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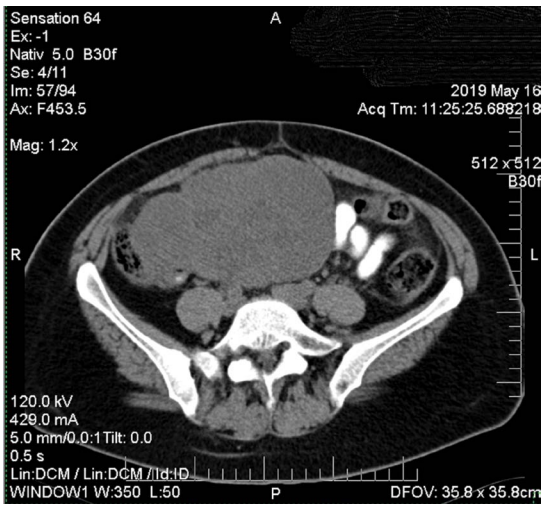

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Metastatic and synchronous ovarian involvement in low-risk endometrial cancer; clinicopathological analysis with detection of DNA mismatch repair deficiency

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ABSTRACT

Objectives: This study aimed to investigate ovarian involvement in low-risk endometrial cancer, the associated risk factors, and impact on overall survival. We attempted to explore the differences in mismatch repair (MMR) deficiency between metastatic and synchronous ovarian tumoral involvement.

Material and methods: This was a retrospective study of patients with low-risk endometrial cancer who were treated at a tertiary center between January 2006 and December 2019. The primary outcome measures were the incidence and risk factors associated with metastatic and synchronous tumoral involvement of the ovary. Overall, survival data were also analyzed. Metastatic and synchronous tumors were compared with each other in terms of MMR deficiency with IHC staining.

Results: From a total of 360 low-risk endometrial cancer patients, 10 (2.8%) had ovarian metastasis and 12 (3.3%) had synchronous ovarian involvement. The median age of patients with metastasis was significantly lower than that of patients without ovarian involvement (49 vs 57 years, $p = 0.004$). Most patients in the metastatic group were in the < 50 age group ($p < 0.001$) and premenopausal period ($p = 0.001$). As a result of IHC staining performed on patients with ovarian involvement, MMR deficiency was found in six (60%) patients in the metastatic group and six (50%) patients in the synchronous group. No significant difference was found in overall survival between groups.

Conclusions: Younger age and premenopausal status were risk factors associated with ovarian metastasis. Overall survival did not show differences between all groups, and MMR deficiency was similar between metastatic and synchronous groups.

Key words: low-risk endometrial cancer; ovarian involvement; ovarian metastasis; synchronous ovarian cancer

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INTRODUCTION

Ovarian involvement in endometrial cancer patients can take two forms: metastasis of cancer in the endometrium and synchronous ovarian cancer. In stage I endometrial cancers, ovarian metastases occur in approximately five percent of cases; diagnosis is often confirmed preoperatively, but in some patients, the cancer can only be detected intraoperatively [1]. In the low-risk population (Endometrioid, < 1/2 myometrial invasion, absence of lymphovascular invasion), the incidence is as low as 0.5% [2]. The incidence of synchronous tumors of the endometrium and ovary ranges from 2–23% in the literature [3, 4].

Deep myometrial invasion, high-grade and non-endometrioid tumor types, lymphovascular invasion, serosal and tubal spread were defined as factors associated with ovarian involvement. Moreover, some studies were performed on stage I patients and most were not carried out on low-risk patient populations [1, 4–6]. It is interesting that a low-grade tumor with no myometrial or lymphovascular invasion can metastasize to the ovary. However, this raises the patient from the low-risk category to stage III. Synchronous tumors, on the other hand, represent a favorable prognosis compared with metastatic tumors [7, 8].

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Although only 5–10% of endometrial cancers with mismatch repair (MMR) deficiency are associated with Lynch syndrome, in fact, 20–40% of endometrial cancers experience MMR loss [9]. Genomic and immunohistochemical (IHC) studies have attempted to understand the biological behavior of synchronous and metastatic tumors. Although the clinical outcome of synchronous tumors is distinct from that of metastatic tumors, the investigation of MMR loss may give a new dimension to the clinicopathologic criteria we use to separate these tumors [10, 11].

It is important to know the frequency of ovarian involvement in endometrial cancer in preoperative counseling, especially if the protection of the ovaries is planned. In this study, we retrospectively analyzed low-risk endometrial cancer cases with ovarian involvement. We aimed to analyze the risk factors associated with metastasis or synchronous tumors and to investigate the impact on overall survival.

MATERIAL AND METHODS

Patient cohort

From January 2006 to December 2019, we conducted a retrospective review of patients with endometrial cancer who were treated at a tertiary center. The Institutional Review Board approved the study (KU GOKAEK 2020/6), and all procedures were performed in accordance with the principles of the Declaration of Helsinki. Demographic, clinical and pathologic data were obtained through the hospital's electronic record system and from paper charts. Age, gravidity, parity, Body Mass Index (BMI), menopausal status, systemic diseases, adjuvant therapies, and pathologic variables were noted. We identified patients with concurrent endometrial and ovarian involvement from a low-risk endometrial cancer cohort (endometrioid type, Grade 1 and 2 tumors, less than ½ myometrial invasion and without lymphovascular spread). All patients underwent hysterectomy with salpingo-oophorectomy, pelvic, and/or paraaortic lymphadenectomy in accordance with the risk category, inspection of the abdomen, and washing cytology procedures. Adjuvant therapies such as chemotherapy and radiotherapy were individualized for all patients, but no patient received neoadjuvant therapy.

The primary outcome measures were the risk factors associated with metastatic and synchronous tumoral involvement of the ovary. Overall survival data were also obtained from the population registry agency, which gives certain information about the patient's death and minimized lost to follow-up. Metastatic and synchronous tumors were compared with each other in terms of MMR deficiency with IHC staining.

Histopathological examination

Pathologic specimens were reviewed by experienced gynecologic pathologists. After fixation in 10% neutralized formaldehyde, all hysterectomy and salpingoophorectomy tissues were cut into 3-mm thick slices for tumor viewing. The materials were completely embedded in paraffin and cut into 5-µm-thick sections. The cut preparations were then dyed with hematoxylin and eosin (H&E) and examined with a light microscope. The Scully criteria were used to separate synchronous ovarian tumors from ovarian metastases of endometrial cancers [12].

Immunohistochemical examination

Immunohistochemical staining of DNA-MMR protein expression was performed on endometrial and ovarian samples in blocks fixed with formalin and embedded in paraffin. Representative whole 5-µm-thick sections were performed with IHC. Anti-PMS2 (A16-4, 1:200; Ventana Medical Systems, Arizona, USA), anti-MLH1 (M1, 1:200 dilution; Ventana Medical Systems, Arizona, USA), anti-MSH2 (G219-11229, 1:50 dilution, Ventana Medical Systems, Arizona, USA), and anti-MSH6 (SP93, 1:200 dilution; Ventana Medical Systems, Arizona, USA) were evaluated. Tissues were stained with antibodies against PMS2, MSH6, MLH1, and MSH2 following deparaffinization. Slides were counterstained with hematoxylin & eosin. Complete loss of nuclear staining for at least one MMR protein was defined as MMR deficiency. Stromal and inflammatory cells of the adjacent normal mucosa with intact nuclear staining were used as an internal positive control.

Statistical analysis

All statistical analyses were performed using IBM SPSS for Windows version 20.0 (SPSS, Chicago, IL, USA). Kolmogorov-Smirnov and Shapiro-Wilk's tests were used to assess the assumption of normality. Categorical variables were summarized as counts (percentages). Continuous variables were presented as the median (25^{th}–75^{th} percentile) since the normality assumption did not hold. Comparisons of continuous variables between groups were carried out using the Kruskal-Wallis test with Dunn's test for multiple comparisons. Associations between two categorical variables were examined by Chi-square test. Multinomial logistic regression analysis was used to determine the factors affecting the outcome variable. The Kaplan-Meier method was used for the survival analysis, and a univariate log-rank test was used to assess statistical significance. Overall survival was defined as the time from surgery to death from any cause. All statistical analyses were carried out with five percent significance and a two-sided p value < 0.05 was considered as statistically significant.

RESULTS

Our patient population consisted of a total of 360 patients with low-risk endometrial cancer, of which 10 (2.8%)

Table 1. Clinicopathologic variables by groups

		Ovarian involvement			p
		None (n = 338)	Metastasis (n = 10)	Synchronous (n = 12)	
Age		57 (24–82)[a]	49 (42–58)[a]	53 (42–69)	0.003
Age group	< 50	71 (21)[a]	8 (80)[a]	4 (33)	< 0.001
	> 50	267 (79)[a]	2 (20)[a]	8 (67)	
Gravida		3 (0–16)	3 (0–7)	3 (0–6)	0.471
Parity		3 (0–13)	2 (0–4)	3 (0–4)	0.405
BMI		28 (27–29)	28.1 (27–29)	27.8 (26–29)	0.919
Menopause	Pre	74 (22)[a]	7 (70)[a]	6 (50)	0.001
	Post	264 (78)[a]	3 (30)[a]	6 (50)	
Hypertension		163 (48)	2 (20)	5 (42)	0.185
Diabetes		88 (26)	1 (10)	1 (8)	0.232
Grade	I	223 (66)	4 (40)	10 (83)	0.093
	II	115 (34)	6 (60)	2 (17)	
Tumor diameter (cm)		2.5 (0.1–9)	2.5 (1.5–6)	2.5 (0.5–6)	0.876
The longest diameter of ovarian mass (cm)			3 (2–8)	6.7 (0.4–15)	0.470
Lymphadenectomy		69 (20)[b]	5 (50)	8 (67)[b]	0.001
Excised pelvic lymph node count		13 (0–44)	13 (0–35)	16 (0–29)	0.371
Patients with pelvic lymph node metastasis		3 (1)	–	–	
Excised paraaortic lymph node count		0 (0–19)[b]	0 (0–10)	0 (0–9)[b]	0.001
Patients with paraaortic lymph node metastasis		1 (0.3)	1 (10)	1 (8)	
Excised total lymph node count		14 (0–55)	17 (0–35)	18 (0–34)	0.158
Total patients with lymph node metastasis		4 (1.2)	1 (10)	1 (8)	
Total metastatic lymph node count		0 (0–2)[a]	0 (0–1)[a]	0 (0–1)	0.006
Chemotherapy		7 (2)[ab]	4 (40)[a]	7 (58)[b]	< 0.001
Radiotherapy		15 (4)	2 (20)	2 (17)	0.041

BMI — body mass index; Data are expressed as median (range) or n (%); [a] Statistically significant difference between 'None' and 'Metastasis' groups; [b] Statistically significant difference between 'None' and 'Synchronous' groups

had ovarian metastasis of the endometrium, and 12 (3.3%) had synchronous ovarian involvement of the endometrium and ovary. The median follow-up time was 74.5 months (Range: 6–167). Table 1 summarizes the clinicopathologic variables by group. The median age of patients with metastasis was significantly lower than that of patients without ovarian involvement (49 vs 57 years, p = 0.004). Most patients in the metastatic group were in the < 50 age group (p < 0.001) when patient age was divided into subgroups below and above 50 years. Furthermore, most of the metastatic patients were in the premenopausal period (p = 0.001).

Patients in the synchronous group had significantly more lymphadenectomy than those in the non-involvement group (p < 0.001). Although there was no difference in total and metastatic pelvic lymph node number among the groups, the number of excised paraaortic lymph nodes in the synchronous group was greater compared with the non-involvement group (p = 0.001). The total metastatic lymph node count was significantly higher in the metastatic group than in the non-involvement group (p = 0.047). In the case of ovarian involvement with metastasis or synchronous tumor, adjuvant chemotherapy (p < 0.001) and radiotherapy (p = 0.041) were used significantly more often in the treatment protocol.

Multinomial logistic regression analysis for ovarian involvement identified that people < 50 years old were 16.1 times more likely to be in the metastasis group than those > 50 years old (Tab. 2). Patients with Grade 1 tumors were 1/0.17 = 5.88 times less likely to be in the metastasis group than those with Grade 2 tumors. Postmenopausal patients were 1/0.13 = 7.69 times less likely to be in the synchronous group than premenopausal patients. Patients without lymphadenectomy were 1/0.08 = 12.5 times less likely to be in the synchronous group than those with lymphadenectomy.

As a result of IHC staining performed on patients with ovarian involvement, MMR deficiency was found in six (60%) patients in the metastatic group and six (50%) patients in

Table 2. Multinomial logistic regression analysis for ovarian involvement

Ovarian involvement*		OR (95% CI)	p
Metastasis	Intercept		0.020
	Tumor diameter	0.87 (0.55–1.39)	0.573
	Age		
	≤ 50	16.10 (1.81–143.25)	0.013
	> 50	1.00 (reference)	
	Menopause		
	Post	0.65 (0.09–4.75)	0.672
	Pre	1.00 (reference)	
	Grade		
	I	0.17 (0.04–0.73)	0.017
	II	1.00 (reference)	
	Lymphadenectomy		
	No Yes	0.17 (0.002–1.65) 1.00 (reference)	0.125
Synchron	Intercept		0.004
	Tumor diameter	1.22 (0.85–1.75)	0.275
	Age		
	≤ 50	0.31 (0.05–1.87)	0.202
	> 50	1.00 (reference)	
	Menopause		
	Post	0.13 (0.02–0.68)	0.016
	Pre	1.00 (reference)	
	Grade		
	I	3.33 (0.63– 17.70)	0.157
	II	1.00 (reference)	
	Lymphadenectomy		
	No Yes	0.08 (0.01–0.68) 1.00 (reference)	0.021

*The reference category is 'None'; OR — odds ratio; CI — confidence interval

the synchronous group. All tumors had the same MMR protein expression status both endometrial and ovarian specimens. Immunohistochemical staining and survey results for metastatic and synchronous tumors are indicated in Tables 3 and 4. The mean age of patients with MMR deficiency was higher than MMR proficient patients (62 vs 51), while the number of premenopausal patients was similar (7/12 vs 7/10). MMR deficient tumors were more likely to be at higher grade when compared to MMR proficient tumors (9/12 vs 3/12).

The average survival was calculated as 144 months (Standard Error [SE]: 3.093, 95% CI: 138–150) for the non-involvement group, 143 months (SE: 16.136, 95% CI: 112–175) for the metastatic group, and 88 months (SE: 12.017, 95% CI: 64–111) for the synchronous group (Fig. 1). In binary comparisons between the non-involvement and metastatic group ($p = 0.748$), between the non-involvement and synchronous group ($p = 0.128$) and between the synchronous group and the metastatic group ($p = 0.353$), no significant difference was found in overall survival.

DISCUSSION

This study showed that 2.8% of low-risk endometrial cancer patients had ovarian metastasis and 3.3% had synchronous ovarian involvement. These rates are similar to those of Stage I endometrial cancer [4–6], though higher than the metastasis rate previously reported for low-risk patients [2]. Most of the metastatic patients in our cohort were young and premenopausal. This finding is contradicted by earlier studies, which concluded that synchronous tumors were more likely to occur in younger, premenopausal patients [4, 13, 14]. In addition, this feature has often been used to explain why synchronous tumors have a more favorable

Table 3. Immunohistochemical staining of mismatch repair in the metastatic group

Patient no.	Age	Menopause	Grade	Diameter of endometrial tumor [cm]	Diameter of ovarian tumor [cm]	MSH2	MSH6	MLH1	PMS2	Dead or alive	Survey [month]
1	49	pre	I	1.5	2	+	+	+	+	Alive	91
2	48	post	II	2	4	+	+	–	–	Alive	130
3	49	pre	I	2.5	MT	+	+	+	+	Alive	101
4	44	pre	II	3	3	–	–	+	+	Alive	96
5	44	pre	I	1.5	3	–	–	+	+	Alive	15
6	42	pre	I	2.5	8	–	–	+	+	Alive	19
7	47	pre	II	3	1	+	+	+	+	Alive	161
8	58	post	II	2	3	+	+	–	–	Dead	23
9	49	pre	II	6	MT	+	+	+	+	Alive	109
10	55	post	II	2	2.5	+	+	–	–	Alive	98

MT — microscopic tumor

Table 4. Immunohistochemical staining of mismatch repair in the synchronous group

Patient no.	Age	Menopause	Type of synchronous tumor	Grade of endometrial tumor	Grade of ovarian tumor	Diameter of endometrial tumor (cm)	Diameter of ovarian tumor (cm)	Capsul invasion	MSH2	MSH6	MLH1	PMS2	Dead or alive	Survey (month)
1	52	pre	Endometrioid	I	I	1	6	+	+	+	–	–	Dead	12
2	56	post	Endometrioid	II	II	5.5	2.5	–	+	+	+	+	Alive	112
3	47	pre	Endometrioid	I	II	4	12	+	–	–	+	+	Dead	70
4	47	pre	Endometrioid	I	II	4	2.5	–	+	+	+	+	Alive	94
5	53	pre	Endometrioid	II	I	4	12	–	+	–	+	+	Alive	18
6	69	post	Clear cell	I	–	3	10	+	–	+	–	+	Alive	78
7	65	post	Endometrioid	I	I	2	14	–	+	+	+	+	Alive	9
8	42	pre	Endometrioid	I	I	6	4	–	+	+	+	+	Alive	57
9	58	post	Granulosa	I	–	1.5	7.5	–	+	+	+	+	Alive	29
10	53	post	Clear cell	I	–	2	15	–	+	+	+	+	Dead	6
11	65	post	Brenner	I	–	1.5	0.4	–	–	–	–	+	Alive	107
12	49	pre	Clear cell	I	–	0.5	1	–	+	+	–	+	Alive	87

prognosis than metastatic tumors [15]. Böss et. al. [16], reported that patients with metastasis to the ovary tended to be younger than patients with synchronous tumors. Similarly, higher rates of ovarian metastasis were detected under the age of 40 when ovarian conservation was performed in early-stage endometrial cancer patients [17].

Well-characterized risk factors that may be responsible for ovarian involvement in endometrial cancer are myometrial invasion, higher tumor grade, and lymphovascular space invasion [5, 6]. Modaress et al. [18], showed a 66-fold increase in ovarian metastasis with myometrial invasion. In addition, serosal invasion, tubal involvement, and positive abdominal cytology emerged as independent risk factors in clinical stage I patients [6]. But there are not many studies examining ovarian involvement in low-risk patients where all these factors are the same-negative. In a study by Ignatov et al., they reported 0.5% rate of ovarian metastasis in low-risk patients, and they could not find a difference in overall survival with ovarian involvement [2].

The size of the endometrial tumor was similar between groups. Also, the diameter of the ovarian tumor was larger in the synchronous group, but the difference was not statistically significant. If the ovary was invaded by a synchronous tumor rather than metastasis, the diameter of the tumor would probably be larger [1, 4]. There were two patients with microscopic ovarian metastasis, and if these patients had not had an oophorectomy, the skipped occult metastasis could have resulted in reduced progression-free survival.

Although more lymphadenectomy was performed in the synchronous group, the total metastatic lymph node count was found to be greater in the metastatic group. Bese et al. [19], reported that performing lymphadenectomy was found to be a significant risk factor for recurrence in synchronous tumors. The larger ovarian mass in the synchronous group is associated with more lymph node resection and may be the cause of the good prognosis observed in this group. In all, 7/12 (58%) of synchronous tumors had the same endometrioid histology. Soliman et al. [14], reported 68% concordant endometrioid adenocarcinoma and noted that the most favorable prognosis was associated with the same endometrioid histology. Young, premenopausal, overweight, and nulliparous women in this study had a median survival of 10 years and a good prognosis. Similarly, Chiang et al. [20], reported a survival of 63 months with the same histology and 48 months with a different histology in synchronous tumors.

In general, the prognosis in patients with synchronous ovarian involvement is better than in metastatic involvement [21]. In a gynecologic oncology group study, the reported five-year survival rates were higher (86% vs 58%) with synchronous tumors [13]. Bese et al. [19], reported

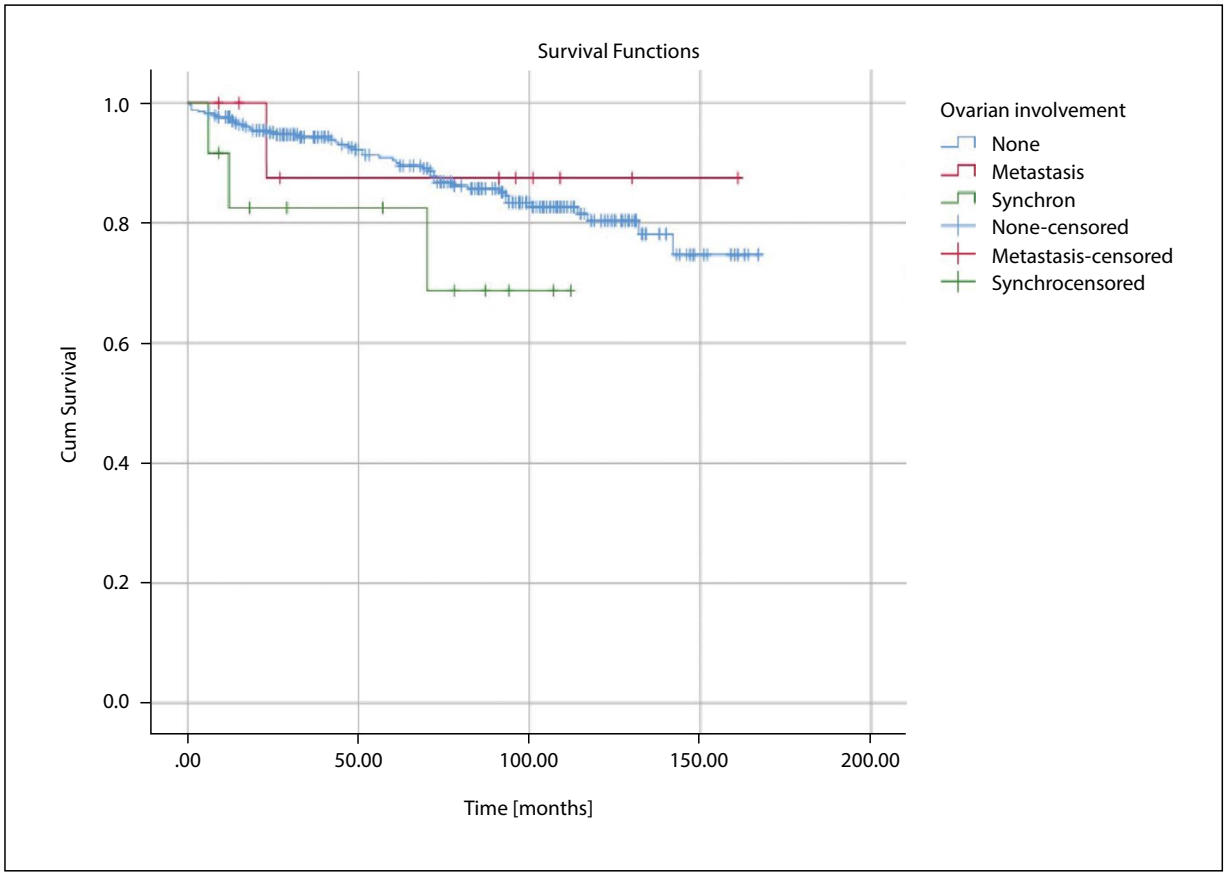

Figure 1. Overall survival analysis of patients

a dramatic change in 10-year survival rates of 61.3% and 36.6% in synchronous and metastatic groups, respectively. The critical point of this study was that only 25% of the study population consisted of Stage patients. Simultaneously detected endometrial and ovarian carcinomas with a grade 1 tumor had a significantly lower five-year recurrence rate (8% vs 22.4%) compared with patients with at least one tumor above grade 1 [13]. In the present study, no significant difference was detected in overall survival between three groups (no involvement, synchronous, or metastatic).

The presence of ovarian involvement elevates endometrial carcinoma to Stage IIIa and assigns it to a high-risk category. However, the treatment options offered by institutions may vary, and the prognosis is therefore uncertain. Adjuvant therapy is often individualized based on stage, pathological outcomes, and risk factors. Some authors advocate not giving adjuvant chemotherapy or radiotherapy because of the lack of a statistically significant difference in overall survival in synchronous primary cancer patients [20]. However, Ayhan et al. [22], suggested adjuvant therapy in patients with advanced stages of ovarian cancer to improve survival. After adjusting risk factors such as stage, grade, and residual tumor tissue Heitz et al. [23], suggested chemotherapy for synchronous tumors and additional radiotherapy if the endometrial component is advanced.

MMR deficiency may be encountered in 20–40% of endometrial cancers and in 6.4% of ovarian cancers [24, 25]. Shikama et al., compared IHC results with clinicopathological findings of endometrium cancer. Patients with MMR proficiency were found to be significantly older, nulliparous, obese, and hypertensive compared to those with MMR deficiency. Overall survival was better in patients with MMR deficiency, but this was not significant [26]. Similarly in our study, MMR-deficient patients with ovarian involvement tended to be older and at higher grade. Clinicopathological features of 7054 patients diagnosed endometrial cancer with MMR deficiency were also evaluated in a systematic review [27]. Patients with MMR-deficient tumors were significantly younger, less likely to have grade I tumor, and had lower BMI.

MMR deficiency was reported 11% to 59% in synchronous tumors [24, 28]. Previous studies have reported that MMR deficiency may be associated with optimal prognosis depending on low stage and grade in endometrial cancers [29, 30]. However, studies in low-risk patients revealed that MMR-deficient tumors had worse progression-free survival

and higher recurrence rates despite similar overall survival [31]. The reason for this condition is that most of these patients had not received adjuvant therapy, and MMR-deficiency can improve the response to treatment [32]. Conversely, in high-intermediate-risk patients, the recurrence rate of endometrial cancer for women with MMR deficiency was significantly higher regardless of adjuvant therapy [33]. In a study by Yoneoka et al. [34], MMR deficiency was observed in 28.3%, MMR expression status was the same for endometrial and ovarian tumors, and no survival advantage was reported. We also found similar MMR expression status and survival between metastatic and synchronous groups.

Recently, a new generation of sequencing (NGS) technology has been used to explain the clonal relationship between endometrial cancer and ovarian cancer. It has been revealed that 95% of synchronous tumors clinically diagnosed as double primary cancers are actually clonal tumors [11, 12]. This means that simultaneous endometrial and ovarian tumors are not independent primary tumors. Despite the clonality, some authors hypothesize indolent spread phenomena instead of a 'fully' metastatic disease [35]. One possible explanation is that these cells cannot spread to distant areas through the bloodstream, but spread transtubally to nearby areas, such as the ovary, and perform pseudometastase [27]. This theory can also help us understand why patients with these tumors often paradoxically exhibit good clinical outcomes.

The limitation of this study is that it was conducted in a single institution and used a retrospective study design. Another limitation is that disease-free survival was not accepted as a primary outcome; rather, the more precise overall survival was used. It is certain that multicentric studies involving greater numbers of patients are needed.

CONCLUSIONS

We found that ovarian involvement in low-risk endometrial cancer is rare, with a similar frequency to those previously reported in the literature. Younger age and premenopausal status were risk factors associated with ovarian metastasis. The probability of postmenopausal patients being in the synchronous group was lower than that of premenopausal patients. Overall survival did not show differences between all groups, and MMR-deficiency was similar between metastatic and synchronous groups.

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Conflict of interests

The authors have no conflict of interest to disclose.

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Predictors of poor neonatal outcomes in fetuses diagnosed with congenital urinary tract anomalies

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ABSTRACT

Objectives: Urinary tract anomalies account for approximately one-quarter of all antenatally detected anomalies. The aim of this study was to identify factors associated with severe adverse neonatal outcomes of a prenatally diagnosed urinary tract anomaly.

Material and methods: A retrospective-prospective study included 101 pregnant women with prenatally diagnosed fetal urinary tract anomalies presented to the Council for Fetal Anomalies. Prenatal diagnoses were compared with autopsy findings in cases of terminated pregnancy or with clinical and operative findings of the infants.

Results: The mortality rate in the group of patients with fetal obstructive uropathy (60 patients) was 10% and in the group of patients with fetal multicystic dysplastic kidney (38 patients) 15.7%. Surgery was performed on 53.4% of the children, whereas more than half of the operations involved resolving associated urinary tract anomalies. Postoperative renal function deterioration occurred in 19% of the children.

Conclusions: The prognosis of renal function in obstructive uropathies is excellent if oligoamnios does not develop prenatally and in case of timely provided surgical care is provided postnatally. The finding of the bilateral multicystic dysplastic kidney is associated with poor prognosis. The prognosis in fetal unilateral multicystic dysplastic kidney depends primarily on the condition of the contralateral kidney and the existence of associated anomalies.

Key words: fetus; congenital; urinary tract; anomalies; outcome

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INTRODUCTION

According to literature data, urinary tract anomalies account for slightly less than one-quarter of all antenatally detected anomalies. As many as 60% of all urinary tract anomalies account for obstructive uropathies and close to 30% for multicystic dysplastic kidney [1, 2]. In obstructive uropathies, antenatal sonography detects not only an anomaly but also the location of the obstruction occurrence, whereas we can also evaluate renal function by biochemical analysis of fetal urine obtained by the bladder puncture. Multicystic dysplastic kidney rarely causes diagnostic dilemmas and is detected easily by a routine prenatal sonographic examination. The kidney itself is enormously enlarged and is the most common cause of sonographic findings of cystic masses in the fetal abdomen, whereas its function is less than 10% [3].

Numerous studies have examined the incidence of fetal urinary tract anomalies, genetics, etiopathogenesis, association with other abnormalities, and surgical procedures conducted on children after birth [4–8]; however, questions remain about prenatally identified factors associated with adverse perinatal-neonatal outcomes.

The objectives of this study were to characterise clinical outcomes of a prenatally diagnosed urinary tract anomaly and to assess prenatal variables associated with the adverse outcome or favourable prognosis for the purpose of adequate counselling of patients.

MATERIAL AND METHODS

A retrospective-prospective study included pregnant women with a congenital fetal urinary tract anomaly pre-

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sented to the Council for Fetal Anomalies at the Institute of Gynaecology and Obstetrics, Clinical Centre of Serbia, and University Children's Hospital, Belgrade within a three-year period. Prenatal evaluation of fetal urinary tract included expert fetal ultrasound examination with fetal echocardiography and, depending on the assessment of the Council team, additional diagnostics such as magnetic resonance imaging, amniocentesis with karyotyping, and fetal urine analysis.

Patients diagnosed with a fetal anomaly incompatible with life or anomalies with poor postnatal outcomes were advised to terminate the pregnancy, whereas the proposals for termination were presented to the Ethics Committee. Patients having a favourable prognosis were referred to their gynaecologists for pregnancy monitoring and completion according to obstetric indications. Postnatal evaluation of the infant urinary tract (ultrasonographic examination, micturating cystourethrography, and radioisotope imaging techniques: MAG-3, DMSA, DTPA), and certain interventions (one or two) if necessary, were performed at the University Children's Hospital. Data used in this study were obtained based on prenatal diagnoses, autopsy findings (in case of lethal outcomes), and clinical and operative findings of the infants.

RESULTS

Within a three-year period, 101 pregnant women with a suspected fetal urinary tract anomaly were referred to the Council For Fatal Anomalies. Fetal urinary tract dilation was diagnosed prenatally in 60 patients (59.4%), whereas the diagnosis of fetal multicystic dysplastic kidney was established in 38 patients (37.6%). The remaining patients were diagnosed with dysfunctions in the number, fusion, and localization of the kidneys and were not included in the study.

Mortality

In the group of patients with an obstructive urinary tract anomaly, the pregnancy was terminated in six patients (10%). After the obtained approval from the Ethics Committee, the termination was performed in two cases of bilateral hydronephrosis, severe oligoamnios, and poor results of the fetal urine analyses indicating the existence of fetal renal insufficiency during early gestation and in four cases of a sonographic finding of megacystis and oligoamnios. The average length of gestation before the pregnancy termination was 26 weeks. The fetal sex was male in all cases.

In patients diagnosed with fetal multicystic dysplastic kidney, the pregnancy was terminated in four patients (10.5%) after obtaining the approval from the Ethics Committee, whereas in two cases (5.2%) child deaths occurred after birth. Excluding two fetuses with multicystic dysplastic kidney confirmed by autopsy findings, in cases of unilateral multicystic dysplasia, the autopsy revealed associated urinary tract anomalies and extrarenal anomalies (Tab. 1).

Surviving children with urinary tract anomalies

Of the 54 patients with a prenatally detected obstructive anomaly of the fetal urinary tract, three were misdiagnosed as verified postnatally. Isolated unilateral or bilateral hydronephrosis, a slightly higher number of the bilateral one, was detected in 30 children (55%). The remaining children had associated urinary tract anomalies. The obstruction cause, the number of operated children, and the number of children with renal function deterioration are shown in Table 2.

The urinary tract of 32 surviving children with a multicystic dysplastic kidney was evaluated postnatally. Radioisotope examination revealed that the kidney altered due to multicystic dysplasia was either entirely dysfunctional or its function was less than 5%.

Ultrasound examination and micturating cystourethrography revealed one or more associated urinary tract anomalies in 27 (84.3%) children (Tab. 3). Surgery was performed on 28 (73.6%) children. In seven (17%) children, renal function deterioration was observed during postoperative follow-up. The remaining children required no interventions and undergo regular check-ups.

DISCUSSION

In the group of patients with congenital fetal obstructive uropathy, the highest number of terminated pregnancies was in fetuses with pronounced megacystis and reduced amniotic fluid volume. Reduced amniotic fluid in early gestation was the main poor prognostic factor in obstructive uropathy. The literature data also indicated high mortality rates in fetuses with this anomaly [9]. In our study, all preg-

Table 1. Fetal autopsy findings (associated renal and extrarenal anomalies) in four cases of terminated pregnancies

	Autopsy findings	
Prenatal diagnosis	Associated urinary tract anomalies	Extrarenal anomalies
Multicystic left kidney and right kidney anomaly	Agenesis of the right kidney	Anal and vaginal atresia
Multicystic right kidney and no amniotic fluid	Hypoplastic bladder and left kidney	Hypoplastic penis
Multicystic left kidney and no amniotic fluid	Agenesis of the right kidney	Cleft lip and palate
Multicystic left kidney and polycistic right kidney	Right kidney dysplasia	Hypoplastic genitalia

Table 2. Postnatal diagnosis in infants with prenatally diagnosed dilated uropathy, the cause of dilation, the number of children who underwent surgery and children with the postoperative renal function deterioration

Postnatal diagnosis	Cause?	No of children	No of the children who underwent surgery	No of children with the postoperative renal function deterioration
Isolated uni/bilateral hydronephrosis	— Stenosis of the pyeloureteral junction — VUR	30 (55.5%)	11 (36.6%)	1 (3.33%)
Hydronephrosis associated with uni/bilateral megaureter	— Stenosis of the pyeloureteral junction — Stenosis of the vesicoureteric junction — Congenital megaureter — Ureter duplex — Posterior urethral valve — VUR	16 (29.6%)	10 (62.5%)	2 (12.5%)
Megacystis	— Posterior urethral valve — Narrowed urethra	5 (9.25%)	5 (100%)	2 (40%)

VUR — vesicoureteral reflux

Table 3. Anomalies of the contralateral kidney, the ipsilateral kidney, and the lower urinary tract in infants prenatally diagnosed with multicystic dysplastic kidney

Type of anomaly	Contralateral kidney (no of anomalies)	Ipsilateral kidney (no of anomalies)	Lower urinary tract (no of anomalies)
Hydronephrosis	3		
Pyelectasis	4		
Megaureter	1	2	
Ectopic ureter	2	2	
Ureterocele	2	1	
Posterior urethral valve			4
Urethral stenosis			1
VUR	8	2	
Total	20	7	5

VUR — vesicoureteral reflux

nancies were terminated before the fetuses were capable of independent life.

The outcome of surviving children with obstructive uropathy was relatively favourable. The results of our study showed that isolated unilateral hydronephrosis is a benign condition, whereas the possibility of spontaneous resolution is very high, especially if the pelvis diameter prenatally at 32 weeks was less than 15 mm. Previous studies have demonstrated similar results [10].

Vesicoureteral reflux (VUR) was responsible for approximately 12% of dilatation detected antenatally, similarly to the percentage reported in the literature (15%) [11].

A high number of interventions were required in children with a prenatal diagnosis of hydronephrosis and megaureter (close to 60%), primarily in those with postnatally detected pyelo-ureteral junction stenosis.

The percentage of interventions was also high in the group of children with a prenatally diagnosed bilateral hydronephrosis and postnatally confirmed VUR with various degrees of severity (close to 30%). Since VUR predisposes patients to urinary tract infection, all children in this study with the dilatation of pyelon greater than 10 mm were postnatally treated with low dose antibiotics terapy in the first three months of life [12]. The highest number of interventions were required in children with megacystis caused by a posterior urethral valve [13, 14].

In general, in the group of children with a dilated uropathy, renal function deterioration occurred only in cases of pronounced bilateral hydronephrosis or pronounced megacystis with the development of oligoamnios requiring labour induction immediately upon achieving fetal lung maturation.

Regarding fetal multicystic dysplastic kidney, our study showed the highest mortality rate in cases of bilateral dysplasia, prenatally diagnosed extrarenal anomalies, and oligoamnios. In comparison to prior research results concerning anomalies of the contralateral kidney, we obtained

similar data. Namely, the contralateral kidney anomalies were found in approximately 32% of children, similar to data from previous studies (21–35%) [15, 16].

VUR was diagnosed in 22% of children. Data from previous research studies indicate a VUR range of 4.8 to 28% [17].

The most frequent anomalies of the ipsilateral side include megaureter, ectopic ureter and VUR, whereas the lower urinary tract anomalies were present in 13.2% of children, slightly higher than reported in previous studies (6%) [18].

Despite conflicting opinions on the application of cystoscopy and nephrectomy in this group cystoscopy revealed an ectopic ureter in 10% of children, whereas colposcopy detected an imperforate hymen and an ectopic ureter with the opening located in the vagina in one girl. The outcome of operated children was generally favourable. Nephrectomy or partial nephrectomy was required in 13 out of 28 children, whereas in other children in this group 28 interventions were performed to resolve the anomalies of the contralateral kidney and the lower urinary tract [19–21]. The remaining children required no interventions and undergo regular check-ups.

CONCLUSIONS

The prognosis of renal function in obstructive uropathies is excellent if oligoamnios does not develop prenatally and in case of timely provided postnatal surgical care. The findings of both bilateral and unilateral MCKD and oligoamnios are associated with poor prognosis. Isolated unilateral MCKD requires serial ultrasound examinations both pre and postnatally since the prognosis depends primarily on the condition of the contralateral kidney and the severity of associated anomalies.

Conflict of interest

None.

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Factors affecting the choice of drospirenone as the component of combined contraceptive pill in daily clinical practice: the results of nation-wide survey

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ABSTRACT

Objectives: The aim of the multicenter, open-label, post-marketing, observational survey was to assess doctors' preferences in choosing the progestogen component of the combined contraceptive pill (CCP) and factors affecting this choice in daily clinical practice as well as non-contraceptive reasons use of CCP containing drospirenone (CCPD) and patients' tolerance and satisfaction with the treatment.

Material and methods: This multicenter, open-label, post-marketing, survey was performed nation-wide with the participation of 222 doctors involving and 10,345 patients treated with CCPD.
The study questionnaire included questions concerning factors affecting the choice of drospirenone as a component of CCP and assessing prescription pattern of the drug as well as tolerance and satisfaction with the use of CCPD.

Results: The doctors frequently declared their choice of drospirenone as the progestogen component of CCP. The most important factors affecting the choice of drospirenone, declared by doctors, were tolerance level, consistent regulation of menstrual cycle and not causing spotting.
CCPD was prescribed to patients with irregular menstrual cycles (62.7%) and painful menstruation (46.8%).
During follow-up, significantly increased percentage of patients assessed the tolerance of treatment with CCPD as very good (52.5% vs 68.0%; $p < 0.01$) and very satisfied with its use (61.9% vs 77.8%, $p < 0.01$).

Conclusions: 1) Drospirenone is frequently chosen progestogen component in CCP by Polish gynecologists due to its good tolerance, consistent regulation of the menstrual cycle and no spotting in patients opinion. 2) CCPD was most frequently used in patients with irregular menstrual cycles and painful menstruation. 3) The patients were satisfied with the use CCPD and treatment was well tolerated.

Key words: combined contraceptive pill containing drospirenone; doctors' preferences; patients' satisfaction; tolerance

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INTRODUCTION

CCP containing 50 µg of ethylene estradiol and progestin is the method of choice in the regulation of fertility in adolescents and young women, unless there are contraindications [1–3]. CCP, apart from being used in contraception, are also used in women with excessive levels of androgens in the blood. The most common cause of excess androgens of ovarian origin is polycystic ovary syndrome (10–15% of women of childbearing age), much less frequently the growth of thecal cells (hypotrichosis) or a hormonally active ovarian tumor. The adrenal causes of androgen excess include non-classical congenital adrenal hyperplasia, Cushing's syndrome or a tumor of the adrenal glands [4].

Apart from treating the clinical features of hyperandrogenism and the contraceptive effect, CCP exerts many other beneficial therapeutic effects, such as: regulation of menstrual cycles, elimination of symptoms occurring in the course of premenstrual syndrome, decrease of menopausal symptoms, treatment of dysmenorrhea and endometriosis, increasing bone mineral density, reduction in the incidence of functional ovarian cysts, decrease in the incidence of uterine fibroids, decrease in the incidence of ectopic pregnancies, decrease in the incidence of mastopathy, decrease

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in the incidence of breast fibroadenomas, decrease in the incidence of chronic cystic changes in the breast, decrease in the incidence of ovarian and endometrial cancers [5–7].

The estrogen component of this tablet causes a reduction in the concentrations of free testosterone and dihydrotestosterone, as well as dehydroepiandrostenedione and androstenedione in the first month of use, it also increases the concentration of SHBG, which further reduces the availability of free androgens [8].

Progestogenic preparations have different affinities for estrogen, androgen, glucocorticoid and mineralocorticoid receptors, thus translate into differences in the clinical activity profile. In the treatment of clinical symptoms of hyperandrogenism, the influence of progestogens on the activity of androgen receptors, i.e., their degree of androgenicity of progestogens or their antiandrogenic effect, is of crucial importance [9]. Drospirenone is a fourth generation progestogen and affects the activity of progesterone receptors, showing also anti-androgenic and anti-mineralocorticoid activity [10, 11]. Thanks to its anti-androgenic and anti-mineralocorticoid activity, drospirenone alleviates symptoms related to water retention and improves the condition of acne-prone skin better than levonogestrel [12]. Drospirenone has also been shown to be more beneficial than other progestogens in women with PCOS and on premenstrual dysphoric symptoms compared to placebo [13, 14].

Currently, there are no Polish data on the preferences of doctors regarding the choice of CCPD and the factors affecting them. It is also unknown how this treatment affects the continuation of therapy and how it is tolerated by the patients. Therefore, the aim of the multicenter, open-label, post-marketing, observational survey was to assess doctors' preferences in choosing the progestogen component of the contraceptive pill and factors affecting this choice in daily clinical practice. The second aim of the study was to assess non-contraceptive reasons use of CCPD as well as patients' tolerance and satisfaction with the treatment.

MATERIAL AND METHODS

Two hundred and twenty-two gynecologists participated in a nation-wide, multicenter, open-label, post-marketing, survey. They interviewed 10,345 patients treated with CCPD. The survey did not meet the criteria of a medical experiment and thus did not require Bioethics Committee approval.

The inclusion criteria for doctors were specialization in gynecology, current license to practice, having in your practice an appropriate number of patients who meet the inclusion criteria for the study, completing and signing the Application Form for the Study and sending it to Europharma.

The inclusion criteria for outpatients were being 18+ years old and the use of CCPD minimum 14 days prior to study inclusion.

The exclusion criterion was inability to obtain answers to questions contained in the survey.

The physicians participating had dual roles in the survey. They answered to the questions regarding their medical practice, filled out questionnaires for a minimum of 40 patients that fulfilled the inclusion criteria during one visit survey resulting from a clinical need of the patient.

The first part of the questionnaire included demographic data of the doctors (specialization, work experience, place of work) and data on their clinical practice [progestogen most often chosen as a component the CCP (chlormadinone acetate/cyproterone acetate/desogestrel/drospirenone/norgestimat/dienogest/gestodene/levonorgestrel), trait the progestogen that most influences its choice (antiandrogenic strength/ tolerance level/ lack of spotting/no effect on body mass/consistent regulation of menstrual cycles/ /elimination of the symptoms of premenstrual syndrome/ /positive action in painful menstruation/ positive effect in endometriosis treatment/drug price)].

The second part of the questionnaire was conducted in two routine outpatient visits resulting from the needs of therapy. The part conducted during the first visit included patient demographic data (age, education level, place of residence and professional activity, staying in a steady relationship), clinical data (nutritional status, number of pregnancies and deliveries, menarche, regularity of menstrual cycles, reason for use the CCPD, previously used contraception, duration of use of current contraception and dose of drospirenone). The part conducted during the second visit (about three months from the previous visit) included data on continuing to use contraception and possible causes of discontinuation.

In addition, during both visits, the patients' opinion on tolerance of the CCPD and satisfaction with the treatment used were assessed based on a four point scale (1-difficult to accept discomfort, 2 — acceptable discomfort, 3 — good tolerance, 4 — very good-tolerance and 1 — the lack, 2 — moderate, 3 — good, 4 — very good, respectively).

Statistical analysis was performed with Statistica 12.0 software (TIBCO Software Inc., Palo Alto, CA, USA). Values of variables were presented as percentages and the mean values with standard deviations (SD). The differences between visits were compared using the chi^2 test and chi^2 test for trend. The value of $p < 0.05$ was considered statistically significant.

RESULTS

Doctors' therapeutic preferences

The study group of doctors' characteristics is presented in Table 1. Drospirenone was the most frequently progestogen included in the CCP chosen by doctors participating in the study (60,4%). The most common trait of progestogen that most influences its choice indicated by doctors were high

tolerance levels (76.1%), consistent regulation of menstrual cycle (59.9%) and not causing spotting (57.2%), Table 2.

The characteristics of study patients and tolerance as well as satisfaction with use CCPD

The study group of doctors' characteristics is presented in Table 3.

In 44.1% of patients included in the study, CCPD was used also for reasons other than contraception. Most often, these reasons were irregular menstrual cycles (62.7%) and painful menstruation (46.8%). 16.5% of the observed patients previously used CCP containing another progestogen, most often levonorgestrel (20.2%) — data not shown. The most common cause of changes in the pill used were no benefit effect on accompanying symptoms (30.3%) — data not shown. 41.8% of the observed group used CCPD for 2-3 months. 98.3% of patients used CCPD at a dose of 3 mg (Table 3).

The second visit was implemented on average 70 days after first visit. The use of the CCPD was continued by 95.8% of the observed patients. Among the 4.2% of patients that discontinued its use, the most common reasons were deliberate decision not to implement prescription (33.7%), deliberate withdrawal of the drug due to discomfort with its' using (23.4%), deciding to terminate treatment under the influence of other people (14.9%) and no beneficial effects on accompanying symptoms (12.4%).

During follow-up, significantly increased percentage of patients assessed the tolerance of treatment with CCPD as very good (52.5% vs 68.0%; $p < 0.01$) and very satisfied with its use (61.9% vs 77.8%, $p < 0.01$). While the percentage of patients who would recommend this form of contraception to a friend was similar (98.3% vs 99.9%), Table 4.

During follow-up in the study group, 12 adverse events in six patients (0.06% of the observed groups) have been reported. One of these adverse events, venous thrombosis of the lower extremities, was serious (Tab. 5).

Table 1. Characteristics of the study group of doctors (n = 222)

Professional experience	n (%)
2–5 years	3 (1.4)
6–15 years	58 (26.1)
16–20 years	11 (5.0)
> 20 years	150 (67.6)
Workplace	n (%)
Public hospital	63 (28.4)
Private hospital	3 (1.4)
Public outpatients clinic	33 (14.9)
Private outpatients clinic	24 (10.8)
Private practice	99 (44.6)
Workplace location	n (%)
Village	1 (0.5)
City < 50,000 residents	62 (27.9)
City 50–200,000 residents	61 (27.5)
City > 200,000 residents	98 (44.1)

Table 2. Doctors preferences and the factors that determine them

Progestogen chosen as a component the CCP [%]	Rarely	Often	The most common
Chlormadinone acetate	47.3	50.9	1.8
Cyproterone acetate	81.5	17.6	0.9
Desogestrel	40.1	53.6	6.3
Drospirenone	2.3	37.4	60.4
Norgestimat	43.2	55.9	0.9
Dienogest	22.1	70.3	7.7
Gestodene	36.5	48.2	15.3
Levonorgestrel	32.0	62.6	5.4
Trait the progestogen decides about its choice [%]	**Not important**	**Important**	**Very important**
Antiandrogenic strength	5.0	65.3	29.7
Good tolerance	0.5	23.4	76.1
The lack of spotting	9.0	33.8	57.2
No effect on body mass	3.6	45.0	51.4
Very good regulation of menstrual cycles	7.7	32.4	59.9
Very good elimination of the symptoms of premenstrual syndrome	13.5	45.9	40.5
Very good action in painful menstruation	6.3	43.2	50.5
Very good effect in endometriosis treatment	23.9	60.4	15.8
Drug price	33.8	60.4	5.9

Table 3. Characteristics of patients study groups treated with CCPD (n = 10.345)	
Sociodemographic	
Age (years) (mean ± SD) (min–max)	28 ± 7 (18–52)
Education levels	**n (%)**
Primary	325 (3.1)
Vocational	1.142 (11.0)
Secondary	5.379 (52.0
Higher	3.499 (33.8)
Professional activity	**n (%)**
Working	6.711 (64.9)
Not working	1.025 (9.9)
Pension	27 (0.3)
Student	2.582 (25.0)
Staying in a solid relationship:	**7.216 (69.8)**
Clinical	
Nutritional status	**n (%)**
Underweight	717 (6.9)
Normal weight	7.795 (75.4)
Overweight	1.712 (16.5)
Obesity	121 (1.2)
Number of pregnancies	**n (%)**
0	4.820 (46.6)
1	2.335 (22.6)
2	2.079 (20.1)
> 2	1.111 (10.7)
Number of births	**n (%)**
0	4.912 (47.5)
1	2.665 (25.8)
2	2.183 (21.1)
> 2	585 (5.7)
Age of menarche	**n (%)**
10–11 years	1.074 (10.4)
12–14 years	8.211 (79.4)
> 14 years	1.060 (10.2)
Regularity of menstrual cycles	**n (%)**
Regular	6.763 (65.4)
Irregular	3.527 (34.1)
Secondary amenorrhea	55 (0.5)
Non-contraceptive reason to use the CCPD	5.787 (55.9)
The factors determining the choice of drospirenone	**n (%)**
Hyperandrogenism	1.039 (22.8)
Overweight	390 (8.6)
Irregular menstrual cycles	2.858 (62.7)
Premenstrual syndrome	1.180 (25.9)
Painful menstruation	2.131 (46.8)
Endometriosis	172 (3.8)
Abundant menstruation	43 (0.9)
Acne	28 (0.6)
Other	21 (0.5)
Duration of taking the CCPD	**n (%)**
< 1 month	1.617 (15.6)
2–3 months	4.327 (41.8)
4–6 months	1.960 (18.9)
7–12 months	1.250 (12.1)
> 12 months	1.191 (11.5)
Drospirenone dose used	**n (%)**
3 mg	10.172 (98.3)
2 mg	173 (1.7)

DISCUSSION

More than half of the doctors participating in the study indicated drospirenone as the most frequently chosen progestogen in the CCP. The most frequently indicated features of the active substance determining its selection were tolerance level, consistent regulation of the menstrual cycles and no spotting. The importance of the non-contraceptive effects of the CCPD for doctors is confirmed by the fact that over 40% of patients included in the study also used it for reasons other than contraception. The most common reasons were irregular menstrual cycles and painful menstruation, which is consistent with the features indicated as important when choosing a progestogen included in the CCP. Moreover, the most common changes in the contraceptive use were made due to the lack of a beneficial effect on the accompanying symptoms. The progestogen most often changed to drospirenone was levonorgestrel. While, the results of a randomized study showed that the CCPD is more effective at relieving the symptoms of painful periods than the pill containing chlormadinone [15]. It should also be noted that in 2010 in Great Britain, similarly to the presented study, in over 40% of women the CCPD was used for non-contraceptive reasons [16].

During the follow-up, the use of the CCPD was continued by 95.8% of the observed patients. Moreover, the percentage of patients assessing the tolerance of the CCPD used as "very good" increased significantly. It should be noted that 98.3% of study women were treated with pills containing 3 mg drospirenone. High tolerance of the drug is also confirmed by the fact that adverse events were reported in 0.06% of the studied group, just one adverse event was severe. The rate of adverse

Table 4. Changes of tolerance and satisfaction of the patients during observation

	Visit 1 (n = 10.345)	Visit 2 (n = 9.909)	P
Tolerance the CCPD	(%)		
Difficult to accept discomfort	0.6	0	< 0.05
Acceptable discomfort	3.2	1.1	< 0.05
Good tolerance	43.7	30.9	< 0.01
Very good tolerance	52.5	68.0	< 0.01
Satisfaction with the use of the CCPD	(%)		
The lack	0.6	0.1	< 0.05
Moderate	2.0	0.4	< 0.05
Good	35.5	21.7	< 0.01
Very good	61.9	77.8	< 0.01
Percentage of patients who would recommend this form of contraception to a friend	98.3	99.9	NS

NS: non-statistical

Table 5. Adverse events related to treatment with CCPD

Adverse event	n
Intolerance	2
Decline in libido	3
Venous thrombosis of the lower extremities	1
Calf pain	2
Constant spotting	1
Periodic spotting	1
Swelling of the breasts	1
Slight swelling of the ankles	1
Total	12

events was much lower than observed in another study. In this study was 1.5%, after subtracting the placebo effect, discontinued the use of CCP containing 3 mg drospirenone [17]. The differences may be the results of the lower number of study women (n = 266) and the indication for the use of CCP (moderate facial acne), the duration of the treatment as well as nature of the study (a randomized, double — blind, controlled placebo vs observational study carried out in the conditions of everyday clinical practice). The high tolerance treatment with CCPD has also been observed in group young adult women with primary dysmenorrhea [18].

During the follow-up, the percentage of patients who were very satisfied with the use of CCPD increased significantly. The percentage of patients recommending this form of contraception to a friend has also increased slightly. Satisfaction with the use of this contraceptive pill may be related not only to its contraceptive efficacy and good tolerability, but also, as suggested by the results of a previously published study with improvement in well-being at the time of application these pills and its deterioration after discontinuation [19]. It is also suggested that the use of a CCP may improve the quality of life [20].

The conducted study describing the daily clinical practice of Polish gynecologists in the use of CCP confirms previous observations on the benefits of using the fourth generation progestogen – drospirenone as a component of CCP [17–20], improves the continuation of contraception and positively affects the quality of life of patients. This may be an indication for doctors that in the event of low tolerance of CCP containing another progestogen, switching to CCPD will encourage the patient to continue the therapy. This is especially important in the group of patients using CCP for other than contraceptive reasons.

The main limitation of the presented study is the lack of control group treated with placebo and the lack of comparisons with CCP containing other progestogens. However, the strengths of the study are study group size and assessment of daily clinical practice.

CONCLUSIONS

Drospirenone is frequently chosen as the progestogen component in CCP by Polish gynecologists due to its good tolerance, consistent regulation of the menstrual cycle and no spotting in patients opinion.

CCPD was most frequently used in patients with irregular menstrual cycles and painful menstruation.

The patients were satisfied with the use CCPD and treatment was well tolerated.

Conflict of interest

Magdalena Olszanecka-Glinianowicz received honorarium for study concept from Europharma.
Violetta Skrzypulec-Plinta received honorarium for co-edition from Europharma.

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The importance of *NFκB1* rs4648068 and *RUNX2* rs7771980 polymorphisms in bone metabolism of postmenopausal Polish women

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ABSTRACT

Objectives: Osteoporosis is a multifactorial disease that causes a loss of bone density. However, genetic factors play an increasingly important role in its development. To thoroughly understand the molecular mechanisms, polymorphic variants of genes candidate for osteoporosis are still being sought. The aim of our study was to investigate the influence of *NFκB1* gene rs4648068 (A>G) and *RUNX2* gene rs7771980 (-1025T>C) polymorphisms on the risk of osteoporosis.

Material and methods: A group of 675 postmenopausal Caucasian women (109 women with osteopenia, 333 with osteoporosis and 233 with normal T-score) were examined. The bone mineral density (BMD) at the lumbar spine (L1-L4) was measured by dual energy x-ray absorptiometry (DXA). The analysis of *NFκB1* and *RUNX2* polymorphisms was performed using real-time PCR method.

Results: Analysis of *NFκB1* gene rs4648068 polymorphism showed that the GG genotype was slightly more frequent in the study groups compared to the control group. In the osteoporosis group, patients with the G allele in the genotype have lower bone mineral density values. For the *RUNX2* rs7771980 polymorphism, in women with osteopenia we observed an increased incidence of TC heterozygotes compared to the control group (29.40% vs 24.90%, $p > 0.05$), and in women with osteoporosis, the TT genotype was more common (78.70% vs 73.80%, $p > 0.05$). No correlation was observed between the genotypes and the clinical parameters.

Conclusions: The analysis showed no significant relationship between the genotypic distribution and the individual clinical parameters. However, it is suggested an association between the rs4648068 polymorphism of the *NFκB1* gene and an increased risk of developing osteoporosis.

Key words: osteoporosis; polymorphism; *NFκB1*; *RUNX2*; postmenopausal women

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INTRODUCTION

Osteoporosis is a multifactorial, chronic metabolic disease of the skeletal system. It is characterized by a progressive decrease in bone density (BMD), which leads to an increased risk of fractures [1]. Initially, it develops asymptomatically, there is a painless deterioration of the state of the skeletal system and destruction of bone mass. Osteoporotic fractures, caused as a result of light injuries, are usually the first noticeable symptom, indicating the very advanced disease [2]. The occurrence of osteoporosis depends on age,

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race, sex and ethnicity. The incidence increases with age; however, most cases are observed in patients over 70 years of age. Osteoporosis is more common in women, especially in postmenopausal women (postmenopausal osteoporosis). The greatest risk of developing osteoporosis was observed in Caucasian and Asian women [2, 3].

In order to determine the genetic basis for the development of osteoporosis, the single nucleotide polymorphisms involved in bone tissue metabolism, such as receptor activator for nuclear factor κ B (RANK), receptor activator for nuclear factor κ B ligand (RANKL) or other genes affecting ossification, are analyzed [4]. RANKL is a protein found on the surface of osteoblasts that participates in the formation of mature osteoclasts.

It binds RANK, located on the surface of osteoclasts, as a result of which these cells differentiate into mature multinucleated forms. Blocking RANKL prevents its attachment to a receptor that inhibits osteoclast maturation and bone resorption. The effect of the RANK and RANKL interaction is the activation of nuclear factor of activated T cells transcription complex 1 (NFATc1), nuclear factor κB (NFκB) i cellular Finkel-Biskis-Jinkins murine osteosarcoma (cFos/Fra-1) transcription factors. The NF-κB protein family regulates the expression of many genes involved in various immune and inflammatory response processes. It includes five transcription factors NF-κB1 (also named p50), NF-κB2 (or p52), RelA (or p65), RelB and c-Rel [5–7]. It is not known exactly how NFκB affects mature osteoclasts. It has been found in mice that the deletion of the gene encoding the NFκB transcription factor, more specifically the p50 and p52 subunits, is responsible for osteoclast-independent, rare, hereditary disease marbled bone called Albers and Schönberg disease or osteopetrosis [8, 9].

Another gene involved in bone formation is runt-related transcription factor 2 (RUNX2), located at the 6p21 locus. It contains two promoters P1 and P2 and seven exons and encodes two protein isoforms: RUNX2-I and RUNX2-II. It is a key transcription factor associated with osteoblast differentiation, RUNX2-I involved in the early stages of osteoclastgenesis, and RUNX2-II in the process of osteoblast maturation. Studies have shown that mice deficient of the transcription factor RUNX2 did not show complete bone formation, and craniofacial dysplasia (CCD) was observed in knockout heterozygous.

The aim of our study was to check whether selected polymorphisms *NFκB1* rs4648068 (A>G) and *RUNX2* rs7771980 (-1025T>C) are more common in postmenopausal women and whether they may predispose to the development of osteoporosis.

MATERIAL AND METHODS

A group of 675 postmenopausal Caucasian women with Polish origin was examined. The patients were divided into three groups: 109 women with osteopenia (mean age 53.24 ± 0.74 years), 333 with osteoporosis (mean age 56.06 ± 0.75 years) and 233 control group with normal T-score (mean age 53.38 ± 1.01 years). During the interview, information was obtained on illnesses, medications taken, patient's age, reproduction age, number of pregnancies and birth weight, and age of first and last menstruation. Women with ovariectomy and taking medicines which might influence the bone metabolism (hormone therapy, selective modulators of estrogen receptors) as well as women with diseases affecting the density and loss of bone mass were excluded from the study.

Bone mineral density (BMD) measurements were performed at the Densitometry Laboratory, Clinical Hospital No. 1, Pomeranian Medical University in Szczecin, using a densitometric apparatus — LUNAR DPX 100 (Lunar Corp., Madison, USA). Each woman was examined in the lumbar spine from L2 to L4 using DEXA (Dual Energy X-ray Absorptiometry). The study determined BMD, T-score and Z-score parameters, as well as the average BMD YA and AM for young-adult and age-matched. Based on the value of the T-score, women were classified into the group with osteopenia (–2.5 < T-score < –1), osteoporosis (T-score < –2.5) and with the correct T-score – control group (T-score > –1). The study was approved by Local Bioethical Committee of Pomeranian Medical University in Szczecin.

The genetic analysis was performed at the Department of Stem Cell and Regenerative Medicine, Institute of Natural Fibers and Medicinal Plants, Poznan. Genomic DNA was isolated from the blood using a commercial QIAamp Blood Kit (Qiagen GmbH, Hilden, Germany) according to the protocol. The LightCycler FastStart DNA Master HybProbe (Roche Diagnostics) and LightCycler®96 instruments were used for *NFκB1* and *RUNX2* genotyping. Determination of the *NFκB1* rs464806 polymorphism and the *RUNX2* rs7771980 polymorphism was performed using LightSNiP *NFκB1* and *RUNX2* (TIBMolbiol, Germany). PCR was carried out according to the manufacturer's protocol.

Data analysis was performed using SPSS Statistics 17.0 using one-way ANOVA test. The value of $p < 0.05$ was considered as statistically significant.

RESULTS

The characteristics of clinical parameters of the study groups and the control group in postmenopausal women was showed in Table 1. The differences in the T-score and Z-score values between the groups (osteoporosis T-score: –3.16 ± 0.06, Z-score: –3.57 ± 1.95, osteopenia: T-score: 1.83 ± 0.04, Z-score: 0.84 ± 0.08, control group: T-score: 0.08 ± 0.11, Z-score: 0.64 ± 0.20) were observed. Studies have shown a correlation between the patients' BMI and individual groups (osteoporosis: 23.79 ± 0.32, osteope-

Table 1. Characteristics of the study population (postmenopausal women with osteopenia, osteoporosis and normal T-score)

		Mean ± SEM	95% CI	
			Min	Max
T-score	Osteopenia*	–1.83 ± 0.04	–1.91	–1.75
	Osteoporosis	–3.16 ± 0.06	–3.28	–3.05
	Controls	0.08 ± 0.11	–0.15	0.30
Z-score	Osteopenia	–0.84 ± 0.08	–1.01	–0.68
	Osteoporosis	–3.57 ± 1.95	–7.46	0.32
	Controls	0.64 ± 0.20	0.24	1.04
Body mass [kg]	Osteopenia*	65.17 ± 1.00	63.20	67.14
	Osteoporosis	61.21 ± 0.94	59.35	63.07
	Controls	68.73 ± 1.49	65.75	71.71
Height [cm]	Osteopenia*	162.63 ± 0.45	161.74	163.52
	Osteoporosis	160.25 ± 0.53	159.20	161.30
	Controls	163.08 ± 0.74	161.61	164.55
BMI [kg/m^2]	Osteopenia*	24.64 ± 0.36	23.94	25.35
	Osteoporosis	23.79 ± 0.32	23.16	24.42
	Controls	25.88 ± 0.56	24.77	26.99
Age [years]	Osteopenia*	53.24 ± 0.74	51.78	54.69
	Osteoporosis	56.06 ± 0.75	54.59	57.54
	Controls	53.38 ± 1.01	51.36	55.40
Birth weight [g]	Osteopenia*	3226.79 ± 77.68	3067.39	3386.18
	Osteoporosis	3141.25 ± 134.08	2855.47	3427.03
	Controls	3628.95 ± 110.29	3397.23	3860.66
Years of reproduction	Osteopenia	36.20 ± 0.64	34.93	37.47
	Osteoporosis	35.62 ± 0.62	34.37	36.86
	Controls	36.38 ± 0.95	34.45	38.30
Age of first menstruation	Osteopenia	13.12 ± 0.31	12.50	13.74
	Osteoporosis	12.94 ± 0.27	12.40	13.47
	Controls	13.38 ± 0.33	12.70	14.05
Age of last menstruation	Osteopenia	49.21 ± 0.50	48.22	50.20
	Osteoporosis	48.16 ± 0.55	47.07	49.25
	Controls	50.17 ± 0.69	48.79	51.56
Number of pregnancies	Osteopenia	1.89 ± 0.10	1.69	2.08
	Osteoporosis	1.96 ± 0.14	1.69	2.22
	Controls	1.94 ± 0.04	1.64	2.24
Years after menopause	Osteopenia*	7.18 ± 0.11	5.63	8.74
	Osteoporosis	10.63 ± 0.08	9.21	12.06
	Controls	7.03 ± 0.08	5.02	9.05
BMD L2-L4 [g/cm^2]	Osteopenia	0.97 ± 0.20	0.93	1.01
	Osteoporosis	0.98 ± 0.81	0.95	1.00
	Controls	0.97 ± 1.00	0.93	1.01
BMD L2-L4 YA [%]	Osteopenia	80.90 ± 1.49	77.49	84.32
	Osteoporosis	81.28 ± 0.66	78.82	83.74
	Controls	81.02 ± 0.45	77.46	84.59
BMD L2-L4 AM [%]	Osteopenia	89.13 ± 0.74	85.50	92.76
	Osteoporosis	89.50 ± 0.32	87.07	91.94
	Controls	89.78 ± 0.36	85.88	93.67

*$p < 0.05$ — comparison between the groups with osteopenia/osteoporosis and normal T-score (one-way ANOVA); BMI — body mass index; BMD — bone mineral density

nia: 24.64 ± 0.36 vs control group: 25.88 ± 0.56, p < 0.05). A similar relationship was observed for birth weight (osteoporosis: 3141.25 ± 134.08 g, osteopenia: 3226.78 ± 77.68 g vs control group: 3628.95 ± 110.29 g, p < 0.05). Other clinical parameters do not differ significantly between the study groups and the control group.

The genotype distribution of the *NFκB1* (rs4648068) and *RUNX2* (rs7771980) polymorphisms between the groups was analyzed (Tab. 2 and 3). For the *NFκB1* rs4648068 polymorphism, no significant differences were observed between the genotypes in the individual groups. The GG genotype was slightly more frequent in the study groups than in the control group (osteoporosis 11.40%, osteopenia 10.10% vs control group 8.20%, p > 0.05). In the case of rs7771980 polymorphism of the *RUNX2* gene in women with osteopenia, a higher frequency of TC heterozygotes was observed compared to the control group (29.40% vs 24.90%, p > 0.05), and in the group with osteoporosis the most common was the TT genotype (78.70% vs 73.80%, p > 0.05). There was no statistically significant difference between the distribution of genotypes of the studied polymorphism in the control and tested groups. No correlation was observed between genotype occurrence and osteoporosis development.

In addition, an analysis of the correlation between the *NFκB1* rs464806 and *RUNX2* rs7771980 polymorphisms with clinical parameters was performed (Tab. 4 and 5). The analysis did not show any statistical significance between the genotypic distribution and the individual clinical parameters analyzed. In the case of the *NFκB1* polymorphism, lower BMI values were observed for patients with the G allele in the genotype in both osteopenia and osteoporosis. Patients with the GG genotype had a higher birth weight compared to the other genetic variants tested. It has been shown that women with the G allele in the osteoporosis group have lower bone mineral density values. It is suggested that the G allele in the genotype is associ-

Table 2. The frequency of alleles and genotypes of *NFκB1* polymorphism (rs4648068) in the group of women with osteopenia, osteoporosis and in the control group

	Osteopenia		Osteoporosis		Control	
	Observed value n (%)	Expected value (%)	Observed value n (%)	Expected value (%)	Observed value n (%)	Expected value (%)
Genotype						
AA	46 (42.20)	43.70	145 (43.50)	43.70	106 (45.50)	47.20
AG	52 (47.70)	44.80	150 (45.00)	44.80	108 (46.40)	43.00
GG	11 (10.10)	11.50	38 (11.40)	11.50	19 (8.20)	9.80
Total	109 (100%)	100.00	333 (100%)	100.00	233 (100%)	100.00
Allele						
A	144 (66.10)	–	440 (66.10)	–	320 (68.70)	–
G	74 (33.90)	–	226 (33.90)	–	146 (31.30)	–
Total	218 (100.00)	–	666 (100.00)	–	466 (100.00)	–

Table 3. The frequency of alleles and genotypes of *RUNX2* polymorphism (rs7771980) in the group of women with osteopenia, osteoporosis and in the control group

	Osteopenia		Osteoporosis		Control	
	Observed value n (%)	Expected value (%)	Observed value n (%)	Expected value (%)	Observed value n (%)	Expected value (%)
Genotype						
TT	77 (70.60)	72.76	262 (78.70)	78.15	172 (73.80)	74.50
TC	32 (29.40)	25.08	65 (19.50)	20.51	58 (24.90)	23.60
CC	0	2.16	6 (1.80)	1.35	3 (1.30)	1.90
Total	109 (100%)	100.00	333 (100%)	100.00	233 (100%)	100.00
Allele						
T	186 (85.30)	–	589 (88.40)	–	402 (86.30)	–
C	32 (14.70)	–	77 (11.60)	–	64 (13.70)	–
Total	218 (100.00)	–	666 (100.00)	–	466 (100.00)	–

Table 4. Characteristics of the postmenopausal women with normal T-score, osteopenia and osteoporosis taking part in the study of the rs4648068 polymorphism of *NFκB1* gene

Genotype	Mean ± SEM	Mean ± SEM	Mean ± SEM
	AA	AG	GG
Controls			
T-score	–0.11 ± 0.13	0.13 ± 0.19	0.83 ± 0.55
Z-score	0.51 ± 0.28	0.65 ± 0.30	1.17 ± 0.76
Body mass [kg]	66.44 ± 2.46	69.83 ± 2.08	75.40 ± 5.33
BMI [kg/m^2]	25.34 ± 0.83	26.45 ± 0.86	27.33 ± 2.41
Birth weight [g]	3587.50 ± 255.26	3.715.00 ± 70.10	3510.00 ± 141.77
BMD L2–L4 [g/cm^2]	0.98 ± 0.03	0.96 ± 0.04	1.03 ± 0.04
BMD L2–L4 YA [%]	81.64 ± 2.86	80.15 ± 2.90	85.25 ± 2.95
BMD L2–L4 AM [%]	91.23 ± 2.97	89.30 ± 3.39	91.00 ± 2.04
Osteopenia			
T-score	–1.79 ± 0.06	–1.80 ± 0.06	–1.90 ± 0.14
Z-score	–0.86 ± 0.14	–0.81 ± 0.13	–0.92 ± 0.18
Body mass [kg]	66.71 ± 1.94	64.52 ± 1.42	64.36 ± 1.88
BMI [kg/m^2]	25.19 ± 0.71	24.27 ± 0.49	24.43 ± 0.63
Birth weight [g]	3290.00 ± 129.25	3148.57 ± 119.18	3342.50 ± 156.70
BMD L2–L4 [g/cm^2]	0.93 ± 0.04	0.99 ± 0.03	0.99 ± 0.04
BMD L2–L4 YA [%]	77.82 ± 3.45	82.51 ± 2.53	82.50 ± 3.01
BMD L2–L4 AM [%]	86.33 ± 3.62	89.85 ± 2.60	92.00 ± 3.95
Osteoporosis			
T-score	–3.13 ± 0.08	–3.20 ± 0.09	–3.39 ± 0.21
Z-score	–1.71 ± 0.15	–6.10 ± 4.52	–1.37 ± 0.21
Body mass [kg]	62.58 ± 1.43	60.45 ± 1.54	57.57 ± 2.72
BMI [kg/m^2]	24.11 ± 0.47	23.52 ± 0.54	23.52 ± 1.08
Birth weight [g]	3220.00 ± 298.50	3010.00 ± 53.63	3600.00 ± 600.00
BMD L2–L4 [g/cm^2]	1.02 ± 0.03	0.96 ± 0.02	0.92 ± 0.02
BMD L2–L4 YA [%]	84.80 ± 2.35	80.16 ± 1.80	76.33 ± 2.00
BMD L2–L4 AM [%]	93.14 ± 2.39	88.24 ± 1.69	85.87 ± 2.28

Data are mean ± SEM values. None of the parameters showed any significant difference among the genotypes; *p value < 0.05; SEM — standard error of the mean; BMI — body mass index; BMD — bone mineral density

ated with an increased risk of developing osteoporosis and may predispose to its development. For the *RUNX2* polymorphism, no correlation between genotype and clinical parameter was observed.

DISCUSSION

Osteoporosis is a multifactorial disease associated with low bone mass and increased risk of fractures. However, the genetic factors may play a large role in its development. Despite ongoing research, little is known about the genetic mechanisms that control bone growth and formation. To thoroughly understand the molecular mechanisms, polymorphic variants of genes candidate for osteoporosis are still being sought [10]. In our study, the association of *NFκB1* rs4648068 and *RUNX2* rs7771980 polymorphisms with osteoporosis was analyzed. Based on the frequency distribution of individual genotypes and alleles, an attempt was made to determine the genotype or allele predisposing to this disease.

Analyzing the *NFκB1* A>G polymorphism, a slightly more frequent occurrence of the GG genotype was observed in women with osteopenia and osteoporosis compared to control group with normal T-score (osteoporosis 11.40%, osteopenia 10.10% vs control group 8.20%). Patients with the G allele in the osteoporosis group showed lower bone mineral density values, suggesting that the G allele is associated with an increased risk of developing osteoporosis. So far, the impact of the rs4648068 *NFκB1* gene polymor-

Table 5. Characteristics of the postmenopausal women with normal T-score, osteopenia and osteoporosis taking part in the study of the rs7771980 polymorphism of *RUNX2* gene

Genotype	Mean ± SEM	Mean ± SEM	Mean ± SEM
	TT	TC	CC
Controls			
T-score	0.04 ± 0.14	0.26 ± 0.23	–0.95 ± 0.35
Z-score	0.46 ± 0.26	1.01 ± 0.29	–0.35 ± 0.12
Body mass [kg]	66.80 ± 1.52	74.00 ± 3.95	76.00 ± 3.86
BMI [kg/m^2]	25.27 ± 0.59	27.95 ± 1.40	30.33 ± 1.12
Birth weight [g]	3582.14 ± 98.52	3812.50 ± 430.30	3550.00 ± 325.5
BMD L2–L4 [g/cm^2]	0.97 ± 0.03	1.00 ± 0.05	0.79 ± 0.04
BMD L2–L4 YA [%]	80.82 ± 2.23	83.92 ± 3.44	66.50 ± 2.45
BMD L2–L4 AM [%]	90.70 ± 2.27	91.25 ± 4.44	69.40 ± 3.12
Osteopenia			
T-score	–1.81 ± 0.05	–1.80 ± 0.08	–
Z-score	–0.88 ± 0.09	–0.74 ± 0.21	–
Body mass [kg]	65.70 ± 1.31	64.75 ± 1.87	–
BMI [kg/m^2]	24.88 ± 0.47	24.18 ± 0.66	–
Birth weight [g]	3189.52 ± 75.98	3338.57 ± 219.35	–
BMD L2–L4 [g/cm^2]	0.96 ± 0.02	0.97 ± 0.06	–
BMD L2–L4 YA [%]	79.94 ± 1.67	81.88 ± 4.80	–
BMD L2–L4 AM [%]	88.13 ± 1.78	89.62 ± 4.95	–
Osteoporosis			
T-score	–3.19 ± 0.07	–3.15 ± 0.11	–2.84 ± 0.05
Z-score	–4.16 ± 2.53	–1.68 ± 0.16	–0.72 ± 0.21
Body mass [kg]	61.23 ± 1.16	61.39 ± 2.03	57.50 ± 2.45
BMI [kg/m^2]	23.85 ± 0.38	23.71 ± 0.74	22.26 ± 0.67
Birth weight [g]	3095.00 ± 148.70	3410.00 ± 384.30	3050.20 ± 285.40
BMD L2–L4 [g/cm^2]	0.97 ± 0.02	1.02 ± 0.04	0.98 ± 0.14
BMD L2–L4 YA [%]	80.53 ± 1.40	85.27 ± 3.44	81.67 ± 11.70
BMD L2–L4 AM [%]	89.11 ± 1.42	92.91 ± 3.38	91.00 ± 8.74

Data are mean ± SEM values. None of the parameters showed any significant difference among the genotypes; *p value < 0.05; SEM — standard error of the mean; BMI — body mass index; BMD — bone mineral density

phism in the Caucasian group on the development of osteoporosis has not been analyzed. The NFκB transcription factor and its effect on the skeletal system are still under investigation. It has been discovered that the deletion of the gene encoding NFκB in mice, more specifically the p50 (NFκB1) and p52 (NFκB2) subunits, is responsible for rare, hereditary osteopetrosis [11]. Therefore, our studies were undertaken to look for a new genetic marker that could differentiate patients with an increased predisposition to developing osteoporosis.

For the rs7771980 polymorphism of the *RUNX2* gene, the TC genotype was more frequent in the osteopenia group compared to the control group, and the TT genotype was more common in the osteoporosis group. No correlation was observed between the genotype and the clinical parameters, which would indicate a predisposition to the development of osteoporosis. Bustamante et al. studied the effects of -330 G>T polymorphism in promoter P1 and -1025 T>C polymorphism (rs7771980) in promoter P2 of *RUNX2* in 821 Spanish postmenopausal women. The analysis showed that the -330 G>T polymorphism was not associated with any of the phenotypes analyzed, and the -1025 T>C polymorphism was associated with bone mineral density in the femoral neck (FN BMD). Patients with TC genotype had higher mean corrected FN BMD values than patients with TT genotype. No relationship was found between the -1025 T>C polymorphism and bone mineral density in the lumbar spine (LS BMD). Due to the small size of the

group with the CC genotype, no association with FN BMD was observed [12]. Lee et al. analyzed two *RUNX2* polymorphisms: -1492 A>T and -1025 T>C among 729 Korean postmenopausal women. In this study, no significant relationship between the -1492 A>T polymorphism and BMD was found. The analysis showed a significant relationship between the CC genotype and the reduced bone mineral density in the lumbar spine and femoral neck compared to TC heterozygotes and TT homozygotes [13].

In another study, Pined's team investigated the effect of -1025 T>C polymorphism (rs7771980) of the *RUNX2* gene on the development of osteoporosis in 776 Spanish postmenopausal women. Like earlier researchers, they observed the relationship of polymorphism with BMD FN, but not with BMD LS. Women with the TC genotype had a higher BMD FN than women with the TT genotype. Unlike previous researchers, they found a relationship between CC genotype and higher BMD FN than women with TT genotype [14].

In addition, various researchers suggest that several other *RUNX2* gene polymorphisms are associated with the development of osteoporosis. Auerkari et al. [10] studied the variability of -330 G>T (rs59983488) polymorphism in 180 Indonesian postmenopausal women. It has been shown that the TT genotype is associated with an increased risk of developing osteoporosis. Vaughan's team studied -336G>A polymorphism of the *RUNX2* gene in 991 Scottish postmenopausal women. Their data suggest that *RUNX2* alleles are associated with BMD in a manner dependent on menopause and body mass [16].

CONSLUSIONS

In conclusion, based on the literature data, no definite conclusions can be drawn. The *NFκB1* gene rs4648068 polymorphism has not yet been studied in connection with the development of osteoporosis. Our studies have shown that the G allele in the genotype is associated with an increased risk of developing osteoporosis and may predispose to its development. Probably the *RUNX2* gene rs7771980 polymorphism predisposes to the development of osteoporosis, but our studies have not confirmed this fact. Additional studies are required to confirm these relationships. All progress in this field has great potential, because understanding the mechanisms leading to the development of osteoporosis could allow the creation of effective therapies and the introduction of appropriate drugs. Early diagnosis of the disease and the implementation of appropriate treatment adapted to the genotype of patients can slow down or completely prevent its further development.

Conflict of interest

None.

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The association between imbalances in vaginal microflora and duration of pregnancy as well as selected maternal and neonatal parameters

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ABSTRACT

Objectives: Abnormal vaginal flora (AVF) is a result of excessive growth of some aerobic bacteria and fungi in relation to the scarce presence of *Lactobacillus spp*. It has been suggested that AVF is responsible for preterm birth and such neonatal conditions as infections or sepsis.

The aim of the study was to assess the influence of excessive vaginal colonization with aerobic bacteria and fungi on the selected postnatal parameters of newborns, duration of pregnancy and length of hospitalisation of neonates.

Material and methods: Retrospective data of all 1057 patients who delivered between 01.2019 and 06.2019 in the Department of Perinatology of Medical University of Lodz was analyzed. Eight hundred nine patients were included in this retrospective study. The study group consisted of 396 patients with abundant growth of aerobic bacteria and fungi obtained between 26 and 42 weeks of gestation, while 413 patients with physiologic vaginal biocenosis constituted the control group. Two hundred forty-eight patients (23.46%) were excluded from the study due to incomplete data.

Results: Patients with abnormal vaginal flora (AVF) gave birth prematurely (9.09%) more often than patients with balanced microflora (5.31%), p = 0.038. Newborns of mothers with AVF obtained an Apgar score under four more frequently (1.21% vs 0%; p = 0.024). Eutrophic neonates were born less frequently in the study group (82.08% vs 88.65%; p = 0.025). Hospitalisation period was longer for children of mothers with AVF (mean of 6.30 ± 9.87 days) than those of mothers from the control group (mean of 5.06 ± 5.30), p = 0.025. Newborns of mothers with AVF developed perinatal infections more often (23.97% vs 15.94%; p = 0.004). Four infants died in the study group whereas no deaths were recorded in the control group (p = 0.045). The most prevalent pathogens were: *Streptococcus agalactiae* (GBS) 57.32%, *Candida spp.* 39.64%, *Klebsiella spp.* 9.85%, *Staphylococcus aureus* 7.32%. Signs of infection were more frequently recorded in newborns of mothers infected with *Klebsiella spp.* (35.90% vs 19.16%; p = 0.011). Premature birth was more prevalent in GBS carriers (11.81% vs 6.28%; p = 0.022).

Conclusions: Abundant growth of aerobic bacteria in the 3rd trimester of gestation contributes to preterm birth, causes the development of infection signs in newborns, increases their mortality rate and prolongs hospitalisation period.

Key words: vaginal microflora; aerobic vaginitis; PROM

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INTRODUCTION

The quantitative and qualitative composition of microorganisms in the vagina changes during a woman's life and depends on many factors such as, age, alterations in hormone levels (during the menstrual cycle, pregnancy, menopause), sexual intercourse and hygiene habits [1–3]. Due to the many improvements in modern microbiological diagnostics and findings of the Human Microbiome Project — a research initiative conducted by the National Institute of Health, our knowledge of the vaginal microflora has significantly increased [4]. Vaginal microbiota is dominated by *Lactobacillus spp. (L. crispatus, L. iners, L. jensenii and L. gasseri)*

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[5]. *Lactobacillus* species are responsible for the acidic pH of the vagina due to the production of lactic acid from glycogen stored in epithelial cells [2]. These symbiotic bacteria cover vaginal mucosa, preventing the adhesion and penetration of pathogens. Moreover, they produce hydrogen peroxide, bacteriocins and bacteriocin — like substances, which strengthen the mechanisms against invasion and colonization by opportunistic pathogens [1].

The pregnancy period is characterized by the exceptional stability of the vaginal microflora [5–7]. This balance is due to the increased estrogen levels, which provide an abundance of glycogen in epithelial cells, resulting in the proliferation of *Lactobacilli* [1, 5].

The most common anomalies associated with microbial imbalance in the vagina are bacterial vaginosis (BV), aerobic vaginitis (AV) and candidiasis. Bacterial vaginosis is a condition characterized by a rapid increase in the anaerobic bacteria population, at the expense of *Lactobacilli*. In this case, *Prevotella, Mobiluncus, Gardnerella vaginalis*, *Ureaplasma* and *Mycoplasma* are detected in vaginal smears. Traditionally we use Amsel's criteria in clinical settings [8, 9] however, Gram staining is the diagnostic standard [10]. Numerous studies confirm the impact of BV on the frequent occurrence of preterm premature rupture of membranes (PPROM), preterm birth [(PTB) delivery before 37 completed weeks of gestation] and low birth weight [(LBW) birth weight of less than 2500] [1, 11, 12].

Vaginal dysbiosis can also manifest as aerobic vaginitis (AV). In this case, reduction of the population of *Lactobacilli* and multiplying aerobic bacteria leads to inflammation [1]. The most common bacteria associated with AV and clinical features are presented in Table 1 [1, 13–15]. AV is associated with adverse obstetric outcomes including PPROM and PTB [16, 17]. Maternal colonization with GBS in pregnant women during delivery could be associated with neonatal pneumonia, meningitis and even severe sepsis [18, 19]. Candidiasis is a fungal infection caused by any type of *Candida*. Pregnancy increases the frequency of vaginal *Candida* colonization, which is favored by high glycogen concentration, resulting from the influence of hormones [20]. The number of studies assessing the relationship between candidiasis and obstetric complications is not sufficient, and the results of many studies are inconclusive [21]. The most convincing analyses confirm the relationship between candidiasis (even asymptomatic colonization) and higher incidence rate of PTB and LBW [22–24].

Considering that the aforementioned pathologies are often asymptomatic, oligosymptomatic or symptoms may imitate physiological changes during pregnancy, and the fact that they have a significant impact on specific obstetric complications, it is important to actively screen for vaginal microflora disorders in pregnant women. Considering the importance of the balance in vaginal microflora during pregnancy we decided to perform a retrospective study to assess the influence of vaginal colonization with pathogenic bacteria and fungi on the adverse perinatal outcomes in mothers and newborns.

Objectives

The aim of the study was to assess the influence of excessive vaginal colonization with aerobic bacteria and fungi on the selected parameters of newborns, duration of pregnancy and length of hospitalisation of neonates.

Table 1. Characteristics of vaginal microflora disorders

	Bacterial vaginosis	Aerobic vaginitis	Candidiasis
Etiology	*Prevotella, Mobiluncus, Gardnerella vaginalis, Ureaplasma, Mycoplasma*	*Escherichia coli, Enterococcus faecalis, Staphylococcus aureus, Staphylococcus epidermidis, group B Streptococcus*	*Candida albicans*, rarely other *Candida* species
Vaginal discharge	thin, homogenous, mostly white or gray	yellowish and sticky	thick or cheesy white
Odor	fishy smell, especially when reacting with KOH	devoid of fishy smell	no odor
pH	> 4.5	> 6	< 4.5
Features of inflammation	often absent, no inflammation	present, often severe	present, mostly vulvar erythema and oedema
Influence on obstetric complications	PPROM, LBW, PTB	PPROM, PTB	LBW, PTB (inconclusive data)
Risk factors	low socioeconomic status, vaginal douching, smoking, multiple sex partners, unprotected intercourse	unmarried status, long-term use of antibiotics, frequent vaginal douching	recent antibiotic use, diabetes mellitus, AIDS, corticosteroid use, immunosuppression

KOH — potassium hydroxide; AIDS — acquired immune deficiency syndrome; PPROM — preterm premature rupture of membranes; LBW — low birth weight; PTB — preterm birth

MATERIAL AND METHODS

Out of 1057 patients who gave birth in the Pirogow Clinical Hospital in Lodz between January and June 2019, there were 809 patients included in this retrospective study. Those patients had their vaginal flora sampled upon hospital admission for delivery. In the given timeline patients gave birth between 26 and 42 weeks of gestation. Swabs were taken from the posterior vaginal wall. Next, smears and bacterial staining were performed, followed by microscopic evaluation. The microscopic evaluation consisted of assessing the *Lactobacillus* count, presence of other bacteria and fungi and leukocyte count. Based on the results, patients were divided into two groups. Patients whose smears did not reveal any abnormalities in bacterial or fungal growth and had high *Lactobacillus* count constituted the control group — 413 patients. The study group consisted of 396 patients whose smears revealed abnormalities (low *Lactobacillus* count, abundant growth of other bacteria and fungi), which will be referred to in the article as abnormal vaginal flora (AVF). The abnormal result was considered an indication to obtain bacterial or fungal cultures. Depending on the species, microorganisms were cultivated between 18–96 hours. The isolated bacteria and fungi were assessed for antimicrobial drug sensitivity using a disk diffusion test. The results were uploaded to an online database. All the patients in the study group and the control group were also tested for GBS presence through rectal and vaginal swabbing. Patients who were not tested for GBS, regardless of their flora composition were excluded from the study as well as patients tested for GBS but not tested for other abundant bacterial or fungal growth — 248 patients (23.46%).

Baseline characteristics and past medical and obstetric history of subjects — age, parity, gravity as well as data concerning the pregnancy in question: way of delivery (C-section/natural birth/forceps or vacuum), gestational age during delivery and the occurrence of PROM were taken. In addition, characteristics of neonates born to mothers enrolled in the study were obtained in order to assess neonatal well-being and post-delivery condition. The characteristics were: neonatal birth weight, Apgar score after the 1st, 3rd, 5th 10th minute after birth, signs of infection in the neonates, signs of respiratory distress, hypotonia, positive bacterial blood culture and the length of post-delivery hospitalisation of the neonates. The following criteria were used as to indicate signs of infection in neonates based on Chan et al. [25], elevated C-reactive protein (CRP) — over 10mg/L and white blood count (WBC) — over 30 000/μL, fever, positive bacterial or fungal blood culture. Respiratory distress was defined using the criteria by Liu et al. and Sochocka et al.: labored breathing (retractions of intercostal muscles, nasal flaring), crackles on auscultation, pulmonary oedema, the necessity to use mechanical ventilatory support, typical x-ray chest findings (diffuse alveolar opacification), metabolic and mixed acidosis or hypoxia/hypercapnia in blood tests [26, 27].

Microsoft Excel 365 (Microsoft, Redmond, Washington, United States of America) and STATISTICA 13.3. (TIBCO Software, Palo Alto, California, United States of America) software were used for statistical analysis. Descriptive data was presented as numbers, percentages, and means with standard deviations. The statistical significance of the association between events was determined with the use of Chi^2 Pearson test. In addition, due to the large study group and the assumed normal distribution of variables, statistical differences in numerical variables were determined using parametric tests, namely the student's T test. P-values were represented to three decimal numbers and 0.05 was used as a cutoff for significance.

RESULTS

Out of the 1057 patients delivered in our hospital between January 2019 and June 2019, a total of 827 underwent vaginal discharge sampling upon hospital admission for delivery (between 26 and 42 weeks of gestation). AVF was observed in the case of 396 patients while 413 had physiological composition of vaginal flora (abundance of *Lactobacillus spp.*, scarce or no other bacterial species, absence of no leukocytes and fungi).

The maternal characteristics are presented in Table 2. There was no significant difference in maternal age, gravity and parity between groups. There was however, statistically significant difference in gestational age between both groups (38.63 vs 38.95 gestational weeks).

Table 2. Basic characteristics of pregnant women

Variable	Study group (n = 396)	Control group (n = 413)	p value
Maternal age [years]	31.32 ± 5.23	31.74 ± 4.59	0.234
Gestational age [weeks]	38.63 ± 2.08	38.95 ± 1.58	0.012
Gravity [median]	2 ± 0.92	2 ± 0.94	0.243
Parity [median]	1 ± 0.82	1 ± 0.69	0.053

Table 3. Delivery data analysis

Variable	Study group	Control group	p value
Preterm birth (< 37 weeks)	9.09%	5.31%	0.038
Vaginal delivery	46.97%	49.15%	0.534
Cesarean section	50.76%	48.18%	0.464
Forceps/vacuum delivery	2.27%	2.66%	0.721
PROM	30.30%	27.12%	0.317

PROM — premature rupture of membranes

Table 4. Neonatal parameters

Variable	Study group	Control group	p-value
Apgar < 8	5.57%	2.9%	0.056
Apgar < 4	1.21%	0%	0.024
Hypotrophy	10.17%	7.08%	0.104
Eutrophy	82.08%	88.65%	0.025
Hypertrophy	7.75%	4.35%	0.057
Signs of infection	23.97%	15.94%	0.004
Respiratory distress	9.44%	7.97%	0.453
Hypotonia	2.18%	2.42%	0.820
Length of post-delivery hospitalisation [days]	6.30 (± 9.87)	5.06 (± 5.30)	0.025
Positive bacterial blood culture (if taken)	11.11% (n = 45)	10.00% (n = 18)	0.018
Neonatal deaths	n = 4	n = 0	0.045

Delivery data analysis is presented in Table 3. Premature birth (26 + 0–36 + 6 weeks of gestation) occurred significantly more often in the study group (9.09% vs 5.31%; p = 0.038).

Neonatal parameters are presented in Table 4. When compared, an Apgar score < 4 signifying bad condition was recorded only in infants of mothers from the study group (1.21% vs 0%; p = 0.02210).

Neonatal assessment also included birth weight analysis which is presented in Table 4. Hypotrophy was more prevalent in the study group (10.17% vs 7.08%), but the difference was not statistically significant (p = 0.104). On the other hand, eutrophy was observed less often in the study group (82.08% vs 88.65%; p = 0.025). Hypertrophy occurred more often in the study group; however, the difference was insignificant (7.75% vs 4.35%; p = 0.057).

Figure 1 represents the prevalence of infection signs among neonates. As shown on the graph, infants born to mothers from the study group developed infections statistically more often than infants born to mothers from the control group (23.97% vs 15.94%; p = 0.004).

There was no significant difference in the development of respiratory distress or hypotonia among infants of both groups.

Regarding perinatal mortality, it was significantly more frequent in the study group — four children of mothers with AVF died, while no deaths were recorded in the control group (p = 0.045). Due to severe post-delivery conditions, two children of mothers from the study group were admitted to the Intensive Care Unit, whereas there was no such necessity for children of mothers from the control group.

Among children of patients with abnormal microflora the average length of hospital stay was 6.30 (± 9.87) days while for children of patients whose microflora did not show any abnormalities, the length was calculated as 5.06 (± 5.30), (p = 0.025).

As for microbiological results, 15 bacteria and fungi species were cultivated from the smears and are presented in Table 5. The most common abundant pathogen growth cultivated from the samples was GBS — 57.32%, followed by *Candida spp.* — 39.64% and *Klebsiella spp.* — 9.85%, two or more pathogens were cultivated from the samples of 104 patients (26.26%).

In the aim of assessing whether any specific type of microbial growth affected neonatal well-being we analyzed such parameters as: signs of infection in newborns, preterm

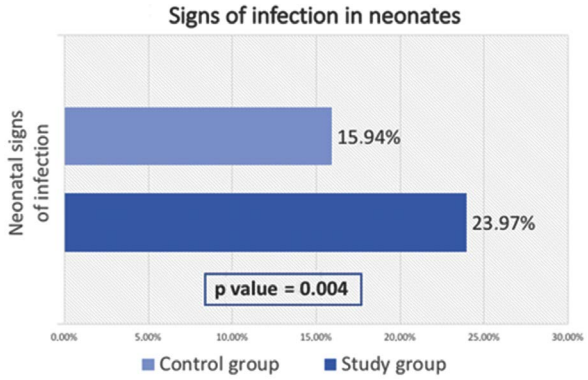

Figure 1. Prevalence of infection signs among neonates

Table 5. Results of cultures in the study group

Pathogen	Presence in % in genital tract in the 3rd trimester
Streptococcus agalactiae (GBS)	57.32%
Candida spp.	39.64%
Klebsiella spp.	9.85%
Staphylococcus aureus	7.32%
Proteus spp.	2.78%
Enterococcus spp.	2.27%
Escherichia coli spp.	2.02%
Pseudomonas spp.	1.52%
Morganella spp.	1.52%
Saccharomyces	1.52%
Citrobacter	1.26%
Enterobacter	1.26%
Serratia	< 1%
Streptococcus group C	< 1%
Leclercia adecarboxylata	< 1%

GBS — *Streptococcus agalactiae*

delivery rate, respiratory distress and reduced Apgar score and calculated correlations between the above mentioned and the prevalence of certain species in the genital tract. Our results are presented in Table 6, 7 and 8.

Signs of infection in newborns: elevated CRP — over 10 mg/L and WBC — over 30 000/μL, fever, positive bacterial or fungal blood culture [25].

The influence of specific bacterial and fungal strains on the occurrence of preterm birth is presented in Table 7. The results showed that the incidence of preterm birth (26 + 0–36 + 6 weeks) was higher among patients infected with GBS than those not infected (p = 0.022).

The results shown in Table 8. indicate that the presence of *Klebsiella spp.* in the genital tract is associated with a higher incidence of postnatal respiratory distress in newborns (p = 0.036).

Table 6. Incidence of signs of infection in newborns according to the type of cultivated vaginal microflora

Pathogen type	Signs of infection in newborn	p value
Klebsiella spp.		
present	35.90%	0.011
absent	19.16%	
GBS		
present	22.78%	0.196
absent	18.81%	
S. aureus		
present	20.69%	0.919
absent	19.92%	
Candida spp.		
present	22.21%	0.651
absent	19.64%	

GBS — *Streptococcus agalactiae*

Table 7. Incidence of preterm delivery (26 + 0–36 + 6 weeks) according to the type of vaginal microflora cultivated from the smears

Pathogen type	Preterm delivery	p value
Klebsiella spp.		
present	12.82%	0.253
absent	7.62%	
GBS		
present	11.81%	0.022
absent	6.28%	
S. aureus		
present	6.90%	0.823
absent	7.90%	
Candida spp.		
present	7.27%	0.486
absent	8.00%	

GBS — *Streptococcus agalactiae*

Table 8. Incidence of respiratory distress signs in newborns according to the type of cultivated microflora

Pathogen type	Respiratory distress signs in newborn	p value
Klebsiella spp.		
present	18.00%	0.036
absent	8.26%	
GBS		
present	9.70%	0.519
absent	8.32%	
S. aureus		
present	6.90%	0.725
absent	8.78%	
Candida spp.		
present	7.88%	0.674
absent	8.93%	

GBS — *Streptococcus agalactiae*

There was no relationship between an Apgar score below 8 and presence of specific bacteria or fungi cultures in the mother's genital tract.

DISCUSSION

The balance in the vaginal microflora is essential for maintaining a healthy vaginal environment and preventing colonization with opportunistic pathogens. Insufficient *Lactobacilli* growth enables bacteria and fungi to thrive and grow abundantly which may cause signs of infection in pregnant females, result in perinatal complications and have consequences on the well-being of their newborns [16, 28]. AV is a newly established condition characterized by the imbalance in the microflora accompanied by an increased inflammatory reaction and followed by a consequential immune response [28]. In addition, the imbalances in the microflora facilitate the invasion and growth of fungi such as *Candida* [15].

Our results showed that patients with abnormal bacterial or fungal growth delivered prematurely more often than those not infected. However, our study included patients who gave birth between 26 and 42 weeks of gestation as this was the specificity of patients admitted to the department in the given timeline. Thus, we only proved a connection between AVF and preterm birth between 26 + 0 and 36 + 6 weeks of gestation. According to literature [29], GBS is significantly associated with preterm birth which was also confirmed in our study. Interestingly, there was no statistical correlation between PTB and *Klebsiella spp.*, *S. aureus* or *Candida spp.* infection. It is well known that the occurrence of PTB is a result of multiple factors, but they were not considered in this study as our prime focus was the influence of vaginal flora.

Many studies confirm that abnormal vaginal flora is associated with deterioration of newborn's condition and need for intensive care for neonates [28]. In our study we confirmed that it is also connected to reduced Apgar score. Abnormal vaginal flora may contribute to the development of signs of infection in the newborns [30]. In our study infants born to mothers with disturbed balance in vaginal microbiota developed infections statistically more often than infants born to mothers without abnormalities.

Special attention should be paid to abundant growth of *Klebsiella spp*. Many sources indicate that *Klebsiella spp.* has a considerable impact on the occurrence of neonatal infections. According to Omwandho et al. [31], this strain of bacteria accounted for over 50% of bacterial infections among neonates and was responsible for 70% of neonatal deaths. Our study recorded a higher incidence of neonatal infections among newborns of mothers infected or colonized with *Klebsiella* as well as a connection between the infection with this pathogen and signs of respiratory distress in newborns.

Due to the recognized impact of GBS on the pregnancy outcomes, screening for GBS is recommended during the last trimester of pregnancy, generally between 35 and 37 weeks of gestation [32]. In addition, antibiotic prophylaxis should be administered to GBS colonized women perinatally [32]. Although there is an evidence of the harmful impact of *Klebsiella* on neonatal well-being, there are no similar recommendations and procedures for patients infected with this bacterium [33]. The prevalence of abnormalities in vaginal microbiota correlated with longer post-delivery hospitalisation. Prolonged hospitalisation of infants, especially those born in bad condition generates higher costs [34]. Regarding the prevention of AV and associated bacterial and fungal colonization, Nv Geneg et al., emphasize that consistent condom uses and college-level education is a protective factor for AV. Unmarried status, menarche at 13–15 years, Intrauterine device (IUD) use, long-term use of antibiotics, use of panty liners and frequent vaginal douching are listed as risk factors [35].

Our study has some limitations. First, the retrospective nature of the study did not allow us to assess the clinical symptoms of vaginitis in patients. Secondly, we were not able to assess the immunological and biochemical characteristics of patients' vaginal discharge which is why the diagnosis of AV could be argued. Our study was conducted in a gynecologic hospital in a big city which does not reflect the general Polish population. Multicenter studies are therefore needed for comparison. As strengths of our study, we consider the big number of patients in the study group — all patients hospitalized after their 30th week of pregnancy in our department in the chosen timeline were included in the analysis.

CONCLUSIONS

We proved a connection between abundant growth of aerobic bacteria in the 3rd trimester of gestation and preterm birth, the development of infection signs in newborns, an increase in their mortality and extension of hospitalisation period. Preventive measures such as screening tests should be carried out regularly and efficient follow-up should be implemented. Those measures should be taken into consideration particularly in the case of *Klebsiella spp.* growth as it was proven to contribute to the development of signs of infection and respiratory distress in newborns.

Author contributions

Conceptualization, M.S., M.W., J.Z., and O.O.; Methodology, M.S., M.W., J.Z, M.Z.; Formal Analysis, M.S., M.W., J.Z., M.Z.; Investigation, M.S., M.W., J.Z and O.O.; Resources, M.S., J.K., J.W.; Data Curation, M.S., O.O; Writing – Original Draft Preparation, M.W, J.Z., O.O., M.Z.; Writing – Review & Editing, M.S. and J.W.; Supervision, J.K., J.W.; All authors have read and agreed to the published version of the manuscript.

Conflict of interest

The authors declare that they have no conflict of interest.

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ORIGINAL PAPER / OBSTETRICS

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Maternal serum IL-22 concentrations are significantly upregulated in patients with preterm premature rupture of membranes

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ABSTRACT

Objectives: This study aimed to compare the serum IL-22 levels between preterm premature rupture of membranes (PPROM) patients and the control group with intact membranes. We also hypothesized whether serum IL-22 upregulation might contribute to defense against inflammatory responses and improve the pregnancy outcomes.

Material and methods: We performed this prospective case-control study between 24–34 weeks of pregnancy. We enrolled 40 singleton pregnant patients with PPROM and 40 healthy gestational age- and gravidity-matched patients without PPROM. The degree of association between variables and IL-22 were calculated by Spearman correlation coefficients where appropriate. Scatter plots were given for statistically significant correlations. ROC curve was constructed to illustrate the sensitivity and specificity performance characteristics of IL-22, and a cutoff value was estimated by using the index of Youden.

Results: Maternal serum IL-22 levels were significantly higher in PPROM patients (60.34 ± 139.81 pg/mL) compared to the participants in the control group (20.71 ± 4.36 pg/mL, $p < 0.001$). When we analyze the area under the ROC curve (AUC), the IL-22 value can be considered a statistically significant parameter for diagnosing PPROM. According to the Youden index, a 23.86 pg/mL cut-off value of IL-22 can be used to diagnosing PPROM with 72% sensitivity and 61.5% specificity. There was no positive correlation between serum IL-22 levels and maternal C-reactive protein (CRP) value, procalcitonin value, latency period, birth week, birth weight, and umbilical cord blood pH value.

Conclusions: Maternal serum IL-22 levels were significantly higher in PPROM patients than healthy pregnant women with an intact membrane. We suggest that IL-22 might be a crucial biomarker of the inflammatory process in PPROM.

Key words: preterm premature rupture of membranes; interleukin-22; neonatal outcomes

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INTRODUCTION

Preterm premature rupture of membranes (PPROM) is described as rupture of the amniotic membranes before 37 weeks of gestation [1]. This common obstetrical syndrome complicates approximately 3–4% of all pregnancies and is the identifiable leading cause of preterm birth, with about 40% of preterm deliveries being associated with PPROM [2]. PPROM is related to short-latency from membrane rupture to labor, infectious complications, and adverse neonatal outcomes associated with preterm birth [3]. These adverse outcomes include neonatal mortality and long-term complications of surviving neonates. Preterm labor is the single direct cause in 35% of neonatal deaths. Surviving neonates often experience long-term consequences, including numerous physical effects (cardiovascular disease, chronic lung disease, hearing or visual impairment), behavioral deficiencies, and neurodevelopmental delay [4]. These complications represent a substantial burden for the family, healthcare system, and society [5].

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Also, neonatal morbidity and mortality rates are higher in PPROM patients than the other subgroups of preterm deliveries [6]. Therefore, it is crucial to determine the mechanisms implicated in PPROM and develop innovative treatments and strategies to prevent or manage this syndrome.

During a healthy pregnancy, the maternal immune system must prosecute in a delicate balancing act as maintaining tolerance to the fetal allograft while preserving adaptive and innate immune mechanisms for protection against microbial infections [7, 8]. Infection and inflammation are implicated in the pathogenesis of PPROM. An imbalance in the production of anti-inflammatory and pro-inflammatory cytokines may activate different humoral and cellular immunologic components, amplifying the membrane weakening and damage. PPROM is considered a disease of the fetal membranes. The inflammation-oxidative stress axis acts a significant role in producing pathways that can cause membrane weakening by several processes, including the activation of matrix-degrading proteases that lyse the collagens and increasing the production of cytokines and prostaglandins [9]. Histological chorioamnionitis (HCA) being reported in about 40–70% of PPROM patients [10]. Immediate and correct HCA diagnosis is essential; however, the event restricts that placental pathology can only be assessed after delivery [11]. The inflammatory response can also be shown in the amniotic fluid and maternal and fetal serum. Previous studies reported that HCA is associated with increased maternal and fetal serum levels of pro-inflammatory cytokines, including interleukin-1 beta (IL-1β), IL-2, IL-6, IL-8, IL-22, and tumor necrosis factor-alpha (TNF-α) [12].

IL-22 is a clinically relevant cytokine, mostly secreted by immune cells, including innate lymphoid cells (ILC), natural killer cells, T-helper 1 (Th1) cells, Th17 cells, Th22 cells, and lymphoid tissue inducer cells [13]. IL-22 is capable of mediating both pro-inflammatory and anti-inflammatory responses, promotes epithelial cell proliferation and survival of epithelial cells, wound repair, and induces the secretion of antimicrobial proteins [14]. However, it remains unclear if IL-22 upregulation might be associated with the pathological processes of the PPROM or it performs a different function. In a recent study, the authors suggested that IL-22 prevents preterm birth and promotes epithelial cell regeneration [15].

In this study, we aimed to compare the serum IL-22 levels between PPROM patients and the control group with intact membranes. We also hypothesized whether serum IL-22 upregulation might contribute to defense against inflammatory responses and improve pregnancy outcomes.

MATERIAL AND METHODS

We performed this prospective case-control study in Kanuni Sultan Süleyman Training and Research Hospital Hospital from July 2019 to January 2020. This study was approved by the Ethics Committee of the same hospital. Informed consent forms were obtained from all participants. All the pregnant women were between the age of 18–40 years and $24^{0/7}$–$34^{0/7}$ weeks of gestation. Of the 80 pregnant women included in the study, we enrolled 40 singleton pregnant patients with PPROM as the study group and 40 healthy gestational age-, gravidity-, and body mass index (BMI)-matched patients without PPROM as the control group. The control group consisted of patients who did not experience any complications associated with pregnancy in the later gestational weeks and had given birth at term.

Patients admitted to our hospital with the complaint or suspicion of PPROM were assessed in the emergency department according to the ACOG criteria [16]. We diagnosed PPROM by using a sterile speculum to evaluate the amniotic fluid leakage from the cervix uteri and then examined utilizing Amnisure®, a rapid test based on the Placental Alpha Microglobulin-1 (PAMG-1) detection in high concentrations in amniotic fluid [17]. The gestational week was determined by sonographic measurement and confirmed according to the last menstrual period and a first-trimester ultrasound exam. Patients with a confirmed PPROM diagnosis were hospitalized and referred to our obstetric department for further evaluation and proper treatment. We collected the blood samples to measure IL-22 levels at the time of the hospitalization. We also took maternal blood samples to analyze complete blood count (CBC) every 72 hours, evaluating clinical chorioamnionitis every eight hours after hospitalization and during the latency period [11]. All pregnant women with PPROM underwent ampicillin treatment daily to prevent chorioamnionitis and four doses of 6 mg of betamethasone for fetal lung maturation. We used Nifedipine to delay the preterm birth during the first 48 hours in all patients.

The pregnancy termination was performed at the end of the 34^{th} gestational weeks or early signs of clinical chorioamnionitis. Clinical chorioamnionitis was diagnosed with the following signs: fever (≥ 38°C orally), maternal tachycardia (> 100 beats/minute), fetal tachycardia (> 160 beats/minute), leukocytosis, purulent vaginal discharge, uterine tenderness, and abdominal pain [18]. We performed labor induction by cervical ripening with a vaginal prostaglandin E2 slow-release system [19]. Indication for cesarean section for non-reassuring fetal status was based on abnormal fetal heart rate monitoring [20].

We excluded patients with gestational hypertensive disorders, hepatic disease, multiple pregnancies, anemia, infections, a history of ruptured amniotic membranes in their previous pregnancies, and co-existing morbidities, including diabetes mellitus, hypothyroidism, chronic hypertension, collagen vascular disease, renal disease, known malignancy, and ischemic heart disease. Patients with unavailable or incomplete medical records were also excluded.

Maternal age, gravidity, parity, BMI, previous history of cesarean section, maternal serum hemoglobin value, white blood cell count (WBC), platelet value, mean corpuscular volume (MCV), red cell distribution width (RDW), C-reactive protein (CRP) value, procalcitonin value, IL-22 value, latency from membrane rupture to labor, and type of delivery (vaginal or cesarean) were recorded. The birth week, birth weight, umbilical cord blood pH, 1- and 5-minute Apgar scores of the newborn were also recorded.

Serum IL-22 concentration was measured using an enzyme immunoassay (Catalog Number: EK0933, Boster Biological Technology 3942 Valley Ave Pleasanton, CA 94566, USA) with a minimum detectable concentration of 15.6 pg/mL and intra- and inter-assay coefficients of variation less than 5.1% and 6.3%, respectively. Absorbance at 450 nm was measured using an SMR 16.1 Smart Microplate Reader (USCN KIT INC.).

Statistical evaluation

We used the Kolmogorov-Smirnov and Shapiro Wilk tests to examine whether the data are normally distributed. We tested the homogeneities of variances by the Levene test. The Chi-square and/or Fisher's exact tests for categorical variables and Student's t-test or Mann-Whitney U test for continuous variables were used to evaluating differences between groups. The degree of association between variables and IL-22 were calculated by Spearman correlation coefficients where appropriate. Scatter plots were given for statistically significant correlations. Receiver operating characteristic (ROC) curve was constructed to illustrate the sensitivity and specificity performance characteristics of IL-22, and a cutoff value was estimated by using the index of Youden. Frequencies (percentages), mean±standard deviation, and median (minimum-maximum) were given as descriptive statistics. We performed statistical analyses using IBM SPSS 20.0 for Windows (SPSS Inc., Chicago, IL, USA), and the p-value < 0.05 was considered statistically significant.

RESULTS

During the study period, 89 patients were enrolled in the study, of which 45 were PPROM patients. After withholding patients with missing medical records and applying the exclusion criteria, 40 patients remained in both groups.

We presented the demographic variables, clinical characteristics, and the perinatal outcomes of the patients in Table 1. There were no significant differences between the two groups in terms of maternal age, gravidity, parity, BMI, history of a previous cesarean section, and delivery type.

Maternal serum IL-22 concentrations were significantly higher in patients with PPROM (60.34 ± 139.81 pg/mL)

Table 1. Comparison of demographic variables, clinical characteristics, and perinatal outcomes between control group and preterm premature rupture of membranes group

	Control group	PPROM group	p value
Age [years]	28.17 ± 5.27	27.69 ± 5.93	0.702
Gravidity	2.92 ± 1.32	2.82 ± 1.68	0.483
Parity	1.56 ± 1.18	1.28 ± 1.39	0.143
BMI [kg/m^2]	27.51 ± 3.79	27.51 ± 4.86	0.997
Previous cesarean section, n (%)	19 (47.5)	14 (35.0)	0.252
IL-22 [pg/mL]	20.71 ± 4.36	60.34 ± 139.81	< 0.001
CRP [mg/L]	9.24 ± 0.49	11.30 ± 12.40	0.116
Procalcitonin [ng/mL]	0.03 ± 0.00	0.04 ± 0.02	< 0.001
WBC [/mm^3 × 10^3]	11.21 ± 3.28	12.48 ± 3.71	0.653
Hemoglobin [g/dL]	11.48 ± 0.55	11.89 ± 1.33	0.116
Platelet [/mm^3 ×10^3]	191.82 ± 6.62	272.07 ± 77.08	< 0.001
MCV [fL]	87.61 ± 1.06	84.12 ± 6.53	< 0.001
RDW [%]	13.46 ± 0.48	13.51 ± 2.08	0.289
Latency period [days]	N/A	19.05 ± 18.00	N/A
Cesarean birth, n (%)	22 (55.0%)	26 (65.0%)	0.352
Birth week	39.15 ± 0.77	29.92 ± 4.11	< 0.001
Birth weight [g]	3662.56 ± 176.24	1746.53 ± 596.71	< 0.001
Umbilical cord blood pH value	7.34 ± 0.04	7.30 ± 0.08	0.007
1-min Apgar	7.66 ± 0.66	4.74 ± 2.42	< 0.001
5-min Apgar	9.41 ± 0.49	7.10 ± 2.45	< 0.001

PPROM — preterm premature rupture of membranes; BMI — body mass index; CRP — C-reactive protein; WBC — white blood cell count; MCV — mean corpuscular volume; RDW — red cell distribution width; N/A — not available

compared to the participants in the control group (20.71 ± 4.36 pg/mL, p < 0.001). When we analyze the area under the ROC curve (AUC), the IL-22 value can be considered a statistically significant parameter for diagnosing PPROM (Tab. 2, Fig. 1). According to the Youden index, a 23.86 pg/mL cut-off value of IL-22 can be used to diagnose PPROM with 72% sensitivity and 61.5% specificity.

There was no positive correlation between serum IL-22 levels and maternal CRP value, procalcitonin value, latency period, birth week, birth weight, and umbilical cord blood pH value (Tab. 3).

DISCUSSION

In the current study, we evaluated the concentrations of IL-22 in the maternal serum of the patients in association with the presence or absence of PPROM. Our study indicates that IL-22 demonstrated significantly increased levels in the serum of patients suffering from PPROM than control patients with intact membranes. However, we found no significant correlation between the upregulation of maternal serum IL-22 levels and pregnancy outcomes.

Inflammation and oxidative stress are keenly associated with the pathogenesis of PPROM. These events are inducted in response to etiological factors with histochemical and biochemical results that may weaken the fetal membranes [9]. The immune mechanisms that play a role in these events may be local or systemic, namely, systemic involvement of immune factors located in circulating blood or local involvement of elements in the fetomaternal unit's layers [4, 21–23]. The amniotic fluid includes inflammatory cytokines and molecules that can be utilized as biochemical markers to predict PPROM, including IL-1, IL-6, IL-22, and TNF-α [4]. However, amniocentesis is an invasive method with concomitant jeopardies. Also, oligohydramnios due to membrane rupture frequently makes this procedure challenging to obtain the amniotic fluid [11]. Therefore, a less invasive and more straightforward procedure of examining these cytokines in maternal serum would be beneficial for the prediction of PPROM. Since PPROM is described as the disease of the fetal membranes, several placental factors and pro-inflammatory cytokines have been implicated in the PPROM pathogenesis. However, few studies investigate the role of maternal serum inflammatory markers for predicting PPROM in the literature. This prediction model is essential for the obstetric units that are not well-resourced in which there is no chance to perform invasive methods for investigating these markers in the amniotic fluid.

IL-22, an IL-10 family member, is a glycoprotein and secreted by cells of the innate and adaptive immune system [24]. The primary biological characteristics of IL-22 are pro-regenerative and anti-apoptotic properties [25].

Table 2. The area under the curve of the IL-22

	ROC	St. error	95% Confidence Interval		p
			Lower	Upper	
IL-22	0.698	0.062	0.577	0.819	< 0.001

ROC — Receiver operating characteristic

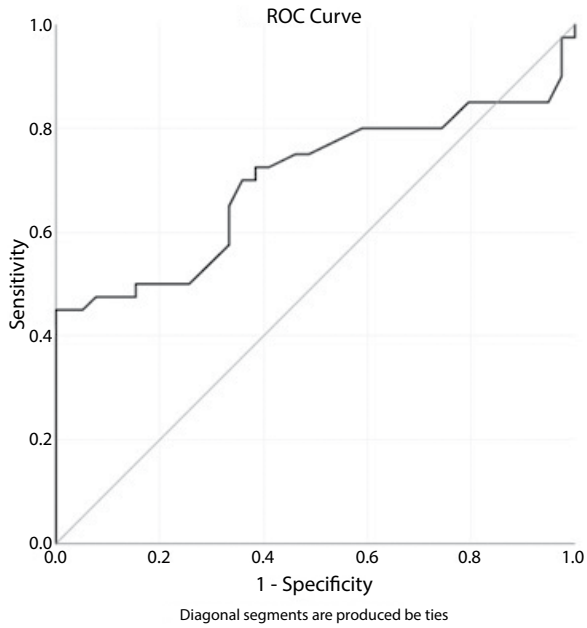

Figure 1. Receiver operating characteristic (ROC) curve for serum IL-22 concentrations in patients with preterm premature rupture of membranes

Table 3. Correlations between IL-22 value and other parameters

		IL-22		
		Control (n = 39)	PPROM (n = 39)	All (n = 78)
CRP [mg/L]	r	0.008	–0.016	0.023
	p	0.969	0.921	0.845
Procalsitonin [ng/mL]	r	0.021	0.266	0.158
	p	0.897	0.102	0.167
Latency period [days]	r	N/A	–0.015	–0.015
	p	N/A	0.926	0.926
Birth week	r	–0.116	–0.207	–0.129
	p	0.482	0.205	0.261
Birth weight	r	–0.067	–0.186	–0.107
	p	0.684	0.257	0.352
Umbilical cord blood pH value	r	–0.062	–0.303	–0.212
	p	0.708	0.061	0.062
1-min Apgar	r	–0.029	–0.264	–0.158
	p	0.861	0.104	0.166
5-min Apgar	r	0.125	–0.165	–0.071
	p	0.448	0.315	0.536

CRP — C-reactive protein; N/A — not available

IL-22 has been demonstrated to modulate the secretion of numerous genes encoding proteins involved in tissue protection, differentiation, remodeling, and survival, and to a more secondary amount, pro-inflammatory proteins [26]. Previous studies reported that IL-22 plays a pivotal role in several immune-mediated inflammatory diseases such as inflammatory bowel diseases, rheumatoid arthritis, psoriasis, and allergic diseases [24].

IL-22 acts primarily in epithelial and stromal cells. In human pregnancy, trophoblast cells are epithelial cells that stemmed fetal origin and promote pregnancy maintenance. Wang et al. stated that IL-22 enhances cell viability, promotes proliferation, and decreases the apoptosis of trophoblast cells. They suggested that IL-22 might be a useful cytokine for the completion of gestation [27]. Dambaeva et al. [14], indicated that IL-22 is upregulated in response to lipopolysaccharide (LPS) injection into pregnant mice's uterus and proposes the probable administration of IL-22 to control inflammation-induced preterm delivery [15]. They also stated that LPS-induced pregnancy loss and fetal death risk in IL-22 k/o mice were significantly reduced with recombinant IL-22 (rIL-22) injection. Moreover, rIL-22 injection inhibited LPS-triggered preterm delivery in an IL-22 +/+ mice. Xu et al. [28] suggested that ILCs are implicated in the localized inflammatory milieu that accompanies preterm birth pathogenesis by expressing a high level of IL-22. Our study showed that maternal serum IL-22 concentrations were higher in women with PPROM (60.34 ± 139.81 pg/mL) than in the control group (20.71 ± 4.36 pg/mL, $p < 0.001$). We think that this result conclusively demonstrated the inflammation in the pathological process of PPROM.

We also assessed whether there is a relationship between maternal serum IL-22 concentration and latency period and neonatal outcomes, including birth week, birth weight, umbilical cord blood pH value, 1- and 5-minute Apgar scores. We found no correlation between maternal serum IL-22 levels and neonatal outcomes. Aris et al. [29] concluded that PPROM in the previous gestation is related to significant adverse neonatal outcomes in the subsequent gestation. We exclude all patients with a history of PPROM to eliminate this risk factor. Martinez-Portilla et al. and Sorokin et al. found no significant association between maternal serum inflammatory markers and adverse neonatal outcomes [11, 30].

To the best of our knowledge, this is the first study to date that has assessed the serum IL-22 concentrations in PPROM patients and compared with healthy pregnant women with intact membranes. Also, we included the control and PPROM patient groups that were matched for maternal age, gestational age at blood sample collection, or BMI. As IL-22 levels may vary with these factors, we eliminate the ones that could introduce potential bias.

This study's main limitation is the absence of confirming the inflammation by the histopathological examination after birth. Further studies are required in which the association between maternal serum IL-22 levels and clinical outcomes are confirmed by postnatal histopathological evaluation.

CONCLUSIONS

Maternal serum IL-22 levels were significantly higher in PPROM patients than healthy pregnant women with an intact membrane. We suggest that IL-22 might be a crucial biomarker of the inflammatory process in PPROM. However, there was no positive correlation between serum IL-22 levels and maternal CRP value, procalcitonin value, latency period, birth week, birth weight, and umbilical cord blood pH value.

Conflict of interest

The authors declared no conflict of interest.

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The effect of epidural analgesia on maternal-neonatal outcomes: a retrospective study

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ABSTRACT

Objectives: Epidural analgesia is commonly used for relieving labor pain in contemporary clinical practice. The rate of pregnant women who request epidural analgesia during labor has been increasing annually, leading to a debate on the effect of epidural analgesia on maternal or neonatal outcomes.

Material and methods: The medical records of nulliparous women with a term singleton pregnancy from January to December 2019 at the Affiliated Hospital of Zunyi Medical University were retrospectively reviewed. The women were divided into those who received epidural analgesia during delivery and those who did not receive it. Maternal and neonatal outcomes were assessed.

Results: A total of 528 women met the inclusion criteria. The overall labor analgesia rate was 43.0% (227). Women with epidural analgesia had a significantly longer second stage [34.5 (22.8–65.3) vs 27.0 (18.0–41.3) min, $p < 0.001$] and total duration of labor [698.5 (493.5–875.0) vs 489.5 (344.0-676.3) min, $p < 0.001$] compared with those without epidural. There were no significant relationships between epidural analgesia and the normal vaginal delivery rate, the incidence of episiotomy, and other adverse maternal or neonatal outcomes ($p > 0.05$).

Conclusions: Epidural analgesia can prolong the second stage of labor, but this is no increased risk for both mother and neonate.

Key words: labor epidural analgesia; maternal and neonatal outcome

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INTRODUCTION

Labor pain is one of the most common pains, which could cause a series of neurophysiological changes such as the increase of maternal oxygen stress hormones, the increase of blood pressure and the decrease of fetal oxygen transport, thus may affecting maternal and fetal well-being [1].

Epidural analgesia (EA) is currently one of the most effective ways of providing excellent intrapartum analgesia for pregnant women [2, 3]. In recent years, the rate of parturients who request EA during labor has widely increased, with a rate of 20–70% of all deliveries [4–7]. Since introduction of EA into the field of labor analgesia, attention has been paid to the effect of EA and pain relief in labor on maternal and neonatal outcomes. However, this effect of EA and pain relief in labor is controversial. Several studies have shown that beneficial analgesic effects come at the expense of prolonged labor, and an increase in instrumental vaginal delivery and emergency cesarean section, among others [8–11]. With regard to analgesic effects on the newborn, the existing literature on the relationship between EA and neonatal outcomes are equivocal [12–15]. In addition, whether the increase in maternal or neonatal morbidity is a consequence of EA is unclear. Anesthetic effects on maternal and neonatal outcomes continue to be investigated. Current and future work in these areas may improve clinicians' ability to individualize obstetric anesthesia treatment.

The aim of this study was to determine the effect of EA on maternal-neonatal outcomes regarding the period of labor.

MATERIAL AND METHODS

The study was conducted in accordance with the Declaration of Helsinki. The study protocol was approved by

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the Ethics Committee of the Affiliated Hospital of Zunyi Medical University, Guizhou, China (KLL-2020-015). Informed consent was waived owing to the retrospective nature of the study design. The study was performed in the Affiliated Hospital of Zunyi Medical University.

The reference population was composed of a group of nulliparous women with a term singleton pregnancy (≥ 37 weeks' gestation) who received care during childbirth in the Affiliated Hospital of Zunyi Medical University from January to December 2019. The exclusion criteria were as follows: planned surgical delivery (elective cesarean section), multipara, gestation < 37 weeks, multiple pregnancies, intrauterine fetal demise, and other anesthetic combinations. The study population was determined using these criteria of exclusion (Fig. 1).

Mothers were divided into the epidural and non-epidural groups according to whether they received analgesia by their choice. EA was performed in women when they requested it, regardless of the size of cervical dilatation during the labor period. The epidural space was located between L2 and L3, and the epidural catheter was inserted into the epidural space for 3 cm. 8 mL 0.1% ropivacaine with 4 μg sufentanil was given as loading dose. An epidural catheter was situated and connected to a patient-controlled epidural analgesia (PCEA) pump containing solutions of ropivacaine 0.1% with sufentanil 0.5 μg/mL. The PCEA regimen was as follows: 8 mL/h for continuous infusion, 8 mL at a bolus dose, and 30 min for locking [16]. PCEA was stopped at the end of the second stage of labor, and the catheter was removed two hours after delivery.

To collect the data, we used electronic medical records of the patients under study. Demographic data that were collected included maternal age, height, weight, gestational weeks, and complications. Maternal complications were defined as follows. Hypertension included essential or gestational hypertension or pre-eclampsia. Diabetes was defined as gestational diabetes, type 1 diabetes or type 2 diabetes. Abnormal results of thyroid function examination could be diagnosed as thyroid disease. Anemia was defined as hemoglobin concentration < 110 g/L. Maternal outcomes included the type of delivery (spontaneous or instrumental vaginal delivery, or emergency cesarean section), meconium-stained amniotic fluid, episiotomy, duration of the first and second stages of labor and the total duration of labor, the amount of postpartum hemorrhage, and length of postpartum hospital stay. Neonatal data included the Apgar score at 1, 5, and 10 min, a 5-min Apgar score ≤ 7, and neonatal intensive care unit admission.

Statistical analyses were performed using the Statistical Package for Social Sciences (SPSS™), Windows version 23.0 (IBM Corp., Armonk, NY, USA). First, the Shapiro–Wilk test was used to assess normal distribution of the data. Because of a lack of agreement with normal distribution, descriptive statistics analysis was performed using frequencies and percentages for categorical variables and the median and interquartile range for quantitative variables. Bivariate analysis was then performed on the obstetric history and maternal or neonatal outcomes with use of EA (no/yes), using Fisher's exact test or Pearson's chi-square test for categorical variables and the Mann–Whitney U test for quantitative variables. For statistical tests, a value of $p < 0.05$ was considered to indicate statistical significance.

RESULTS

The reference population consisted of 4085 pregnant women of whom 2296 (56.2%) were excluded for elective

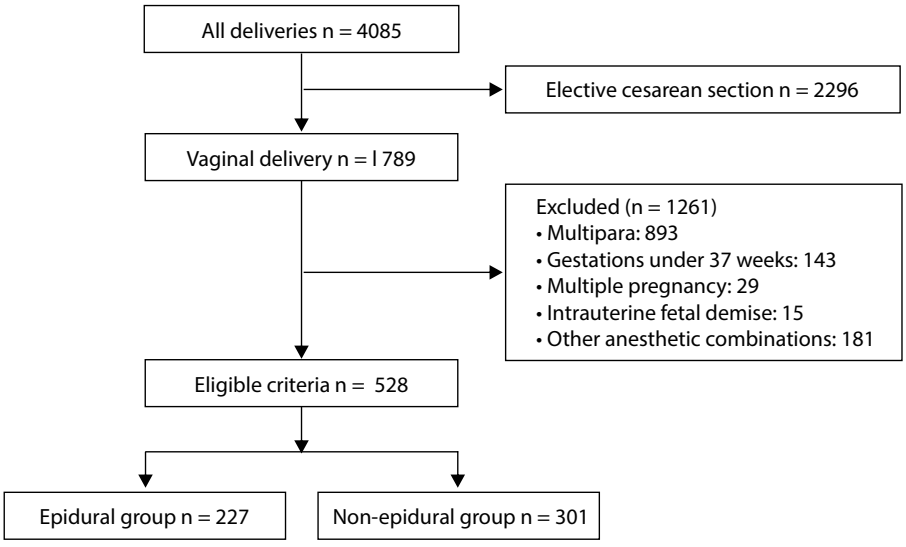

Figure 1. Flow chart of women in the study

cesarean section and 1261 (30.9%) for various reasons, with a final total of 528 (12.9%) pregnant women. The study cohort was divided into the epidural group (227 women) and non-epidural group (301 women). The overall epidural rate was 43.0% (Fig. 1).

Women who received EA were more likely to be older compared with those without an epidural ($p < 0.01$). There were no differences in maternal height, weight, gestational age, and complications between the two groups. Demographics of the women are shown in Table 1.

Maternal outcomes are shown in Table 2. The times of the first ($p < 0.001$) and second ($p < 0.001$) stages of labor were longer in the epidural group than in the non-epidural group. Additionally, the total duration of labor was significantly longer in the epidural group than in the non-epidural group ($p < 0.001$). However, there was no significant difference in the method of delivery between the groups. Additionally, the rate of spontaneous vaginal delivery. The amount of postpartum hemorrhage and the mother's hospital stay after delivery were not significantly different between the groups.

Regarding neonatal outcomes, there were no significant differences in the Apgar score at 1, 5, and 10 min, and admission to the neonatal ward between the two groups (Tab. 3).

DISCUSSION

In this study, we found that EA was associated with longer duration of the second and total stages of labor. However, this did not affect the normal vaginal delivery rate, the inci-

Table 1. Demographics of the women

Variables	Epidural Analgesia		p value
	No (n = 301)	Yes (n = 227)	
Maternal age [years]	26.0 (23.0–28.0)	27.0 (25.0–29.0)	< 0.01
Maternal height [cm]	158.0 (155.5–160.0)	158.0 (155.0–162.0)	0.29
Maternal weight [kg]	67.0 (60.0–72.3)	67.0 (62.0–72.0)	0.66
Gestational week, [weeks ± days]	39.6 (38.9–40.3)	39.7 (39.0–40.3)	0.19
Complications			
Hypertension	6 (2.0)	3 (1.3)	0.56
Diabetes	32 (10.6)	33 (14.5)	0.18
Thyroid disorders	37 (12.3)	25 (11.0)	0.65
Anemia	56 (18.6)	28 (12.3)	0.05

Data are presented as n (%) or median (25^{th}–75^{th} percentiles); Diabetes — gestational diabetes mellitus, type 1 diabetes mellitus, or type 2 diabetes mellitus; hypertension — essential or gestational hypertension or pre-eclampsia; thyroid disorders — abnormal results of thyroid function tests; anemia — a concentration of hemoglobin < 110 g/L

Table 2. Intrapartum and maternal outcomes

Variables	Epidural Analgesia		p value
	No (n = 301)	Yes (n = 227)	
Type of delivery, n (%)			
Normal Vaginal	241 (80.0)	196 (86.3)	0.06
Instrumental	5 (1.7)	2 (0.9)	0.44
Emergency CS	55 (18.3)	29 (12.8)	0.09
Meconium-stained amniotic fluid	81 (26.9)	54 (23.8)	0.42
Episiotomy*	122 (49.6)	92 (46.5)	0.51
First stage of labor duration [minutes]	445.0 (306.0–621.3)	655.0 (454.3–820.5)	< 0.001
Second stage of labor duration [minutes]	27.0 (18.0–41.3)	34.5 (22.8–65.3)	< 0.001
Total time of labor [minutes]	489.5 (344.0–676.3)	698.5 (493.5–875.0)	< 0.001
Postpartum haemorrhage			
< 0.5 L	244 (81.1)	197 (86.8)	0.79
≥ 0.5 L	57 (18.9)	30 (13.2)	0.79
Maternal postnatal length of stay	2 (2–3)	2 (1–2)	0.21

CS — cesarean section; *Women who achieved a vaginal birth

Table 3. Neonatal outcomes

Variables	Epidural Analgesia		p value
	No (n = 301)	Yes (n = 227)	
Apgar score at 1 min	10 (10–10)	10 (10–10)	0.56
Apgar score at 5 min	10 (10–10)	10 (10–10)	0.93
Apgar score at 10 min	10 (10–10)	10 (10–10)	0.88
5-min Apgar score ≤ 7	1 (0.3)	1 (0.4)	0.84
NICU admission	62 (20.6)	47 (20.7)	0.98

NICU — neonatal intensive care unit

dence of episiotomy, and other adverse maternal or neonatal outcomes. Our results are consistent with recent studies that EA during delivery does not increase the rate of vaginal delivery, and EA during delivery is safe for both mothers and fetuses [17, 18]. A 2018 Cochrane review suggested that EA had no effect on the risk of cesarean section [19]. This review also showed that EA did not appear to have an immediate effect on neonatal status as determined by Apgar scores or in admission to neonatal intensive care. These review findings are in contrast to those of the Cochrane review of 2011 [8]. Similarly, we found that although the second stage of labor in the epidural group was longer compared with that in the non-epidural group, the instrumental delivery rate, emergency cesarean section, and neonatal outcomes were similar between the two groups. However, unlike our study, previous studies showed that while a longer second stage of labor may increase vaginal delivery rate, this may be at the expense of increasing maternal and neonatal morbidity [20, 21].

Because of concern of a prolonged second stage of labor and its adverse outcomes, some obstetric nurses ask to reduce or terminate the epidural infusion rate in order to improve the maternal expulsive efforts in the second stage of labor [22]. This practice varies from center to center, but it is reported to occur in 46% of deliveries (range: 14–85%) [22, 23]. Increased maternal pain or decreased satisfaction with EA may be balanced with the successful benefits of vaginal delivery. However, this is not an ethical solution. Chestnut et al. [24], found that continuous epidural infusion of 0.0625% bupivacaine had no effect on the duration of the second stage of labor. This finding suggested that there should be a dose-response relationship between the concentration of epidural local anesthetics and the effect of the second stage of labor. These authors' findings are similar to recent findings that minimum local analgesic concentrations of epidural sufentanil or ropivacaine provided satisfactory and safe analgesia for parturients, while they had a low incidence rate of side effects [18, 25]. The potential dose-response mechanism of EA on the success of the second stage of labor needs further study. We used a low concentration of ropivacaine (1%) with a relative potency of about 0.06% bupivacaine [26]. We found that the second stage of labor in the epidural group was 34.5 min (range: 22.8–65.3 min) compared with 27.0 min (range: 18.0–41.3 min) in the non-epidural group. Interestingly, we found that the instrumental delivery and emergency cesarean section rates were similar between the epidural and non-epidural groups.

Due to the nature of our research, it has some limitations, which are inherent in retrospective research and may be the cause of some bias. Data, such as maternal satisfaction and dose-response analyses, were missing, which lead to difficultly in further analyzing the underlying reasons and mechanisms of epidural-related maternal or neonatal outcomes. We also did not clarify whether EA is a risk factor, or whether other factors related to analgesia are the causes of adverse outcomes. We plan to add further monitoring in future studies. In addition, the small sample size of this study is a limitation. Therefore, we need to further increase the sample size in the future to further verify our results.

CONCLUSIONS

EA can prolong the duration of labor, but there is no increase in the normal vaginal delivery rate or incidence of episiotomy, as well as no increase in other adverse effects in mothers or newborns. In summary, EA may be safe for the mother and neonate.

Conflict of interest

The authors declare no conflict of interest.

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Nutrition quality of pregnant women based on body mass index and the content of selected nutrients and energy in the daily diet

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ABSTRACT

Objectives: BMI of pregnant women is influenced by the percentage of energy and the content of individual nutrients in the daily diet. The aim of the study was to evaluate nutrition quality based on BMI values of women with physiological course of pregnancy and to determine correlations between BMI and the content of selected nutrients and energy in the daily diet.

Material and methods: The study was carried out among healthy women between the first and fourth day after childbirth. It was conducted using a standardized questionnaire of the National Health Institute: DHQ II. In total, 103 women met the inclusion criteria. The analyses were performed with the use of a data analysis software system called Statistica 10.0.

Results: The mean BMI before pregnancy was 22.30 ± 3.19 kg/m^2. The mean BMI before delivery was 27.87 ± 3.9 kg/m^2. The analysis of selected nutrient intake in relation to the nutritional status based on BMI before pregnancy showed no statistically significant differences. It was found that women with normal BMI (18.5–24.9 kg/m^2) consumed foods of lower energy value than those with BMI over 25 kg/m^2. These differences were statistically significant for daily energy intake and for the mean content of carbohydrates in the daily diet. Intake of selected nutrients was correlated in a statistically significant way with the nutritional status during pregnancy based on pre-partum BMI values. The higher the percentage of energy in the daily diet, the higher the pre-partum BMI values. Similar correlations were found for total fats, carbohydrates, protein, saturated fatty acids, mono- and polyunsaturated fatty acids, calcium, magnesium, vitamin D, water contained in foods, fluids and total sugars.

Conclusions: Dietary energy and carbohydrate content has a significant impact on BMI of pregnant women. During pregnancy, BMI increases with an increase in saturated fatty acid consumption. Intake of selected nutrients was correlated in a statistically significant way with the nutritional status during pregnancy based on BMI values.

Key words: nutrition in pregnancy; nutritional status of pregnant women; DHQ II

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INTRODUCTION

The quality of women's nutrition before and during pregnancy as well as their eating habits are becoming the main determiners of external factors affecting the course of pregnancy [1]. Nutrition during pregnancy affects fetal growth, birth weight and morbidity [2]. Body weight before pregnancy and weight gain during pregnancy play a significant role in normal fetal development. Studies based on body mass index (BMI) indicate that 10% of women younger than 30 years of age are malnourished before conception (BMI < 18.5 kg/m^2), whereas the percentage of obese and overweight women increases with age to 50%. Fewer than 50% of women change their eating habits during pregnancy, but this is not always related with improved diet adjusted to requirements, which increases the risk of vitamin and nutrient deficiency. Pregnancy is one of natural causes of weight gain, but uncontrolled, excessive weight gain is a significant risk factor of complications during pregnancy, childbirth or puerperium [3–5].

Aim of study

The aim of the study was to evaluate nutrition quality in women with physiological course of pregnancy according to their BMI values and to determine correlations between

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BMI and the content of selected nutrients and energy in their daily diet.

MATERIAL AND METHODS

The study enrolled healthy pregnant women aged 18–38 years (mean age 29.9 ± 3.89 years) and was conducted in the period between the first and fourth days post-labor in maternity units of hospitals in the Silesian Province of Poland.

The study was conducted using a standardized questionnaire of the National Health Institute: Diet History Questionnaire (DHQ II), and an author's own survey. The standardized DHQ II questionnaire evaluates eating habits in the past 12 months. That is why the authors enrolled women directly after the conclusion of a physiological pregnancy. DHQ II was prepared based on food intake reports generated in the Diet* Calc program version 1.5.0 [6].

DHQ II is an available food frequency questionnaire (FFQ) prepared by the team from the Risk Factor Monitoring and Methods Branch (RFMMB). DHQ II contains a list of food products updated according to the current nutrition data and consists of 134 questions concerning food products and eight questions concerning dietary supplements. Data obtained from a paper version of DHQ II were analyzed in the Diet* Calc program. This program enables one to interpret data from DHQ II and determine estimated intake of individual food groups and nutrients [6]. The Diet*Calc provided reports on estimated daily intake of nutrients, energy, micro- and macroelements and the remaining food components. The reports contain a list of 176 nutrients and food groups.

Data analysis/statistical methods

Statistical hypotheses were verified with the significance level of $p < 0.05$. Significance of the differences between groups was evaluated based on the Student's T test or, in the case of a higher number of groups, analysis of variance (ANOVA). The analyses were performed with the use of a data analysis software system called Statistica 10.0.

The analysis included 103 women who met the following inclusion criteria: age 18–38 years, physiological course of pregnancy, pre-pregnancy BMI below 30, consent to participation and correctly completed questionnaire (100% of main questions). The BMI index was calculated twice: before pregnancy and before labor.

RESULTS

The first BMI measurement was based on body weight before pregnancy, and the second on body weight before labor. The mean body weight before pregnancy was 60.76 ± 8.86 kg, and during pregnancy (measured before labor): 75.74 ± 10.11 kg. The mean pre-pregnancy BMI was 22.30 ± 3.19 kg/m^2, and the mean BMI measured for the last time before childbirth was 27.87 ± 3.9 kg/m^2. Considering the pre-pregnancy body weight, the group was divided into three subgroups based on the international classification of underweight, overweight and obesity according to BMI (WHO): underweight women (BMI < 18.5), normal body weight women (BMI 18.5–24.9) and overweight women (BMI: 25.0–29.9). Women with pre-pregnancy obesity (BMI ≥ 30.0) were excluded from the study. In the analyzed group, pre-pregnancy BMI was normal in most of the women (68.9%), 8.7% were underweight and 22.3% were overweight. Before delivery, 29.1% of women had the correct body weight (BMI ranging from 18.5 to 24.9 kg/m^2), 41.7% were overweight (BMI 25.0–29.9 kg/m^2) while BMI ≥ 30.0 kg/m^2 was found in 29.1% of the respondents. The analysis of BMI values before and during pregnancy showed that the mean pre-pregnancy BMI value was lower in a statistically significant way ($p < 0.05$) than BMI during pregnancy (22.30 ± 3.19 kg/m^2 vs 27.80 ± 3.66 kg/m^2). Weight gain during pregnancy was 14.99 ± 4.90 kg. Weight gain in pregnant should follow IOM guidelines and refer to pre-pregnancy BMI. The analysis showed that the higher the pre-pregnancy BMI level, the greater the pregnancy weight gain. The study showed statistically significant differences in individual BMI groups before pregnancy and before delivery (Tab. 1).

The analysis of selected nutrient intake in relation to the nutritional status before pregnancy based on BMI showed no statistically significant differences. However, the data indicate quantitative differences between intake of individual nutrients in relation to BMI. Women who were overweight (based on BMI) before pregnancy consumed foods of a considerably higher energy value compared with underweight women or women with normal body weight (2951.48 ± 1247.93 kcal vs 2001.33 ± 613.51 kcal and 2576.35 ± 1215.83 kcal). The energy value of food consumed daily before pregnancy averaged 2,609.9 ± 1,199.86 kcal. The comparison in terms of the remaining nutrients shows that overweight women consumed the greatest amount of fat (102.76 ± 48.65 g), protein (101.83 ± 47.62 g), carbohydrates (420.18 ± 205.39 g), cholesterol (313.48 ± 151.87 mg), saturated fatty acids (SFA) (37.45 ± 17.82 g), monounsaturated fatty acids (MUFAs) (35.78 ± 18.38 g) and polyunsaturated fatty acids (PUFAs) (20.65 ± 12.81 g) in their daily diet (Tab. 2).

Table 1. Nutrition status of women before and during pregnancy (body mass index before and during pregnancy)

Nutritional status based on BMI	Mean ± SD	Min–Max	p (Shapiro-Wilk test)
BMI before pregnancy	22.30 ± 3.19	16.4–29.7	0.00220
BMI before labor	27.80 ± 3.66	21.1–36.2	0.00332

p — level of significance; SD — standard deviation; BMI — body mass index

The analysis of the nutritional status during pregnancy according to BMI (measured before labor) in relation to the level of selected nutrients and energy (collective data) is shown in Table 3.

When analyzing the level of nutrient intake and the percentage of energy in the daily diet in different subgroups of women depending on BMI measured during pregnancy, it was found that women with normal BMI (18.5–24.9 kg/m^2) consumed foods of lower energy value than those with BMI over 25 kg/m^2.

Pregnant women with normal BMI (measured before delivery) consumed fewer calories (2193.0 ± 887.28 kcal) compared with those with overweight or obesity according to the pre-partum BMI values. Women with BMI ≥ 30 (3004.63 ± 1156.49 kcal) were characterized by the highest energy intake.

The situation is similar for the remaining nutrients. Apart from alcohol consumption and percentage of energy from fats, women with the lowest BMI consumed foods with a lower nutrient value than women with BMI ranging from 25–29.9 kg/m^2 or with BMI ≥ 30 kg/m^2. These differences were statistically significant for daily energy intake (p = 0.030517) and for the average content of carbohydrates (p = 0.052135) in the daily diet. There were no statistically significant differences for other nutrients, but quantitative differences between patients with various BMI values were noted.

The highest % of energy is derived from carbohydrates (> 50%) and fats (over 30%). They are followed by protein (approximately 15%) and saturated fatty acids (approximately 12%).

There were no statistically significant differences in the percentage of energy derived from individual diet compo-

Table 2. Pre-pregnancy nutritional status according to body mass index and the percentage of nutrients and energy in the daily diet (collective data)

Energy Nutrients		Pre-pregnancy BMI			
	p	< 18.5 kg/m^2	18.5–24.9 kg/m^2	25.0–29.9 kg/m^2	Total
ENERGY_KCAL_USD/d	0.120009	2001.33 ± 613.51	2576.35 ± 1215.83	2951.48 ± 1247.93	2609.9 ± 1199.86
TOTAL_FAT_G_USDA/d	0.106986	67.47 ± 23.91	89.99 ± 42.01	102.76 ± 48.65	90.87 ± 42.97929
CARBOHYDRATE_G_USDA/d	0.240070	290.67 ± 111.26	363.48 ± 208.2	420.18 ± 205.39	369.78 ± 202.41
PROTEIN_G_USDA/d	0.121956	67.5 ± 27.8	90.91 ± 41.77	101.83 ± 47.62	91.3 ± 42.69
ALCOHOL_G_USDA/d	0.121472	0.2 ± 0.49	1.02 ± 1.79	0.41 ± 0.69	0.81 ± 1.55
CHOLESTEROL_MG_USDA/d	0.327650	229.1 ± 106.9	311.23 ± 164.42	313.48 ± 151.87	304.55 ± 158.03
TOTAL_SATURATED FATTY_ACID G/d	0.176772	23.74 ± 10.41	34.03 ± 19.54	37.45 ± 17.82	33.90 ± 18.74
TOTAL_MONOUNSATURATED_FATT G/d	0.163302	24.79 ± 8.24	31.24 ± 14.37	35.78 ± 18.38	31.69 ± 15.10
TOTAL_POLYUNSATURATED_FATT G/d	0.076744	12.92 ± 4.61	16.96 ± 8.03	20.65 ± 12.81	17.43 ± 9.25
%Energy from TOTAL_FAT	0.798575	30.92 ± 7.59	32.22 ± 6.14	31.54 ± 6.61	31.95 ± 6.32
%Energy from CARBOHYDRATE	0.714628	57.66 ± 9.48	55.34 ± 8.00	56.18 ± 9.61	55.73 ± 8.45
%Energy from PROTEIN	0.599670	13.37 ± 2.75	14.47 ± 2.66	14.34 ± 4.22	14.35 ± 3.06

BMI — body mass index; p — level of significance; d — day

Table 3. Nutritional status during pregnancy according to body mass index (measured before labor) and the average level of selected nutrients

Energy Nutrients Skłp	p	BMI before labor			
		BMI 18.5–24.9	BMI 25.0–29.9	BMI ≥ 30	Total
ENERGY_KCAL_USDA	0.030517	2193.0 ± 887.28	2625.30 ± 1339.24	3004.63 ± 1156.49	2609.87 ± 1199.86
TOTAL_FAT_G_USDA	0.068546	78.56 ± 32.28	90.21 ± 47.05	104.12 ± 43.70	90.87 ± 42.98
CARBOHYDRATE_G_USDA	0.052135	302.93 ± 137.70	375.26 ± 230.30	428.77 ± 200.15	369.78 ± 202.41
PROTEIN_G_USDA	0.105732	79.70 ± 31.97	91.21 ± 47.92	103.04 ± 42.19	91.30 ± 42.69
ALCOHOL_G_USDA	0.654246	0.71 ± 1.04	0.98 ± 2.12	0.68 ± 0.92	0.81 ± 1.55
CHOLESTEROL_MG_USDA	0.293446	271.20 ± 133.08	306.44 ± 183.43	335.2 ± 138.83	304.55 ± 158.03
%Energy from TOTAL_FAT_G_USDA	0.865717	32.47 ± 4.38	31.81 ± 7.33	31.64 ± 6.58	31.95 ± 6.32
%Energy from CARBOHYDRATE G USDA	0.788274	54.83 ± 6.32	56.10 ± 9.10	56.10 ± 9.48	55.73 ± 8.45
%Energy from PROTEIN_G_USDA	0.818819	14.65 ± 2.71	14.21 ± 2.84	14.24 ± 3.72	14.35 ± 3.07

BMI — body mass index

nents in pregnant patients taking into account the division based on BMI during pregnancy (measured before labor). However, it was observed that pregnant women with BMI in the range of 18.5–24.9 kg/m^2 consumed more energy with fats and protein compared with other groups. The percentage of energy derived from long-chain polyunsaturated fatty acids (PUFAs), which are considered one of the most important dietary components, was the highest in women with normal BMI and reached 6.69%. This value was the lowest in women with BMI ≥ 30 kg/m^2 and equaled 5.86%.

The study led to a conclusion that intake of selected nutrients is correlated in a statistically significant way with nutritional status during pregnancy based on pre-partum BMI values. The higher the percentage of energy in the daily diet, the higher the pre-partum BMI.

Similar correlations were found for total fats, carbohydrates, protein, saturated fatty acids, mono- and polyunsaturated fatty acids, calcium, magnesium, vitamin D, water contained in foods and fluids, and total sugars (Tab. 4).

Table 4. Correlations between the nutritional status during pregnancy according to body mass index (measured before labor) and intake of selected nutrients)

Nutrients	BMI during pregnancy
ENERGY	R = 0.2665, p = 0.0065
TOTAL FAT	R = 0.2338, p = 0.0175
CARBOHYDRATE_G_USDA	R = 0.2392, p = 0.0150
PROTEIN_G_USDA	R = 0.2377, p = 0.0156
ALCOHOL_G_USDA	R = 0.0011, p = 0.9911
CHOLESTEROL_MG_USDA	R = 0.1508, p = 0.1285
TOTAL_SATURATED_FATTY_ACID G_USDA	R = 0.2394, p = 0.0149
TOTAL MONOUNSATURATED FATTY ACIDS G_USDA	R = 0.2056, p = 0.0372
TOTAL POLYUNSATURATED FATTY ACIDS G_USDA	R = 0.1780, p = 0.0721
DIETARY_FIBER_G_USDA	R = 0.0978, p = 0.326
RETINOL_MCG_USDA	R = 0.1205, p = 0.225
VITAMIN_E_AS_ALPHA_TOCOPHEROL	R = 0.0496, p = 0.619
VITAMIN_K_MCG_USDA	R = 0.1194, p = 0.230
VITAMIN_C_MG_USDA	R = 0.1888, p = 0.056
CALCIUM_MG_USDA	R = 0.2314, p = 0.019
MAGNESIUM_MG_USDA	R = 0.2187, p = 0.026
IRON_MG_USDA	R = 0.0595, p = 0.551
ZINC_MG_USDA	R = 0.1390, p = 0.161
PFA_20_5_EICOSAPENTAENOIC_USDA	R = 0.2197, p = 0.026
PFA_22_5_DOCOSAPENTAENOIC_USDA	R = 0.2282, p = 0.020
PFA_22_6_DOCOSAHEXAENOIC_USDA	R = 0.2201, p = 0.026
CAFFEINE_MG_USDA	R = 0.0640, p = 0.521
BETA_CAROTENE_MCG_USDA	R = –0.0517, p = 0.604
FOLIC_ACID_MCG_USDA	R = –0.0586, p = 0.557
TOTAL_SUGARS_G_USDA	R = 0.2438, p = 0.013
VITAMIN_A_RAE_MCG_USDA	R = –0.0361, p = 0.717
WATER_G_NDSR	R = 0.3424, p = 0.000
VITAMIN_D_CALCIFEROL	R = 0.2173, p = 0.0275
CHOLINE_MG_NDSR	R = 0.1838, p = 0.063

BMI — body mass index; R — correlation coefficient; p — level of significance

DISCUSSION

The analysis of the percentage of energy in relation to pre-partum BMI values revealed that the highest energy % derived from carbohydrates was observed in women with BMI in the range of 25.0–29.9 kg/m^2 and ≥ 30 kg/m^2. Carbohydrates, sugar in particular, is a significant factor determining a BMI increase during pregnancy and excessive weight gain. Similar results were presented by Maslov [7]. Positive correlations were also observed by Diemert who found that increased weight gain and BMI in pregnant women accompanies an increase in energy content and carbohydrate intake [8].

It was observed that intake of total protein and protein of animal origin is positively correlated with an increase in the nutritional status according to the pre-partum BMI values. The content of vegetable protein does not affect the nutrition status, as evaluated by BMI. Similar results were presented by Ostachowska-Gąsior, who observed an increase in BMI values during pregnancy with increased consumption of animal protein [9].

As for recommendations concerning saturated fatty acid consumption in the studied groups with respect to BMI (measured before delivery), there were no statistically significant differences. Intake of saturated fatty acids exceeded 10% of dietary energy requirement, which was not consistent with current guidelines, as their maximum limitation is recommended [3, 10]. The percentage of energy from polyunsaturated fatty acids in the daily diet of the surveyed pregnant women based on their BMI (measured before delivery) averaged slightly more than 6% in women with BMI ranging from 18.5 to 24.9 kg/m^2 and 25.0–29.9 kg/m^2, with the minimum recommended value of 6% and the maximum value of 10% [11, 12]. Pregnant women with BMI ≥ 30kg/m^2 consumed less polyunsaturated fatty acids than recommended. A low percentage of these acids in the diet of pregnant women has also been observed by Wawrzyniak et al. [13]. Delivering more energy from fats than specified in the recommended referential norms during pregnancy can have adverse effects in the child in the form of, *e.g.*, lipid accumulation in the liver, atherosclerosis or insulin resistance [14].

Authors of various studies on nutrient content in the daily diet of pregnant women indicate deficiencies as the main causes of health-related complications. However, excessive consumption of nutrients is an equally dangerous situation.

Research shows that balanced diet during pregnancy is the main determiner of fetal programming [15]. According to Renault, obesity during pregnancy is caused by consumption of sugar and saturated fat. Limiting snacks, sweets and non-alcoholic beverages might protect pregnant women from excessive weight gain to a greater extent than following a given diet. However, research does not clearly specify which nutrient is primarily responsible for a BMI increase and obesity during pregnancy [16].

The results suggest that limiting dietary carbohydrates can have a greater impact on reducing weight gain during pregnancy than increasing protein content. Higher protein intake during pregnancy increases satiety and attenuates hunger. A reason for increased food intake may be the activation of the so-called "reward system" by consuming foods of high fat and sugar content. Reward system stimulation promotes overeating, thereby leading to energy homeostasis disorders and thus to higher intake of energy than is actually utilized [10, 17].

The present study investigated a BMI increase and correlations of selected nutrients in pregnant women. Studies on nutritional factors and body weight determiners during pregnancy are a significant aspect in light of a growing epidemic of obesity and attempts to optimize body weight during pregnancy.

According to WHO guidelines, nutritional counselling and education should be based on improving nutrition quality of pregnant women, adjusting individual nutrients and their optimal dietary content. Education should also encompass advice on possible supplementation, including iron and folic acid. Moreover, promotion of pro-health and elimination of anti-health behaviors, particularly in terms of tobacco, alcohol or psychoactive substance use, should be an important aspect of such education [18]. Nutritional errors made by pregnant women should be eliminated at the very beginning of pregnancy, and preferably even in the preconception period. That is why instructing pregnant women or those planning pregnancy is relevant as it is a form of early prophylaxis of complications resulting from improper nutrition. Nutritional education of pregnant women is a significant element of obstetric care. Its aim is to improve nutrition quality of women and health outcomes of both women and children.

CONCLUSIONS

Dietary energy and carbohydrate content has a significant impact on BMI in pregnant women. BMI of pregnant women increases with an increase in saturated fatty acid and carbohydrate intake. Total protein content in the daily diet and animal protein consumption were found to be positively correlated with a BMI increase during pregnancy.

Ethics approval and consent to participate

The study protocol was approved by the Ethics committee of the Hamburg State Board of Physicians (06.91.2011, PV3694) and conducted according to the principles of the Declaration of Helsinki. Written informed consent was obtained from all participants.

Conflict of interest

None.

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Pregnancy-related comorbidities and labor induction — the effectiveness and safety of dinoprostone compared to misoprostol

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ABSTRACT

Objectives: The aim of the study was to evaluate whether the presence of the disease in pregnancy influences the effectiveness and safety of delivery preinduction with prostaglandins: misoprostol vaginal insert and dinoprostone vaginal gel.

Material and methods: This is a retrospective cohort study conducted of 560 pregnant women. The concomitant diseases mainly recorded were diabetes mellitus, hypertensive diseases, intrahepatic cholestasis of pregnancy, asthma, thrombocytopenia, and hypothyroidism. The primary study outcome was a successful vaginal delivery. The study above others evaluates the time from treatment implementation to the beginning of a labor and to a final delivery, the rate of Cesarean sections, and the presence of delivery complications.

Results: Among women with a concomitant disease, Caesarean section was observed more frequently in the misoprostol group. In the dinoprostone group, mothers with the concomitant disease as compared to healthy mothers required more time to the delivery and to achieve the beginning of labor. There were no differences in postpartum complications regardless of the prostaglandins, comorbidities or mothers' age. Neonates of mothers ≥ 35 years old with concomitant disease had lower average Apgar scores.

Conclusions: Our study showed that comorbidities seem to increase the caesarean section risk in the misoprostol preinduction group but in the dinoprostone group they prolong the time needed to achieve an active labour phase and a delivery.

Key words: comorbidities; dinoprostone; labor induction; misoprostol

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INTRODUCTION

In the era of postponing pregnancy to an advanced age of women, which has both social and economic determinants, various consequences of such decisions must be considered. Among older pregnant women, especially over 40 years old, the risk of comorbidities increases [1].

Hypertension in pregnancy concerns 6–10% of pregnancies [2, 3]. It is associated with numerous complications during pregnancy [4, 5]. The delivery beyond 37 weeks' gestation in pregnancies with the mild hypertensive disease was associated with improved maternal outcomes [6]. It has been proven, that labour induction at 38 or 39 weeks in pregnant women with uncomplicated chronic hypertension appears to reduce the risk of serious neonatal morbidity and mortality [7].

It is well known that diabetes type II is highly correlated with obesity and unfortunately obesity among women of reproductive age (20–39 years) increases, which altogether is concerning [8–9]. Obesity is a popular risk factor for stillbirth [10]. Fetal hypertrophy may lead to a disproportion of labour, shoulder dystocia during delivery, the need for urgent caesarean section with an increased risk of preoperative complications [11]. Both maternal gestational diabetes mellitus and obesity are independently associated with an unfavourable course of pregnancy and both have an even greater impact than either one alone [12]. In order

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to reduce the risk of fetal complications in pregnancy with pregestational diabetes and gestational diabetes, Polish Gynaecological Society recommends labour induction after 38 weeks and after 39 weeks of gestation, respectively [13].

Pregnant women older than 35 years have also increased risk of placenta previa, placental abruption or preterm birth and small-for-gestational age neonates. When comparing the adjusted perinatal mortality rates between women aged 20–24 with 35–39 and 40 years old, the rates were 63% ($p = 0.04$) and 183% ($p = 0.01$), respectively. Also, the rates of the adjusted perinatal mortality and morbidity rates were much higher in over 35 years-old pregnant group comparing with women under 25 years old [14]. There is the real risk of stillbirth in pregnant women aged 40 and more and that is why The Polish Society of Gynecologists and Obstetricians recommends to treat those pregnancies as biologically mature and to induct labour at 39 weeks of gestation [13].

As mentioned above there are studies showing the need for active rather than expectant management according to varies pregnancy complications and finishing the pregnancy before 40 weeks of gestation. The choice of the method, in accordance with the recommendations of The Polish Society of Gynecologists and Obstetricians, is based mainly on the assessment of obstetric state in each patient, the preferences of the deciding physician and, most often, the availability of a given procedure in a hospital.

The crucial role plays the maturity of the cervix mostly assessed by scale introduced by Bishop in 1964 [15]. There are many possible ways of preparing the cervix to the delivery which is called a labour pre-induction. The most often used ones include the mechanical ways (a Foley or a double-balloon catheter, membrane stripping) and the pharmacological way with the usage of prostaglandins in a numerous dosage and routs of administration (dinoprostone-prostaglandin E2 and misoprostol-prostaglandin E1) [16].

Available research results show effectiveness and safety of a use of prostaglandins for preinduction purposes, after a control for several covariates, and, as mentioned above, there are several clinical characteristics of the pregnant woman which are indications for the use of preinduction. The knowledge, however, on how the presence of a disease in pregnant woman influences clinical outcomes in those patients is very limited.

Objectives

The aim of the study was to evaluate whether the presence of the disease in pregnancy influences the effectiveness and safety of prostaglandins which are the most often used in routine clinical practice for preinduction, meaning: the misoprostol vaginal insert at a dose of 0.2 mg (Misodel, Ferring Pharmaceuticals Poland sp. z o.o) and dinoprostone gel at a dose of 0.5 mg (Prepidil, Pfizer Polska Sp. z o.o.). In details, the study assessed whether the presence of disease influences the effectiveness of the two aforementioned drugs measured by the time from treatment implementation to the beginning of a labour and to a final delivery and safety measured by the rate of emergency Caesarean sections, the presence of delivery complications, and some health indicators in newborns. Additionally, we addressed an issue of mothers' age as a potential contributing factor.

MATERIAL AND METHODS

The study included 560 pregnant women hospitalized at the Obstetric and Perinatology Department at the University Hospital in Cracow between January 2015 and April 2019. This was a retrospective cohort design for which all available medical records had been identified and reviewed. The list of collected information covered among others: maternal age, body mass index (BMI), number of pregnancies, parity history, gestational age. The mode of delivery, indications for caesarean section and other maternal outcomes including, episiotomy, anemia requiring blood transfusion, uterine hyperstimulation were also counted.

All patients identified as eligible for the study had to have singleton gestation with cephalic presentation and they required labour induction for medical indications. The cervical ripening was performed with dinoprostone gel or misoprostol insert. There were no known selection rules implemented by physicians at a clinic which might favor the use of one drug over the other due to patient's characteristics or preferences. Other inclusion criteria were the Bishop's score ≤ 4 and an absence of an active labour before administration of the drug. Exclusions included expected fetal weight over 4500 g or any known contraindication to vaginal delivery, or any contraindication for prostaglandins. For the presented study, pregnant women with any diagnosed disease were included. These were mainly: any tape of diabetes mellitus, hypertensive diseases, intrahepatic cholestasis of pregnancy, asthma and thrombocytopenia, hypothyroidism.

The primary study outcome was a successful vaginal delivery. Secondary effectiveness outcome measures were time from drug administration to delivery (both, vaginal and Caesarean section), induction-active labour interval time and durations of the first three delivery stages. The safety outcomes covered any complication observed during a labor such as blood transfusion, uterine hyperstimulation, curettage after delivery, episiotomy, rupture of perineum, and additionally emergency Caesarean delivery.

Statistical analysis

For the purpose of the study, all participants have been classified into two groups, a dinoprostone and

a misoprostol group. The categorization was made by the implementation of the intention to treat (ITT) principle. Thusly, mothers who were intended to begin their labour with dinoprostone and received dinoprostone as a first drug after admission were categorized as dinoprostone group members, and those who received misoprostol first composed a misoprostol group. There was also a group of women, in which, in the lack of effect of one drug, the other had been implemented. These were included according to the intention to treat (ITT) criteria in the appropriate group in the effectiveness analyses and additionally were analyzed as a separate group when complications were considered.

The descriptive characteristics of the investigated groups have been presented by the mean, SD, median and first (Q1) and third quartile (Q3). Median and quartiles were used as majority of data distributions were skewed causing the mean and SD were not informative enough to provide appropriate group depiction. To test whether there were differences in the study outcomes across analyzed groups the following strategy had been implemented for categorical data: 1. a chi-square test was used provided the expected values exceeded 5, otherwise, the Fisher's exact test was used; 2. to test whether there is a difference between mothers with a disease as compared to mothers without a disease across strata by mother's age (< 35 yrs vs 35 + yrs) the Cochran-Mantel-Haenszel statistics were used. This answered a question of whether the effect size caused by the presence of a disease across the two treatments differed between younger and older mothers. For continuous data: 1. firstly, the assumption of normal distribution had been tested using Shapiro-Wilk test; 2. as the variables analyzed were skewed the U-Mann-Whitney test was used to test for significance of a difference. The results with a $p < 0.05$ were considered statistically significant. The pairwise procedure was used for missing data, consequently all the available data were used for analyses. All analyses had been made by the IBM SPSS Statistics, version 26.

RESULTS

There were 560 women identified as admitted for a labour induction in the calendar period covered by the study. In this group, the misoprostol insert was applied to 210 pregnant women, and dinoprostone gel was used in 350 patients. In the dinoprostone group 100 women, who received additionally misoprostol as a second drug, were identified. In total, there were 320 women with at least one diagnosed disease 117 in the misoprostol and 203 in the dinoprostone group. Out of these 57 and 87, respectively, were diagnosed with hypothyroidism, 27 and 28 with hypertension, 23 and 65 had diabetes, 3 and 15 had both, diabetes and hypertension, and 7 and 8 had some other diseases. Women diagnosed with any concomitant disease had higher body mass and higher BMI in both dinoprostone and misoprostol groups. Women representing 35 + age category characterized a higher number of pregnancies. All the other characteristics were similar across analyzed groups (Tab. 1 and 2).

Among women with concomitant disease vaginal delivery was observed more frequently in the dinoprostone group as compared to misoprostol (66.5% vs 52.1%, $p = 0.013$). Consequently, Caesarean sections were observed more frequently in the misoprostol group. Moreover, mothers with a disease treated by misoprostol as compared to dinoprostone more frequently were referred to Caesarean section in emergency (Tab. 3). When we took into account the misoprostol group only, a higher proportion of pregnant women with a concomitant disease (as compared to women without the disease) underwent Caesarean section (47.9% vs 31.2%; $p = 0.016$), and also more of them experienced emergency Caesarean section (being a part out of total deliveries) (35.9% vs 20.4%; respectively, $p = 0.015$). Those differences were not observed in the dinoprostone group (Tab. 3). Some detailed analysis of Caesarean indications revealed that pregnant women with a disease treated by misoprostol more frequently presented preeclampsia and placenta abruption (both, when they were compared with mothers with a disease treated by dinoprostone, and with mothers treated by misoprostol but having no concomitant disease) (Tab. 3).

There were no differences in postpartum complications in the group of study participants regardless of the prostaglandin combination, any concomitant disease, or mothers' age, apart from more often need for episiotomy and an occurrence of rupture of perineum in dinoprostone group. (Tab. 4a and 4b).

Interesting findings are shown in Table 5 with time intervals from drug implementation to delivery (vaginal only or any delivery). It has been observed that in the group treated by dinoprostone, mothers with the concomitant disease as compared to mothers without the disease required more time to the delivery (vaginal route only: 39.6 vs 31.3 hours, $p = 0.014$, or any rout: 42.8 vs 35.6 hours, $p = 0.023$) and to achieve the beginning of a labor (33.5 vs 25.3, $p = 0.009$). After analysis of mothers' age, we have found no differences. In the misoprostol group, no significant differences in time intervals were found. The investigation of dinoprostone – misoprostol differences analyzed in the concomitant disease group we noticed that the time from the drug implementation to the onset of regular contraction activity of the uterus and to the delivery of the newborn was shorter for misoprostol as compared to dinoprostone and the differences were statistically significant (Tab. 5).

Table 1. Clinical characteristics of the study "ITT dinoprostone group" across study participants

	No concomitant disease			Any concomitant disease		
	Whole group [n = 147]	**Mothers < 35 y [n = 119]**	**Mothers 35 + [n = 28]**	**Whole group [n = 203]**	**Mothers < 35 y [n = 164]**	**Mothers 35 + [n = 39]**
Maternal age [years] Mean (SD) Median (Q1-Q3)	 30.4 (4.7) 30.0 (28.0–34.0)	 28.7 (3.5) 29.0 (27.0–31.0)	 37.4 (2.3) 37.0 (36.0–38.9)	 30.6 (4.4) 30.0 (28.0–33.0)	 29.1 (3.2) 29.0 (27.0–32.0)	 37.0 (2.1) 37.0 (35.0–38.0)
Weight at admission [kg] Mean (SD) Median (Q1-Q3)	[n = 83] 78.1 (12.6) 76.0 (69.0–85.0)	[n = 64] 77.9 (12.2) 74.9 (68.6–84.8)	[n = 19] 78.9 (14.2) 78.0 (70.0–88.0)	[n = 113] 81.3 (14.7) 79.0 (71.5–89.0)	[n = 90] 80.9 (15.1) 79.0 (70.8–89.0)	[n = 23] 82.7 (13.2) 80.0 (72.0–94.0)
Height [cm] Mean (SD) Median (Q1-Q3)	[n = 130] 167.2 (5.9) 168.0 (164.0– 171.0)	[n = 103] 167.9 (5.6) 168.0 (164.0–172.0)	[n = 27] 164.6 (6.6) 165.0 (160.0–170.0)	[n = 182] 165.6 (6.3) 165.0 (161.8–170.0)	[n = 147] 165.7 (6.3) 165.0 (162.0–170.0)	[n = 35] 164.9 (6.0) 165.0 (160.0–170.0)
Body mass index at admission [kg/m^2] Mean (SD) Median (Q1-Q3)	[n = 83] 27.7 (4.1) 27.1 (24.9–30.4)	[n = 64] 27.3 (3.7) 26.3 (24.7–29.3)	[n = 19] 29.4 (4.9) 30.1 (26.7–31.9)	[n = 113] 29.8 (4.8) 29.7 (25.9–32.1)	[n = 90] 29.6 (4.9) 29.7 (25.3–32.1)	[n = 23] 30.8 (4.4) 30.4 (27.7–33.3)
Number of pregnancies, n (%)						
1	97 (66.0%)	89 (74.8%)	8 (28.6%)	130 (64.0%)	113 (68.9%)	17 (43.6%)
2	27 (18.4%)	20 (16.8%)	7 (25.0%)	47 (23.2%)	37 (22.6%)	10 (25.6%)
≥ 3	23 (15.6%)	10 (8.4%)	13 (46.4%)	26 (12.8%)	14 (8.5%)	12 (30.8%)
Parity history (current delivery included), n (%)						
1	112 (76.2%)	99 (83.2%)	13 (46.4%)	155 (76.4%)	134 (81.7%)	21 (53.8%)
2	24 (16.3%)	17 (14.3%)	7 (25.0%)	34 (16.7%)	25 (15.2%)	9 (23.1%)
≥ 3	11 (7.5%)	3 (2.5%)	8 (28.6%)	14 (6.9%)	5 (3.0%)	9 (23.1%)
Nulliparous, n (%)	111 (75.5%)	100 (84.0%)	11 (39.3%)	151 (74.4%)	129 (78.7%)	22 (56.4%)
Miscarriage history, n (%)						
no	120 (81.6%)	103 (86.6%)	17 (60.7%)	169 (83.3%)	137 (83.5%)	32 (82.1%)
yes	27 (18.4%)	16 (13.4%)	11 (39.3%)	34 (16.7%)	27 (16.5%)	7 (17.9%)
Pre-ripening cervical characteristics, n (%)						
Dilatation ≤ 1 cm	138 (93.9%)	114 (95.8%)	24 (85.7%)	191 (94.1%)	154 (93.9%)	37 (94.9%)
Effacement ≤ 50%	140 (95.2%)	114 (95.8%)	26 (92.9%)	195 (96.1%)	157 (95.7%)	38 (97.4%)
Gestational age [weeks]# Mean (SD) Median (Q1-Q3)	 40.1 (1.0)* 40.0 (40.0–41.0)	 40.1 (1.0) 40.0 (40.0–41.0)	 40.1 (1.0) 40.0 (40.0–41.0)	 39.6 (1.4) 40.0 (39.0–41.0)	 39.6 (1.3) 40.0 (39.0–41.0)	 39.3 (1.6) 40.0 (38.0–40.0)
Estimated birth weight [g] Mean (SD) Median (Q1-Q3)	[n = 54] 3553.6 (49.8) 3615.5 (3241.3–3868.8)	[n = 48] 3554.6 (416.3) 3607.5 (3257.5–3874.3)	[n = 6] 3545.7 (388.6) 3653.0 (3115.0–3875.0)	[n = 54] 3529.2 (514.6) 3662.5 (3300.0–3862.5)	[n = 47] 3536.7 (510.2) 3671.0 (3358.0–3855.0)	[n = 7] 3478.1 (583.0) 3300.0 (3262.0–3975.0)

*p < 0.05 by the Shapiro-Wilk test for normal distribution; #at a time of administration of the first dose of the drug

Interestingly, there were no significant differences observed between investigated drugs in the duration of the 1st, 2nd, and 3rd stage of labor. The effect of age was noticed in the dinoprostone group only (Tab. 5).

Finally, neonatal outcomes were analyzed. In the Apgar score analyses the only statistically significant difference was found in the group of mothers with a disease treated by misoprostol, as in this group older (35 +) mothers delivered babies with lower Apgar scores on average (9.0 vs 9.7 pts, p < 0.001) and additionally, significantly higher proportion of babies with a score of ≤ 6 (7.4% vs 2.2%) and Apgar 7–8 (22.2% vs 3.3%) was observed (Tab. 6).

DISCUSSION

The comorbidities in a pregnant woman, like hypertension, diabetes mellitus, alloimmune disease, intrahepatic cholestasis or renal disease, may be a serious medical conditions influencing a wellbeing of a woman and her baby. The states mentioned are often indications for a labour induction. The several national obstetrical associations have established recommendations for most common diseases pointing out the need of the elective and active management before the due date at 40 weeks of gestation in order to reduce the perinatal and maternal risk [13,17–19]. There is still an open question, however, about the best (the saf-

Table 2. Clinical characteristics of the study "ITT misoprostol group" across study participants

	No concomitant disease			Any concomitant disease		
	Whole group [n = 93]	**Mothers < 35 y [n = 73]**	**Mothers 35 + [n = 20]**	**Whole group [n = 117]**	**Mothers < 35 y [n = 90]**	**Mothers 35 + [n = 27]**
Maternal age [years] Mean (SD) Median (Q1-Q3)	 31.1 (4.4)* 31.0 (28.5–34.0)	 29.5 (3.4) 30.0 (28.0–32.0)	 36.8 (2.5) 36.0 (35.0–38.0)	 30.8 (4.0) 31.0 (28.0–34.0)	 29.2 (3.0) 29.0 (27.0–31.3)	 36.1 (1.4) 36.0 (35.0–37.0)
Weight at admission [kg] Mean (SD) Median (Q1-Q3)	[n = 47]* 76.8 (10.9) 75.0 (69.0–83.0)	[n = 34] 76.6 (10.9) 75.0 (68.8–83.0)	[n = 13] 77.4 (11.4) 73.0 (70.0–84.5)	[n = 66] 84.2 (16.2) 83.0 (71.5–93.3)	[n = 46] 86.6 (16.5) 85.0 (75.8–94.5)	[n = 20] 78.6 (14.2) 77.0 (70.0–88.5)
Height [cm] Mean (SD) Median (Q1-Q3)	[n = 84] 165.7 (5.7) 166.5 (162.0–170.0)	[n = 68] 166.2 (5.6) 167.0 (163.0–170.0)	[n = 16] 163.4 (5.6) 164.5 (158.5–167.8)	[n = 110] 166.9 (5.7) 167.0 (163.8–170.0)	[n = 83] 166.9 (6.1) 167.0 (162.0–170.0)	 167.0 (4.3) 168.0 (164.0–170.0)
Body mass index at admission [kg/m^2] Mean (SD) Median (Q1-Q3)	 [n = 46] 28.5 (3.7)* 27.4 (25.9–30.4)	 [n = 34] 28.1 (3.4) 27.3 (25.7–29.8)	 [n = 12] 29.7 (4.2) 29.3 (26.1–31.7)	 [n = 66] 30.2 (5.4) 29.9 (25.9–33.4)	 [n = 46] 31.0 (5.5) 30.5 (27.3–33.8)	 [n = 20] 28.4 (4.6) 27.6 (24.6–31.8)
Number of pregnancies, n (%)						
1	52 (55.9%)	45 (61.6%)	7 (35.5%)	74 (63.2%)	58 (64.4%)	16 (59.3%)
2	20 (21.5%)	16 (21.9%)	4 (20.0%)	23 (19.7%)	17 (18.9%)	6 (22.2%)
≥ 3	21 (22.6%)	12 (16.4%)	9 (45.0%)	20 (17.1%)	15 (16.7%)	5 (18.5%)
Parity history (current delivery included), n (%)						
1	64 (68.8%)	54 (74.0%)	10 (50.0%)	95 (81.2%)	75 (83.3%)	20 (74.1%)
2	18 (19.4%)	14 (19.2%)	4 (20.0%)	17 (14.5%)	12 (13.3%)	5 (18.5%)
≥ 3	11 (11.8%)	5 (6.8%)	6 (30.0%)	5 (4.3%)	3 (3.3%)	2 (7.4%)
Nulliparous, n (%)	62 (66.7%)	53 (72.6%)	9 (45.0%)	88 (75.2%)	70 (77.8%)	18 (66.7%)
Miscarriage history (n, %)						
no	70 (75.3%)	57 (78.1%)	13 (65.0%)	89 (76.1%)	67 (74.4%)	22 (81.5%)
yes	23 (24.7%)	16 (21.9%)	7 (35.0%)	28 (23.9%)	23 (25.6%)	5 (18.5%)
Pre-ripening cervical characteristics, n (%)						
Dilatation ≤ 1 cm	86 (92.5%)	69 (94.5%)	17 (85.0%)	108 (92.3%)	83 (92.2%)	25 (92.6%)
Effacement ≤ 50%	85 (91.4%)	67 (91.8%)	18 (90.0%)	112 (95.7%)	85 (94.4%)	27 (100.0%)
Gestational age [weeks]# Mean (SD) Median (Q1-Q3)	 39.7 (1.8)* 40.6 (38.9–40.9)	 39.4 (1.8) 40.0 (39.0–41.0)	 38.9 (1.8) 40.0 (37.3–40.0)	 38.9 (2.0) 40.0 (38.0–40.0)	 39.0 (2.0) 40.0 (38.0–40.0)	 38.6 (2.0) 39.0 (38.0– 40.0)
Estimated birth weight [g] Mean (SD) Median (Q1-Q3)	[n = 54] 3325.0 (552.1)* 3450.0 (3000.0–3747.8)	[n = 43] 3375.4 (513.2) 3456.0 (3075.0–3800.0)	[n = 11] 3127.9 (675.1) 3250.0 (2800.0–3500.0)	[n = 59] 3288.5 (608.6) 3400.0 (2922.0–3786.0)	[n = 49] 3302.0 (576.3) 3400.0 (2939.0–3758.0)	 3222.4 (780.7) 3414.5 (2446.3–3850.0)

*$p < 0.05$ by the Shapiro-Wilk test for normal distribution; #at a time of administration of the first dose of the drug

est, and effectively leading to vaginal birth) way of a labour induction in a specific clinical situation. Several of observational studies have suggested that induction of labour at term is associated with reduction of perinatal mortality and morbidity and maternal complications [20] without increasing the Caesarean rate risk [21–22].

In our investigation we tried to reveal whether one of the two prostaglandins, dinoprostone or misoprostol, preponderate the other considering effectiveness and safety in high-risk pregnancy. Our study showed statistically important differences in Caesarean section rate and time intervals from drug implementation to delivery between groups. Our findings, however, are difficult to compare with other results, as, by our knowledge, there are no such studies published. The study investigated pregnancies with different kinds of complications presented that misoprostol usage in a group of small-for-gestational age neonates at delivery was not associated with an increased risk of Caesarean section when compared with dinoprostone or Foley catheter preinduction. The authors concluded then, that all investigated cervical ripening agents had similar efficacy and safety in small-for-gestational age pregnancies which is not in consistence with our results [23]. On the other hand, literature data indicate an increased risk of Caesarean sec-

Table 3. Mode of delivery and indications for caesarean section across drug and the presence of concomitant disease (ITT groups)

	Dinoprostone				Misoprostol				p value for dinoprostone vs misoprostol in 'any concomitant disease' group
	No concomitant disease [n = 147]	Any concomitant disease [n = 203]	No disease vs any concomitant disease		No concomitant disease [n = 93]	Any concomitant disease [n = 117]	No disease vs any concomitant disease		
			Mothers < 35 y [283]	Mothers 35 + [n = 67]			Mothers < 35 y [n = 163]	Mothers 35 + [n = 47]	
Caesarean section	27.2%	33.5%	25.2% vs 32.9%	35.7% vs 35.9%	31.2%	47.9%	27.4% vs 42.2%	45.0% vs 66.7%	$p^{chi2} = 0.013$
	$p^{chi2} = 0.241$		$P^{MH} = 0.256$		$p^{chi2} = 0.016$		$P^{MH} = 0.022$		
Emergency Caesarean delivery out of total deliveries	12.2%	14.8%	11.8% vs 14.6%	14.3% vs 15.4%	20.4%	35.9%	15.1 % vs 31.1%	40.0% vs 51.9%	$p^{chi2} < 0.001$
	$p^{chi2} = 0.532$		$P^{MH} = 0.256$		$p^{chi2} = 0.015$		$P^{MH} = 0.022$		
Emergency Caesarean delivery out of total Caesarean sections	[n = 40] 45.0%	[n = 68] 44.1%	[n = 30 vs 54] 46.7% vs 44.4%	[n = 10 vs 14] 40.0% vs 42.9%	[n = 29] 65.5%	[n = 56] 75.0%	[n = 20 vs 38] 55.0% vs 73.7%	[n = 9 vs 18] 88.9% vs 77.8%	$p^{chi2} < 0.001$
	$p^{chi2} = 0.999$		$P^{MH} = 0.925$		$p^{chi2} = 0.447$		$P^{MH} = 0.515$		
Vaginal delivery	72.8%	66.5%	74.8% vs 67.1%	64.3% vs 64.1%	68.8%	52.1%	72.6% vs 57.8%	55.0% vs 33.3%	$p^{chi2} = 0.013$
	$p^{chi2} = 0.241$		$P^{MH} = 0.256$		$p^{chi2} = 0.016$		$P^{MH} = 0.022$		
Indications for Caesarean section	[n = 40]	[n = 68]	[n = 30 vs 54]	[n = 10 vs 14]	[n = 29]	[n = 56]	[n = 20 vs 38]	[n = 9 vs 18]	
• Foetal distress	45.0%	36.8%	46.7% vs 38.9%	40.0% vs 28.6%	62.1%	62.5%	50.0% vs 57.9%	88.9% vs 72.2%	
• Preeclampsia	–	–	–	–	0%	3.6%	0% vs 2.6%	0% vs 5.6%	
• Placenta abruption	0%	7.4%	0% vs 5.6%	0% vs 14.3%	0%	8.9%	0% vs 13.2%	–	
• Labour arrest during first stage (First-stage Caesarean)	40.0%	48.5%	40.0% vs 48.1%	40.0% vs 50.0%	20.7%	25.0%	25.0% vs 26.3%	11.1% vs 22.2%	
• Labour arrest during second stage (Second-stage Caesarean)	15.0%	7.4%	13.3% vs 7.4%	20.0% vs 7.1%	4 (13.8%)	0 (0%)	20.0% vs 0%	–	
• Fetal hand prolapse	–	–	–	–	3.4%	0%	5.0% vs 0%	–	
	$p^{F} = 0.161$		#		$p^{F} = 0.015$		#		$p^{F} = 0.002$

^{chi2} — the chi-squared test with 1 degree of freedom; F — the exact Fisher's test; # — due to no data in all contingency tables the p-value for the common odds ratio has not been estimated; MH — the Cochran-Mantel-Haenszel statistics

Table 4a. Postpartum complications among study participants (ITT groups)

	Dinoprostone				Misoprostol				p value for dinoprostone vs misoprostol in 'any concomitant disease' group
	No concomitant disease [n = 147]	Any concomitant disease [n = 203]	No disease vs any concomitant disease		No concomitant disease [n = 93]	Any concomitant disease [n =117]	No disease vs any concomitant disease		
			Mothers < 35y [283]	Mothers 35 + [n = 67]			Mothers < 35y [n =163]	Mothers 35 + [n = 47]	
Any complication	14.3%	10.8%	11.8% vs 11.0%	25.0% vs 10.3%	15.1%	9.4%	12.3% vs 6.7%	25.0% vs 18.5%	$p^{chi2} = 0.709$
	$p^{chi2} = 0.410$		$P^{MH} = 0.420$		$p^{chi2} = 0.283$		$P^{MH} = 0.275$		
Blood transfusion	2.7%	2.5%	1.7% vs 2.4%	7.1% vs 2.6%	2.2%	0.9%	2.7% vs 0%	0% vs 3.7%	$p^{F} = 0.421$
	$P^{F} = 0.999$		$P^{MH} = 0.850$		$p^{F} = 0.585$		$P^{MH} = 0.835$		
Uterine hyper-stimulation	1.4%	0%	0.8% vs 0%	3.6% vs 0%	2.2%	0.9%	2.7% vs 1.1%	0% vs 0%	$p^{F} = 0.366$
	$P^{F} = 0.176$		$P^{MH} = 0.343$		$p^{F} = 0.585$		$P^{MH} = 0.855$		
Curettage after delivery	8.2%	7.9%	8.4% vs 8.5%	7.1% vs 5.1%	8.6%	3.4%	6.8% vs 2.2%	15.0% vs 7.4%	$p^{chi2} = 0.151$
	$p^{chi2} = 0.999$		$P^{MH} = 0.916$		$p^{chi2} = 0.138$		$P^{MH} = 0.180$		
Episiotomy	40.1%	40.4%	45.4% vs 44.5%	17.9% vs 23.1%	28.0%	27.4%	32.9% vs 28.9%	10.0% vs 22.2%	$p^{chi2} = 0.021$
	$p^{chi2} = 0.999$		$P^{MH} = 0.956$		$p^{chi2} = 0.999$		$P^{MH} = 0.926$		
Rupture of perineum (any type)	19.0%	13.3%	16.8% vs 12.2%	28.6% vs 17.9%	16.1%	12.0%	17.8% vs 13.3%	10.0% vs 7.4%	$p^{chi2} = 0.862$
	$p^{chi2} = 0.180$		$P^{MH} = 0.189$		$p^{chi2} = 0.425$		$P^{MH} = 0.519$		
Rupture of perineum									
• No rupture	81.0%	86.7%	83.2% vs 87.8%	71.4% vs 82.1%	83.9	88.0%	82.2% vs 86.7%	90.0% vs 92.6%	
• I-stage	15.6%	12.3%	13.4% vs 11.0%	25.0% 17.9%	15.1%	6.8%	16.4% vs 7.8%	10.0% vs 3.7%	
• II-stage	1.4%	1.0%	1.7% vs 1.2%	0% vs 0%	1.1%	3.4%	1,4% vs 4.4%	0% vs 0%	
• III-stage	2.0%	0%	1.7% vs 0%	3.6% vs 0%	0%	1.7%	0% vs 1.1%	0% vs 3.7%	
	$p^{F} = 0.149$		#		$p^{F} = 0.093$		#		$p^{F} = 0.036$

chi2 — the chi-squared test with 1 degree of freedom; F — the exact Fisher's test; # — due to no data in all contingency tables the p-value for the common odds ratio has not been estimated; MH — the Cochran-Mantel-Haenszel statistics

Table 4b. Postpartum complications among study participants in the group receiving both drugs (i.e. dinoprostone and misoprostol)

	Dinoprostone followed by misoprostol			
	No concomitant disease [n = 39]	Any concomitant disease [n = 61]	No disease vs any concomitant disease	
			Mothers < 35 y [n = 89]	Mothers 35 + [n = 11]
Any complication	23.1%	16.4%	15.2% vs 14.3%	66.7% vs 40.0%
	$p^{chi2} = 0.282$		$P^{MH} = 0.824$	
Blood transfusion	5.1%	4.9%	3.0% vs 3.6%	16.7% vs 20.0%
	$P^{F}=0.999$		$P^{MH}=0.780$	
Uterine hyper-stimulation	5.1%	0%	3.0% vs 0%	16.7% vs 0%
	$P^{F} = 0.150$		$P^{MH} = 0.400$	
Curettage after delivery	7.7%	9.8%	9.1% vs 10.7%	0% vs 0%
	$P^{F} = 0.999$		$P^{MH} = 0.906$	
Episiotomy	43.6%	37.7%	48.5% vs 41.1%	16.7% vs 0%
	$p^{chi2} = 0.676$		$P^{MH} = 0.521$	
Rupture of perineum (any type)	10.3%	14.8%	9.1% vs 14.3%	16.7% vs 20.0%
	$p^{chi2} = 0.561$		$P^{MH} = 0.$	
Rupture of perineum				
No rupture	89.7%	85.2%	90.9% vs 85.7%	83.3% vs 80.0%
I-stage	7.7%	13.1%	9.1% vs 12.5%	0% vs 20.0%
II-stage	0%	1.6%	0% vs 1.8%	0% vs 0%
III-stage	2.6%	0%	0% vs 0%	16.7% vs 0%
	$P^{F} = 0.471$		#	

^{chi2} — the chi-squared test with 1 degree of freedom; F — the exact Fisher's test; # — due to no data in all contingency tables the p-value for the common odds ratio has not been estimated; MH — the Cochran-Mantel-Haenszel statistics

tion in women with pre-eclampsia in the dinoprostone induced labour group, regardless of the number of deliveries and gestational age, but no differences were found in the group with hypertension without pre-eclampsia and in the group without hypertensive diseases at all [24]. This is in conformity with our data showing no differences according to presence of concomitant disease in dinoprostone group. There were also no differences in the risk of Caesarean section, depending on the gestational age in the dinoprostone induced group of women with gestational hypertension [25]. In view of these results, we speculate that the higher rate of Caesarean rate in the misoprostol group might be related to the comorbidity of pregnant women with no such effect in the dinoprostone group.

No differences were found in perinatal outcomes when misoprostol was used in the groups with and without hypertensive diseases [26] as well as the dinoprostone insert did not adversely affect the perinatal outcomes compared to the group of women with spontaneous or oxytocin-stimulated delivery in the group of women with hypertension [27]. In our study, only babies in the subgroup of mothers over 35 years old with any concomitant disease had statistically significant lower average Apgar scores comparing with younger mothers with comorbidities. These findings require more detailed analyses on larger study groups. Regarding the neonatal safety of a preinduction of a labour in a pregnancy with any comorbidity, because only the Apgar points at the first minute were assessed, we cannot draw a definite conclusion. Nevertheless, the data we have gained show no differences in Apgar score between dinoprostone and misoprostol in any concomitant disease groups.

In our study we did not find significant differences in postpartum complications among pregnant women with any concomitant disease after labour induction using either dinoprostone or misoprostol, what is similar to other retrospective study concerning the induction of labour in hypertensive and normotensive patients with misoprostol and dinoprostone vaginal inserts. The authors also showed no differences in time to achieve active labour or to overall delivery when considering such confounding variables as BMI, gestational age, Bishop's scale or the time from drug administration to the active phase of labour [28]. Nevertheless, they showed that women with hypertension need more time to achieve active labour or overall delivery both in misoprostol and dinoprostone groups. Similarly, it has been proven that pregnant women with diabetes need more time to maturation of the cervix measured by the Bishop scale and simply need a longer time to reach the active stage of

Table 5. Time intervals to delivery across drug and the presence of concomitant disease (ITT groups)

	Dinoprostone				Misoprostol				p value for dinoprostone vs misoprostol in 'any concomitant disease' group
	No concomitant disease [n = 147]	Any concomitant disease [n = 203]	Any concomitant disease		No concomitant disease [n = 93]	Any concomitant disease [n = 117]	Any concomitant disease		
			Mothers < 35y [n = 164]	Mothers 35 + [n = 39]			Mothers < 35y [n = 90]	Mothers 35 + [n = 27]	
Time admission to delivery (vaginal or Caesarean section) [h] Mean, (SD) Median (Q1–Q3)	67.3 (73.0)* 51.2 (31.3–81.3)	88.1 (95.1)* 63.4 (35.5–97.8)	92.9 (102.0)* 63.9 (35.5–103.4)	67.6 (54.2)* 56.8 (32.3–82.3)	47.0 (69.3)* 25.8 (14.0–44.0)	62.1 (133.0)* 23.2 (13.9–45.8)	61.4 (145.0)* 22.7 (14.0–45.4)	64.6 (83.4)* 33.3 (12.7–82.5)	$P^{UMW} < 0.001$
	$P^{UMW} = 0.007$		$P^{UMW} = 0.185$		$P^{UMW} = 0.896$		$P^{UMW} = 0.561$		
Time drug application to delivery (vaginal or Caesarean section) [h] Mean, (SD) Median (Q1–Q3)	35.6 (25.0)* 28.8 (13.5–51.9)	42.8 (29.1)* 36.0 (18.6–59.0)	44.0 (30.4)* 36.9 (18.5–65.1)	37.7 (22.8) 35.0 (21.5–54.5)	14.5 (13.8)* 11.0 (8.0–17.4)	12.9 (8.3)* 11.0 (7.8–15.9)	12.9 (8.3)* 11.0 (8.0–15.2)	12.9 (8.4)* 10.5 (7.0– 16.8)	$P^{UMW} < 0.001$
	$P^{UMW} = 0.023$		$P^{UMW} = 0.447$		$P^{UMW} = 0.445$		$P^{UMW} = 0.727$		
Time drug application to vaginal delivery (Caesarean sections excluded) [h] Mean, (SD) Median (Q1–Q3)	[n = 107] 31.3 (24.4)* 26.0 (12.0–47.2)	[n = 135] 39.6 (28.6)* 33.8 (15.7–54.0)	[n = 110] 40.7 (30.0)* 34.4 (16.0–54.2)	[n = 25] 34.7 (21.1) 32.0 (15.2–51.9)	[n = 64] 15.1 (15.6)* 11.0 (8.7–17.8)	[n = 61] 12.7 (5.3)* 11.0 (9.0–15.0)	[n = 52] 14.0 (12.7)* 11.0 (9.0–14.4)	[n = 9] 13.0 (5.9) 11.4 (7.8– 16.9)	$P^{UMW} < 0.001$
	$P^{UMW} = 0.014$		$P^{UMW} = 0.662$		$P^{UMW} = 0.942$		$P^{UMW} = 0.924$		
Time drug application to the beginning of a labour [h] Mean, (SD) Median (Q1–Q3)	[n = 115] 25.3 (23.0)* 20.9 (5.8–40.8)	[n = 144] 33.5 (27.7)* 27.2 (10.9– 47.9)	[n = 118] 34.4 (29.1)* 27.2 (10.2–48.1)	[n = 26] 29.7 (20.3) 25.3 (10.9–48.4)	[n = 68] 9.9 (15.0)* 6.2 (3.9–11.5)	[n = 61] 7.3 (5.4)* 5.8 (3.8–9.3)	[n = 52] 7.2 (5.3)* 5.8 (3.9–8.4)	[n = 9] 7.7 (6.1) 5.7 (2.8–11.0)	$P^{UMW} < 0.001$
	$P^{UMW} = 0.009$		$P^{UMW} = 0.858$		$P^{UMW} = 0.425$		$P^{UMW} = 0.908$		
I stage of labour duration [h] Mean, (SD) Median (Q1–Q3)	[n = 115] 5.4 (2.7)* 5.0 (3.0–7.0)	[n = 144] 5.2 (2.2)* 5.0 (4.0–6.0)	[n = 118] 5.3 (2.2)* 5.0 (4.0–6.3)	[n = 26] 4.4 (2.2)* 4.0 (3.0–6.0)	[n = 68] 4.8 (2.2)* 4.8 (3.0–6.0)	[n = 61] 4.8 (2.2)* 4.0 (4.0–6.0)	[n = 52] 4.8 (2.3)* 4.0 (3.0–6.0)	[n = 9] 4.8 (1.1)* 4.0 (4.0–5.8)	$P^{UMW} = 0.192$
	$P^{UMW} = 0.796$		$P^{UMW} = 0.025$		$P^{UMW} = 0.991$		$P^{UMW} = 0.530$		
II stage of labour duration]min] Mean, (SD) Median (Q1–Q3)	[n = 111] 37.7 (33.4)* 30.0 (15.0–60.0)	[n = 135] 32.6 (28.2)* 20.0 (10.0– 45.0)	[n = 110] 33.1 (27.5)* 20.0 (15.0–45.0)	[n = 25] 30.4 (31.3)* 15.0 (7.5–45.0)	[n = 68] 30.0 (28.6)* 20.0 (10.0– 40.0)	[n = 61] 34.7 (31.6)* 25.0 (10.0–47.0)	[n = 52] 35.8 (32.1)* 30.0 (10.0– 54.8)	[n = 9] 27.8 (29.1)* 15.0 (12.5–35.0)	$P^{UMW} = 0.791$
	$P^{UMW} = 0.246$		$P^{UMW} = 0.221$		$P^{UMW} = 0.266$		$P^{UMW} = 0.483$		
III stage of labour duration [min] Mean, (SD) Median (Q1–Q3)	[n = 106] 8.6 (4.2)* 10.0 (5.0–10.0)	[n = 127] 8.9 (4.9)* 10.0 (5.0–10.0)	[n=104] 9.1 (5.1)* 10.0 (5.0–10.0)	[n=23] 8.0 (3.6)* 10.0 (5.0–10.0)	[n = 63] 8.8 (5.6)* 10.0 (5.0–10.0)	[n = 60] 9.3 (4.8)* 10.0 (5.0–10.0)	[n = 51] 9.0 (4.2)* 10.0 (5.0–10.0)	[n = 9] 11.1 (7.4)* 10.0 (7.5–10.0)	$P^{UMW} = 0.373$
	$P^{UMW} = 0.770$		$P^{UMW} = 0.383$		$P^{UMW} = 0.197$		$P^{UMW} = 0.450$		

* -p < 0.05 by the Shapiro-Wilk test for normal distribution; UMW — the U Mann-Whitney test;

Table 6. Neonatal outcomes across drug and the presence of concomitant disease (ITT groups)

	Dinoprostone				Misoprostol				p value for dinoprostone vs misoprostol in 'any concomitant disease' group
	No concomitant disease [n = 147]	Any concomitant disease [n = 203]	Any concomitant disease		No concomitant disease [n = 93]	Any concomitant disease [n = 117]	Any concomitant disease		
			Mothers < 35y [n = 164]	Mothers 35 + [n = 39]			Mothers < 35y [n = 90]	Mothers 35 + [n = 27]	
Apgar score (points) Mean, (SD) Median (Q1–Q3)	9.8 (0.6)* 10.0 (10.0–10.0)	9.6 (1.1)* 10.0 (10.0–10.0)	10.0 (1.2)* 10.0 (10.0–10.0)	9.6 (0.9)* 10.0 (9.0–10.0)	9.4 (1.6)* 10.0 (10.0–10.0)	9.6 (1.1)* 10.0 (10.0–10.0)	9.7 (0.8)* 10.0 (10.0–10.0)	9.0 (1.5)* 10.0 (8.0–10.0)	$p^{UMW} = 0.216$
	$p^{UMW} = 0.164$		$p^{UMW} = 0.079$		$P^{UMW} = 0.883$		$P^{UMW} < 0.001$		
Apgar score ≤ 6 points at the 1st min (n, %)	1.4%	3.0%	3.7%	0%	8.6%	3.4%	2.2%	7.4%	
Apgar score 7-8 points at the 1st min (n, %)	2.7%	4.9%	3.7%	10.3%	4.3%	7.7%	3.3%	22.2%	
Apgar score 9–10 points at the 1st min (n, %)	95.9%	92.1%	92.6%	89.7%	87.1%	88.9%	94.4%	70.4%	
	$p^{F} = 0.368$		$p^{F} = 0.150$		$p^{chi2} = 0.175$		$p^{F} = 0.003$		$p^{F} = 0.548$
Birth weight [g] Mean, (SD) Median (Q1–Q3)	[n = 146] 3623 (417) 3625 (3320–3955)	3459 (450)* 3510 (3200–3760)	3470.5 (421.7)* 3515.0 (3202.5–3760.0)	3410.8 (556.5) 3510.0 (3110.0–3800.0)	3385 (530) 3420 (3045–3750)	3293 (565)* 3330 (2970–3700)	3304.2 (543.3)* 3335.0 (3032.5–3682.5)	3256.3 (643.1) 3250.0 (2750.0–33880.0)	$p^{UMW} = 0.011$
	$p^{UMW} = 0.001$		$p^{UMW} = 0.898$		$P^{UMW} = 0.305$		$P^{UMW} = 0.764$		
Birth length [cm] Mean, (SD) Median (Q1–Q3)	[n = 146] 56.0 (3.0)* 56.0 (54.0–58.0)	55.2 (2.9)* 56.0 (53.0–57.0)	55.2 (2.7)* 56.0 (53.0–57.0)	55.2 (3.6) 55.0 (53.0– 57.0)	54.9 (3.4) 55.0 (53.0–57.0)	54.4 (3.3)* 55.0 (53.0–57.0)	54.6 (3.4)* 55.0 (53.0–57.0)	53.9 (3.0) 54.0 (52.0–56.0)	$p^{UMW} = 0.050$
	$p^{UMW} = 0.008$		$p^{UMW} = 0.880$		$P^{UMW} = 0.372$		$P^{UMW} = 0.302$		
Female (n, %)	46.3%	49.8%	48.8%	53.8%	47.3%	55.6%	51/1%	70.4%	$p^{chi2} = 0.353$
	$p^{chi2} = 0.588$		$p^{chi2} = 0.597$		$p^{chi2} = 0.267$		$p^{chi2} = 0.121$		

* -p < 0.05 by the Shapiro-Wilk test for normal distribution; UMW — the U Mann-Whitney test; ^{chi2} — the chi-squared test with 1degree of freedom; F — the exact Fisher's test; # — due to no data in all contingency tables the p-value for the common odds ratio has not been estimated

a labor, but without differences in its duration. The study also showed that women with diabetes needed a statistically significant longer time to give birth after administration of prostaglandins when compared to women without diabetes regardless the prostaglandin used [29]. Both cited studies are partially in agreement to our study showing pregnant women with any concomitant disease need statistically more time from drug application to the beginning of labour or to the delivery in dinoprostone preinduction group with the opposite, but not statistically important, observations in misoprostol group. The present analysis of women with comorbidities undergoing labour preinduction using misoprostol vaginal inserts showed strong statistical differences in time intervals from drug implementation to active phase achievement and to delivery when comparing with dinoprostone gel. That may lead to the conclusion of obtaining a faster effect of misoprostol used in the group of pregnant women with concomitant diseases.

Our study has several strengths, as the access to the data enables us to analyze a fair number of pregnant women, which increases the power of the study, the analysis of clinical data using cohort retrospective design provided an opportunity to assess effectiveness rather than efficacy, but in that way provided information on how the investigated treatments lead to the effect in real clinical practice. Next, we were able to analyze the clinical features of mothers and her babies which provided information on safety. An additional benefit is the ability to analyze the effects across the mother's age categories.

The provided results however are not free from some limitations, as mothers with a disease were investigated as one group, but the group was represented by different comorbidities. Primarily, we believed, that our investigation would be able to answer whether there is an effect of concomitant diabetes or hypertension in pregnancy on the pregnancy outcomes if labour induction took place, but due to the limited number of women with these comorbidities, we could not provide reliable answers. Additionally, our study is a retrospective cohort which, due to lack of randomization, may be a source of bias.

CONCLUSIONS

The presented study has shown that concomitant disease during pregnancy may have an impact on some safety and effectiveness outcomes. Pregnant women with a disease compared to healthy ones had higher risk of Caesarean section if were treated by misoprostol, however, this effect was not observed for dinoprostone. On the other side, the presence of a disease caused the time between drug implementation and delivery was longer if dinoprostone was used. Dinoprostone was also more beneficial than misoprostol to get vaginal delivery if these two drugs were compared exclusively in the group of mothers with a disease. Considering child's health, the presence of a disease and mother's age over 35 was associated with lower Apgar scores if preinduction method was by misoprostol.

Although, our results are novel in this area, and require further investigation, we believe, they may help clinicians to make better clinical decisions even at this stage of research.

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Conflict of interest

The authors declare no conflict of interest.

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On the border of medical specialties: ovarian metastasis from colorectal cancer

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ABSTRACT

The colon cancer (CC) is the fourth most common cancer in the world. It is associated with metastatic spread in 50% of cases in the course of the disease. Common sites for synchronous metastases from colorectal cancer are the lung, liver, peritoneum, bone and brain. The frequency of ovarian metastasis from CC varies widely from 1.6 to 7.4%. This type of metastasis is difficult to distinguish clinically from primary ovarian neoplasms. We present a case of a 49-years old woman admitted to the Department of General Surgery at the 5th Military Clinical Hospital in Cracow for elective surgery for metastatic obstructive sigmoid cancer. Computed tomography (CT) showed a large tumor in the right ovarian field. Brief recommendations regarding that issue based on the available literature has been summarized as well.

Key words: colorectal cancer; metastasis; ovarian tumor

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INTRODUCTION

The colon cancer (CC) is the fourth most common cancer in the world. About 576,000 men and 521,000 women, respectively, are projected to be diagnosed with CC in 2018. This incidence constitutes a 1.51% cumulative risk of CC among men aged 0–74 years, and a 1.12% risk among women. [1]. CC is associated with metastatic spread in 50% of cases in the course of disease [2]. Common sites for synchronous metastases from colorectal cancer are the lung, liver, peritoneum, bone and brain [3]. The frequency of ovarian metastasis from CC varies widely from 1.6 to 7.4% (the rate of ovarian metastases from CC is reported to be up to 30%, but this refers to autopsy patients who died from CC). This type of metastasis is difficult to distinguish clinically from primary ovarian neoplasms — even up to 45% of CC metastases are clinically mistaken for primary ovarian tumors. The optimal first-line treatment strategy is debatable [3–6].

CASE REPORT

We present a case of a 49-years old woman admitted to the Department of General Surgery at the 5th Military Clinical Hospital in Cracow for elective surgery for metastatic obstructive sigmoid cancer.

She was diagnosed with a growing tumor in the meso- and hypogastric area and abdominal pain. Computed tomography (CT) showed a large tumor (15 × 11 × 9 cm) in the right ovarian field (Fig.1). CT also confirmed the presence of the sigmoid wall thickening on the section about 7 cm long with blurred borders. Furthermore, numerous minor liver lesions were noted, most likely metastatic on imaging.

Colonoscopy revealed in the sigmoid (18 cm upwards from the anal sphincter) a circular obstructive infiltrate impervious to the endoscope. Biopsy specimen on histopathology confirmed the diagnosis of adenocarcinoma.

Due to impending bowel obstruction patient was scheduled for primary resection of sigmoid with further systemic therapy afterwards. On admission patient was in good general condition, no vomiting, normosthenic, without signs of cachexia (normal total protein and albumin level); abdominal wall arched at the level of the chest, with tumor palpable in the right iliac fossa, no peritoneal signs and normal peristalsis. Laboratory tests found mild anemia (HGB

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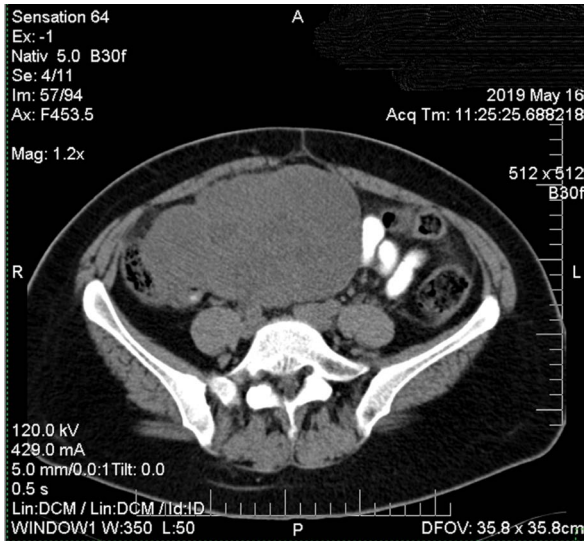

Figure 1. Computed tomography showed a large tumor in the right ovarian field

10.8 g/dL) and elevated tumor markers (CEA 11 ng/mL, Ca 19–9 125 IU/mL, Ca 125 362,2 IU/mL).

Intraoperatively, the right and centrally located 25 × 15 cm tumor was found, as well as the lower sigmoid tumor of 5–6 cm in size, significantly narrowing the intestinal lumen. Additionally, multiple neoplastic seeds were noted in the pouch of Douglas and massive metastatic lesions of both liver lobes. Surgery was performed as planned (sigmoid resection with primary anastomosis); additionally, liver metastasis biopsy was done. Remnant of the right ovary and right oviduct extensively infiltrated by the tumor were noted and resected en bloc as well. Clinical diagnosis of metastasis to the right ovary was seen. Postoperative course was uneventful, and the patient was discharged home.

Final histopathological report confirmed the diagnosis of sigmoid cancer (G2 adenocarcinoma pT3 N0 M1a). The infiltration to the right ovary was metastatic, while the sample taken from the liver was non-diagnostic on histopathology.

DISCUSSION

Apart from primary ovarian malignancies, which warrant appropriate gynecological diagnostic work-up, ovaries are also relatively common site of secondary tumors. According to Yvonne et al., metastasis to the ovary accounted for 15% of all ovarian malignancies identified and the gastrointestinal tract was the most common primary site (39%) [11]. During the initial laparotomy, up to 3.4–10.3% of patients with CC are found to have synchronous metastases to the ovary [6]. An analysis by Segelman et al. [13], (> 3000 patients with CC) reported total incidence rate of synchronous ovarian metastases reaching 1.1%. Main results of this study are shown in Table 1. Metastases are commonly bilateral

Table 1. Incidence of metastases to the ovary in patients with colon cancer according to Segelman et al. [13], 2010

No. of metastases to the ovary in patients with CC (%)	
Synchronous	**Metachronous**
34/3712 (1.1%)	22/1971 (1.1%)

CC — colon cancer

on presentation and usually not larger than 10 cm in its largest dimension [6, 10, 11] — on the contrary of the case presented here (15 cm). They are also more commonly seen in premenopausal women [10].

The process by which CC metastasizes more frequently to the ovary versus other intraabdominal organs is still not clearly explained. Some theories suggest hematogenous spread or contact dissemination (migration of malignant cells through peritoneal space) [3].

Hematogenous pathway is convergent with the fact that some authors indicate that a younger premenopausal female which has higher blood flow to the premenopausal ovary present more often with ovarian metastasis [4, 6, 8].

The optimal treatment for ovarian metastasis from CC depends on the advancement of disease, whether solitary metastasis or multiple foci are present, general status of the patient and numerous other clinical factors. Multidisciplinary approach is mandatory to include at least gynecologists, surgeons and medical oncologists in the decision process. Some recommend surgery for metastatic ovarian lesion if resectable [3]. It is claimed that even if only one ovary is involved, bilateral oophorectomy should be performed, as autopsy series frequently shows bilateral ovarian involvement on the histopathology despite being clinically limited to one ovary only [6, 9]. The prognosis is generally poor and long-term survival has been reported relatively rare, as ovarian involvement reflects massively advanced disease with microscopic intraperitoneal spread (even if clinically negative on inspection). In CC the detection rate of malignant cells in peritoneal effusion has been reported as 1.4–35.5%. Due to the wide range of cytologic positivity rate for malignant cells in peritoneal effusion, cytologic evaluation of peritoneal fluid is not routinely performed, thus peritoneal fluid has not been regarded as a reliable indicator [12]. The median survival in patients with residual disease after ovariectomy for metastasis is 10 months. [3 ,6]. A better prognosis have females without concomitant peritoneal spread. According to Miller et al., they had median survival time 25.2 months versus 10.8 months [6, 8, 10]. Considering generally poor prognosis some authors suggested palliative surgical management only or emergency surgery, leaving the patient mainly to systemic therapy or best supportive care if not fit enough or with very limited expected survival [6].

Table 2. General remarks on ovarian metastasis from colon cancer

General remarks on ovarian metastasis from CC	
1.	Prophylactic excision and collection of tissue samples of normal-appearing ovaries in patients with CC is neither necessary nor supported by data.
2.	Clinical suspicion of ovarian metastasis requires detailed inspection of the entire abdominal cavity in the search of other primary or secondary tumors.
3.	After ruling-out other than ovarian intraabdominal seeds which could not be radically resected/ablated and following radical resection of colon segment with primary focus, unilateral (in premenopausal women, involving the diseased ovary) or bilateral (in postmenopausal women, involving the diseased and the contralateral healthy ovary) ovariectomy is justified.
4.	Ovariectomy with metachronic metastases from CC is warranted if primary or secondary excision or ablation of other extragonadal disease lesions is possible.
5.	Different guidelines apply to patients with CC who have hereditary syndromes like HNPCC, Lynch syndrome, Peutz-Jeghers syndrome and BRCA1 and BRCA2 gene mutation-associated syndromes. In this case, the risk of primary ovarian cancer is higher than in the general population, therefore these patients, in addition to treatment of CC, require an appropriate and comprehensive prophylactic plan, including the ovaries.
Based on: Wysocki W. et al. [16], 2013	

CC — colon cancer

Due to impending bowel obstruction, this particular patient was scheduled for primary resection of sigmoid with further systemic therapy afterwards, however in the non-urgent settings an International Ovarian Tumor Analysis protocol is recommended [14].

The concept of prophylactic ovariectomy in patients with CC, described in the past literature, resulted from observed clinical predilection of CC to metastasize to the ovaries. However, there are only a few evidence-based data concerning this issue with conclusions which did not supported the rationale for prophylactic ovariectomy [15]. It seems that prophylactic adnexectomy does not provide any additional benefit [16, 17]. Brief recommendations regarding that issue based on the available literature has been summarized in the Table 2.

CONCLUSION

We conclude that a female patient, especially in the premenopausal age with a mass in the ovarian region, should always be also diagnosed for ovarian metastasis deriving from other intraabdominal malignancies. Surgeons and gynecologists who had diagnosed an ovarian metastasis from an unknown origin should keep in mind that the CC is most likely the primary tumor. Multidisciplinary approach is mandatory, as the optimal treatment might encompass gynecologists, surgeons and medical oncologists. Family history taking can be helpful during diagnostic process, with particular focus on hereditary syndromes with increased colon cancer risk — including Hereditary Non Polyposis Colorectal Cancer (HNPCC) and Familial Adenomatous Polyposis (FAP), as well as inflammatory bowel diseases (Crohn's disease, ulcerative colitis) which as well increase the risk of colorectal cancer in younger age women.

Conflict of interest

None declared.

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Inflammatory rheumatic diseases and pregnancy

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ABSTRACT

Pregnancy in a patient diagnosed with systemic connective tissue disorder is a challenge that requires a close co-operation between a rheumatologist and gynaecologist. Good control over the activity of the underlying condition and the choice of appropriate time for planning a pregnancy have direct effect on the pregnancy results in these patients. Applying gynaecological supervision adequate to the increased risk of complications is also very important.

The aim of this study is to present the current knowledge on the care over pregnant patients with systemic connective tissue diseases and to draw attention to the importance of pregnancy planning in this group of patients.

Key words: inflammatory rheumatic diseases; pregnancy; lupus erythematosus; adverse pregnancy outcomes

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INTRODUCTION

Systemic autoimmune connective tissue diseases are a heterogeneous group of rheumatological conditions with common pathogenesis: autoimmune inflammation of the connective tissue. Depending on a disease, symptoms from many systems and organs determine various clinical manifestations.

According to the 1983 American Rheumatism Association (ARA) classification of rheumatological diseases, systemic connective tissue diseases include:

Systemic lupus erythematosus, rheumatoid arthritis, juvenile idiopathic arthritis, scleroderma, polymyositis, and dermatomyositis, vasculitis, Sjögren's syndrome, overlap syndromes, including unspecified and mixed connective tissue disease, and others.

Typical age of diagnosis of systemic connective tissue diseases are typically found in patients between 20 and 40 years old, *i.e.*, in their reproductive age. Rheumatic diseases, with rheumatoid arthritis being the most common one, are rare. Their prevalence is estimated at 0.001 to 1.0% [1].

The reason why connective tissue diseases affect women more often than men is unknown. Due to the rare occurrence of these disorders, resulting in limited experience in care over pregnant women with connective tissue diseases and the possible deterioration of mother and foetus condition it seems that these patients should be treated at reference centres.

Based on the analysis of the course of pregnancy, and pregnancy outcomes of patients suffering from connective tissue disorders, pregnancy in this group of women is associated with a higher risk of complications and adverse pregnancy outcomes compared to the healthy population. The principal factors affecting the risk include organ complications and high activity of the underlying disease [2, 3].

Effective symptom control due to proper pharmacotherapy, motivates patients to make a conscious decision to get pregnant.

The aim of this study is to present the current knowledge on the care over pregnant patients with systemic connective tissue diseases and to draw attention to the importance of pregnancy planning in this group of patients.

PREGNANCY MANAGEMENT

Preparation for getting pregnant

The time of becoming pregnant

Proper timing for trying to get pregnant in the case of patients with systemic connective tissue diseases is crucial. It should be the time of low disease activity, obtained with pharmacotherapy that may be continued safely during pregnancy [4]. The recommended period of symptom reduction, meeting the remission criteria, prior to getting pregnant differs between various diseases. In the case of lupus erythematosus, it is at least six months [5]. In patients diagnosed with other connective tissue diseases, without

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extraarticular symptoms, three months of remission are deemed sufficient.

Pharmacotherapy

Another important element of preparation involves the analysis of medications used by the patient and the possibility of treatment continuation during pregnancy. The necessity to discontinue teratogenic drugs, if they are used to maintain remission, is associated with the risk of increased disease activity. Therefore, it is important that patients can continue their treatment and control the activity of the underlying disease also during pregnancy. Literature data demonstrate that in patients with systemic lupus erythematosus using hydroxychloroquine discontinuation of the therapy is a significant risk factor for exacerbation of the underlying disease and adverse pregnancy outcomes [6–8]. Therefore, all pregnant patients with lupus should receive hydroxychloroquine, unless it is contraindicated.

The disease controlling drugs with known teratogenic effect that should be discontinued in advance before getting pregnant include methotrexate - three months; cyclophosphamide - three months; mycophenolate mofetil — six weeks [9–11].

It is recommendable to discontinue the drugs that are contraindicated in pregnancy, whose effects on pregnancy have not been sufficiently studied, at least one month prior to the planned pregnancy. They include targeted synthetic disease-modifying antirheumatic drugs [9].

In the case of biologic drugs, their ability to penetrate the foetal circulation is varied; therefore, only some of them are approved for use in pregnancy [12].

Continuation of certain TNF inhibitors during pregnancy is acceptable, and the recommended time for their discontinuation before the planned delivery depends on the half-life of a given drug. This is to ensure that during the delivery the medication will not be present in the child's organism, as it may be a risk factor for infections in the case of using live vaccines [13].

Organ dysfunction

Another step involves the assessment of organ dysfunction associated with the underlying disease. If the patient had a history of organ failure at any time, despite the subsequent improvement or normalisation of the organ's function, this fact significantly increases the risk of pregnancy complications, both foetal and maternal [14].

In the case of pulmonary hypertension, interstitial lesions in the lungs, heart failure, renal failure or multidrug-resistant hypertension in a previous pregnancy, the decision regarding pregnancy should be taken by a multidisciplinary group of experts, due to the risk of increased pregnancy complications.

Presence of anti-SSA and anti-SSB antibodies

Another aspect to be considered when preparing for pregnancy is the assessment of anti-SSA and anti-SSB antibodies. Anti- Sjögren's syndrome-related antigen-A antibodies (anti-SSA) /RO and anti-SSB/LA antibodies may be present not only in patients with Sjögren's disease, but also with other systemic connective tissue diseases [15].

These antibodies actively penetrate the placental barrier from approximately 16th week of gestation, which may cause atrioventricular blockage in the heart of the foetus, or neonatal lupus [16]. In most cases, heart blockage develops between 18 and 24 weeks of gestation. The risk of complete heart blockage in the foetus of an SSA-positive or SSB-positive mother is two percent; however, it increases to 18% if a blockage occurred already in a previous pregnancy [17]. Complete foetal heart blockage is the most dangerous complication, almost always requiring cardiac stimulation in the neonate, due to the irreversible changes in the electrical conduction system of the heart.

Determination of the anti-SSA or anti-SSB status of the mother already when planning pregnancy or in its early stage will enable proper supervision — ultrasound assessment of the atrioventricular conductivity in the heart of the foetus.

If an early blockage is detected, therapy with steroids penetrating the placental barrier (dexamethasone, betamethasone) should be applied. [18]. However, the effectiveness of this treatment was not clearly demonstrated.

The use of hydroxychloroquine was associated with a proven reduction of the rate of atrioventricular block in the foetuses of anti-SSA-positive and anti-SSB-positive mothers, as well as with decreased recurrence of this complication in subsequent pregnancies [19–21].

Skin, haematological and hepatic manifestations of neonatal lupus in most cases resolve after six to nine months following the birth, when maternal antibodies cease to circulate in the child's organism [22].

Obstetric history

A detailed analysis of the previous obstetric history of the patient with systemic connective tissue disease is an essential element of preparation for pregnancy. If the information from the obstetric history reveals a negative pregnancy outcome, the cause should be established, and it should be determined whether it coincided with exacerbation of the underlying disease. The patient should be informed that proper preparation for pregnancy and appropriate period of symptom remission increase the chances of successful pregnancy outcome.

Negative pregnancy outcomes that meet one of the clinical criteria of antiphospholipid syndrome (APS) require verification of this diagnosis in laboratory tests before the

patient gets pregnant again. Patient's blood serum should be tested for antiphospholipid antibodies (anticardiolipin antibody, beta-glycoprotein 1 antibody and lupus anticoagulant). The diagnosis of antiphospholipid syndrome must be supported by two positive results for at least one of three antibodies at medium or high titres, performed at least 12 weeks apart, together with a clinical criterion [23].

Presence of anticardiolipin antibody doubles the risk of venous thrombosis in patients with systemic lupus. The risk is six times higher in patients with positive test results for lupus anticoagulant, compared to lupus patients without these antibodies [24]. In patients with antiphospholipid syndrome, anticoagulatory prevention with low-molecular-weight heparin is recommended throughout the pregnancy and the postpartum period is recommended.

In the context of anti-SSA/anti-SSB antibodies, it is always necessary to ask patients about the occurrence of atrioventricular blockage or neonatal lupus in their children.

The effect of the underlying disease on the course of pregnancy

Due to a limited prevalence of connective tissue diseases, their effect on the course of pregnancy has been studied most extensively in the population of patient with the most common disorders within this group: lupus and rheumatoid arthritis. Other connective tissue diseases also increase the risk of pregnancy complications, especially when the activity of the disease is high, antibodies are present, or organ complications occur.

The data from retrospective studies indicate that in patients with RA pregnancy complications, i.e., pregnancy-induced hypertension, pre-eclampsia, FGR and premature birth occur significantly more often than in the healthy population of pregnant women. These pregnancies also required Caesarean section delivery more frequently [25–27].

A meta-analysis of studies from the years 2001–2016, including 3,395 patients with lupus demonstrated nearly a double increase of the relative risk (RR) of pregnancy-induced hypertension and pre-eclampsia, over three times higher risk or premature birth, and over four times higher risk of growth retardation in the child [28].

Pregnancy supervision

Care over a patient with a systemic connective tissue disease should be provided by a multidisciplinary team, including a rheumatologist, obstetrician and, depending on the organ complications specific for the patient, specialists in other fields of medicine.

For a patient with a connective tissue disease pregnancy is a special time, and it requires a regular monitoring of disease activity. Systematic control of the disease activity markers conducted by the patient's rheumatologist will enable early detection of exacerbations, and potential modification of pharmacotherapy. According to the presence of risk factors, determined before the conception, the supervision over the patient must be individualised. In addition to the gynaecological examination and blood pressure tests performed at every visit, laboratory studies should be performed to assess renal function (creatinine, general urinalysis, presence of protein in urine), liver function (AlAT, AspAT), and complete blood count. If arterial hypertension occurs, it should be controlled regularly, both by Holter and home blood pressure monitoring to optimise pharmacology treatment.

All pregnant patient with a systemic connective tissue disease, especially lupus erythematosus, are at high risk of pre-eclampsia, so preventive treatment with low doses of acetylsalicylic acid (≤ 150 mg) is recommended [5, 29]. The suggested time for initiation of the prophylactic therapy is 12–16 weeks of pregnancy.

The factors additionally increasing the risk of pre-eclampsia in patients with lupus include active disease at six months prior to conception, lupus nephritis, chronic hypertension, presence of antiphospholipid antibodies, low levels of complement components and thrombocytopaenia [30]. Doppler ultrasound examination of the flow in the uterine arteries in the second trimester is also recommended. Presence of bilateral early diastolic notches in these arteries between 23 and 25 weeks of gestation is a predictive factor for pre-eclampsia and pregnancy hypertension [31].

Differentiation between pre-eclampsia and lupus nephritis poses a significant challenge in the management of patients with lupus. In both cases, the clinical manifestation may include proteinuria, oedema, impaired renal function, hypertension and thrombocytopaenia. Lupus nephritis is characterised by reduced concentrations of complement components C3 and C4, increased titres of anti-dsDNA antibodies, active urinary sediment (presence of dysmorphic erythrocytes, erythrocyte casts and granular casts), and manifestation of other dermatological, articular and haematological symptoms of disease exacerbation. In pre-eclampsia, the levels of complement components C3 and C4 typically increases [32]. If the two conditions cannot be differentiated clinically, a kidney biopsy may be required. The only effective management in the case of intensified symptoms posing a threat to the lives of the mother or the child due to severe pre-eclampsia is premature delivery of the child, which may also be necessary to administer proper immunosuppressants for exacerbated nephritis.

In patients diagnosed with antiphospholipid syndrome, anticoagulatory prevention during pregnancy with low-molecular-weight heparin is recommended [33]. These pregnant patients, and women with other rheumatic diseases,

especially with systemic lupus, should receive antiplatelet therapy with low doses of aspirin.

In patients positive for anti-SSA and anti-SSB antibodies ultrasound monitoring of the atrioventricular conduction time in the foetus is required. The conduction time can be measured in an ultrasound examination using the M-mode technique, pulsed Doppler and tissue Doppler. Normal atrioventricular conduction time in a foetus is 110–150 ms [34]. Following the recommendations of the American Heart Association, monitoring of the foetus of a patient positive for anti-SSA or anti-SSB antibodies should start at 16 weeks of gestation. Measurements should be performed weekly, until 24 weeks of gestation.

SUMMARY

Despite pregnant women diagnosed with inflammatory rheumatic diseases are in the group of greater risk of adverse pregnancy outcomes, following up to date principles of pregnancy planning and supervision can rise the chance of motherhood of those patients.

Due to the risk of disease exacerbation and sudden deterioration of both mother and feats condition those patients require multidisciplinary monitoring and should be referred to reference centre in case of the necessity of advance obstetric and neonatal care.

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VIA MEDICA

RECOMMENDATIONS

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Updating the recommendations of the Working Group for the Preservation of Fertility in Oncological and Hematological Patients and Other Patients Treating Gonadier Therapies "ONCOFERTILITY" (GROF) of the Polish Society of Oncological Gynecology regarding cryopreserves and autologous transplant

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ABSTRACT

Update of the recommendations of the Fertility Preservation Working Group in Oncological, Hematological and Other Patients Treated with Gonadotoxic Therapies "ONCOFERTILITY" (GROF) of the Polish Society of Oncological Gynecology regarding cryopreservation and autologous ovarian tissue transplantation.

The Fertility Preservation Working Group in Oncological, Hematological and Other Patients Treated with Gonadotoxic Therapies "ONCOFERTILITY" (GROF) of the Polish Society of Oncological Gynecology has developed current clinical guidelines and recommendations to improve the quality of healthcare provision in the area of reproductive health in patients undergoing therapy that may impair their reproductive potential.

The guidelines are based on current scientific evidence available at the time of writing this document. In the absence of scientific evidence on some aspects, a consensus was reached among GROF stakeholders.

The purpose of the guidelines is to assist healthcare professionals in making decisions in specific clinical situations regarding the selection of an appropriate and effective diagnostic and therapeutic process. The document provides practical guidelines for the management of cryopreservation and autologous ovarian tissue transplantation.

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INTRODUCTION

In fewer and fewer countries, using ovarian tissue cryopreservation (OTC) as a method of preserving fertility in women who require chemotherapy is still considered an experimental treatment. In Poland, in accordance with the 2017 recommendations of the Polish Cancer Society's Working Group for the Preservation of Fertility in Cancer Patients (GROF), it was recommended that OTC be used only

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in centers with appropriate experience [1], using protocols approved by the Bioethics Committee.

However, due to the increasing use of OTC as a method of securing fertility prior to systemic treatment around the world and increasing evidence of its effectiveness, this method is no longer considered a medical experiment. In the 2019 recommendations of the Executive Committee of the American Society for Reproductive Medicine (ASRM) [2], we read that OTC is no longer considered an experimental method and is the only option for prepubertal girls and those women who cannot be stimulated for an IVF procedure. The European Society of Human Reproduction and Embryology (ESHRE) has also changed its position on OTC and in the recommendations of 2020 [3] we read that ovarian tissue freezing may be proposed as an alternative treatment to preserve fertility in young patients who are at risk of developing premature ovarian insufficiency (POI).

ADVANTAGES AND LIMITATIONS OF OTC (OVARIAN TISSUE CRYOPRESERVATION)

OTC can be used in prepubertal girls, in women who do not have time or are not advised to stimulate ovulation prior to oncological intervention and in those who do not accept assisted reproductive techniques. In addition, it should be noted that the collection and retransplantation of ovarian tissue (OTT) is the only method of securing fertility that allows conception without further medical interventions. It is also a method of restoring the hormonal function of the ovary and, consequently, a cardioprotective effect, reducing the risk of osteoporosis and senile dementia, which with such a high percentage of autograft acceptance (95%) seems no less important than procreation itself [4]. The disadvantage of this method is the necessity to perform laparoscopy at least twice and the lack of reimbursement of costs of freezing ovarian tissue from public funds in Poland. In the case of hematological neoplasms, there is a theoretical risk related to the possibility of re-implantation of neoplastic cells in a frozen fragment of the ovary (depending on the type and stage of the neoplasm), but so far, no such case has been reported. [5]. Due to the risk of retransplantation of neoplastic cells in patients with haematological neoplasms, the collection of ovarian tissue in this group should be performed only after induction chemotherapy and complete remission of the tumor in the blood.

EFFECTIVENESS

OTC indications and exclusion criteria differ depending on the centers that carry them out. The age of the enrolled patients seems to be crucial. In various recommendations, we find the upper age limit from 35 years [6] to even 49 years [7–9]. However, pregnancy was rarely achieved in women over 35 years of age, and none over 38 years of age was found [10]. The effectiveness of this method for women younger than 36 years is confirmed by the study, which compared the effectiveness of OTC in comparison with oocyte cryopreservation (OC). It showed the superiority of OC for women over 36 years of age, in whom 30% of pregnancies obtained with this method were found, while no pregnancies were achieved with the OTC method. In the group of younger patients, the effectiveness of both methods was comparable [11]. By 2019, autologous ovarian tissue transplantation was performed in over 300 patients, over 140 pregnancies obtained by this method were reported, of which over 100 children were born. In 85% of cases, ovarian tissue cryotransplant function was restored within four months. The effectiveness of the method was assessed at 40%, counting at least one child per patient treated with this method [10, 12]. More recent data estimate the efficacy of ovarian tissue autograft measured as restoration of menstrual function and a reduction in FSH < 20 IU/mL as 94%, while the return of procreative function, measured as at least one pregnancy, was estimated at 50%, and delivery to nearly 42% [4]. Unfortunately, there is no data on the number of babies born for all women who started treatment with this method, and a relatively low number of procedures performed. The largest percentage of patients undergoing the OCT procedure are patients with breast cancer. In this group of women, the damage to the ovarian tissue structure as a result of chemotherapy occurs not only by damaging the DNA structure in egg cells and granular cells, but also by accelerating the recruitment of primordial follicles [13]. Recently, the loss of the ovarian reserve through oocyte apoptosis has also been postulated [14]. Therefore, it seems that special emphasis should be placed on the collection of ovarian tissue before the implementation of systemic therapy in neoplasms other than hematological.

OVARIAN FRAGMENT CRYOPRESERVATION PROCEDURE — OTC

There are two methods of collecting ovarian tissue:

1. Ovarian cortex biopsy 1/3–2/3 ovarian surface (OCB), used for large ovaries or high ovarian reserve (AMH > 2).
2. Unilateral removal of the ovary in the case of low ovarian reserve, small ovaries.

The treatment can be performed on any day of the cycle. The collected tissue must be transported to the reference embryology laboratory under strict conditions within 1–20 hours [5].

There are no studies comparing the effectiveness of both methods of obtaining ovarian tissue. The advantage of OCB is that it leaves both ovaries as a potential site for ovarian tissue transplantation and reduces the invasiveness of the procedure. A potential disadvantage of removing

one ovary is the acceleration of menopause after chemotherapy/radiotherapy, although no comparative studies have been performed in these groups of patients [10].

Preparation for cryopreservation consists of dividing the ovarian cortex in sterile conditions into fragments of approximately 1 mm. This is because effective freezing requires tissue thickness up to 2 mm, and that the vast majority of primordial follicles are located less than 1 mm from the ovary surface. The fragments prepared in this way are individually frozen by slow freezing or vitrification. The 2018 study describes the recovery of pregnancy from ovarian tissue retransplantation, frozen using the slow-freezing method and stored for over 14 years. Since the procedure of ovarian tissue collection cannot be repeated, the preparation and freezing of the tissue should be performed by trained embryologists and in appropriately adapted laboratories.

OVARIAN TISSUE TRANSPLANTATION (OTT)

Autotransplantation of ovarian fragments can be done either orthotropically or heterotropically. The orthotropic sites are the remaining ovaries, the broad ligament, and the peritoneal pocket at the ovary. There were no significant differences between these sites [10].

Heterotropic sites for autotransplantation of ovarian fragments have been described, such as the subcutaneous tissue of the forearm and abdominal integuments, or only one birth from heterotropic transplantation [15], while the rest from orthotropic location, with as many as 60% of these pregnancies conceived naturally.

Patients who became pregnant after OTT were on average younger than those who failed (26.4 ± 6.3 vs 29.6 ± 5.4 years) [10]. One group describes the inclusion criteria for OCT based on the age of patients under 35 years of age and the measurement of ovarian reserve (AMH above 0.4 ng/mL and AFC > 5 antral follicles) [16]. The average ovarian transplant lifetime is 24.9 month (4–144 months), three live births over seven years after OTT were described in one patient [10].

There is no consensus on the amount/volume of ovarian tissue transplanted. In a meta-analysis of 309 OTT, 255 women had 1/3 ovaries transplanted, and 45 patients who required two transplants to become pregnant were also reported. Three such procedures were described in only one percent of cases. There is also no universally accepted upper age limit for women undergoing OTT. The oldest reported patients were 47 years old and in these cases, attention is drawn to the maternal risk associated with pregnancy [10, 17].

OTHER METHODS COMBINED WITH OTC

In order to increase the chances of getting pregnant, the ESHRE recommendations allow the combination of OTC with other fertility preservation techniques, such as OC (oocyte cryopreservation) and the movement of the ovaries beyond the small pelvis when irradiation in this area is necessary. In the case of oocyte cryopreservation, it is recommended to stimulate ovulation immediately after the OTC procedure or immediately before [3].

SAFETY OF THE METHOD

Surgical complications

Both the collection of ovarian tissue and its retransplantation are associated with a low risk of surgical complications, estimated at about one percent [18, 19]. Retransplantation surgery may be combined with other procedures, such as hysteroscopy, tubal patency assessment, and other procedures depending on the clinical context. It is recommended that the OTT procedure and ovarian thawing take place in the same facility. Although there are no reports of infectious complications, it is recommended to consider prophylactic perioperative antibiotic therapy.

Risk of reintroducing cancer cells

Ovarian metastases are found in slightly more than 20% of autopsies in women who died due to non-gynecological neoplastic diseases. For this reason, the decision about OTT should be made with utmost caution in patients suffering from leukemia and CSN neoplasms, such as medulloblastoma or neuroblastoma. In other neoplasms, OTT seems safe if the invasion of small pelvis is excluded. For this reason, it seems unlikely that the risk of reintroduction of cancer cells in ovarian and adnexal cancers (even in the case of graft removal after pregnancy) could be so limited that OTT could be recommended as safe in these cancers. Before OTT, the patient should be in good condition and cured oncologically in accordance with the accepted treatment criteria. After retransplantation, she should be subject to at least two years of oncological follow-up [5]. It seems reasonable to perform a histopathological examination of an ovarian section taken during the OTC procedure, as well as another histopathological inspection before cryopreservation of the tissue.

Perinatal complications

Recent meta-analyzes in patients after cancer treatment indicate an increased risk of prematurity (RR 1.56; 95% CI 1.37–1.77 — mainly due to oncological indications for early termination of pregnancy), low birth weight (RR 1.47; 95% CI 1.24–1.73), urgent Caesarean sections (1.22; 95% CI 1.15–1.30), elective cesarean sections (RR 1.38; 95% CI 1.13–1.70), and postpartum haemorrhages (RR 1.18; 95% CI 1.02–1.36) [20].

Risk to the fetus

There is no evidence of an additional risk of fetal malformations after OTT [10, 21]. The risk is about 1.2%, which is comparable with the occurrence of major fetal malforma-

tions in the general population [17]. The latest data on the occurrence of fetal malformations in 22 patients who underwent the first course of chemotherapy before OTC indicate the birth of eight healthy children from 13 pregnancies [22].

Long-term risk

As the first cryotransplantation took place almost 20 years ago and there are no reports of negative breasts related to this method, the long-term risk should be assumed to be low. A separate problem is patients treated for breast cancer with mutations in the BRCA1 or BRCA2 genes. In these patients, a site of transplantation (heterotropic transplantation) may be considered, where the observation of the graft will be easier, or orthotropic transplantation, followed by removal of the appendages, as soon as possible after birth, to the number of children that the patient established, but not later than the age of 40 [23, 24].

RECOMMENDATIONS OF THE WORKING GROUP

1. The Working Group recommends the recognition of the OTC/OTT procedure as a therapeutic method.
2. It is recommended to consider OTC/OTT in patients with low ovarian reserve (AMH < 0.4 ng/mL, AFC < 5 follicles in both ovaries)
3. In the case of blood cancers and CSN, individual consideration of the case regarding the risk of tumor reimplantation seems justified.
4. It is recommended to use OTC after the initiation of chemotherapy only for hematological malignancies

FINAL REMARKS

The guidelines do not replace and do not override the individual responsibility of healthcare professionals to make the right decisions about the diagnosis and treatment of individual patients. Ultimately, it is healthcare professionals who make clinical decisions on a case-by-case basis, using their clinical judgment, knowledge and experience, and considering the condition, circumstances and wishes of the patient, in consultation with the patient and/or their caregiver and taking into account current guidelines issued by relevant public health organizations.

The team of experts reserves the right to update this statement in the event of new significant scientific reports.

Conflict of interest

None.

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VIA MEDICA

CLINICAL VIGNETTE

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Evisceration of the small intestine through the vagina as a rare complication after laparoscopic pectopexy

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Key words: apical defect; pectopexy; pelvic organ prolapse; vaginal evisceration

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A 63-year-old woman (gravida 2, para 2, body mass index of 34 kg/m^2) presented with vomiting, diarrhea, lower abdominal pain and vaginal bulging symptoms was referred to the nearest, secondary referral hospital by emergency medical care providers. The presented symptoms appeared during the routine, daily activities. The patient had undergone laparoscopic pectopexy (LP) in our tertiary medical center 14 months previously due to stage IV apical prolapse (Fig.1). Moreover, she underwent total vaginal hysterectomy (TVH) eight years prior to LP. Vaginal examination revealed a small intestine protruding from the vagina. The patient was taken urgently to the operating room. Lower midline laparotomy showed a 5-cm perforation in the vaginal vault located medial to the site of mesh insertion. The mesh continued to be affixed to the vagina, causing tension. The eviscerated small intestine was not incarcerated and could be reduced manually. The opened vaginal vault was accomplished with two layers of absorbable sutures (Vicryl 2.0). No further mesh repair or insertion was performed. The patient was discharged on postoperative day five. After two months, vaginal examination revealed an intact suture line at the vaginal vault and no evidence of apical defect recurrence or mesh-related problems.

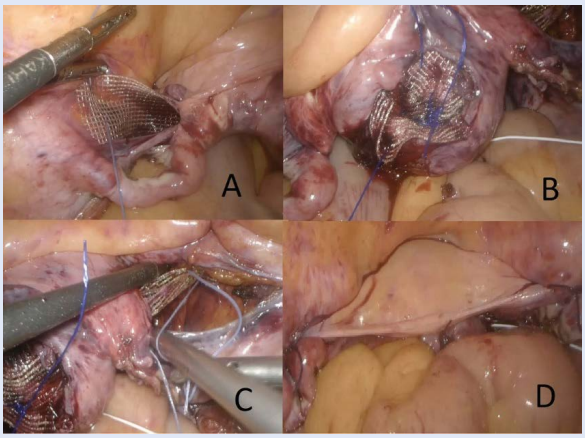

Figure 1. Procedure of laparoscopic pectopexy in our patient: mesh fixation to the left and right iliopectineal ligaments (**A, C**), to the vaginal vault (**B**) and the final view (**D**) just before the end of the surgery.

To the best of our knowledge, this has been the first reported case of vaginal evisceration (VE) after LP. VE is defined as the disruption of the vaginal vault and extrusion of intraperitoneal contents [1]. Its incidence ranging from 0.14% to 4.1% [2]. In our patient, VE occurred spontaneously with gradually increasing intra-abdominal pressure and a thin, atrophic vaginal wall as the possible cause. The past TVH was an additional trigger factor. The literature offers modest data about severe LP complications [3]. Complications after LP described in the literature are presented in Supplementary Material S1 (see in Supp./Additional Files).

Apical vaginal support has since become the focus of clinical research. In the light of communications published by the United States Food and Drug Administration (U.S. FDA) regarding synthetic meshes, careful attention must be paid to complications such as mesh exposure, dyspareunia, organ perforation and urinary problems. Research on a modified, uterus-preserving pelvic organ prolapse (POP) procedures, fixing the mesh or autologous grafts to the anterior abdominal wall or sacrospinous ligaments and the uterus, are ongoing [4, 5]. So far, mesh exposure after LP occurred only in one study [6].

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In POP surgery, VE is mainly reported after sacrocolpopexy [7]. During sacrocolpopexy, the Y-shaped polypropylene mesh is attached to the vaginal walls and the anterior longitudinal ligament. In LP, a polyvinylidene fluoride monofilament mesh is sutured to iliopectineal ligaments and fixed to the vaginal vault. The mesh used in sacrocolpopexy has the larger contact area between the mesh and vaginal walls as compared to LP (approx. 52.75 cm^2 vs 12.25 cm^2, respectively) (Supplementary Material S2 see in Supp./Additional Files).

VE after LP constitutes a gynecological emergency. Careful attention to restore the normal vaginal axis, with a tension-free and meticulous mesh attachment to the vaginal vault or cervix is essential to prevent VE after LP. Vaginal estrogen therapy should be considered, if not contraindicated.

Conflict of interest

The authors state that there are no conflicts of interest to disclose.

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