized.

A strategy aiming to promote and support breastfeeding should be carried out in every maternity or children's hospital where premature infants are born or treated and cared for after birth. Early intervention with milk expression after delivery (ideally within 6 hours) is critical for milk production; therefore, mothers should be educated a method of milk expression within this time frame. Presence of an HMB does not compete with breastfeeding, but decreases the utilization of formula in a NICU and increases exclusive breastfeeding rates at discharge [20–22]. In our analyses the vast majority of infants received either exclusive or partial MOM at discharge, both in the group of gestational age > 37 weeks (82.4%) and in premature infants (93.1%).

CONCLUSIONS

Neonates born before 32 0/7 week of GA, as expected, received the smallest volume of DHM, but, the time of supply was almost the same irrespective of GA. The initiation and

maintenance phase of lactation of newborn infants' mothers allowed to obtain the sufficient volume of MOM in 5–7 days after delivery. Despite many scientific studies and published clinical trials, it has not been clearly established and there are no recommendations regarding the supply of DHM in NICU, i.e. the time of supply, volume and type of patients who should receive breast milk. However, replenishing the MOM and the initiation and maintenance of lactation allowed exclusively breastfeeding or feeding only with MOM for all newborns. Further studies on the short-and long-term effects of DHM on child development are needed, as well as the guidelines for the use of DHM in the NICU.

Based on the obtained data, we recommend supplying DHM to all newborns treated in NICU when mother's milk is not available or if its volume is too small to fulfill the infants' nutritional needs. However, it is to be remembered that DHM should be used as a supplement to breast milk and not instead of MOM. Further research is needed to help building universally accepted recommendations.

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The study was approved by Bioethical Committee at the Medical University (177/2015 and 242/2017). Permission to apply DHM had to be given by the child's legal guardian. Thanks to Brian Hughes for proofreading.

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Complete placenta previa in the second trimester: clinical and sonographic factors associated with its resolution

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ABSTRACT

Objectives: This study was carried out to evaluate outcomes of pregnancies with complete placenta previa diagnosed in mid-pregnancy, and evaluate whether a history of caesarean section and placenta location effect the resolution of placenta previa.

Material and methods: A prospective observational study was conducted on patients diagnosed with complete placenta previa by ultrasound examination between 20+0 weeks and 25+6 weeks of gestation. Patients were grouped in terms of placenta location (anteriorly or posteriorly located) and presence/absence of prior caesarean section. Maternal demographics, ultrasound findings and pregnancy outcomes were subsequently compared between these groups. Statistical analysis was performed by using SPSS version 16.0.

Results: 70 patients with the above characteristics were recruited in our study. Of the 70 patients, 21 (30%) had prior caesarean section, and 41 (58.6%) had an anteriorly located placenta. Patients with prior cesarean delivery delivered earlier (36.9 ± 2.2 weeks versus 38.0 ± 1.8 weeks, P = 0.039). Furthermore, 74.3% of the placenta previa resolved by delivery. Prior caesarean section (RR 2.941, 95% CI 0.938–9.216, P 0.024) and anterior placenta (RR 3.805, 95% CI 1.126–12.855, P 0.031) were related to greater risk of persistence of placenta previa to term.

Conclusions: Prior caesarean section and anteriorly located placenta are important factors that modify the risk that previa will complicate delivery. Our findings may be useful for patient counselling and future management of the condition.

Key words: placenta previa; cesarean section; prenatal ultrasonography; pregnancy outcome

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INTRODUCTION

Peripartum hemorrhage is one of the most preventable causes of maternal mortality worldwide [1]. Complete placenta previa (CPP) is a major contributor to severe postpartum hemorrhage (PPH), especially when it is associated with placenta accreta. CPP is associated with increased maternal perinatal morbidity and mortality [2]. As revealed by ultrasound examination, the incidence of CPP during the second trimester is reportedly between 0.49% and 5.6% [3, 4]. Although more than 90% of placenta previa discovered at mid-pregnancy resolves prior to delivery, CPP is more likely to persist [5].

Several studies show that CPP might be an entity clinically different from incomplete placenta previa and associated with worse pregnancy outcomes [6–10]. Development of ultrasonic imaging has led to better understanding of the relationship between the internal cervical os and the placental margin and allowed us to more precisely identify the location of the placenta and the type of placenta previa. Nonetheless, data are still limited concerning the pregnancy outcomes of patients with CPP diagnosed at mid-pregnancy.

Furthermore, studies have reported widely different results regarding the resolution of placenta previa [11–13]. Multiple investigators have studied the impact of placenta location and prior caesarean section on the resolution of placenta previa but have reached notably different conclusions [5, 11, 14–16]. It is not known whether these factors exert any effect on the resolution of CPP.

Objectives

This study was carried out to evaluate the pregnancy outcomes of patients diagnosed with CPP at mid-pregnancy

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to better understand the influence of prior caesarean section and placenta location on the resolution of placenta previa.

MATERIAL AND METHODS

This prospective cohort study examined patients with singleton pregnancies who underwent ultrasound examination during mid-pregnancy. The study protocol was approved by the local Institutional Review Board, and an informed consent for the research was obtained from all subjects in accordance with the World Medical Association Declaration of Helsinki. Patient anonymity was preserved. This study does not violate the policies and/or procedures described in 'Specific Inappropriate Acts in Publication Process. Women were enrolled if they were diagnosed with CPP between 20^{+0} weeks and 25^{+6} weeks of gestation. To evaluate whether resolution occurred, the women were sonographically examined every 4 to 6 weeks. On each ultrasonic examination, gestational age (GA) at the examination and the distance in centimetres between the placental margin and the internal cervical os were recorded. All participants were followed until they delivered, and data were collected, including intraoperative confirmation of placenta previa. Patients whose pregnancies were terminated because of malformations and who delivered in other hospitals were excluded from the evaluation.

Between April 2014 to January 2015, 70 patients in total were recruited in our study. Patients were grouped in terms of placenta location (anteriorly or posteriorly located) and presence/absence of a history of caesarean section. In this study, CPP was defined when a placenta covered the internal os of the cervix completely, while the position was defined as normal when placental–cervical distance was more than 2 cm. Maternal demographics, ultrasound findings and pregnancy outcomes were then compared between these groups. Postpartum hemorrhage in this study is defined as a blood loss of 1000 mL or greater, or a blood loss with associated signs or symptoms of hypovolemia, that occurs within 24 h of delivery, regardless of the mode of delivery.

SPSS version 16.0 (SPSS, Chicago, IL) was adopted to perform statistical analysis. Continuous variables were expressed as the mean ± standard deviation or medians. Qualitative variables were presented as absolute frequency and percentage. Cox regression analysis was used for statistical analysis. P value < 0.05 was considered significant.

RESULTS

70 women were enrolled in this study. 21 women had a prior caesarean delivery, and 49 did not. 41 CPPs were located anteriorly and 29 posteriorly. Patients with prior cesarean delivery tended to be advanced in age (34.7 ± 4.8 vs 30.5 ± 4.0, P = 0.000), gravidity (4.1 ± 1.6 vs 2.0 ± 1.2, P = 0.000) and parity (0.8 ± 0.6 vs 0.1 ± 0.2, P = 0.000). Incidence of prior dilatation and curettage was also increased in this group. However, there was no significant difference in these maternal characteristics between anterior and posterior groups (Tab. 1).

While mean gestational age at initial diagnosis was similar for cesarean group and non-cesarean group, mean gestational age at resolution was obviously later in cesarean group (36.4 ± 2.7 vs 30.5 ± 5.3, P = 0.000), indicating that placenta migrated slower in these patients (Tab. 2). Patients with prior cesarean delivery resolved less frequently (33.3% vs 91.8%, P = 0.000) and delivered earlier (36.9 ± 2.2 vs 38.0 ± 1.8, P = 0.039). Mean GA at initial diagnosis, at resolution and at delivery were the same for anterior group and posterior group. However, resolution of CPP occurred more often in women with posteriorly located placenta (55.2% vs 87.8%, P = 0.002).

Table 3 shows odds for the persistence of placenta previa to term. In a Cox regression model, after adjusted for maternal age ≥ 35 and prior abortion, prior caesarean section (RR 2.941, 95% CI 0.938–9.216, P 0.024) and anterior placenta

Table 1. Demographic data stratified by prior CS and placenta location

	Prior cesarean section			Placenta location		
Characteristic	**Yes (n = 21)**	**No (n = 49)**	**P**	**Anterior (n = 41)**	**Posterior (n = 29)**	**P**
Maternal age [years]	34.7 ± 4.8	30.5 ± 4.0	0.000	32.7 ± 4.2	31.1 ± 4.8	0.159
Gravity	4.1 ± 1.6	2.0 ± 1.2	0.000	3.1 ± 1.9	2.3 ± 1.2	0.051
Parity	0.8 ± 0.6	0.1 ± 0.2	0.000	0.4 ± 0.6	0.2 ± 0.5	0.092
Prior dilatation and curettage	17 (81.0%)	26 (53.1%)	0.028	20 (69.0%)	23 (56.1%)	0.276
Prior uterine surgery	5 (23.8%)	8 (16.3%)	0.687	8 (27.6%)	5 (12.2%)	0.103
Assisted reproductive technology	4 (19.0%)	11 (22.4%)	1.000	7 (24.1%)	8 (19.5%)	0.642
Posterior placenta	10 (47.6 %)	31 (63.3%)	0.223	—	—	—
Prior cesarean section	—	—	—	11 (37.9%)	10 (24.4%)	0.223

Data are presented as mean ± SD or number (percent)

Table 2. Data of placental migration stratified by prior CS and placenta location

	Prior cesarean section			Placenta location		
Characteristic	**Yes (n = 21)**	**No (n = 49)**	**P**	**Anterior (n = 41)**	**Posterior (n = 29)**	**P**
Gestational age at initial detection	23.2 ± 1.3	22.8 ± 1.9	0.416	23.3 ± 2.0	22.7 ± 1.5	0.144
Gestational age at resolution	36.4 ± 2.7	30.5 ± 5.3	0.000	31.7 ± 6.0	30.8 ± 5.1	0.331
Rate of resolution	7 (33.3%)	45 (91.8%)	0.000	36 (87.8%)	16 (55.2%)	0.002
Gestational age at delivery [weeks]	36.9 ± 2.2	38.0 ± 1.8	0.039	37.3 ± 2.2	37.9 ± 1.8	0.615

Data are presented as mean ± SD or number (percent)

(RR 3.805, 95% CI 1.126–12.855, P 0.031) were significantly related to greater risk of persistence of placenta previa to term. 52 (74.3%) CCPs eventually resolved. The mean GA at resolution was 31.2 ± 3.4 weeks (Tab. 4 and 5). Overall, 10% of placenta previa resolved before 28 weeks of gestation, 31.4% before 32 weeks and 62.9% before 36 weeks, while a small number [8 (11.4%)] resolved at or after 36 weeks.

Data for 18 patients whose placenta previa did not resolve by delivery are summarized in Table 6. These patients consisted of 12 patients with CPP; 1 with partial placenta previa, 3 with marginal placenta previa and 1 with a low-lying placenta at last ultrasound examination or at delivery. All 18 patients had caesarean deliveries. 3 patients were delivered emergently and 3 suffered from postpartum haemorrhage.

Our results showed no significant difference in obstetric outcomes and neonatal outcomes between cesarean group and non-cesarean group, and between anterior group and posterior group (Data was not shown). No subjects received hysterectomy in this series.

Table 3. Odds for the persistence of placenta previa

Characteristic	RR	95% CI	P
Maternal age ≥ 35 years	1.276	0.454–3.588	0.664
Prior abortion	3.127	0.760–12.873	0.114
Prior cesarean section	2.941	0.938–9.216	0.024
Anterior placenta	3.805	1.126–12.855	0.031

Table 4. Clearance of placenta based on GA at initial diagnosis of a CPP

GA at diagnosis [weeks]	Patients		Cleared		Mean GA at clearance [weeks]
	n	%	n	%	
20.0–21.6	42	60.0	35	83.33	30.1 ± 1.2
22.0–23.6	22	31.4	14	63.63	33.0 ± 2
24.0–25.6	6	8.6	3	50.00	36.3 ± 1.4
Total	70	100	52	74.26	31.2 ± 2.3

GA — gestational age

Table 5. Patients whose placentas cleared by a specific GA range

GA at clearance [weeks]	Cleared		Cumulative clearance, %
	n	%	
24.0–27.6	7	10.00	10.00
28.0–31.6	15	21.43	31.43
32.0–35.6	22	31.43	62.86
36.0–delivery	8	11.40	74.26

GA — gestational age

DISCUSSION

This study evaluated the outcomes of CPP discovered in mid-pregnancy and the impact of prior caesarean section and placental location on the resolution of CPP.

The significant decrease in maternal perinatal mortality has been ascribed to two major progress in the management of placenta previa: the liberal use of cesarean section plus maternal blood transfusion supply and expectant treatment of placenta previa. Nevertheless, placenta previa still contributes to a prominent proportion of maternal perinatal morbidity and mortality. However, no serious complications, such as hysterectomy or foetal death, occurred in our study.

The resolution rate of CPP before delivery in our study was 74.3% with a mean GA of 31.2 ± 3.4 weeks at clearance. Overall, 10% of placenta previa resolved before 28 weeks of gestation, 31.4% before 32 weeks and 62.9% before 36 weeks. To date, reports on the resolution of CPP diagnosed in mid-pregnancy are scanty, and their findings are inconsistent. A study conducted by Townsend in 1986 suggested that the placenta did not migrate in cases of central previa discovered between 14 and 26 weeks of gestation [17]. Over the past 30 years, ultrasonographic examination in the diagnosis of placenta previa has greatly advanced; therefore, the study may not be relevant. Another study in 2000 found that the entire placenta previa did not migrate during the third trimester[12]. However, the power of their study may be limited due to a small sample size of CPP subjects. Recently, Blouin et al. [18] carried out a retrospective cohort study on 714 cases of complete or incomplete previa. Coincidently with our findings, their study showed that 12% of CCP discovered between 15 and 19 weeks of

Table 6. Summary of 18 patients whose placenta previa persist to delivery

GA at diagnosis [weeks]	Age [years]	Prior CS	Placental location	GA at delivery [weeks]	Previa type	Emergency CS	PPH	Hysterectomy
22.0	31	No	Anterior	36.5	Complete	No	No	No
22.6	34	Yes	Anterior	38.3	Complete	No	No	No
22.3	29	No	Anterior	38.6	Complete	No	No	No
22.3	40	Yes	Posterior	39.5	Marginal	No	No	No
23.1	32	No	Anterior	38.6	Complete	Yes	No	No
22.0	38	Yes	Posterior	38.6	Marginal	No	No	No
22.5	35	Yes	Anterior	37.3	Complete	No	Yes	No
24.1	37	Yes	Anterior	39	Partial	No	No	No
23.3	32	Yes	Anterior	39.6	Complete	No	No	No
23.1	24	Yes	Posterior	38.2	Complete	No	No	No
23.3	36	Yes	Anterior	38	Marginal	Yes	No	No
25.1	30	Yes	Posterior	39	Complete	No	No	No
23.0	33	Yes	Posterior	37.4	Complete	No	No	No
22.3	32	Yes	Anterior	36.1	Complete	No	No	No
21.0	40	Yes	Anterior	40.2	Low-lying	Yes	No	No
25.2	41	Yes	Anterior	37.1	Complete	No	Yes	No
23.3	36	Yes	Anterior	37.1	Complete	No	No	No
21.1	31	No	Anterior	40	Complete	No	Yes	No

GA — gestational age; CS — cesarean section; PPH — postpartum hemorrhage

gestation and 34% of those discovered between 20 and 23 weeks of gestation persisted to delivery. Similarly, Lal et al. and Osmundson et al. showed that the resolution rates in CPP diagnosed during the second trimester were 84% and 59.1%, respectively [13, 19].

While it is well-documented that placental migration occurs during the second half of pregnancy in most mid-pregnancy placenta previas, the exact mechanism has not been thoroughly elucidated to date. One of the explanations is that thin placental margins gradually atrophy due to poor vascularization, meanwhile other regions continue to develop, and consequently, migrate towards better vascularized regions. However, it seems that the placental migration rate is not constant. Some factors, such as type of placenta previa, placental location, prior caesarean section, degree of coverage over internal cervical os, gestational week and distance of placental edge from the internal os at initial detection, were reportedly associated with placental migration [4, 5, 14, 19–23].

The influence of prior caesarean delivery on placental migration has been previously reported. Recently, Naji et al. [14] demonstrated that the presence of a caesarean section scar influenced the site of placental implantation but exerted no effect on placental migration in future pregnancies. Inconsistent with that finding, other studies showed that prior caesarean section related to a smaller chance of resolution. The scarred lower uterine segment caused by prior surgery was believed to impede placental migration, resulting in less frequent resolution [11]. Furthermore, caesarean section served as the primary contributor to placenta accreta or increta [24], which may impede placental migration. Consistent with these findings, our study showed that prior caesarean section significantly decreased the likelihood of resolution of placenta previa by delivery.

In studies by Lal et al. [11] and Eichelberger et al. [19], migration rates in anteriorly situated placentae showed no difference from that of posteriorly situated ones. However, Magann et al. [16] showed a higher possibility of resolution in posteriorly located previa, and attributed the phenomenon to the disproportion in the growth of uterine smooth muscles between anterior placentas and posterior ones. Conversely, other studies believed that placenta previa with an anteriorly located placenta was more likely to migrate, and the migration was secondary to a thinner lower uterine segment on the anterior portion of the uterus, leading to a more pronounced upward migration [11, 25]. While Lal et al. [11] demonstrated that placental location did not influence the resolution of placenta previa. we found that resolution was more frequent in women with posteriorly located CPP. Since the two studies were of prospective design, and had a similar number of subjects, the difference might be ascribed to the racial difference.

The power of the study lay in its prospective nature. The main limitations included: the relatively small size of the subject population and that it was only a single-center study. A larger and multi-center study is warranted to further confirm the findings in this study.

CONCLUSIONS

In summary, when a complete placenta previa is diagnosed mid-pregnancy, a small percentage of the cases will persist to delivery. What is more, prior caesarean section and anteriorly located placenta are important factors that modify the risk that previa will complicate delivery. Such information may be useful for counseling patients and assisting with future management decisions.

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Preferences and expectations among Polish women regarding prenatal screening

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ABSTRACT

Objectives: Patients' attitudes and expectations of prenatal screening for genetic abnormalities throughout pregnancy are rarely analyzed by researchers as emotions and fears are both important and challenging factors. Prenatal counselling has never been so difficult as we live in the era of detailed ultrasound scans, cell-free fetal DNA and detailed microarray testing.

The aim of this study was to investigate Polish women's attitudes towards screening for chromosomal abnormalities and fetal defects.

Material and methods: The study was a prospective survey conducted among a population of Polish women. An electronic questionnaire regarding prenatal diagnostics was distributed to a total number of 1072 female volunteers.

Results: 1044 patients (97.30%) stated that they were motivated to undergo prenatal diagnostics and would want to be informed about fetal abnormalities. Over 90% of the respondents would want to be informed about serious defects with a high mortality rate (including trisomy 13 or 18). More than half the Polish women (54.83%) stated they were willing to consider terminating pregnancy in the case of a severe abnormality.

Conclusions: Polish women expect prenatal screening. Almost all Polish women would want to be informed about both genetic and anatomical abnormalities and over half of them would consider terminating pregnancy in the case of a severe abnormality. Willingness to learn about a defect increased with average household income, and the statement of a will to terminate pregnancy depended mostly on maternal age and type of fetal abnormality.

Key words: genetics; prenatal counselling; ultrasound

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INTRODUCTION

Prenatal diagnostics has an important role in contemporary perinatal medicine. Structural defects or genetic disorders occur in approximately 3–5% of pregnancies. Such a high rate of adverse pregnancy outcomes points to the significance of prenatal diagnostics. In Poland the annual number of deliveries is approximately 400,000. Considering the rate of 3–5% adverse outcomes, each year 12,000 abnormalities may occur in infants. However, different approaches exist to prenatal screening, invasive procedures and termination of pregnancy, due to personal and religious preferences [1, 2]. Major advances in prenatal medicine now offer a variety of diagnostic tools for parents expecting a baby. Medical professionals should always discuss all the options with patients. It has to be emphasized and properly acknowledged by medical professionals that not all patients expect exactly the same counselling and prenatal diagnosis. Does a perfect diagnostic algorithm for pregnant women exist at all? Do women want to be informed about all abnormalities? Which factors influence their attitude? Are the best diagnostic strategies for physicians perhaps not the most convenient for and acceptable to patients? This study aims to answer these questions and describe future parents' expectations towards prenatal diagnostics adjusted for their needs.

MATERIAL AND METHODS

The total number of patients who participated in this prospective survey was 1,072. An electronic questionnaire regarding prenatal diagnostics was distributed to volunteers

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via social media and e-mails between November 2016 and March 2017. There was no specific algorithm for patient selection, but the only condition necessary for enrolment was access to the Internet and female gender. The consent for this survey study was obtained from all respondents. Demographic (age, ethnicity, chronic diseases), social (residence, education, religion, economic status) and obstetrical data were investigated. Further on in the questionnaire respondents were provided with a basic explanation of fetal abnormalities and intellectual disabilities (including trisomies 13, 18 and 21). Congenital anomalies were described in details and marked as five different types with decreasing severity and labeled as: type 1 (most die or handicapped if survive), type 2 (moderately handicapped, likely to have several common health problems), type 3 (health problems in only some of the individuals affected), type 4 (autism, intellectual disability) and type 5 (abnormal result of uncertain meaning). Description of abnormalities as presented in the questionnaire is summarized in Table 1. Questions regarding preferences for being informed about specific fetal disorders were asked. The local Ethical Committee of Warsaw Medical University (Poland) approved this study.

Statistical analysis

The data collected were cleaned, tabulated, and subjected to statistical analysis. Apart from the calculation of proportions and contingency tables, a series of χ^2 (Chi-Square) tests were performed in order to check for relationships between survey questions.

RESULTS

Study group characteristics

In total 1,072 women participated in the questionnaire. The majority of them were aged 25–29 years (36.07%) and 30–34 years (33.46%). The number of relatively younger (20–24 years) and older women (35–39 years) was comparable (12.24% and 12.18%, respectively). Almost all (1,062 out of 1,072) of the women participating were born in Poland (99.07%), as were most of their partners (described as "father of the baby") (96.45%). The vast majority of respondents had

Table 1. Detailed description of abnormalities presented in the questionnaire

Type of abnormality detected prenatally	Detailed description of abnormality
Type 1	There are anomalies identified in some tests, which are surely known to cause problems for all the babies affected, and such problems are so severe that most will not survive; that is, most babies affected with such anomalies, but not all, will die before they are born or soon after being born. The few that survive will be very severely handicapped and will need complicated care while they live, for all their lives, which will, most often, be short — examples of this type of anomalies are Trisomy 18, an anomaly that causes a disease called syndrome of Edwards, and Trisomy 13, an anomaly that causes a disease called syndrome of Patau.
Type 2	There are anomalies identified in some tests, which are surely known to cause problems for all the babies affected, although not as severe as Type 1; most of the babies, in which those anomalies were detected, will survive. However, the vast majority of the surviving babies will be moderately handicapped and will need someone taking some care of them for all their life, that may be long, although, on average, slightly shorter than the population's average. They are more likely to have several common health problems throughout their lives. Some, but not all, of those problems, will be treatable and cured, some partially repaired and some improved. There are also interventions that may ameliorate their mental health, although not cure it. One frequently mentioned example of this type of defect is Trisomy 21, a defect that causes a disease called Down syndrome.
Type 3	There are anomalies identified in some tests, which are (not as surely as in type 1 or 2, though) known to cause health problems in only some of the individuals affected, but not in all. Even in those that will eventually develop health problems caused by the anomalies identified by the tests, such health problems are generally considered by many people to be not very severe. For instance, babies, in which those anomalies were detected by the tests and that will have health problems, may, when grown-ups, have abnormally short or, reversely, tall stature, and are frequently infertile, that is, they cannot have babies on their own; sometimes it will be possible to help them having babies, sometimes not. They may have, more frequently than other children, difficulties in school with some disciplines, but many times get better with early intervention. Examples of this type of defect are some anomalies of the number of the so-called sex chromosomes, the biological determinants of sex.
Type 4	There are anomalies identified in some tests that make individuals carrying them more likely to develop some relatively severe neurologic or psychiatric problems. This means that only a proportion of these babies that are found to have the test anomaly, but not all, will develop certain mental diseases, such as autism, intellectual disability or schizophrenia, for example. That proportion may vary with the test result but the exact value of that proportion may be imprecise and poorly known. Also, not all persons that will eventually get affected will have equally severe diseases. Some individuals may have severe symptoms, some may have moderate symptoms and some may have mild symptoms. It is important to also understand that only a small proportion of individuals with autism, intellectual disability or schizophrenia will have this type of test defects. That is, if the baby test results are normal, that does not mean that s/he will not have any of those conditions – autism, intellectual disability or schizophrenia. There are many causes for these diseases, only a few of those causes are known, and from those, only a few can be detected by the tests.
Type 5	There are anomalies identified in some tests, for which there are still not enough information to predict, with certainty, that the baby will have a health problem. It will only be possible to say that, most likely, but not surely, the baby will have a health problem, although it will not be possible to say which problem and its severity.

had higher education: 79.50% (57.05% of partners), while 18.92% (39.03% of partners) had had secondary education and 1.58% (3.92% of partners) reported an elementary education level. More than 58% of the women taking part considered themselves religious, with over 71% being Christians (other religions: 7.55%, no answer 20.55%). Similar results concerned partners. A total of 43.04% women were pregnant, 6.91% within the 6 weeks after delivery and half (50.05%) of the respondents were neither pregnant nor in the puerperium period. Within the group of pregnant respondents most women had been pregnant before (73.07%), as opposed to women having their first babies (26.93%). In total, 20.71% had had at least one spontaneous miscarriage and 4.38% of respondents had had a termination due to medical reasons. In 6.52% of cases fetal abnormalities of some sort had been detected, as opposed to 82.67% who had had no defects detected and 10.81% who did not answer this question.

Patients' preference

A total number of 1,044 participants (97.30%) stated that they were motivated to undergo prenatal diagnostics of some kind as early as in the first trimester of pregnancy and in general would want to be informed about fetal abnormalities (without specifying exactly which defects — "the anomalies possible to detect in routine tests"); 2.7% of respondents would not want to be informed about these abnormalities. Within the group of women willing to undergo prenatal tests the percentages of women and their partners who considered themselves Christians were 96.73% and 97.24%, respectively. Further on in the questionnaire fetal abnormalities were more precisely described. Over 90% of respondents would want to be informed about a very serious defect with a high mortality rate (including trisomy 13 or 18), as opposed to 2.61% who would want to be informed about such an abnormality only after delivery (and not during pregnancy). A total of 5.78% of respondents were not sure whether they would want to be informed during pregnancy or after delivery. The group of women who stated their wish to be informed about severe abnormality also stated that they would consider termination of pregnancy (54.83%), as opposed to 15.71% who would not consider termination of pregnancy and 29.47% who were not sure what would they do in such circumstances. 92.72% of respondents would want to be informed about less serious defects with a low mortality rate (including life-long defects or health problems), as opposed to 3.26% who would want to be informed about such an abnormality only after delivery (and not during pregnancy). 0.19% of respondents would not want to be informed about such issues either before or after delivery. In cases of less severe health problems, 41.55% of patients would terminate the pregnancy, as opposed to 22.43% who would not consider pregnancy termination at all. As for the third type of abnormality described (only a certain number of children with minor health problems like infertility in adulthood, short stature or learning difficulties), 87.97% of respondents would want to be informed during pregnancy. In such circumstances, 7.21% participants would terminate the pregnancy, as opposed to 60.45% who would not consider pregnancy termination at all. In cases of less severe abnormalities (autism, schizophrenia, higher risk of health problems but in some cases no symptoms at all) 83.58% of respondents would want to be informed about these during pregnancy. In such circumstances, 6.58% patients would terminate the pregnancy, as opposed to 59.26% who would not consider pregnancy termination at all. In cases of health issues difficult to detect or confirm before birth, 75.02% of respondents would want to be informed about these during pregnancy. In such circumstances, 4.97% patients would terminate the pregnancy, as opposed to 62.86%, who would not consider pregnancy termination at all. There is a relationship between income and the willingness for prenatal diagnosis of lethal defects [χ^2 (12) = 33,600, p = 0.0008]. Regardless of the average monthly income per household, the majority of respondents stated that they were willing to undergo prenatal diagnosis and would want to know about the type 1 defect ("the majority of neonates will die"). However, there was a tendency for willingness to learn about the defect to increase with average income (75% with an income of < €250, 87.1% with an income of €250–500, 88.9% with an income of €500–1,000 and 94.0% with an income of > €1,000). These data are presented in Table 2. There is a relationship between income and the willingness for prenatal diagnosis of milder defects (type 3) [χ^2 (12) = 24,205, p = 0.019]. Regardless of the average monthly income per household, the majority of respondents stated they were willing to undergo prenatal diagnosis for defect 3. Regardless of parity, motivation to recognize defects with a different prognosis was the same for all respondents. Over 90% of patients would want to be tested for a type 1 defect, about 90% for type 2, around 80–90% for type 3, around 80% for type 4 and around 70% for a type 5 defect. However, the trend is decreasing: the better the clinical prognosis for the defect, the fewer the patients (regardless of parity) stating their willingness for prenatal diagnosis of these conditions.

There is a relationship between the age of the respondents and their statement of willingness to terminate pregnancy in the case of a serious fetal abnormality [χ^2 (19) = 19,558 p = 0.034]. Willingness to terminate the pregnancy is most frequently stated by patients aged 40–44 (60%), 35–39 (53.6%) and 16–19 (42.8%). These data are presented in Table 3.

It is not surprising that in the subgroup of women considering themselves Christian Catholics the percentage of

Table 2. Relationship between stated willingness for prenatal tests concerning lethal defects and average monthly income per household [χ^2 (12) = 33,600, p = 0.0008]

		Average monthly income per household			
		< €250	€250–500	€500–1,000	> €1,000
Stated willingness to know if a fetus has type 1 defect (most children die, individual cases live until they reach the age of 1)	I do not understand the question/ description of this type of defect	0.00%	1.61%	0.47%	0.00%
	No, I would not like to know either during pregnancy or after delivery	0.00%	0.00%	0.24%	0.69%
	I am not sure whether I would like to know during pregnancy or after delivery	16.67%	9.68%	8.98%	2.08%
	No, I would not like to know about it during pregnancy, but only after delivery	8.33%	1.61%	1.42%	3.24%
	Yes, I would like to know during pregnancy	75.00%	87.10%	88.89%	93.98%

Table 3. Relationship between age of respondents and their statement of willingness to terminate pregnancy in the case of type 2 fetal abnormality [χ^2 (19) = 19,558 p = 0.034]

		Age					
		16–19	20–24	25–29	30–34	35–39	40–44
Would you consider termination of pregnancy if your type 2 defect was confirmed (the majority of children survive the neonatal period, but live with serious defects that impair their quality of life)?	No, I would most likely not choose this option	28.57%	21.95%	26.84%	22.02%	13.60%	12.00%
	I do not know what choice I would make	28.57%	39.02%	37.29%	36.90%	32.80%	28.00%
	Yes, I would consider termination in such circumstances	42.86%	39.02%	35.88%	41.07%	53.60%	60.00%

respondents stating termination of pregnancy as a possibility is lower than in the entire population studied: the overall percentage of respondents declining pregnancy termination was 41.5%, but in the Christian Catholic group it was 31.5%.

DISCUSSION

The overall conclusion derived from an analysis of the survey is that in general Polish women desire prenatal diagnostics (97.30%). It has to be underlined that Poland is considered a Catholic country with 88.8% of Poles identifying themselves as Roman Catholic in 2016 [census conducted by the Central Statistical Office (GUS)] [3]. This is also consistent with data gathered in this study — almost all respondents and their partners stated that they were Roman Catholics (96.73% and 97.24%, respectively). Polish women would definitely like to be informed about various health problems their baby might have, before the delivery. This study has several other interesting findings, many of which may differ from common assumptions regarding the population of women living in a homogeneous conservative country. For instance, more than half the respondents would consider termination of pregnancy for the most severe abnormalities like Patau and Edwards' syndrome (54.83%) but not in cases of minor health problems like infertility, short stature or learning difficulties (7.21%). In our study the less severe the defect, the lower the determination to detect the abnormality. This seems reasonable as couples who receive a diagnosis of unknown or uncertain significance may experience a difficult and stressful pregnancy though still have a final chance of having a healthy infant [4–6].

As expected, and as confirmed by other studies, advanced maternal age plays an important role in the decision to undergo prenatal diagnostic testing [7, 8]. The statement of willingness to terminate pregnancy was stronger with advancing maternal age: 53% and 60% within age groups 35–39 and 40–44, respectively.

Prenatal counselling has never been so difficult. We live in the era of cell-free fetal DNA and detailed microarray testing. It is important to understand the benefits and the threads that can ensue from each possible screening and testing method [9]. But the most important thing is — to ensure patients understand their choices and receive accurate information and counselling before making informed decisions. This is even more important after realising that expectations of prenatal tests may be different for health professionals and for patients [10]. The study by Hill et al. [11] revealed that women placed a greater emphasis on test safety and having comprehensive information than health professionals, who placed more emphasis on accuracy and early testing than women. Unfortunately, patients' attitudes towards and expectations of prenatal diagnostics throughout pregnancy are rarely analysed by researchers as emotions and fears are important, challenging factors to be translated into scientific language [12].

CONCLUSIONS

The results of this study have important implications for health professionals and clinical management in Poland. Although the social, ethnic or religious background of a couple may alter the final decision on types of prenatal tests, almost all women in Poland (97%) demand accessibility to prenatal testing. It has to be emphasised that there is also a group of women who are seeking prenatal testing primarily to obtain information without any intention to terminate pregnancy due to abnormal results.

Study limitations

This study has some limitations. The survey was an Internet-based study; it was distributed via e-mail and social media. Therefore, it has to be acknowledged that only women with a basic education, Internet and social media access would gain access to the survey. It has to be assumed that mostly women with a higher socio-economic status had access to the survey. As for all survey studies there is a selection bias related with the type of the study. It can never be accurately foreseen who will agree to participate therefore proper randomization in this case is not possible. It has to be acknowledged that this selection bias is a major weakness of this study. Although the authors took the greatest care to explain all the medical terms in the survey, some terms may not have been clear to patients who might have answered differently after further clarification. The strengths of this study include the large sample of both pregnant and non-pregnant women who provided the answers.

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