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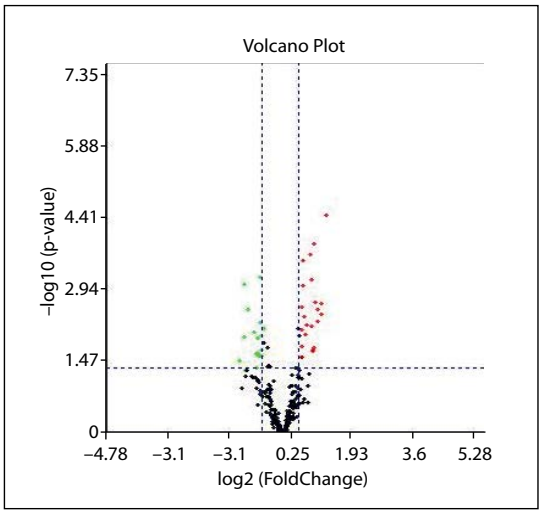

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Editorial

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Breast cancer is a heterogeneous disease of significant social importance. For many years it has been the most common malignant tumor in women in Poland and in many countries throughout the world. The incidence of breast cancer in women over 30 is systematically increasing. In Poland in 2018, according to the National Cancer Registry, there were 18,869 cases of BC in women and 154 in men. At the same time, a total of 6,895 and 75 deaths were recorded for women and men, respectively [1, 2]. The neoplasm is characterised by a varied clinical course and a wide spectrum of morphological images in radiological studies. In recent years, there have been many developments in terms of the knowledge base, diagnostic methods, and new therapeutic options for breast cancer. Currently, breast cancer treatment consists of a comprehensive approach to the diagnostic and therapeutic processes. Three main imaging methods are used in the diagnosis of breast cancer: ultrasonography, mammography, and magnetic resonance imaging [1, 3, 4]. Each of these methods plays a special role in diagnostics. Ultrasonography is used mainly in young women and those with glandular or mixed breast structure [4]. Contemporary breast ultrasonography means not only mapping the morphology of focal lesions and their surroundings but also involves a combination of additional techniques such as sonoelastography and colour Doppler. These techniques allow an increase in the accuracy of imaging and qualification of patients for biopsy or observation [1, 5]. Early diagnosis of breast cancer and knowledge of its oncological characteristics based on biopsy findings facilitate the choice of optimal therapy, including surgical treatment which, in selected cases, is preceded by neoadjuvant chemotherapy. Treatment of early breast cancer is complex and includes a combination of surgical methods (breast conserving therapy, BCT), radiotherapy, systemic therapies (chemotherapy, hormone therapy, molecularly targeted therapies), and adjunctive therapy in various sequences [1, 3]. The use of predictive bio- markers such as the histological type of BC (invasive or preinvasive forms), the expression of ER/PgR (estrogen receptor (ER) and progesterone receptor), Ki67 (proliferation index) and HER2 (human epidermal growth factor receptor 2), genomic signatures, if available, stage of the primary tumor, condition of the axillary lymph nodes, and patient's preferences, affect the choice and sequence of therapies. These methods, especially systemic treatment, have undergone significant changes over the years. Neoadjuvant chemotherapy (NAC), first introduced in 1970, has been used in locally advanced breast cancer (LABC) and inflammatory BC to reduce tumor size and improve the radical nature of surgical treatment, including BCT. Currently, decisions regarding neoadjuvant treatment should be based on the anticipated sensitivity to particular types of treatment, the benefits of their use, and the individual risk of relapse. Additionally, short-term and long-term toxicity, the biological age of the patients, and their general health and comorbidities should be considered. In the current recommendations of all scientific oncological societies, neoadjuvant chemotherapy is recommended not only in locoregional advanced breast cancer but also in the early stages of the following subtypes: triple-negative breast cancer (TNBC) and in combination with molecularly targeted treatment in the subtypes with the presence of HER2 receptors (luminal B HER2 positive and HER2 positive non-luminal subtypes [1, 5]. Neoadjuvant chemotherapy can also be used in cases of HER2 negative luminal B cancer with low expression of hormone receptors, high grade (G3), and in young individuals (≤ 35 years of age), stage II or III [1, 3] (Fig. 1. A–C).

Many processes, both benign and malignant can mimic primary breast cancer [6, 7]. Many of the can be differentiated from the breast cancer based on imaging tests, whereas other will finally require a histopathological confirmation. Most common benign breast tumors in women are fibroadenomas and cysts [6]. High-resolution imaging test as mammography and ultrasonography (USG) and exact criteria of assessment and images interpretation application in most cases allow to differentiate breast cancer from fibroadenomas and cysts.

However, due to partial convergence in image of benign and malignant lesions, new or growing breast lesion that

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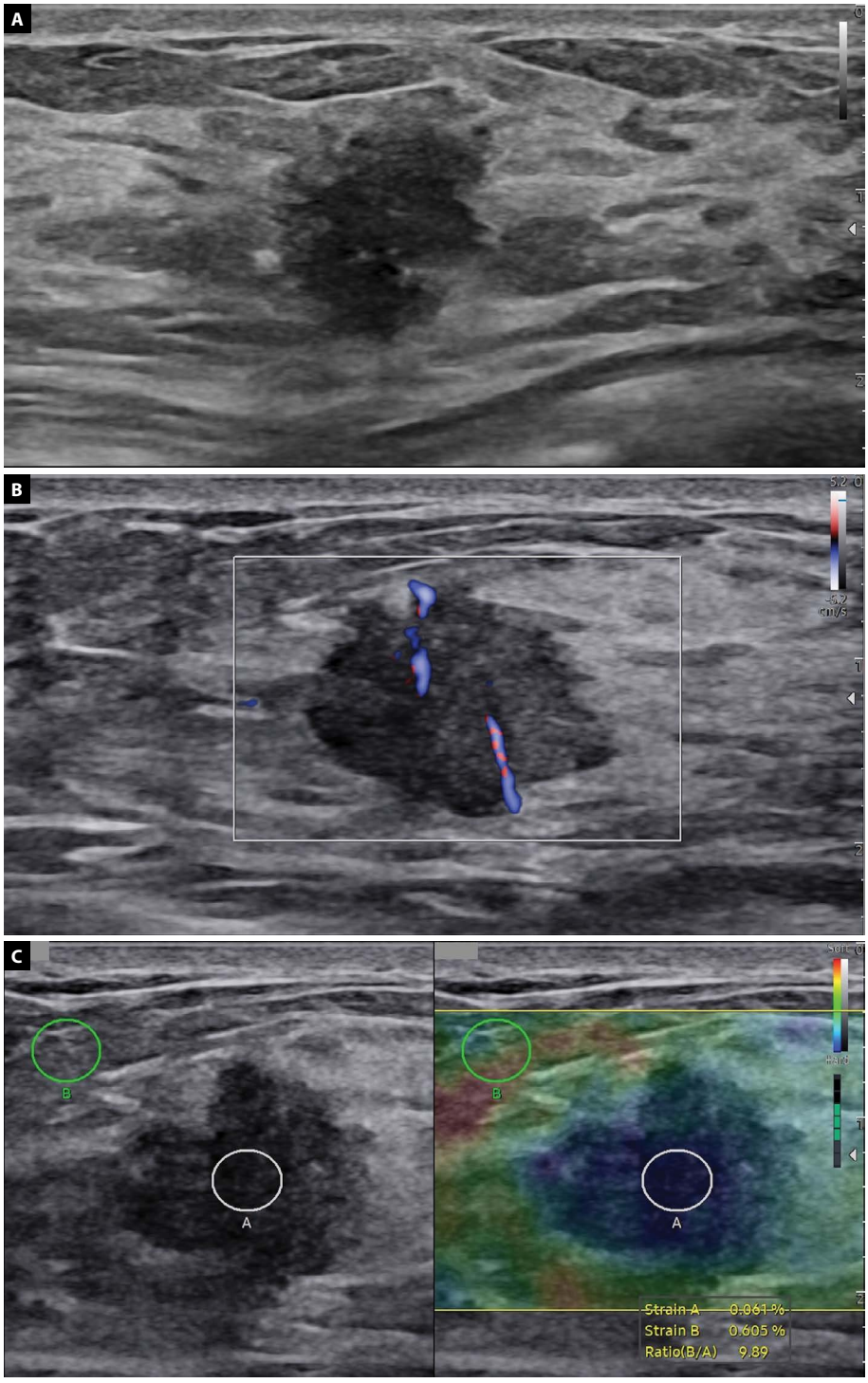

Figure 1. A–C. A 31-year-old patient. The B-mode examination shows an irregularly shaped tumour with indistinct margins, with enhancement behind the lesion (**A**). In the PD small vessels are visible on the periphery of the lesion and inside (**B**). SE – strain elastography on, the lesion is hard; Ratio 9,89. BIRADS 5 (**C**). Histopathology: Luminal B subtype

does not present all typical features of benign lesion (*e.g.*, hamartoma) requires performing a biopsy.

Apart from lesions associated with ducto-lobular system, structures originating from mesenchymal stroma of the breast may mimic a breast cancer.

Such structures include typical tumors originating from the stroma like pseudovascular stromal hyperplasia (PASH) and other, which originate from supporting tissues, including fibrous, vascular, lymphatic, nervous tissues and skin. The second group includes focular fibrotic lesions (diabetic

mastopathy) [8], fibromatosis, malignant histiocytic tumors, vascular malformations, vascular sarcomas, neuromas, lymphomas and sarcomas form the adipose tissue. In addition, image mimicking breast cancer may arise due to inflammation (reaction to foreign body, breast inflammation, abscess), trauma (hematoma, steatonecrosis), lactation related changes and metastasis of other, not related to breast, cancers.

Additionally, multiparametric ultrasonography analysis of breast cancer features is helpful in detecting aggressive subtypes, assigning the appropriate BIRADS classification category, and referring patients for biopsies [1].

Another interesting method with possible future application is contact thermography, which was proven to be a safe, practical a complementary method of breast pathologies diagnosis in the GP's or gynecologist's office [9]. While its future practical applications are yet to be implemented, it should be noted that contact thermography is not a sufficient method for breast cancer prevention, and it can be only regarded as a complementary method in the diagnosis of breast pathologies.

Despite large and various possibilities of imaging techniques, in some cases options of certain radiological diagnosis are limited, even when few of the techniques are combined [10]. Ultrasonography plays a role of easy to access, available technique, however its results should be later confirmed in more accurate and specific techniques like, magnetic resonance imaging or computed tomography.

I encourage you to read the current issue of our magazine. As usual, we publish many very interesting articles that can be fascinating reading even during the holidays.

By recommending the content, they record more interesting and interesting materials with the new issue of Polish Gynecology, I wish you a wonderful and eventful holiday.

Conflict of interest

None declared.

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Variant type of leiomyomas: 13 years of experience in a single institution

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ABSTRACT

Objectives: Our understanding of a variant type of leiomyoma lags far behind of leiomyoma/leiomyosarcoma of the uterus. The rarity of variant type leiomyomas limits epidemiologic study, evidence-based guidance for diagnosis and treatment. We aimed to analyze clinical, pathologic and radiological features of variant type of leiomyomas in women who underwent surgical therapy for symptomatic disease in a tertiary center. We furthermore intended to put forth the recurrence patterns of variant type of leiomyoma after uterine-conserving therapies.

Material and methods: Pathology results and inpatient files of women undergoing surgery (vaginal or abdominal hysterectomy; total abdominal hysterectomy and bilateral salphingoopherectomy; abdominal myomectomy; polipectomy) for symptomatic disease and with a histologic diagnosis of variant type of leiomyoma were assessed. Patient gravida, parity, menopausal status, patient complaint, type of initial surgical procedure, size of neoplasms, number of mitosis, presence of atypia, and necrosis, MRI evaluation, recurrence and any subsequent therapy were documented.

Results: A total of 3275 patients' medical records were evaluated between 2005–2018. The study sample comprised of 185 women with a diagnosis of variant type of leiomyoma. The patients ranged from 23 to 79 years of age. One hundred thirty-five cases were postmenopausal and 50 cases were during the reproductive period. The most common presenting symptom was menometrorrhagia (38.9%). Four point nine percent of cellular leiomyoma, 14.2% of smooth muscle tumors of uncertain malignant potential (STUMP) and 4.7% of atypical leiomyomas were recurred with clinical follow-up.

Conclusions: Clinicians should be aware of variant type leiomyomas and their associated clinical, imaging, and pathologic issues.

Key words: leiomyoma; leiomyosarcoma; recurrence; variant type of leiomyoma

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INTRODUCTION

Uterine leiomyoma and leiomyosarcoma are at opposite poles of the pathologic spectrum of uterine smooth muscle tumors. In between, there are variant type of leiomyomas including mitotically active leiomyoma, cellular leiomyoma, lipoleiomyoma, atypical leiomyoma, angiolipoleiomyoma and smooth muscle tumors of uncertain malignant potential (STUMP) [1–6].

Leiomyomas are benign smooth muscle tumours and are the most common solid tumors in women with an estimated incidence of 70% [7]. Variant type of leiomyomas were relatively less and it is important to differentiate them from malignant neoplasms of the myometrium, since they have a good prognosis. Variant type of leiomyomas exhibit the same symptoms and signs as usual leiomyomas. Most variant type of leiomyomas present as typical fibroids and are excised if they are symptomatic. A woman with a uterine mass presumed to be a myoma is found to have a variant type of leiomyoma at pathologic analysis, with approximately 10 in 100 cases [8]. The rarity of this diagnosis limits epidemiologic study, evidence-based guidance for diagnosis and treatment. Most variant types of leimyomas are restricted to case reports and small case series. There are no imaging modalities that can distinguish histologic variants from other leiomyomas. They are diagnosed by pathology examination following myomectomy or hysterectomy.

Our understanding of a variant type of leiomyoma lags far behind of leiomyosarcoma/leiomyosarcoma of the uterus. The recurrence risk of variant type of leiomyoma has never been fully characterized because of the use of hysterectomy as the primary therapeutic option. However, the evolution of uterus preserving surgeries require un-

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derstanding of the pathophysiology, clinical phenotype and natural history of these lesions.

Objectives

Clinicians should be aware of variant typeleiomyomas and their associated clinical, imaging, and pathologic issues. The aim of this study was to analyze clinical, pathologic and radiological features of variant type of leiomyomas in women who underwent surgical therapy for symptomatic disease in a tertiary center. We furthermore intended to put fort the recurrence patterns of variant type of leiomyoma after uterine-conserving therapies.

MATERIAL AND METHODS

Medical records between 2005–2018 of Department of Obstetrics and Gynecology at Health Science University, Istanbul Training and Research Hospital, a tertiary center, were retrospectively evaluated. Pathology results and inpatient files of women undergoing surgery (vaginal or abdominal hysterectomy; total abdominal hysterectomy and bilateral salphingoopherectomy; abdominal myomectomy; polipectomy) for symptomatic disease and with a histologic diagnosis of variant type of leiomyoma were assessed. Patients with histopathological diagnosis of mitotically active leiomyoma, cellular leiomyoma, lipoleiomyoma, atypical leiomyoma, angiolipoleiomyoma, vascular leiomyoma, myxoid leiomyoma and STUMP were included. The following data were documented: patient gravida, parity, menopausal status, patient complaint, type of initial surgical procedure, size of neoplasms, number of mitosis, presence of atypia, and necrosis, magnetic resonance imaging (MRI) evaluation, recurrence and any subsequent therapy. Tumor size was based on gross pathology. The histologic features including presence of atypical cells, overall cellularity, mitotic index defined as the highest number of mitotic figures (MF) counted in 10 high-power fields (HPF), presence and type of necrosis were recorded.

Dysmenorrhea, menorrhagia, menometrorrhagia, pelvic pain, pelvic mass, vaginal discharge, postmenopausal bleeding and prolapsus were considered to be presenting symptoms. Premenopausal status was defined as the occurrence of at least one menstrual period in the 12 months before surgery. Patients who had a concomitant gynecologic cancers were excluded from the study.

Statistical analysis

IBM SPSS Statistics 22.0 program was used for statistical analysis. Descriptive statistical methods (mean, standard deviation) were used. Qualitative data were compared using the Chi-Square test. Significance was evaluated at $p < 0.05$.

RESULTS

A total of 3275 patients' medical records were evaluated between 2005-2018. Our study sample comprised of 185 women with a diagnosis of variant type of leiomyoma (102 cellular leiomyomas, 32 lipoleiomyomas, 21 atypical leiomyomas, 8 mitotically active leiomyomas, 7 STUMP, 5 myxoid leiomyomas, 5 angiomyolipomas, 5 vascular leiomyomas).

The surgical procedures of the cohort consisted of 110 total abdominal hysterectomies and bilateral salphingo-oopherectomies, 39 abdominal myomectomies, 24 total abdominal hysterectomies, 5 polypectomies, and 3 vaginal hysterectomies. Demographic features of patients were given in Table 1. The patients ranged from 23 to 79 years of age (mean age 47.80 ± 11.29). One hundred thirty-five cases

Table 1. Demographic features of patients

		n	%
Gravida	<5	120	64.9
	≥ 5	65	35.1
Parity	< 5	163	88.1
	≥ 5	22	11.9
Menopausal status	Premenopause	135	73
	Postmenopause	50	27
Presenting symptom	Vaginal discharge	2	1.1
	Menorrhagia	21	11.3
	Menometrorrhagia	72	38.9
	Menorrhagia and dysmenorrhea	23	12.4
	Pelvic pain	44	23.8
	Pelvic pain and mass	1	0.5
	Pelvik pain and prolapsus	3	1.6
	Postmenopausal bleeding	19	10.3
Operation	TAH + BSO	110	59.5
	TAH	24	13
	Myomectomy	39	23.2
	Polipectomy	5	2.7
	VAH	3	1.6
Diagnosis	Angiolipoleiomyom	5	2.7
	Atypical leiomyom	21	11.4
	Lipoleiomyom	32	17.3
	Myxoid leiomyom	5	2.7
	Mitotically active	8	4.3
	Cellular leiomyom	102	55.1
	STUMP	7	3.8
	Vascular leiomyom	5	2.7

n — number; TAH — total abdominal hysterectomy; BSO — bilateral salphingoopherectomy; STUMP – smooth muscle tumors of uncertain malignant potential

were post menopausal, 50 cases were in reproductive period. The most common presenting symptom was menometrorrhagia (n: 72, 38.9%), followed by pelvic pain (n: 44, 23.8%).

Distribution of tumor characteristics were given in Table 2. The size of the variant type of leiomyoma ranged from 2 cm to 26 cm, with a median of 8 cm. By the highest count method, 140 cases were found to have 0 MF/10HPF, 23 showed 1 to 3 MF/10HPF, and 22 cases were found to have ≥ 3 MF/10HPF. While 29 (15.7%) of the cases had atypia, 156 (84.3%) had no atypia. The necrosis was observed in 9 (4.9%) of the cases and not observed in 176 (95.1%). One hundred seventy-nine (96.75%) of tumors affected the uterine corpus, and 6 (3.25%) was in the cervix uteri.

Thirty-six of the patients had MRI evaluations. Eighty-three point three percent of cases showed hypointensity on T1 weighted images, 75% of cases showed hyperintensity on T2 weighted images, 66.7% of the cases had positive fat substraction and all of the 36 cases showed contrast enhancement.

None of mitotically active leiomyomas, lipoleiomyoma, myxoid leiomyomas, angiomyolipomas and vascular leiomyomas were recurred; however, 5 of 102 (4.9%) cellular leiomyomas and one of 21 (4.7%) atypical leiomyoma were recurred during clinical follow-up.

Evaluation of clinical parameters according to pathologic diagnosis were given in Table 3. There was a statistically significant difference between the number of gravida and parity according to diagnosis ($p < 0.01$). The incidence of myxoid leiomyoma and STUMP were higher in cases with gravida and parity number ≥ 5. Angiolipoleiomyoma was not observed in patients with gravida number ≥ 5. Angiolipoleiomyoma, mitotically active leiomyoma and vascular leiomyoma were not observed in patients with parity number ≥5.

Tablo 2. Distribution of tumor characteristics

		Min–Max	Mean ± SD (median)
Tumor diameter (cm)		2–26	8.55 ± 5.21 (8)
		N	%
Number of mitosis	0	140	75.7
	1	15	8.1
	2	8	4.3
	≥ 3	22	11.9
Atypia	–	156	84.3
	+	29	15.7
Necrosis	–	176	95.1
	+	9	4.9
T1 (n = 36)	Isointense	6	16.7
	Hypointense	30	83.3
T2 (n = 36)	Isointense	1	2.8
	Hypointense	8	22.2
	Hyperintense	27	75
Fat substraction (n = 36)	–	24	66.7
	+	12	33.3
Contrast enhancement (n = 36)	+	36	100

n — number; SD — standard deviation

Tablo 3. Evaluation of clinical parameters according to pathologic diagnosis

	Angiolipoleiomyoma	Atypical leiomyoma	Lipoleiomyoma	Miksoid leiomyoma	Mitotically active leiomyoma	Cellular leiomyoma	STUMP	Vascular Leiomyoma
	n; %	n; %	n; %	n; %	n; %	n; %	n; %	n; %
**Gravida ≥ 5	0; 0	8; 38.1	14; 43.8	5; 100	3; 37.5	26; 25.5	7; 100	2; 40
**Parity ≥ 5	0; 0	1; 4.8	5; 15.6	5; 100	0; 0	4; 3.9	7; 100	0; 0
**Tumor Diameter ≥ 10	0; 0	2; 9.5	6; 18.8	5; 100	0; 0	22; 21.6	7; 100	3; 60
**Menometrorrhagia	5; 100	7; 33.3	10; 31.3	0; 0	6; 75	42; 41.2	0; 0	2; 40
TAH + BSO	0; 0	11; 52.4	22; 68.8	5; 100	5; 62.5	56; 54.9	7; 100	4; 80
TAH	0; 0	2; 9.5	3; 9.4	0; 0	2; 25	16; 15.7	0; 0	1; 20
Myomectomy	5; 100	7; 33.3	4; 12.5	0; 0	1; 12.5	26; 25.5	0; 0	0; 0
Polipectomy	0; 0	0; 0	2; 6.3	0; 0	0; 0	3; 2.9	0; 0	0; 0
VAH	0; 0	1; 4.8	1; 3.1	0; 0	0; 0	1; 1	0; 0	0; 0
**Mitosis ≥ 3	0; 0	2; 9.5	0; 0	0; 0	5; 62.5	8; 7.8	7; 100	0; 0
**Atypia	0; 0	16; 76.2	0; 0	0; 0	0; 0	6; 5.9	7; 100	0; 0
**Necrosis	0; 0	1; 4.8	0; 0	0; 0	0; 0	1; 1	7; 100	0; 0

Ki — Kare test was used; **p < 0.01; n — number; TAH — total abdominal hysterectomy; BSO — bilateral salphingoopherectomy; VAH — vaginal hysterctomy; STUMP — smooth muscle tumors of uncertain malignant potential

There was a statistically significant difference between tumor diameters according to diagnosis ($p < 0.01$). The incidence of myxoid leiomyoma, STUMP and vascular leiomyoma were higher in patients with tumor diameter of ≥ 10 cm. Angiolipoleiomyoma and mitotically active leiomyoma were not observed in those patients.

There was a statistically significant difference between menometrorrhagia symptom according to diagnosis ($p < 0.01$). The incidence of angiolipoleiomyoma was higher in patients with menometrorrhagia than other diagnoses. Myxoid leiomyoma and STUMP diagnoses were not observed in those patients.

There was a statistically significant difference between the number of mitosis according to diagnosis ($p < 0.01$). The incidence of mitotically active leiomyoma and STUMP were higher in cases with mitosis number ≥ 3. Angiolipoleiomyoma, lipoleiomyoma, myxoid leiomyoma and vascular leiomyoma were not observed in those patients.

There was a statistically significant difference between the presence of atypia according to diagnosis ($p < 0.01$). The incidence of atypical leiomyoma and STUMP were higher in patients with atypia. Angiolipoleiomyoma, lipoleiomyoma, myxoid leiomyoma and vascular leiomyoma were not observed in those patients.

There was a statistically significant difference between the presence of necrosis according to the diagnosis ($p < 0.01$). The incidence of STUMP was higher in patients with necrosis compared to other diagnoses. Angiolipoleiomyoma, lipoleiomyoma, myxoid leiomyoma and vascular leiomyoma were not observed in those patients.

DISCUSSION

In the present study, we aimed to reveal our 13 year clinical experince of variant type of leiomyomas. Since variant type of leiomyomas have a greater risk for recurrence than benign leiomyomas, careful analysis of clinical and pathological features will help treatment planning and follow-up strategies.

Variant type of leiomyomas were relatively less, but it is important to differentiate them from malignant neoplasms of the myometrium, as they have good prognosis. Tumor size, presence or absence of necrosis, cytological atypia and vascular invasion, nature of tumor margins are most important histological features for differentiation. Variant type of leiomyomas include mitotically active leiomyoma, cellular leiomyoma, lipoleiomyoma, atypical leiomyoma, angiolipoleiomyoma, vascular leiomyoma, myxoid leiomyoma and smooth muscle tumors of uncertain malignant potential (STUMP) [1–6].

Cellular leiomyoma constitues 5% of leiomyomas. The clinical data on cellular leiomyoma are scanty. The recurrence rate after myomectomy is 8–12% for patients underwent myomectomy [9, 10]. They have increased cellularity compared to the adjacent myometrium [7, 11,12]. The disease is often considered benign but should not be considered as having a completely benign course. Hysterectomy is an option for patients who do not wish to preserve their fertility. Women who wish to retain fertility deserve a close follow-up. Close follow-up is also recommended even if total hysterectomy has been performed because disease recurrence, metastases and malignant transformations can occur even after 10 years [13, 14]. In our study, 55.1% of variant type of leiomyoma cases were cellular leiomyoma. Four point eighty-eight percent of cellular leiomyomas originated from cervix uteri. The rest of the cases originated from corpus uteri. One of the cases diagnosed as cellular leiomyoma after myomectomy procedure was presented with a mass two years later and hysterectomy was performed. The pathological diagnosis was leiomyoma. Another mass at the pelvis with a diameter of 4 cm was detected at the same patient two years following second operation. The pathological result of pelvic mass was cellular leiomyoma.

Two cases with cellular leiomyoma diagnosis were presented with mass three and eight years following first operations (myomectomy). Pathological examination of the materials were leiomyoma and adenomyosis. One other case with cellular leiomyoma recurred from the cervix uteri with a diameter of 6 cm five years after myomectomy, was hysterectomized and pathology was cellular leiomyoma.

One of the cases had polipectomy. The histology was variant type of leiomyoma (cellular leiomyoma). Two years following first operation, the patient had another polipectomy procedure. The pathologic result was adenosarcoma with 3 cm diameter. Surgical staging was performed and the follow-ups were unremarkable.

Lipoleiomyomas are uncommon and their reported incidence constitutes 0.03 to 0.2% of benign uterine tumors [15, 16, 17]. Since most cases are not involved due to their benign behaviour and they show histological features of admixture of varying amounts of mature adipose tissue with smooth muscle cells, their exact incidence is unknown. These tumors usually occur in postmenopausal women between 50–75 years of age [17]. Cytological atypia, necrosis, and calcification were not seen. The mitotic rate was zero in all cases. In our study; the incidence was 17.3%. Lipoleiomyomas sometimes are accompanied by anomalous blood vessels surrounded by smooth muscle cells and called angiomyolipoma [17]. In our case the 2.7% of the variant type of leiomyomas was angiomyolipoma. None of the lipoleiomyoma and angiomyolipoma cases were recurred.

Myxoid leiomyoma is consist of benign smooth muscle cells with myxoid material separating the tumor cells. The margins are circumscribed and neither cytological atypia nor mitotic figures are present. [18–20]. In our cohort; 2.7%

of the variant type of leiomyomas was myxoid leiomyoma. None of them were recurred.

Mitotically active leiomyoma is defined as tumours having 5–15 mitoses/10 HPFs but lacking necrosis or cytological atypia. The clinical behaviour is like that of a benign neoplasm and may be seen in patients with pregnancy or taking exogenous hormones [11, 21]. In our cohort; 4.3% of the variant type leiomyomas was mitotically active leiomyoma and none of them was recurred.

Atypical leiomyoma shows the presence of atypical cells and demonstrates moderate-severe cytologic atypia [11]. They resemble leiomyosarcomas. Most noticeable marker is low mitotic activity and absence of necrosis [5]. Twenty-one (11.4%) cases in our study, showed only nuclear atypia without necrosis or significant mitoses and hence were diagnosed as atypical leiomyoma. Five out of seven recurrent cases were cellular leiomyoma. Only one of the seven recurrent cases was atypical leiomyoma. The first operation was myomectomy and recurred after seven years. Myomectomy was performed again due to fertility preservation demand of the patient. The pathological result of second specimen was atypical leiomyoma.

Uterine smooth muscle tumor of uncertain malignant potential (STUMP) is a rare diagnosis. It is defined by the World Health Organization (WHO) as a smooth muscle tumor between benign and malignant criteria [5]. It is mostly seen in patients in their forties, who were operated with a leiomyoma diagnosis. Risk factors and prognosis are not exactly known, but there is risk of recurrence or metastasis in long term follow-up. The following histologic findings including a smooth muscle tumor with an uncertain type of necrosis, the presence of focal or diffuse cytologic atypia but the mitotic count is < 10/10 HPF, the presence of coagulative tumor necrosis but mitosis is < 10/10 HPF, and cellular tumors with > 15 mitosis/10 HPF are frequently encountered [22]. A retrospective study of Dańska-Bidzińska et al., evaluated the clinical and pathological features and outcomes of ten patients diagnosed with STUMP. Uterine bleeding was the second most frequent symptom. They performed conservative procedure in three cases, whereas in other patients hysterectomy was performed. Diameter of the tumors ranged from 3 to 29 cm. In all tumors mitoses were less than 10 per 10/hpf, atypia of middle or severe type, and in three cases necrosis was observed. They revealed no recurrence during the follow-up period [23]. In our study; 7 (3.8%) of the variant type of leiomyomas was STUMP. Diameter of the tumors were > 10 cm in all cases. They all showed mitosis < 10/10 HPF, atypia and necrosis. Hysterectomy was performed in all seven patients. One of them (14.2%) was recurred.

The exact diagnosis of a variant type of leiomyoma made with pathologic examination. But hypointense T1 signal intensity, moderate T2 signal intensity, hyperintensity on Diffusion-weighted imaging (DWI), if present, might raise the possibility of a leiomyoma variant [24]. In our sample, 36 of the patients had MRI evaluations. Eighty-three point three percent of cases showed hypointensity on T1 weighted image, 75% of cases showed hyperintensity on T2 weighted image, 66.7% of the cases had positive fat substraction and all of the 36 cases showed contrast enhancement.

In our study; 4.9 % of cellular leiomyoma, 14.2% of STUMP and 4.7% of atypical leiomyomas were recurred with clinical follow-up. In the literature; Zhang et al., [25] reported that none of six mitotically active leiomyomas and none of 17 cellular leiomyomas were recurred. Three out of 31 atypical leiomyomas and three of 14 STUMP with clinical follow-up were recurred. Kim et al., [26] reported an isolated case of a mitotically active leiomyoma recurrence as a leiomyosarcoma. Taran et al., [13] reported two out of 99 patients with cellular leiomyomas (2%) had recurrent disease. Studies in the literature suggest that atypical leiomyomas and uterine STUMPs may have a greater risk of recurrence [27–29].

CONCLUSIONS

Clinicians should be aware of variant type leiomyomas and their associated clinical, imaging, and pathologic issues. Understanding the diversity of variant type of leiomyoma in both pathology and symptomatology will lead to targeted therapy in the short term and prevention strategies in the long term in clinical practice. Since most variant type of leiomyomas mimic malignancy in one or more respects, diagnosis should be done by experienced pathologists due to the fact that they might be misdiagnosed. Though the frequency with which they occur remains less, their correct diagnosis was essential for a conservative management in patients wishing to preserve fertility.

Also, as we reveal, there is increasing evidence that variant type of leiomyomas may have recurrence potential. In clinical practice, the importance of exhaustive histopathological examination should be emphasized once again. Confirmed diagnosis is mandatory and has paramount importance for optimal management, and surveillance of the concerned patients. We emphasize on imperative submission of all hysterectomy specimens for histopathology, thorough sampling, and diligent quest for associated pathologies in routine hysterectomy specimens, few of which may need further management and surveillance for the patient's well-being. Early identification of these lesions may be beneficial for adequate treatment and follow-up. Prospective studies with longer follow-up would be important to gain insight into the pathogenesis of this subgroup of variant type of leiomyoma.

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Conflict of interests

No conflict of interest.

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Plasma microRNAs can be a potential diagnostic biomarker for endometriosis

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ABSTRACT

Objectives: Plasma microRNAs are considered potential diagnostic biomarkers for endometriosis. Increasing evidence has shown that a huge number of miRNAs are abnormally expressed in endometriosis plasma and play irreplaceable roles in diagnosis.

Material and methods: The aim of our study was to identify the differential expression of circular miRNA by reviewing the PubMed, ScienceDirect, and Cochrane databases between normal women and women with endometriosis and analyzing the miRNA data downloaded from the GEO database.

Results: Because of the differential miRNA expression in this review, we evaluated the diagnostic values of the differentially expressed miRNAs, particularly during the menstrual phases. According to the cut-off criteria with $|\log 2\,FC| > 1.0$ and $P < 0.05$, 36 differentially expressed miRNAs were identified, including 13 upregulated miRNAs and 23 downregulated miRNAs. We developed miR-155, miR-574, miR-23a, and miR-520d via a Venn diagram. Functional enrichment analysis considered that the target miRNAs might be involved in various pathways related to endometriosis, including neurotrophin, Hippo, oocyte meiosis, ubiquitin mediated proteolysis, HTLV-Infection, FoxO, and Rap1 signaling pathways. CTNNB1, MYC, and ES R1 of transcription factors were related to the differentially expressed miRNAs.

Conclusions: In summary, our study suggested that a four-miRNA could be included as a prognostic marker in endometriosis.

Key words: endometriosis; circular; microRNA; diagnosis; plasma

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INTRODUCTION

MicroRNAs (miRNAs) are composed of 21–23 nucleotides. miRNAs have the characteristics of high conservation, timing, and tissue specificity. miRNAs are stable in serum and may be used as non-invasive diagnostic indicators of diseases [1]. Two small non-coded RNAs, namely, Lenin4 and elet-7, which have been recognized as being related to various human diseases, were found in *Caenorhabditis elegans* for the first time by Lee in 1993 [2, 3]. Global expression profiling studies have identified hundreds of misaligned miRNAs in several diseases. miRNAs are involved in a number of steps, such as inclusion, addition, transfer out of the nucleus, processing in the fine cytoplasm, and translation or stimulation [4].

miRNAs mature by not fully binding to the 3′ end of the non-coding region of the target gene, inhibition of their translation, or binding to RNA silent complexes composed of multiple proteins. Target gene expression can be suppressed by completely binding to the non-coding region of the target gene 3′ [5, 6]. It is important that miRNA can target multiple mRNA expressions, and one mRNA can be regulated by multiple miRNAs at the same time through this complex post-transcription regulatory network [7, 8]. miRNA is involved in almost all pathophysiological processes in the body. To date, more than 1,881 miRNA precursors, encoding more than 2,500 miRNAs, have described as mature miRNA in humans. With the increased understanding of the mechanism of action of miRNAs and the study of the biogenesis, function, role, and characterization of miRNA, candidate biomarkers for many diseases have emerged, such as cancer, coronary artery disease, and gynecological diseases, including endometriosis [9–13]. Therefore, miRNAs have substantial potential as promising markers for diagnosis, prognosis and personalized targeting.

Endometriosis (EMS) refers to a common estrogen-dependent chronic disease in the endometrium (glands and interstitial substances) that occurs in other parts of the uterus and affects nearly 10% of women of childbearing age [14–16].

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This disease primarily causes pelvic pain and infertility. The prevalence of this disorder is an estimated global average of 176 million individuals, in whom the diagnosis is delayed by seven years, and the mean diagnostic age is 32.5–36.4 years, depending on the research population [17]. Although significant progress has been made in the study of the etiology and pathogenesis of EMS, unfortunately, compared to other chronic diseases, it is difficult to diagnose, and the diagnosis of EMS is often delayed because there are currently no accurate, accessible and non-invasive diagnostic tools. Early diagnosis and treatment of EMS remain difficult. Therefore, it is urgent to further explore the etiology and pathogenesis of EMS to identify specific and sensitive detection indicators and treatment targets and provide new ideas and strategies for early clinical diagnosis and treatment [18]. In several studies, a specific miRNA has been identified as a potential biomarker of the disease. These and other miRNAs have been associated with target genes and functional pathways in the disease-specific pathophysiology. The occurrence of endometriosis involves various factors, such as hormones, inflammatory factors, and hypoxic microenvironments. In recent years, studies have shown that tiny RNA also plays an important role in the development of endometriosis. There are differences in the expression of miRNA between ectopic endometrial tissue cells and normal tissue cells. These differences in the expression of miRNA may be related to the occurrence and development of EMS. The expression pattern of miRNA in the endometrium in endometriosis is based on patients and control women as well as different individuals who have endometriosis. miRNA may be an attractive candidate for new diagnostic markers and treatment interventions for endometriosis. These small non-coding molecules have become attractive candidates as new biomarkers for early non-invasive diagnosis [19–22]. Study of this disease may lead to valuable benefits for patients by reducing the recurrence rates in terms of prognosis and improvements.

In this study, a systematic review was conducted of the key serum miRNAs predicted for endometriosis diagnosis. GEO (Gene expression omnibus) is a gene expression database created and maintained by the NCBI (National Biotechnology Information Center of the United States). The purpose of this study is to identify miRNA data downloaded from the GEO database to determine serum differences between normal women and patients with endometriosis. In miRNA high-throughput analysis, miRNA target genes are shown to be differentially expressed and their function is annotated, and a miRNA feature that can effectively diagnose endometriosis is constructed. In addition, the TFactS database was analyzed using analytical transcription factors. This study shows the importance of miRNA in the diagnosis of endometriosis.

MATERIAL AND METHODS

A systematic review was conducted of all the pertinent studies that were identified in the electronic PubMed, ScienceDirect, and the Cochrane Central Register of Controlled Trials (CENTRAL) databases that examined plasma microRNAs as potential diagnostic biomarkers for endometriosis from 1966 to January 2019. The search strategy included the terms miRNA, microRNA, circular, blood, serum, and plasma. The search was concluded by 1) perusal of the reference sections of all relevant studies in English and 2) a manual search of the key journals and abstracts from the major annual meetings in the fields of endocrinology and obstetrics and gynecology. Articles were excluded from the analysis that lacked adequate disease-matched control groups. The control groups consisted of women without endometriosis.

Screening of the endometriosis miRNA expression dataset

The Series Matrix file of GSE46735 was downloaded from the GEO (http://www.ncbi.nlm.nih.gov/geo/) database. The inclusion criteria were as follows: 1) Diagnosis of endometriosis and a normal female control group; 2) sample sequencing data and clinical information of miRNA; and 3) processed bold parts in the properties of natural cells. The platforms included GPL 15634 (Applied Biosystems Human TaqMan Low Density Array (TLDA, v2 .0, Card A)) and GPL 15647 (Applied Life, dispensers TaunqMan Dense). The datasets of GSE46735 were used to recalibrate the relationship between control women and women with quiet division endometriosis (n = 8 in each group). Each programmed soft space in the early portfolio included the public and personal spaces of the natural class (n = 47 total spaces). The better case is better than the better. RNA was made available to study the identified microRNAs. miRNA sequencing data were processed using R language packets. The difference between endometriosis and normal female blood samples expressed by miRNAs was analyzed by Lima packets in R. Multiples in individual expression (FCs) were used to calculate miRNA and express miRNA considerations and GT with $|\log2\ FC| > 1.0$ and $p < 0.05$. Importantly, differential expression of miRNA at different stages of the menstrual cycle was associated with the diagnosis of endometriosis. Differentiated expression of the miRNA spectrum was normalized by log2 conversion. We used FunRich (http://www.Funrich.org) to obtain the overlapping differential expression of miRNA among GSE46735. A Vern diagram and volcano map were also constructed by FunRich. We used Heml 1.0 (http://hemi.biocuckoo.org/down.php) to obtain the differential expression of miRNA among GSE 46735. A heatmap was also constructed by Heml.

Prediction of the functional enrichment of microRNA target genes in endometriosis serum

Identification of miR target genes was performed with Targetscan (http://www.targetscan.org/), miRanda (http://miranda.org.uk), miRDB (http://www.mirdb.org/mirdb/), Pictar (https://pictar.mdc-berlin.de), miRWalk (http://zmf.umm.uni-heidelberg.de/apps/zmf/mirwalk2/), and RNA22 (http://cbcsrv.watson.ibm.com/rna22.html/) online analysis tools. To improve the reliability of the bioinformatic analysis, a Venn diagram was used to identify overlapping target genes. Then, The Date for Annotation, Visualization and Intrusion analyze the overlapping gene bioinformatic tool (DAVID) (https://david.ncifcrf.gov/) was used. DAVID is the web-based, online and bioinformatic tool designed to provide investigators with a complete series of functional annotation tools to identify biological mechanisms associated with numerous genes or proteins. GO (Gene Ontogirl) and KEGG (Kyoto Engineering of Genes and Genomes) pathway events were analyzed for particular genes. A P-value < 0.05 was set as the cut-off for significance.

Analysis of the regulation of miRNA targeting in endometriosis serum was used to determine up- and down-regulation of miRNA (Essaghir et al.) using the TFactS database (2010) (http://www.tfacts.org/). Only four indicators (P-value, Q-value, E-value, and FDR) were used in advance to indicate that a value which was less than 0.05 was considered a reliable transcription factor scope. State on translation factors (TF) of target DEMs of up and down-protected miRNA regulated objects where we must go to the special study.

RESULTS

The electronic search strategy identified 160 potentially relevant articles (PubMed, 136; ScienceDirect, 24; and Cochran Library, 0), which filtered articles by the title, summary, full text, or a combination of these factors. Of these 160 articles, 84 articles were excluded because of not meeting the inclusion criteria after reading the abstracts. The full studies of the remaining 76 studies, which focused on miRNAs used in the diagnosis of endometriosis, were then carefully read. An additional 65 articles were excluded because the sample originated from peritoneal fluid or urine. We excluded trials as follows: data on the diagnosis of endometriosis via a blood test identifying microRNAs were not available from the papers and could not be obtained from the investigators by e-mail contact and the microRNA detection method used reverse transcriptase quantitative real-time PCR. Eleven studies that investigated the role of miRNA expression changes as blood biomarkers in endometriosis samples were included. Eleven studies analyzed the expression of miRNAs by comparing endometriosis cases vs healthy controls [19, 21–31]. A total of 472 endometriosis serum samples and 357 normal corresponding serum samples were collected (some articles studied serum and some studies studied plasma; for simplicity, we used serum instead of serum/plasma). The subjects' age in the studies ranged from 26 to 53 years old. Table 1 summarizes the quality of the trials included in the review.

By summarizing 11 studies that studied the difference in the expression of miRNA in peripheral blood between endometriosis patients and normal individuals, the expression of miRNA was obtained, and the increased expressions included: miRNA-365, -125b, -150, -342, -143, -145, -500a, -451a, -18a, -154, -196b, -378a, -33a, -199a, -122, -4645, -636, -24-2, -3127, -185, -542, -502, -296, -550a, -424, -451a, -16, -191, -195, -1978, -1979, -4284, -1973, and -1974; the decreased expressions included: miRNA-let7, -135a, -200a, -141, -363, -6755, -145, -141, -542, -9, -889,-432, -1381, -410, -584, -99b, -127, -30c, -215, and -17. Quantitative real-time polymerase chain reaction detected the expression in blood and peritoneal fluid (PF) samples for miR-122 and miR-199a, and serum miR-122 and miR-199a detected endometriosis with a sensitivity of 95.6 and 100.0 and specificity of 91.4 and 100, respectively. MiR-199a ($p < 0.05$) and miR-122 could be used to distinguish between severe and mild endometriosis. MiR-199a was closely related to pelvic adhesion and lesions ($p < 0.05$) and was also related to hormone mediated signaling pathways. Moreover, it was confirmed that the best combinations of miR-199a, miR-122, miR-145 and miR-542-3p were reliable in terms of sensitivity and specificity, and the tested feature lines (Receiver Opera Charitable Curve, ROC) Under the Curve Area (Area Under Curve, AUC) was 0.994 (95% CI: 0.984–1.000). In addition, the AUC associated with miR-17-5p, miR-20a, and miR-22 was 0.9 (95% CI: 0.8–1.0). At the same time, the combination of serum le-7b, 7D and 7f during the proliferation period could be used as a diagnostic marker for endometriosis according to the differential expression of circulating miRNA between the endometriosis and control groups. The level of miRNA varied with the time of blood collection, and miR-200a and miR-141 have potential as new non-invasive biomarkers of endometriosis. In addition, the plasma levels of miR-200a, miR-200b and miR-141 varied with the sampling time; thus, the sampling time is critical. The specificity and sensitivity of plasma miR-17-5p, miR-20a and miR-22 in the diagnosis of phase III/IV endometriosis were 90.0 and 70.0, respectively [19].

2 GEO analyses

In the present study, 242 differentially expressed miRNAs in GSE46735 were identified in the plasma of endometriosis samples compared to control samples. Among the differentially expressed miRNAs, 124 miRNAs were upregulated, while 118 miRNAs were downregulated. The hierarchical

Table 1. Characteristics of eligible studies considered in the report

Author	Groups	miRNA (n)	n	Age	Infertility (n, %)	ARSM stage (n, %)	DIE (n, %)
Jia et al. 2013	Endometriosis	132	23	34.1 ± 5.03	5, 21.74	III: 10, 43.48 IV: 13, 15.52	11, 47.83
	Control		23	32.1 ± 6.95	3, 13.04	NA	NA
Suryawanshi et al. 2013	Endometriosis	286	33	36.2 ± 10.20	24, 100	NA	NA
	Control		20	38.8 ± 14.11	NA	NA	NA
Wang et al. 2013	Endometriosis	765	60	30.00	26	I: 17 II: 5 III: 14 IV: 24	18
	Control		25	20.65	22	NA	NA
Wang et al. 2016	Endometriosis	108	30	32.5 ± 6.5	13	I/II: 30	NA
	Control		20	34.0 ± 5.8	13	NA	NA
Nothnick et al, 2017	Endometriosis	miR-451a	41	23–44	NA	I/II: 12 III/IV:29	NA
	Control		40	21–45	NA	NA	NA
Maged et al, 2018	Endometriosis	miR-122 miR-199a	45	29.6 ± 3.44	25	I: 9 II: 1 III: 19 IV: 6	
	Control		45	29.5 ± 4.48	1		
Wang et al. 2018	Endometriosis	miR-17	80	22–45		I: 22 II: 28 III: 20 IV: 10	
	Control		60	22–45			
Cho et al. 2015	Endometriosis	let-7a-f, miR-135a, miR-135b	24	33.1 ± 6.63		III: 11, 45.8 IV: 13, 54.2	8, 33.3
	Control		24	32.2 ± 9.46			
Rekkr et al. 2015	Endometriosis	miR-200–family	61	27–39	39	I/II: 33 III/IV:28	
	Control		35	26–37	25		
Cosar et al. 2016		36354	24	33.1 ± 6.63			
			24	32.2 ± 9.46			
Pateisky et al. 2018	Endometriosis	372	51	27–40		I/II: 20 III/IV:31	23
	Control		41	29–45			

NA – not available

clustering heat map is shown in Figure 1, and the volcano map is shown in Figure 2. The identified miRNAs were well distinguished from differentially expressed miRNAs.

Has-miR-155-5p, hsa-miR-128-3p, hsa-miR-1-3p, and hsa-miR-532-5p of the upregulated differentially expressed miRNAs (LogFC > 1, P < 0.05) and hsa-miR-574-3p, hsa-miR-23a-3p, hsa-miR-520d-5p, hsa-miR-433-3p, hsa-miR-485-5p, and hsa-miR-122-5p of the downregulated differentially expressed miRNAs (LogFC < –1, P < 0.05) were significantly different. With respect to patients who provided blood samples in the early proliferative, late proliferative and mid luteal phases of the menstrual cycle (n = 47 total plasma samples), the cycle phase was verified according to the hormonal profile. RNA was extracted from each sample, and the expression of microRNAs was assessed using TaqMan Low Density Human miRNA arrays. Has-miR-155, hsa-miR-218, hsa-miR-301b, hsa-miR-128, hsa-miR-532-5p, hsa-miR-22, hsa-miR-1, hsa-miR-339-5p, and hsa-miR-143 in early proliferation; has-miR-155, hsa-miR-218, hsa-miR-532-5p, hsa-miR-22, hsa-miR-1, hsa-miR-339-5p, hsa-miR-331-5p and hsa-miR-362-3p in late proliferation; and has-miR-155, hsa-miR-218, hsa-miR-301b, hsa-miR-128, hsa-miR-133a,

Figure 1. The hierarchical clustering heat map of upregulated and downregulated miRNA

and hsa-miR-143 in the mid luteal phase were upregulated and differentially expressed (LogFC > 1, P < 0.05). Has-miR-574-3p, hsa-miR-23a, hsa-miR-500, hsa-miR-98, hsa-miR-7f, hsa-miR-451, hsa-miR-122, hsa-miR-520d-5p, hsa-miR-15a and hsa-miR-409-5p in early proliferation, hsa-miR-574-3p, hsa-miR-23a-3p, hsa-miR-98, hsa-miR-122, hsa-miR-874, hsa-miR-381, hsa-miR-520d-5p, hsa-miR-452, hsa-miR-369-3p, hsa-miR-224, hsa-miR-502-5p, hsa-miR-320, hsa-miR-433 and hsa-miR-23b in late proliferation and has-miR-574-3p, hsa-miR-382, hsa-miR-23a, hsa-miR-10b, hsa-miR-485-5p, hsa-miR-520d-5p, hsa-miR-433, hsa-miR-452, hsa-miR-130b and hsa-miR-874 in the mid luteal phase were downregulated and differentially expressed (LogFC < –1, P < 0.05) and were significantly different. The consistently

upregulated and downregulated genes in independent cohorts in all three phases were identified using Venn analysis, and a Venn diagram was generated by FunRich (Fig. 3). As a result, we identified has-miR-155-5p as having unregulated expression and hsa-miR-574-3p, hsa-miR-23a-3p, and hsa-miR-520d-5p as having downregulated expression.

Three Target prediction and function analysis

The target genes of four miRNAs were predicted using the TargetScan, miRDB, RNA22, miRWalk and miRanda online analysis tools. Thirty-nine overlapping genes of miR-155-5p, 4 overlapping genes of miR-574-3p, 70 overlapping genes of miR-23a-3p, and 107 overlapping genes of miR-520d-5p were identified. Enrichment analysis of the target genes was subsequently performed to elucidate the biological function of the consensus target genes.

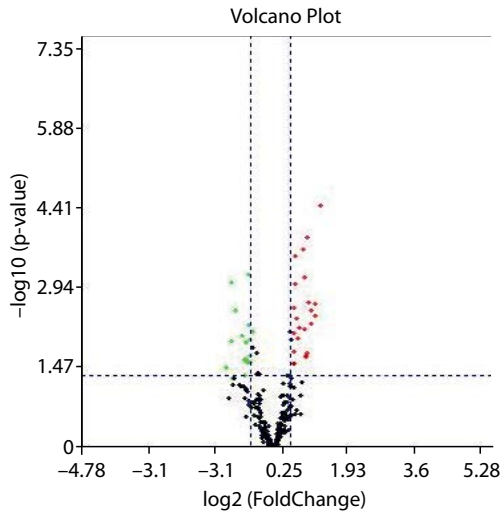

Figure 2. The volcano map of upregulated and downregulated miRNA

The biological processes (BP) were mainly enriched in axon guidance, peptidyl-tyrosine phosphorylation, negative regulation of an extrinsic apoptotic signaling pathway, positive regulation of cell migration, positive regulation of transcription, liver development, transmembrane receptor protein tyrosine kinase signaling pathway, positive regulation of transcription from RNA polymerase II promoter, retinal ganglion cell axon guidance, and negative regulation of transcription from RNA polymerase II promoter (Fig. 4A). The cellular components (CC) were significantly enriched in the cell-cell adherens junction, transcriptional repressor complex, cell surface, protein-DNA complex, Golgi membrane, cytoplasm, cytosol, nucleus, nucleoplasm, and perinuclear region of cytoplasm (Fig. 4B). The KEGG pathways that were primarily significantly enriched were the neurotrophin signaling pathway, hippo signaling pathway, oocyte meiosis, ubiquitin mediated proteolysis, HTLV-Infection, FoxO signaling pathway, Rap1 signaling pathway, pathways in cancer, signaling pathways regulating pluripotency of stem cells, and osteoclast differentiation (Fig. 4C). In addition, the molecular functions (MF) were mainly enriched in ubiquitin protein ligase binding, insulin-like growth factor receptor binding, chromatin binding, ubiquitin protein ligase activity, SMAD binding, transcription corepressor activity, transcriptional repressor activity, protein binding, and RNA polymerase II core promoter proximal region sequence-specific DNA binding (Fig. 4D).

Four Analysis of the transcription factors (TFs) of target genes

The corresponding TFs were analyzed and compared. The results showed that there were 61 TFs corresponding to the target. Among them, 56 genes correspond to upregulated relating TFs and 17 genes correspond to downregulated relating TFs. Comparative analysis suggested that of the 61 TFs, 12 TFs were shared between the two target genes, accounting for 19.67% of the total TFs. In addition, the TFs

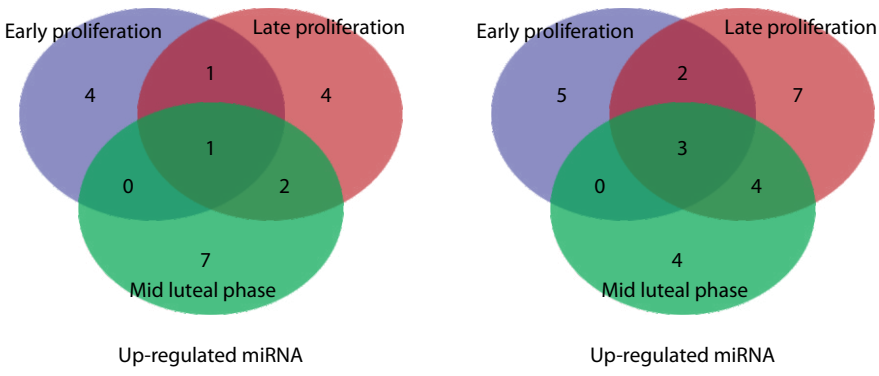

Figure 3. The Venn diagram of upregulated and downregulated miRNA in all three phases of menstruation

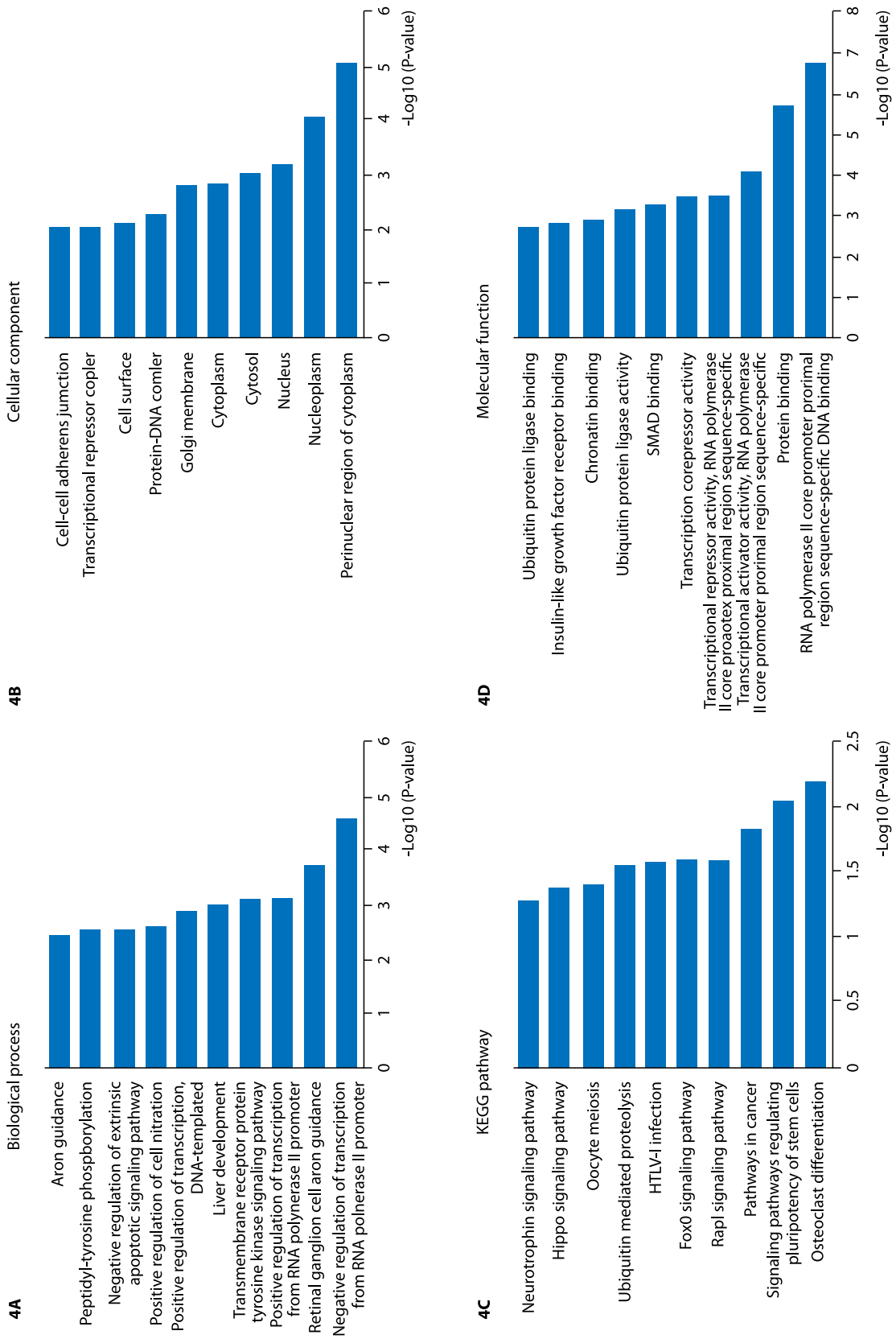

Figure 4. Target prediction and function analysis in the target genes of miR-155, miR-574, miR-23a, and miR-520d (**4A** — biological processes; **4B** — cellular components; **4C** — KEGG pathways; **4D** — molecular function)

corresponding to the regulation of miRNA target genes showed high specificity, consistent with the results of the GO analysis, and enriched the regulation of miRNA target genes during the regulation of transcription. According to the results of the analysis, the main TFs with credibility E values and cross ratios were not more than 0.05, and only the TFs CTNNB1, MYC, and ES R1 had a hard cross rate.

DISCUSSION

Endometriosis is the main cause of pelvic pain and low fertility. However, it is difficult for the diagnosis of endometriosis, and there is no clear diagnostic biomarker. Laparoscopy is currently the gold standard for the endometriosis diagnosis; however, it is traumatic. Many clinicians evaluate a series of clinical symptoms of endometriosis prior to seeking a definitive diagnosis by laparoscopy. Moreover, experimental treatment drugs have significant side effects and are typically not completely eradicated [31, 32]. At the same time, 70–75% of visually diagnosed lesions are confirmed histologically in laparoscopy, thus hindering their widespread use [33]. In addition, CA125 is only 21–50% sensitive for the diagnosis of endometriosis. Therefore, there is a need to develop a non-invasive diagnostic test for endometriosis. In recent years, studies on miRNAs have shown that their expression levels are closely related to the occurrence, development and metastasis of EMS; thus, it miRNAs are expected to be non-invasive diagnostic markers for EMS.

miRNA achieves the regulation of EMS through its regulation [34]. Using TaqMan microRNA chips to detect changes in serum miRNA expression levels in EMS patients and healthy control groups, studies showed that miR-199 and miR-122 were increased in the serum of EMS patients compared to healthy control groups [24]. miR-141, miR-9, MiR-145, and miR-542-3p were downregulated, and miR-199 and miR-122 could be used to distinguish between severe and mild EMS patients. In addition, the area under the ROC curve measured jointly by miR-199, miR-122, miR-145 and miR-542-3p was 0.994, and the sensitivity and specificity were 93.22% and 96.00%, respectively. It was proven that the combined detection of miR-199, miR-122, miR-145 and miR-542-3p as non-invasive biomarkers of EMS had significant diagnostic significance. At the same time, it was found that 27 miRNAs were differentially expressed in the serum of EMS patients compared to the healthy control group using TaqMan microRNA chips [19]. After testing with Real-time PCR, it was found that miR-17-5p, miR-20a and miR-22 showed significant downward expression, indicating that these miRNAs can be used as serum markers to diagnose endometriosis. EMS is characterized by the growth of the endometrium outside the endometrium. This process is closely related to factors such as vascular endothelial growth factor-A, which regulates angiogenesis, and thrombin-sensitive protein, miR-222, and miR-17-5p, which regulate the expression of angiogenic factors and play important roles in the pathogenesis of EMS. MiR-199a can inhibit the invasion of endometrial stromal cells by inhibiting the IKKβ/NF-κB signaling pathway and decreasing IL-8 expression, and it can be used as a serum marker for metastasis in EMS patients [36, 37]. Therefore, circulating miRNA can be used as a biomarker for the early diagnosis of small and mild endometriosis.

Because of the differential expression of miRNAs in the review, we downloaded a dataset from the GEO database to validate the exact plasma miRNA levels. Unexpectedly, we found that miR-155, miR-128, miR-1 and miR-532 of the upregulated miRNAs and miR-574, miR-23a, miR-520d, miR-433, miR-485 and miR-122 of the downregulated miRNAs were differentially significantly expressed and associated with the diagnosis of endometriosis patients in the present study. With respect to the phases of the menstrual cycle, we found that miR-155, which upregulated miRNA expression, and miR-574, miR-23a, and miR-520d, which downregulated miRNAs expression, could be used as a multi-marker-based model to provide more powerful information for the prediction of EMS in patients. When it is performed enrichment analysis of the four-miRNAs for the prediction and function analyses of biological processes, cellular components, KEGG pathways, and molecular function. Furthermore, we also assessed the miRNA target genes during the regulation of transcription. The results of the functional enrichment analysis implied that the three target genes of miRNAs related to endometriosis might be involved in various pathways, including neurotrophin, Hippo, oocyte meiosis, ubiquitin mediated proteolysis, HTLV-Infection, FoxO, and Rap1 signaling pathways. Unsurprisingly, only the transcription factors CTNNB1, MYC, and ES R1 agreed with this conclusion.

In short, in recent years, with the in-depth study of miRNAs, the different stages of disease occurrence and development have been shown to be accompanied by changes in miRNA expression, and a deep understanding of miRNAs helps to scientifically grasp the internal mechanism of disease occurrence. In addition, miRNA expression levels are expected to be important markers for disease diagnosis, treatment selection, efficacy evaluation, and prognosis evaluation. In summary, a number of miRNAs have been found to be differentially expressed in the plasma of women with endometriosis, and the mechanism of serum miRNA dysregulation remains unknown. To date, as indicated by the different results from the review and microarray datasets, circulating miR-155, miR-574, miR-23a, and miR-520d may be powerful biomarkers for diagnosis of endometriosis, accurate chemotherapy and targeted therapy; however, additional research is required to determine the repeatability and consistency of the results. These findings pro-

vide new insights into the early diagnosis and detection of endometriosis.

CONCLUSIONS

Comprehensive analysis of the pooled data provides strong evidence that circulating unregulated miR-155 expression and downregulated miR-574, miR-23a, and miR-520d expression are significantly associated with the diagnosis of endometriosis. Abnormal expression of aberrant miR-155 and low expressions of miR-574, miR-23a, and miR-520d may be promising diagnostic biomarkers for non-invasive endometriosis testing.

Ethics approval and consent to participate

We clarify the source of the materials used in our study, and any permissions necessary to collect such samples. Field studies should be conducted in accordance with local legislation, and the manuscript should include a statement specifying the appropriate permissions and/or licenses.

Consent for publication

We have given our consent for our manuscript, pictures or tables to be published in the journal. We have seen and read the material to be published.

Availability of data and material

We declared that materials described in the manuscript, including all relevant raw data, will be freely available to any scientist wishing to use them for non-commercial purposes, without breaching participant confidentiality.

Author contributions

ZZ contributed to the conception of the study. ZZ and WC contributed significantly to analysis and manuscript preparation. ZZ, GL, and YH performed the data analyses and wrote the manuscript.

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Conflict of interests

No conflict of interest.

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Analysis of incidence and overall survival of patients with vulvar cancer in Poland in 2008–2016 — implications for cancer registries

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ABSTRACT

Objectives: To analyze the incidence and overall survival rate of patients with vulvar cancer in Poland, based on the reporting data from the National Health Fund.

Material and methods: The incidence of vulvar cancer in Poland in 2008–2016 (9-year follow-up period) by voivodship and the number of patients undergoing combined hospital treatment were analyzed. For the group of patients treated systemically, overall survival (OS) probability was calculated using the Kaplan-Meier estimation method.

Results: In the period 2008–2016 in Poland, the diagnosis of malignant neoplasm of the vulva (C51% group) was made in 29,702 patients. The mean annual prevalence rate per 100,000 inhabitants was 8.3 ± 1.2 for Poland. The largest numbers of patients were reported in Mazowieckie and Slaskie voivodeships and the lowest in Opolskie and Podlaskie voivodeships. The median overall survival of patients treated with the combined method in 2008–2016 in Poland was 64.7 months (95% CI: 58.0–70.0). One-year survival rate was observed in 77.6% of patients, 2-year in 64.4%, 3-year in 58%, over 5 years — 54.22%.

Conclusions: In the years 2008–2016 in Poland, based on the data reported to the National Health Fund, the incidence of vulvar cancer was 4 times higher than the statistics of the National Cancer Registry, the WHO or the USA, which indicates either substantive or reporting errors. In Poland, 54% of patients treated with the combined therapy survive over 5 years which is a much lower result compared to highly developed countries.

Key word: vulvar cancer; overall survival; combined therapy; retrospective analysis; Poland

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INTRODUCTION

Malignant neoplasms of the vulva occur most often after the age of 60 [1] and by some are classified as diseases of the menopausal age. Observations in recent years indicate an increase in the incidence amongst younger patients [2]. Malignant neoplasm of the vulva is a rare neoplasm, it accounts for only 2–5% of all malignant neoplasms of female genital organs [2]. However, in the last decade, an increase in new cases was observed from about 0.6% each year, which resulted in an increase in mortality due to this cancer by an average of about 1.2% in the period between 2005 and 2014 [4]. Malignant neoplasms of the vulva jointly with malignant neoplasms of the vagina, account for only one percent of all malignant neoplasms in women in Poland. Similarly, malignant neoplasms of the vulva and vagina are responsible for one percent of cancer deaths in women in Poland [3, 4]. According to the studies of the National Cancer Registry (NCR), in patients diagnosed with malignant neoplasm of the vulva and vagina (NCR studies those tumours jointly), the one-year survival rate in 2000–2002 was

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71.2% and in 2003–2005 it was 69.4%. The five-year survival rates in the group of patients with vulvar and vaginal cancer in the years 2000–2002 accounted for 51.8% and in the years 2003–2005 for 48.6% of patients, respectively [4].

In the Polish literature, there are practically no in-depth data on the prevalence and overall survival rate of patients diagnosed with vulvar malignant neoplasm. Even the data of the Polish National Cancer Registry combine this information with the data on malignant tumours of vagina. Therefore, the aim of this study was to analyze the incidence and overall survival rate of patients with vulvar cancer in Poland, based on the reporting data from the National Health Fund.

MATERIAL AND METHODS

From the reporting database of the National Health Fund, the only public payer in Poland, the data of patients were collected for analysis from 2008-2016, who were shown to the payer with the diagnosis from C51% group — vulvar malignant neoplasm, according to ICD-10 [5]. The PESEL number (personal identification number) [6] was recognized as the unique identifier of the patient. Then, from those data, further information was extracted on patient hospital treatment. The analysis included data in which there was a simultaneous occurrence of the unique individual patient number (PESEL number) and diagnosis from the selected group. Then, a subset was created in the database in order to distinguish the data of patients undergoing combined treatment (chemotherapy, radio[chemo]therapy, surgery). Overall survival was analyzed in this group. The analysis covered the data of patients treated in the period from 1st January 2008 to 31st December 2016. The start date was the first date of the treatment given; the observation cut-off date was set on 31st December 2016. The number of neoplasms diagnosed according to the ICD-10 classification reported to the NHF was analyzed [5] in given types of services (health care subsegments) [7]. The number of diagnoses was analyzed by voivodship (reporting to NHF regional departments) in the nine-year period, separately for each year. In addition, for the group of patients undergoing combined therapy within hospital treatment (subsegment 03 — Hospital Treatment) 12, 24, 36 and 60-month survival rates were calculated using the Kaplan-Meier estimator. The median follow-up time was calculated based on the censored observation time (the median follow-up time value represents the time during which 50% of living patients were observed until the end of the analysis, i.e., until 31st December 2016). Data on the date of patient death was obtained based on the PESEL database from the Home Office. Overall survival analysis was performed with the Kaplan-Meier estimator and use of survival tables [8]. The results were developed in SAS Enterprise software Guide 7.1.

RESULTS

In Poland, there are 17 types of health services otherwise referred to as health care subsegments [7]. In the period 2008–2016 in Poland, the diagnosis of malignant neoplasm of vulva (C51% group) was made in 29,702 patients, on average annual approximately 3,300 patients per year. The percentage distribution of those patients among individual health care segments in Poland is presented in Table 1. The largest number of patients diagnosed in the analyzed group occurred in the Outpatient Specialist (Secondary) Care (ambulatory specialized services — 45%); then in primary care (general practitioners — 21%) and in hospital treatment care (17.3%).

The number of patients diagnosed with C51% in individual voivodeships directly correlates with the size of the voivodeship and frequency of highly specialized centres (Tab. 2). The largest numbers of patients were reported in the following voivodships: Mazowieckie (average annual about 500 people); Slaskie (approx. 490 people average annual) as well as in Wielkopolskie and Dolnoslaskie (approx. 280 people on average annual).

The lowest number of patients was reported in the following voivodships: Opolskie (about 70 people on average annual) and Podlaskie (approx. 90 people on average annual) as well as Swietokrzyskie and Podkarpackie (approx. 120 people on average annual). Mean annual prevalence rate per 100,000 inhabitants was 8.28 ± 1.23 for Poland.

The mean age of the patient with malignant neoplasm of vulva (C51% diagnosis) at the time of providing with healthcare services increased with the year of observation (Tab. 3)

On average, 24% of patients from a cohort of patients diagnosed with malignant neoplasm of vulva (C51% diagnosis) received treatment as part of inpatient therapy. The number of these patients by voivodship is presented in Table 4.

The highest percentage of people receiving hospital treatment was observed in the following voivodships: Mazowieckie (56.2%), Slaskie (51.8%), Malopolskie (35.2%); the lowest percentage is in the following voivodeships: Lubuskie (6.87%), Opolskie (7.2%), Warminsko-Mazurskie (9.7%).

Overall survival was based on a cohort of patients undergoing combination therapy as part of hospital treatment (Fig. 1). The median overall survival in the analyzed cohort of patients (4319 people) in the years 2008–2016 (9 years) was 64.7 months (95% CI: 58.0–70.0). 1783 were full observations and 2536 (58.72%) were censored. one-year (12 months) survival occurred in 77.6% of patients, two-year (24 months) in 64.4%, three-year (36 months) in 58.43 (months), over five years (60 months) — 54.22%.

Table 1. Distribution of patients with malignant neoplasm of vulva (C51% diagnosis) between types of health services in Poland (healthcare subsegments) in the years 2008–2016

Type of healthcare service according to the National Health Fund classification	Percentage of patients receiving the healthcare service
1. Primary care	21%
2. Ambulatory specialized services	45%
3. Hospital treatment	17.3%
4. Psychiatric care and treatment of addictions	0.0%
5. Medical rehabilitation	1.2%
6. Long-term care	5.9%
7. Dental treatment	0.0%
8. Sanatorium treatment	0.0%
9. Emergency assistance and sanitary transport	0.0%
10. Preventive health programs	6.4%
11. Separately contracted services	0.8%
12. Supplied of orthopedic equipment, auxiliaries and medical technical measures	0.0%
13. Drug price reimbursement	0.0%
14. Nursing and care services	1.0%
15. Palliative and hospice care	1.4%
16. Emergency Medical services	0.0%
17. Emergency assistance and sanitary transport from 2009	0.0%

DISCUSSION

Cancer of vulva makes 2–5% of all malignant neoplasms of the female genital organs and one percent of all malignancies in women. The incidence rate ranges from 0.1–2.6 per 100,000 in various populations and regions of the world. The world average is 1.2 [1–4].

In Poland, vulvar cancer ranks fourth in terms of the incidence of malignant neoplasms of the reproductive organs: after cervical, ovarian and endometrial cancer. There are approximately 350 new cases of this cancer diagnosed in Poland every year. Every year 200 women die from vulvar cancer in Poland (National Cancer Registry data). The average (raw) incidence rate in our country is 1.4 per 100,000 [4]. According to the data reported to the National Health Fund, this ratio is 8.3 per 100,000, which may indicate over-diagnosing or errors in reporting. The mean age at diagnosis is 69 years. In the group of patients diagnosed with vulvar cancer, only one in four (24%) was qualified for systemic treatment. There is a significant difference in the number of patients undergoing combined inpatient treatment between the voivodships: Mazowieckie 56%, Slaskie 51% *vs.* Lubuskie 6.8%, Warmińsko-Mazurskie 9.7%. These data indicate organizational problems (distance from reference medical centres), insufficient specialist knowledge amongst medical personnel, difficulties with access to highly specialized services, but also probably low patient health awareness in the age group over 60 and their health condition related to multiple co-morbidities disqualifying them from combined therapy. The consequence of the above-mentioned problems is the result of only 54% of five-year survival in the group of patients treated with combined therapy.

For comparison, according to data from the United States, 0.3% of the female population is at risk of being diagnosed with vulvar cancer. Every year, there are 6,070 new cases (2.2 per 100,000) and 1,280 deaths (0.5 per 100,000), 71.1% will survive five years — these data have remained unchanged for 40 years. Cancer of vulva is diagnosed in locally advanced stage in 59% of patients, in 29% in regionally advanced stage and in six percent in the stage of dissemination beyond the regionally advanced stage. The mean age of patients diagnosed with vulvar cancer is 69 years and death 78 years [9, 10]. These values are comparable with the data of the International Federation of Gynaecology and Obstetrics [11] and the data from Australia [12].

The above differences between Polish and American data indicate that despite the same age of patients at the time of diagnosis with vulvar cancer, it occurs four times more often in the population of Polish women and five-year survival rates are recorded only in 54% of Polish women [13–15] (only group treated with combined therapy) versus 71% of American women (the whole group). The comparison of the data suggests that vulvar neoplasms are diagnosed in more advanced clinical stages in Poland. Another explanation may be less effective treatment in

Table 2. The prevalence of patients diagnosed with malignant neoplasm of vulva (C51% diagnosis) in Poland in 2008–2016 in all types of services and by voivodship

Provincial Branch of the National Health Fund (Voivodeship)	Year of observation									Annual average in the province 2008–20016	Morbidity rate per 100 000 inhabitants in voivodeship
	2008	2009	2010	2011	2012	2013	2014	2015	2016		
Dolnoslaskie	228	274	247	262	280	310	292	300	288	**275.67**	**9.46**
Kujawsko-Pomorskie	145	167	169	160	166	196	196	191	191	**175.67**	**8.34**
Lubelskie	153	157	153	157	167	178	179	186	194	**169.33**	**7.71**
Lubuskie	75	85	70	83	100	87	87	86	80	**83.67**	**8.27**
Lodzkie	150	189	191	193	209	221	199	204	197	**194.78**	**7.71**
Malopolskie	205	242	236	236	276	240	255	263	259	**245.78**	**7.31**
Mazowieckie	469	496	510	550	531	486	496	543	511	**510.22**	**9.66**
Opolskie	81	63	63	62	62	57	75	72	80	**68.33**	**6.59**
Podkarpackie	109	122	120	124	126	144	117	136	127	**125.00**	**5.89**
Podlaskie	78	78	91	88	78	95	93	109	98	**89.78**	**7.44**
Pomorskie	190	184	184	219	205	201	196	210	182	**196.78**	**8.74**
Slaskie	492	506	538	469	465	479	484	462	500	**488.33**	**10.55**
Swietokrzyskie	94	114	125	127	138	132	117	127	121	**121.67**	**9.60**
Warminsko-Mazurskie	122	118	107	110	106	120	99	109	126	**113.00**	**7.74**
Wielkopolskie	235	277	263	286	323	286	264	290	288	**279.11**	**8.07**
Zachodnio-pomorskie	158	189	165	159	148	155	144	168	182	**163.11**	**9.41**
Poland in total	2984	3261	3232	3285	3380	3387	3293	3456	3424	Total: 29702 Annual average: 3300.22	
Average in Voivodeship X+/–SD*	186.5 +/–125.6	203.8 +/–132.84	202.0 +/–139.21	205.3 +/–135.88	211.3 +/–34.71	211.7 +/–126.47	205.8 +/–129.29	216.0 +/–131.92	214.0 +/–131.55	206.26 +/–131.17	8.28 +/–1.23

*Average value +/–Standard deviation

Table 3. The mean age of the patient with malignant neoplasm of vulva (C51% diagnosis) at the time of providing with healthcare services in years 2008–2016 in Poland

Year of observation	Average age, Average value +/–standard deviation
2008	65.61+/–13.04
2009	66.17+/–13.48
2010	66.58+/–13.28
2011	67.29+/–13.20
2012	67.60+/–12.90
2013	68.58+/–12.54
2014	68.24+/–12.53
2015	68.78+/–12.66
2016	69.08+/–12.64

Table 4. Number of patients diagnosed with malignant neoplasm of vulva (C51% diagnosis) treated with the combined method in hospital care in individual years 2008–2016

Provincial Branch of the National Health Fund (Voivodeship)	Year of observation									Annual average in the province 2008–2016	Morbidity rate per 100 000 inhabitants in voivodeship
	2008	2009	2010	2011	2012	2013	2014	2015	2016		
Dolnoslaskie	72	57	49	80	80	96	82	102	99	**79.67**	**2.66**
Kujawsko-Pomorskie	33	45	43	33	54	53	52	60	56	**47.67**	**2.24**
Lubelskie	38	33	46	46	49	48	41	54	50	**45.00**	**2.06**
Lubuskie	25	10	3	11	17	11	19	20	22	**15.33**	**1.43**
Lodzkie	45	55	60	60	60	68	58	65	54	**58.33**	**2.33**
Malopolskie	63	82	81	81	83	73	94	90	76	**80.33**	**2.42**
Mazowieckie	128	99	120	147	118	120	133	140	148	**128.11**	**2.38**
Opolskie	9	17	16	17	12	14	15	21	26	**16.33**	**1.49**
Podkarpackie	32	32	32	42	38	41	37	38	40	**36.89**	**1.72**
Podlaskie	25	27	30	23	30	21	24	32	30	**26.89**	**2.22**
Pomorskie	43	43	42	54	44	58	56	56	50	**49.56**	**2.18**
Slaskie	104	118	145	99	106	118	119	113	141	**118.11**	**2.50**
Swietokrzyskie	28	25	28	31	27	37	31	45	34	**31.78**	**2.48**
Warminsko-Mazurskie	23	17	17	23	16	27	24	22	30	**22.11**	**1.47**
Wielkopolskie	83	69	70	82	81	77	70	99	71	**78.00**	**2.29**
Zachodniopomorskie	41	28	34	42	38	40	38	48	60	**41.00**	**2.26**
Poland in total	792	757	816	871	853	902	893	1005	987	Total: 7876 Annual average: 875.11	
Average in Voivodeship X+/–SD*	49.5 +/–32.4	47.31 +/–31.06	51.0 +/–37.79	54.43 +/–35.92	53.31 +/–32.24	56.37 +/–33.85	55.81 +/–35.46	62.81 +/–36.10	61.69 +/–38.20	54.69 +/–33.96	2.13 +/–0.39

*Average value +/–Standard deviation

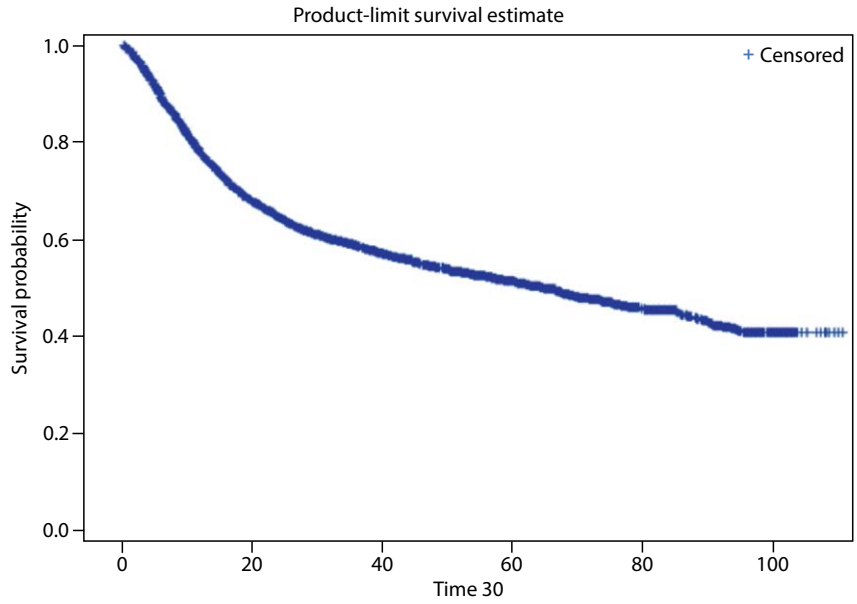

Figure 1. Kaplan-Meier estimation of overall survival in patients with malignant neoplasm of vulva (C51% diagnosis)

this group of patients. Organizational problems mainly related to pathomorphological diagnostics may be an indirect cause of suboptimal therapies. The above presented data require further detailed analysis within the framework of the national statistics (Statistics Poland, Social Insurance Institution, National Health Fund, National Cancer Registry).

This study has several limitations. Firstly, our study is based on the data collected from the registry of the National Health Fund and the quality of reported data may influence the obtained results. Secondly, our analysis is limited to nine-year period and further analysis are needed to assess the epidemiology of vulvar cancer in Poland. However, our study also has practical implications. The incidence of vulvar cancer presented in this study and differences between data from the registry of the National Health Fund and other public institutions collecting data on cancer (including vulvar cancer) indicate an urgent need to verify the existing caner registers and introduce methods to improve the quality of collected data and ensure their comparability between institutions. In addition, data on the prevalence of vulvar cancer can be used to plan health policy programs at both the national and regional levels.

CONCLUSIONS

1. In the years 2008–2016 in Poland, based on the data reported to the National Health Fund, the incidence of vulvar cancer was four times higher than in the statistics of the National Cancer Registry, data from the WHO or the USA, which indicates either substantive or reporting errors.
2. Systemic treatment covered a greater percentage of patients in voivodships where oncology reference centres were located.
3. In Poland, 54% of patients treated with combined method survive over five years. Compared to highly developed countries, this result is unsatisfactory, in the USA this percentage is as high as 71%.
4. Joint data from Statistics Poland, Social Insurance Institution, National Health Fund, National Cancer Registry and oncology registries are essential to develop standards of care and improved treatment outcomes for vulvar cancer patients.

Conflict of interest

All authors declare no conflict of interest.

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There is no significant correlation of adenomyosis with benign, premalignant and malignant gynecological pathologies. Retrospective study on 647 specimens

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ABSTRACT

Objectives: The aim of this study is to identify the prevalence of benign, premalignant and malignant gynecological pathologies in women with adenomyosis who underwent gynecological surgery.

Material and methods: The medical records collected between 1985 and 2020 were retrospectively reviewed. The pathology reports were studied from 647 cases where adenomyosis was presented. The estimated prevalence of benign, premalignant and malignant gynecological disorders in the general population was further evaluated.

Results: The mean age of women with adenomyosis was 54.1 ± 10.4 years old. Out of 647 patients, in 18.5% of the specimens we detected isolated adenomyosis and in 81.5% of cases a coexistence of one or more gynecological diseases, while in 84 out of 647 patients (13%) there was coexistence of adenomyosis with more than one gynecological condition (benign or malignancy). Among all cases, uterine leiomyomas were observed in 61.3% of patients, followed by endometrial polyps (11.9%), endometriosis (11.6%), endometrial hyperplasia (7.1%), endometrial cancer (3.6%), ovarian (1.4%) and cervical cancer (0.8%) ($p < 0.001$). Additionally, we found that women with a simultaneous co-existence of adenomyosis, leiomyomas and endometrial polyps or hyperplasia were younger ($p < 0.01$) in comparison to cases with malignancy.

Conclusions: Adenomyosis presents a common benign but often progressing myometrial condition that it is underestimated in clinical practice. Even though some studies suggest a potential association with several gynecological pathologies, we did not confirm a significant difference of adenomyosis prevalence between benign, premalignant and malignant gynecological conditions compared with the general population. Further investigation is required to confirm our results.

Key words: adenomyosis; endometriosis; benign gynecological diseases; gynecological malignancy

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INTRODUCTION

Adenomyosis is an enigmatic benign myometrial lesion characterized by the overgrowth of ectopic endometrium, into myometrium layers, resulting in a diffusely or focally enlarged uterus [1]. In 1860, Carl von Rokitansky was the first who described this entity as "cystosarcoma adenoids uterinum" [2].

With prevalence ranges reported between 10–70%, it is detected more often in women between 40-55 years old. Vercellini et al. [3], postulated that adenomyosis can be observed in 30–60% of resected uterine specimens.

According to the literature, it can coexist with endometriosis lesions and myomas cases. Although being different entities, 35–55% of women diagnosed with myomas

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share similar clinical characteristics to adenomyosis such as abnormal vaginal bleeding, painful menstrual cycles and chronic pelvic pain. Additionally, there have been reports of a coincidence with endometrial hyperplasia, polyps and endometrial cancer [4–7].

The risk factors for adenomyosis include age in the mid-forties, multiparity, smoking habits and elevated hormonal levels such as FSH and prolactin. Moreover, prior cesarean section and uterine surgery represent a major risk due to their potential to damage the junctional zone [2].

Objectives

The design of this study aims to investigate and highlight a possible notable relationship between adenomyosis and benign, premalignant and malignant gynecological diseases in women underwent gynecological surgery.

MATERIAL AND METHODS

Characteristics of study population

We reviewed the medical records of patients that underwent gynecological surgery between 1985 and 2020, from the department of Obstetrics and Gynecology of the Venizeleio General Hospital of Heraklion and between 2009 and 2020 from the 3rd Department of Obstetrics and Gynecology of Aristotle University of Thessaloniki. A total of 647 women with adenomyosis, which were confirmed by histology were retrospectively examined. Data were recorded including age, the type and cause of surgery performed and the concurrency of other benign and malignant gynecological conditions. We excluded cases without histological evidence. The pathologic features of the gynecologic diseases were classified according to the criteria of FIGO [8]. The Ethics Committee of the Department of Obstetrics and Gynecology of Venizeleio Hospital of Crete and the 3rd Department of Obstetrics and Gynecology of Aristotle University of Thessaloniki approved the protocol. The data that support the findings of this study are available from the corresponding author upon reasonable request.

Statistical analysis

Student-t test and x^2 tests were used for comparison of the mean of the various characteristics. The Mann-Whitney U test was performed if data were not distributed normally. The results are reported as mean ± SD or as percentages where appropriate. Differences were considered statically significant at $p < 0.05$.

RESULTS

In the present study we included patients with a diagnosis of adenomyosis based on histopathological results from uterine-sparing and non-uterine-sparing specimens. A total of 647 women with adenomyosis were identified with or without other gynecological pathology. We detected 120 (18.5%) cases with isolated adenomyosis and 527 (81.5%) cases with coexistence of one or more gynecological pathologies. Furthermore, we reported the coincidence of adenomyosis with more than one gynecological disease in 13% (84/647) of the overall cases of patients with adenomyosis (Tab. 1).

Table 1. Coexistence of adenomyosis with more than one gynecological condition

Gynecological conditions	No
Total number of cases with coexisted pathology	84/647 (13%)
Coexistence with leiomyomas and endometrial polyps	43
Coexistence with leiomyomas and endometrial hyperplasia	27
Coexistence with complex hyperplasia with atypia, endometrial polyps and leiomyomas	1
Coexistence with ovarian serous cystadenoma, leiomyomas and endometrial polyps	1
Coexistence with ovarian serous cystadenofibroma and leiomyomas	1
Coexistence with ovarian serous cystadenoma and endometrial polyps	1
Coexistence with ovarian serous-mucinous cyst and endometriosis	1
Coexistence with ovarian fibroma and leiomyomas	2
Coexistence with ovarian fibroma, endometrial polyps and leiomyomas	1
Coexistence with ovarian mucinous adenofibroma and leiomyomas	1
Coexistence with brenner tumor and serous cystadenoma	1
Coexistence with cini and leiomyomas	1
Coexistence with cervical cancer and endometriosis	1
Coexistence with breast cancer and leiomyomas	1
Coexistence with endometriosis and leiomyomas	1

Number of cases (No), percentage (%). This table describes the frequency of occurrence of malignant gynecological pathologies in 647 women with adenomyosis

The mean age of patients was 54.1 ± 10.4 years old (at the time of operation). The main indications for operation were uterine bleeding, benign and malignant gynecological pathology of the genital tract and/or pelvic pain. Out of all cases, uterine leiomyoma was reported in 61.3% (397/647) of cases, followed by endometrial polyps (11.9 % [77/647]), endometriosis (11.6 % [75/647]) and endometrial hyperplasia (7.1 % [46/647]) ($p < 0.001$) (Tab. 2).

Table 3 shows the co-existence of adenomyosis with gynecological malignancies. Among them, 3.6 % (23/647) had endometrial cancer, 1.4 % (9/647) ovarian and 0.8 % (5/647) cervical, respectively.

Table 2. Histological confirmation of benign and premalignat gynecological pathology in 647 women with adenomyosis

Gynecological pathologies	No (%)
Uterine Leiomyomas	397 (61.3%)
Endometriosis	75 (11.6%)
Endometrial polyps	77 (11.9%)
Endometrial hyperplasia	46 (7.1%)
Endometrial hyperplasia with atypia	10 (1.5%)
Benign ovarian cyst	22 (3.4%)
Ovarian fibroma-thecoma	1 (0.15%)
Ovarian fibroma	4 (0.6%)
Ovarian mucinous cystadenofibroma	1 (0.15%)
Ovarian serous cystadenoma	18 (2.8%)
Ovarian mucinous cystadenoma	1 (0.15%)
Ovarian mucinous adenofibroma	1 (0.15%)
Brenner tumor	1 (0.15%)
Ovarian mucinous cystadenoma (borderline)	1 (0.15%)
CIN (cervical intraepithelial neoplasia)	7 (1.1%)

Number of cases (No), percentage (%). This table describes the frequency of occurrence of benign and premalignant gynecological pathologies in 647 women with adenomyosis. Note that the sum of all gynecological conditions exceeds the total number of cases, because of the occurrence of coexisting pathologies

Table 3. Coexistence of gynecological cancer and adenomyosis

Gynecological malignancy	No (%)
Endometrial cancer	23 (3.6%)
Cervical cancer	5 (0.8%)
Stump (uterine smooth muscle tumor of uncertain malignant potential)	1 (0.15%)
Ovarian cancer	9 (1.4%)

Number of cases (No), percentage (%). This table describes the frequency of occurrence of malignant gynecological pathologies in 647 women with adenomyosis

Additionally, we observed that benign lesions were more prevalent in younger ages ($p < 0.01$). Diversely, endometrial and ovarian cancers were prominent in postmenopausal women.

DISCUSSION

Adenomyosis has become a clinical challenge rather than solely a histological diagnosis. Although it has been correlated with various gynecological pathologies, in the present study, we did not confirm a significant difference of adenomyosis prevalence in benign, premalignant and malignant cases compared to the general population.

It has been shown previously that the gynecological benign tumors may develop as a result of inflammatory, dietary, genetic and environmental factors [9]. In 1972, Bird defined adenomyosis as a chronic benign invasion of endometrium (glands and stroma) into myometrium, producing an enlarged uterus that is characterized by hyperplasia and hypertrophy of tissue [10]. Even though, the exact pathophysiology of adenomyosis is not clear yet, the classical theory attributes to the disruption of the boundary between endometrial basalis layer and the underline myometrium. Moreover, the de novo metaplasia of embryonic or adult stem cells in the myometrium and the altered lymphatic drainage present well accepted alternative pathogenic theories. In recent years, a notable number of studies have shown that various inflammatory molecules, sex steroid hormone receptors, extracellular matrix enzymes, growth and neuroangiogenic factors play an important role in the pathogenesis of this condition [1]. Considering the multifactorial character of the pathophysiology of adenomyosis, genetic alternations in signaling pathways also interact in the manifestations of such patients. In parallel, it is well known that endometriosis arises from the interplay between environmental and genetic factors. Thus, many studies aimed to the identification of potential shared genetic factors involved in the development of adenomyosis, endometriosis, uterine leiomyoma and endometrial polyps. Whilst the difference observed in the expression levels of estrogen receptor (ER) and progesterone receptor (PR) between patients with adenomyosis and leiomyoma [11], significantly elevated levels of metalloproteinases (MMPs) MMP-2 and MMP-9 and some specific cytokines have been found in patients with adenomyosis, leiomyoma and endometrial polyps [12].

An oestrogen receptor-alpha (*ERa*) *Pvu*II gene polymorphism was also found to be associated with endometriosis, adenomyosis and leiomyoma [13]. On the other hand, genetic polymorphisms of *MMP-1*, *MMP-7* and peroxisome proliferator activated receptor γ *(PPAR γ)* genes have been characterized as risk factors for adenomyosis and endometriosis but not for leiomyoma [14]. A recent next generation sequencing (NGS)-based study showed that the presence of *KRAS* mutations in adenomyosis is associated with the co-occurrence of endometriosis [15]. Of note, polymorphisms of two angiogenic factors, namely fibroblast growth factor (*FGF*) -1 and -2 may be involved in the initiation of angiogenesis in endometriosis and adenomyosis [16]. In sum, the aforementioned findings point out that the co-existence of adenomyosis with other gynecological conditions can be attributed to some shared genetic risk factors; obviously, there are various additional genes that are disease-specific.

Of note, four parameters describe adenomyosis. The presence of endometrial glands and stroma within the myometrium, the depth of penetration, the extend of spread in terms of number of foci and the arrangement of the lesion [2]. In last decades, although adenomyosis is

rarely diagnosed before hysterectomy, the improvement of diagnostic approaches such as Ultrasonography and Magnetic resonance imaging (MRI) allows us to identify the disease by means of non-invasive methods. Common transvaginal ultrasound (TVUS) findings represent reliable criteria to strongly suggest the diagnosis of adenomyosis. Additionally, minimally invasive techniques such as sonography, hysteroscopy and laparoscopy can also be useful for imaging [2].

As far as the clinical signs and symptoms are concerned, patients can be asymptomatic or nonspecific features can be present like dysmenorrhea, dyspareunia, chronic pelvic pain, abnormal uterine bleeding and infertility. These overlapping symptoms can also be a manifestation of other concomitant gynecologic disorders; thus, adenomyosis has largely been a postoperative diagnosis made by the pathologist [2].

More in depth, previous studies have suggested that a co-morbidity associating exists between adenomyosis and benign and malignant gynecological tumors [4–7, 17]. Results from a large retrospective study on patients undergoing hysterectomy showed that women with leiomyoma and adenomyosis were more likely to report similar complaints [18]. Despite the hyper estrogenic environment that may share these gynecological conditions [19], in the present study, we noticed a quite expected percentage of adenomyosis coexisting with leiomyoma cases (61.3%), followed by endometrial polyps (11.9%), endometriosis (11.6%) and endometrial hyperplasia (7.1%). By taking into consideration the epidemiological standards of current literature related to earlier mentioned benign pathologies in the general population, we did not notice a prominent appearance of such conditions in women diagnosed with adenomyosis. More specific, it is already known that up to 70% of women develop leiomyoma by the age of menopause [20]. Furthermore, depending on the different geographical areas and population studied, the prevalence of endometrial polyps varies from 7.8% to almost 35% [21]. Apart from that, 10% of premenopausal and 6% of menopausal women report the coexistence of an abnormal uterine bleeding and endometrial hyperplasia at some point during their life time [22].

In association with endometriosis, from a pathogenic standpoint, they are considered two distinct diseases because of specific causative pathways and clinical presentation, despite appearing together in patients; although for over 90 years endometriosis and adenomyosis were considered as the same entity with the exception of endometriomas [1, 19]. Worth of note, in general community endometriosis affects 10 to 15% of patients of reproductive age [23]. In the present work, we confirmed the concurrence of adenomyosis with 75 endometriosis cases (11.6%).

Interestingly, as reported in the literature, adenomyosis may be the precursor of cancerous transformation due to the pattern of growth, invasion and angiogenesis of such lesions [24]. Well of note, malignant transformation of adenomyosis is more observed in postmenopausal and elderly women and in preexisting benign gynecological lesions [7]. Malignant changes in adenomyosis have been reported in 6.8% of patients with endometrial cancer [25]. Recently, it was postulated that women with adenomyosis are at higher risk of endometrial and thyroid cancer, while cases with endometriosis are in danger of endometrial and ovarian cancers [17, 19]. Even thought, the association of adenomyosis in the pathogenesis of endometrial cancer is unclear, endometrial cancer involving adenomyosis is influenced by hormonal imbalances and it is associated with a better outcome [7, 19]. Additionally, the malignant transformation of adenomyosis is suggested to be due to its endometrial epithelium transition to cancerous cells, which results to tumorigenesis [7].

Lately, Koray et al., determined the effects of adenomyosis on the aggressiveness of endometrial cancer. Although, adenomyosis was not noticed to be an independent prognostic factor for endometrial tumor, they detected a better prognosis on such cases [26]. On the other hand, in a large pilot study, the authors did not find any significant difference between patients with coexistence of endometrial cancer and adenomyosis in comparison to isolated endometrial cancer cases in terms of epidemiologic, clinopathologic and prognostic characteristics [27]. Moreover, recently, Raffone A et al., in a systematic review and meta-analysis confirmed that adenomyosis and endometrial cancer pathology present two unrelated conditions. In that study they assessed the prevalence of adenomyosis in women with endometrial cancer. They did not detect a difference in adenomyosis prevalence in endometrial cancer cases compared to those reported for other gynecological pathologies requiring surgery [28]. Furthermore, it has be revealed that the presence of adenomyosis may be a principal factor for the determination of adenocarcinoma prognosis, due to *de novo* malignant transformation of adenomyotic foci and the simultaneous malignant transformations in the eutopic endometrium and adenomyosis. In a previous study, Koshiyama et al., reported four cases with adenocarcinoma out of 564 women with adenomyosis [19, 29]. Thus, a possibility of increased risk for endometrial cancer in patients with adenomyosis is yet to be confirmed.

As far as the ovarian cancer is concerned, Shen et al. [30], in a large case control study confirmed that adenomyosis importantly raise the risk of developing ovarian cancer. Opposed to that, Jeh et al., reported that adenomyosis did not increase the risk for ovarian cancer [17]. Even

though, it is known that adenomyosis and ovarian cancer are characterized by estrogen disturbance and menstrual disorders, further investigation is required in order to establish a correlation between these two entities. In our series, we confirmed that endometrial cancer appears in 3.6% of adenomyosis patients, followed by ovarian cancer (1.4%) and cervical cancer (0.8%) (Tab. 3). Well of note, the National Cancer Institute mentions that approximately 3.1% of women will be diagnosed with uterine cancer, less than 2% with ovarian cancer and 0,6% with cervical cancer at some point during their lifetime [31]. Thus, according to our data, we did not observe a significant risk of developing gynecological malignancy in women with adenomyosis compared to cases with no previous pathology of adenomyosis.

On a gene level, although adenomyosis can be a precursor of some carcinomas, the exact molecular mechanisms leading to the malignant transformation are poorly understood, taking into account that studies in this field reporting genetic alterations, epigenetic changes and mutational analysis are very few. Therefore, to date, there have not been accumulated sufficient genetic and epigenetic data for the mechanisms leading to the malignant transformation of adenomyosis through a multi-step process. Both adenomyosis and (type 1) endometrial cancer have been linked to sex steroid action, while the gene expression profile of this condition is reminiscent of cancer, cell death and cell cycle networks [32]. Furthermore, reduced levels of mRNA of Phosphatase and Tensin Homolog (*PTEN* mRNA) were observed in adenomyosis and it is worth noting that respective gene has been characterized as a tumor suppressor gene that is mutated in a large number of cancers [33]. The relationship between *PTEN* and endometrial cancer has been sufficiently documented [34], while two more features strengthening the speculation for a possible link between adenomyosis and endometrial cancer deals with the implication of *KRAS* and *BCL2* gene mutations [32]. A meta-analysis of two genome wide association studies (GWAS) of patients with uterine leiomyomas revealed shared signals with endometriosis, including two variants at the *GREB1* gene as well as the rs2202282 variant of *SULT1E1* gene that is located in a cluster of sulfotransferase genes and the rs765333492 variant of *SCFD2* gene; substantially, this study presented evidence for a shared risk factor between leiomyoma and endometrial cancer (EC), rs10917151 variant of *CDC42/WNT4* locus [35]. However, no association with adenomyosis was detected.

The retrospective nature of the study represents a limitation of this work. Additionally, the prevalence of adenomyosis is slightly deviated due to the postmenopausal age at the time of operation. On the other hand, strong points are the large number of patients and the selection of all cases based on histological biopsy.

CONCLUSIONS

To summarize, in the present retrospective study, the supposed association between adenomyosis and benign, premalignant and malignant gynecological diseases appears unsupported. Compared to women with no previous pathology of adenomyosis, we did not report a significant correlation of adenomyosis and other gynecological pathologies. Further studies are required in order to confirm our findings.

Acknowledgment

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Ethical approval

The Ethics Committee of the Department of Obstetrics and Gynecology of Venizeleio Hospital of Crete (no. 124/17/2019) and the 3rd Department of Obstetrics and Gynecology of Aristotle University of Thessaloniki [no.94/23-4-20] approved the protocol. This article does not contain any studies with animals performed by any of the authors.

Informed Consent

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

Conflict of interest

The authors report no conflict of interest.

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Increased clitoral artery pulsatility index and decreased sexual desire level in women with polycystic ovary syndrome

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ABSTRACT

Objectives: Polycystic ovary syndrome (PCOS) is claimed to effect the sexual desire, and recently, blood flow in the clitoral artery (CA) was measured by Doppler ultrasound (USG) examination and the level of sexual desire was objectively demonstrated by determining the pulsatility index (PI).

In the present study, it was aimed to quantitatively determine the sexual desire levels in women with PCOS using Doppler USG and to compare the data with healthy women.

Material and methods: The study included 71 patients diagnosed with PCOS and 78 healthy women who applied to our tertiary hospital gynecology clinics and for control purposes. Pulsatility indices were determined by measuring blood flows in the clitoral artery, uterine artery, ovarian artery and labial artery using Doppler USG in all participants.

The clitoral artery pulsatility index was found to be increased significantly in women with PCOS.

Results: The mean age was 28.5 ± 3.7 in the polycystic ovary syndrome group and 30.0 ± 5.2 in the control group. The mean clitoral artery pulsatility index (1.4 ± 0.5 cm/sec) in the PCOS group was significantly higher than the control group (1.2 ± 0.4 cm/sec) (p = 0.033 cm/sec).The mean ovarian artery pulsatility index (0.8 ± 0.2 cm/sec) in the PCOS group was also significantly higher than the control group (0.7 ± 0.2 cm/sec) (p = 0.015 cm/sec).

PCOS is showed to influence sexual desire with an objective measurement.

Since trying to obtain objective data about the level of sexual desire, questionnaires were not applied to the participants and no questions were asked.

Conclusions: In our study, it was found that the clitoral artery pulsatility index, that is, the rate of resistance in the blood flow to the clitoral region, increased significantly in women with PCOS. This finding shows that the level of sexual desire in women with PCOS has decreased compared to healthy women.

Key words: polycystic ovary syndrome (PCOS); clitoral artery blood flow; pulsatility index; PI; clitoral volume

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INTRODUCTION

Polycystic ovary syndrome (PCOS) is an endocrinological disease that affects 5–10% of women. At least two of the major findings such as cysts, hyperandrogenism, and ovulatory dysfunction are present in PCOS [1, 2]. As a result of endocrinological disorders occurring in PCOS, follicle-stimulating hormone (FSH) is inadequate and luteinizing hormone (LH) is excessive. This leads to the production and release of large amounts of androgens in the ovaries, resulting in ovulatory dysfunction [2–4].

Endocrine disorders seen in PCOS, menstrual disorder, diabetes, cardiovascular disease, and infertility lead to the development of many important complications [4, 6]. In addition to this, the appearance of hirsutism with obesity and excessive hair causes the patient to experience psychological and social problems and decrease the quality of life.

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In addition, it is stated that PCOS can significantly reduce the level of sexual desire. It has been reported that when womens' sexual desires decreases, they can also experience sexual and/or marital life problems [7–9].

The level of decrease in sexual desire of women has been attempted to be evaluated subjectively with some questionnaires [10, 11]. However, recently, blood flow in the clitoral artery (CA) was measured by Doppler ultrasound (USG) examination and the level of sexual desire was objectively demonstrated by determining the pulsatility index (PI) [12–14].

To date, sexual desire level in PCOS patients was attempted to be shown using only questionnaires in a subjective way. However with the present study, it was aimed to show the sexual desire level using a quantitative method for clitoral blood flow with Doppler USG. The present study was aimed to calculate the pulsatility indices and quantify the sexual desire levels by comparing these data with healthy women by measuring the blood flow in the clitoral artery, uterine artery, ovarian artery and labial artery with Doppler USG in women with PCOS.

MATERIAL AND METHODS

This study was approved by the local ethics committee and was planned prospectively.

Patients and tests

The study included 71 patients diagnosed with PCOS and 78 healthy women who applied to our tertiary hospital gynecology clinics for control purposes. A signed consent form was received from all participants.

To avoid selection bias, we recruited women between the ages of 20–45 and not of reproductive age to obtain reliable results about sexual desire and accordingly about clitoral blood flow.

Women who are not of reproductive age, those with chronic diseases and those with a history of gynecological surgery were excluded. PCOS was diagnosed according to the Rotterdam criteria [1, 2].

Doppler USG

Clitoral artery blood flow in all women was measured using colored Doppler USG. Doppler USG was performed with the Aplio Ultrasound System (SSA-790; Toshiba, Tokyo, Japan) using a convex 7.5 MHz probe. This procedure was performed by at least five years of experienced Obstetrics and Gynecology specialist.

Each woman was placed in gynecological position for Doppler USG procedure. The Doppler translabial probe was placed sagittally on the clitoris at an angle of less than 20°, so as not to press on the tissues. After determining the crotroal artery by color flow mapping, the Doppler probe was placed on the artery and at least three sequential Doppler waveforms were obtained. In this way, pulsatility indices were measured and recorded. The same procedure was repeated for uterine artery, ovarian artery, and labial artery, and pulsatility indexes were measured and recorded [14].

In addition, right (RO) and left ovary (LO) volumes and follicle numbers were measured and recorded.

Statistical analysis

All statistical analyzes in the study were done using SPSS 25.0 software (IBM SPSS, Chicago, IL, USA). Whether continuous variables are suitable for normal distribution was confirmed by the Kolmogorov-Smirnov Test. The differences between the groups in terms of continuous variables were analyzed using Independent Samples' t Test, and the comparison of mean values between multiple groups by variance analysis. The relationship between continuous variables was tested using Pearson's correlation analysis. The results were evaluated within the 95% confidence interval, and $p < 0.05$ values were considered significant. Bonferroni correction was made where appropriate.

We performed a power analysis using the software G*Power (version 3.1.9.4, Düsseldorf, Germany) with an effect size 0.6, and according to the analysis, a total of 148 subjects would be needed to obtain statistical power at the level 0.95.

RESULTS

The mean age in the polycystic ovary syndrome group was 26.5 ± 3.7, and in the control group it was 30.0 ± 5.2. The mean body mass index (BMI) (26.7 ± 4.8 kg/m^2) was significantly higher in the PCOS group compared to the control group (24.8 ± 4.6 kg/m^2) ($p = 0.017$).

The mean right ovarian volume (14.5 ± 5.0) in the PCOS group was significantly higher than the control group (6.4 ± 2.7) ($p < 0.001$). Similarly, the mean left ovarian volume (13.3 ± 4.5) in the PCOS group was significantly higher than the control group (7.3 ± 4.9) ($p < 0.001$).

The mean clitoral artery pulsatility index (1.4 ± 0.5 cm/sec) in the PCOS group was significantly higher than the control group (1.2 ± 0.4 cm/sec) ($p = 0.033$ cm/sec). The mean ovarian artery pulsatility index (0.8 ± 0.2 cm/sec) in the PCOS group was also significantly higher than the control group (0.7 ± 0.2 cm/sec) ($p = 0.015$ cm/sec). However, the mean clitoral volume was similar between the groups ($p = 0.18$). The mean menstruation time (13.2 ± 14.5 days) in the PCOS group was also significantly higher than the control group (8.0 ± 9.5) ($p = 0.014$) (Tab. 1).

In correlation analysis, the clitoral artery pulsatile index was found to be significantly correlated with clitoral volume ($p = 0.001$; $r = 0.364$), the uterine artery pulsatile index ($p = 0.028$; $r = 0.255$) and the labial artery pulsatile index ($p = 0.006$; $r = 0.333$) (Tab. 2).

Table 1. Comparison between polycystic ovarian syndrome group and control group in terms of mean Doppler measurements

	PCOS group		Control group	
	Mean	SD	Mean	SD
Age [years]	28.5	3.7	30.0	5.2
RO volume	14.5	5.0	6.4	2.7
LO volume	13.3	4.5	7.3	4.9
Clitoral volume	1.2	0.6	1.1	0.4
CA PI [cm/sec]	1.4	0.5	1.2	0.4
OA PI [cm/sec]	0.8	0.2	0.7	0.2
UA PI [cm/sec]	1.9	0.5	2.0	0.6
LA PI [cm/sec]	1.8	0.7	1.8	0.6
BMI [kg/m^2]	26.7	4.8	24.8	4.6
Duration of menstruation [days]	13.2	14.5	8.0	9.5

*Significant at the 0.001 level (99.9% CI); **Significant at the 0.05 level (95% CI). Independent Samples' t Test was used; PCOS — polycystic ovary syndrome; SS — standard deviation; RO — right ovary; LO — left ovary; CA — clitoral artery; PI — pulsatile index; OA — ovarian artery; UA — uterine artery; LA — labial artery; BMI — body mass index

Table 2. Correlation analyzes in polycystic ovarian syndrome group

		Age	RO volume	LO volume	Number of follicles	Clitoral volume	CA PI	OA PI	UA PI	LA PI	BMI
RO volume	r	0.052									
	p	0.659									
LO volume	r	0.065	0.691								
	p	0.583	< 0.001								
Number of follicles	r	0.047	–0.078	0.064							
	p	0.698	0.517	0.595							
Clitoral volume	r	0.076	0.151	0.014	–0.238						
	p	0.518	0.200	0.903	0.046						
CA PI	r	–0.051	0.092	0.147	–0.084	0.364					
	p	0.664	0.436	0.210	0.485	0.001					
OA PI	r	–0.077	–0.163	–0.043	–0.191	–0.055	–0.157				
	p	0.513	0.166	0.716	0.110	0.639	0.181				
UA PI	r	–0.154	0.044	0.071	–0.092	0.111	0.255	0.079			
	p	0.191	0.711	0.545	0.444	0.345	0.028	0.505			
LA PI	r	–0.088	–0.107	–0.078	–0.024	–0.167	0.333	–0.137	0.148		
	p	0.477	0.387	0.527	0.847	0.175	0.006	0.267	0.227		
BMI	r	0.057	0.186	0.209	–0.089	0.126	–0.143	0.060	0.095	–0.040	
	p	0.635	0.120	0.080	0.471	0.296	0.233	0.617	0.430	0.754	
Duration of menstruation	r	–0.205	0.197	0.196	0.030	–0.064	–0.140	0.072	0.047	–0.202	0.103
	p	0.107	0.122	0.123	0.818	0.621	0.275	0.577	0.714	0.128	0.422

Pearson's correlation analysis was used for all analyzes; RO — right ovary; LO — left ovary; CA — clitoral artery; PI — pulsatile index; OA — ovarian artery; UA — uterine artery; LA — labial artery; BMI — body mass index

Right and left ovarian volumes were significantly correlated with each other ($p < 0.001$; $r = 0.691$). The clitoral volume was negatively correlated with the number of follicles ($p = 0.044$; $r = –0.235$).

DISCUSSION

The pulsatility index is a flow parameter calculated using the maximum, minimum and average Doppler frequency during a cardiac cycle [PI = (Vmax–Vmin)/(Vmean);

PI = (peak systolic flow-peak diastolic flow)/(mean flow)]. It is used in conjunction with the resistance index to evaluate resistance in a vascular system. The pulsatility index increases when there is an obstacle ahead of the measured artery. Resistance index, systolic flow/diastic flow ratio and pulsatility index can be measured easily and quickly and provide information about the resistance of the flow. However, in cases where diastolic flow is absent or decreases to zero, only the pulsatility index can be used [12–18]. Khalife et al. [12] measured the clitoral blood flow resistance with Doppler USG by determining the pulsatility index and stated that this method is a non-task, cheap and quantitative method. They also suggested that the clitoral blood flow resistance determined by this method could quantitatively determine the level of sexual desire in women [12]. Oiwa et al. [13] measured the clitoral artery pulsatility index after surgery and stated that this method can be used as a useful parameter related to genital circulation and sexuality in women. Mercier et al. [17] showed that there is no significant difference in repeated measurements and that the pulsatility index can be used to provide reliable data in determining the resistance of the clitoral blood flow. Karatas et al. [11] found the clitoral blood flow measurements they made using Doppler USG correlated with the survey values they made to determine the level of sexual desire and showed that the clitoral blood flow measurement reflects the level of sexual desire. Rosato et al. [14] stated that the clitoral blood flow shows the level of sexual desire and therefore they tried to determine the level of sexual desire by measuring the amount of blood flow in the clitoral artery by Doppler USG. In our study, the clitoral artery pulsatility index was measured using Doppler USG and the sexual desire levels of women with PCOS were determined.

It is a matter of debate whether women with PCOS have decreased levels of sexual desire compared to healthy women due to the different hormonal levels of healthy women, the development of hirsutism, and their predisposition to obesity [7, 9, 19]. Stovel et al. [10] Hashemi et al.[20] and Yildiz et al. [21] found that women with PCOS had the same level of sexual desire as control groups in their studies using questionnaires. In all three studies, only the average orgasm score was found lower than the control group [10, 21, 22]. Eftekhar et al. [19] showed that the level of sexual desire in women with PCOS decreased significantly compared to healthy women. In our study, the mean clitoral artery pulsatility index (1.4 ± 0.5 cm/sec) in the PCOS group was significantly higher than the control group (1.2 ± 0.4 cm/sec) (p = 0.033 cm/sec). The mean ovarian artery pulsatility index (0.8 ± 0.2 cm/sec) in the PCOS group was also significantly higher than the control group (0.7 ± 0.2 cm/sec) (p = 0.015 cm/sec). These findings suggest that the level of sexual desire in PCOS patients may be lower than that of healthy women.

Battaglia et al. [15] reported that there was no significant difference in depression level between women diagnosed with PCOS and the healthy control group with similar age and BMI values. Morotti et al. [22] did not find a significant difference between PCOS group and control group in terms of mean clitoral volume, clitoral artery pulsatility index and labial artery pulsatility index in their study to measure the level of sexual behavior in weak women with PCOS. These data suggest that psychological status and sexual desire levels are associated with obesity in women with PCOS. These findings mean that the sexuality level of women with PCOS but without obesity does not differ from healthy women. However, in our study, no significant correlation was found between BMI and clitoral volume, clitoral artery pulsatile index, and labial artery pulsatile index in the PCOS group. This result may be attributed to the fact that the number of patients in our study group is not very high, however, this finding suggests that it may not be very accurate to completely link the level of sexual desire in women with PCOS to obesity. It should be taken into consideration that both hormonal levels differ in women with PCOS and excessive hairiness such as hirsutism can affect sexual desire levels.

Özay et al. [23] and Mala et al. [24] found that the ovarian artery pulsatility index in women with PCOS was significantly lower than the control group. In our study, the mean ovarian artery pulsatility index was found significantly higher in the PCOS group. Battaglia et al. [15] Adali et al. [25] and Mala et al. [24] found that the uterine artery pulsatility index in women with PCOS was significantly higher than the control group. In our study, no significant difference was found between the two groups in terms of both the average uterine artery and the labial artery pulsatility indexes. These differences between the results of the studies may have resulted from the differences in the formation of the groups. Because both the average age and the average BMI in the groups in our study are much higher than these two studies. In our study, the ages of women were tried to be kept in a wider range and the average age was higher in order to better reflect the situation of women of reproductive age.

Battaglia et al. [15] reported in two separate studies that there was no significant difference between patients with PCOS and healthy women in terms of the mean clitoral volume [14, 15]. In our study, the mean clitoral volume was similar among the groups. These data mean that the clitoral volume does not show a significant change in PCOS patients.

In the correlation analysis performed in our study, the clitoral artery pulsatile index was found to be significantly correlated with both the uterine artery pulsatile index (p = 0.028; r = 0.255) and the labial artery pulsatile index (p = 0.006;

r = 0.333). These findings mean that the blood supply resistance in the sexual areas can be evaluated together in patients with PCOS.

There were some limitations in our study. Since the blood flow to the clitoral region was measured only with Doppler USG in the study, it was tried to obtain objective data about the level of sexual desire, and questionnaires were not applied to the participants and no questions were asked in order to avoid statistical bias due to subjective responses. Therefore, how the participants feel subjectively about their sexual desire levels was not evaluated. Since the study was also cross-sectional, long-term changes of women could not be analyzed.

CONCLUSIONS

In the present study, it was found that the clitoral artery pulsatility index, that is, the rate of resistance in blood flow to the clitoral region, increased significantly in women with PCOS. This finding shows that the level of sexual desire in women with PCOS has decreased compared to healthy women.

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Conflict of interests

All the authors declare that they do not have any conflict of interests.

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Influence of prenatal steroid therapy on the incidence of respiratory disorders in late premature infants

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ABSTRACT

Objectives: This study was conducted because of conflicting data on the role of corticosteroids administered before delivery in the late premature period. The aim of the study was to assess the frequency of respiratory disorders in 'late premature infants' and the impact of using prenatal steroid therapy.

Material and methods: The study included 513 newborns born between the 34–36 week of pregnancy. They were divided into two groups. In the first group, there were 439 newborns (85.58%) who did not receive prenatal steroid therapy, and in the second group, there were 74 newborns (14.42%) born after the prenatal steroid course. The frequency of occurrence of respiratory disorders requiring the use of non-invasive respiratory support methods as well as intubation and mechanical ventilation was compared in both groups.

Results: In the group of premature infants after steroid therapy 43/74 (58.12%) did not require respiratory support compared to the group of infants without prenatal steroid therapy where in 368/439 (83.8%) cases no respiratory disorders were found.

Conclusions: If there is a risk of preterm labor in the 34–36 week of pregnancy, the use of steroid therapy should be considered. Steroidotherapy at this moment of gestation may not be such beneficial, like in the more premature delivery, before 34 weeks of pregnancy.

Key words: prenatal steroid therapy; late preterm; RDS; respiratory support

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INTRODUCTION

Preterm labor is a serious health problem around the world and is associated with other challenges to doctors, in comparison to the cases of term newborns [1]. Late preterm labors between 34–36 week account for approximately 75% of all preterm labors and are the fastest-growing subgroup of premature infants [2]. Fortunately, the increase in the incidence of late preterm deliveries has stalled in recent years, and the estimated frequency of occurrence in 2013 was 8.0% and remains on a similar level until now [3]. Preterm infants stay longer in hospital and generate higher care costs. They are also at higher risk of developing some diseases (hypoglycemia, hypothermia, eating problems, sudden infant death syndrome), as well as three times higher mortality compared to full-term newborns. More than 1/3 of premature infants requires a stay in the neonatal intensive care unit, mainly due to respiratory system diseases [5].

Hence, the potential public health effects as well as the economic effects of reducing the incidence of late prematurity complications by administering glucocorticoids before labor, are worth investigating.

Compared with infants delivered between the 39 and 40 week of pregnancy, infants delivered in the 34 week are at higher risk for respiratory complications, including RDS/hyaline disease of the newborn [odds ratio (OR): 40.1; 95% CI: 32.0–50.3], transient tachypnea of the newborn (OR: 14.7; 95% CI: 11.7–18.4), pneumonia (OR: 7.6; 95% CI: 5.2–11.2), respiratory failure (OR: 10.5; 95% CI: 6.9–16.1),

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and the need to assist breathing with a respirator (OR: 13.9; 95% CI: 11.0–17.6). The risk of lung disease incidence decreases with increasing gestational age at delivery [6].

In 1972 Liggins and Howie started looking for a method to reduce the occurrence of respiratory diseases in the group of premature newborns. They published a study, in which they proved the beneficial effect of prenatal corticosteroid therapy in cases of inevitable deliveries before the 32nd weeks of pregnancy [7]. The premise of the therapy is to stimulate faster development of the newborn's lungs so that they reach the level of maturity sufficient for efficient work in the extrauterine environment. Such treatment reduces the incidence of the respiratory distress syndrome (RDS) and the incidence of intraventricular bleeding or necrotizing enterocolitis (NEC) [8].

The use of corticosteroids in the prenatal period, in cases of risk of preterm labor, gained popularity after the National Institute of Child Health and Human Development (NICHD) consensus meeting in 1994 [9]. There have been recommendations that corticosteroids should be given to all women with a gestational age of 24–34 at risk of preterm labor, which is now the standard of antenatal care. However, there is no unambiguous data to support treatment with corticosteroids in the late premature period [2].

Currently, numerous studies on the influence of betamethasone administration before parturition on the incidence of late prematurity complications from the respiratory system in newborns are being developed [10]. C. Gyamfi-Bannerman et al. [10] investigated the effect of administering betamethasone in two injections at a dose of 12 mg to pregnant patients from 34–36 weeks, who were at high risk of late preterm delivery, on the incidence of complications in newborns. Severe respiratory complications, transient neonatal rapid breathing, the need for surfactant and bronchopulmonary dysplasia were less common in the betamethasone treatment group compared to the placebo. However, it was associated with a higher incidence of hypoglycaemia in newborns in the test group.

Objectives

This study was conducted because of conflicting data on the role of corticosteroids administered before delivery in the late premature period. The aim of the study was to assess the frequency of respiratory disorders in 'late premature infants' and the impact of using prenatal steroid therapy.

MATERIAL AND METHODS

The study included 513 newborns born between the 34–36 week of pregnancy. They were divided into two groups. In the first group, there were 439 newborns (85.58%) who did not receive prenatal steroid therapy, and in the second group, there were 74 newborns (14.42%) born after the prenatal steroid course. The frequency of occurrence of respiratory disorders requiring the use of non-invasive respiratory support methods as well as intubation and mechanical ventilation was compared in both groups.

RESULTS

In the group of premature infants after steroid therapy 43/74 (58.12%) did not require respiratory support. In 27/74 newborns (36.49%), respiratory disorders requiring non-invasive ventilation were found. 4/74 (5.41%) of the infants required intubation and mechanical ventilation.

In the group of infants without prenatal steroid therapy 368/439 (83.8%) no respiratory disorders were found. 55/439 (12.53%) infants had breathing disorders requiring the use of non-invasive breathing support methods (CPAP, Duopap), and 16/439 (3.65%) infants had respiratory failure requiring intubation and mechanical ventilation (Tab. 1).

DISCUSSION

The effect of the administration of antenatal corticosteroids in the late premature period is controversial. Data concerning lack of a beneficial effect of prenatal steroid therapy in 'late premature infants' might be found in literature.

Mohammad K. Ramadan et al. [2] described 295 children who were divided into two groups: the test group

Table 1. Incidence of respiratory disorders

	Steroids		No steroids	
	n	%	n	%
No respiratory distress	43	58.1	368	83.8
Non-invasive ventilation	27	36.5	55	12.5
Mechanical ventilation	4	5.4	16	3.6
Total	74	100.0	439	100.0

Chi 2 = 28.471; p = 0.0000

(n = 74 patients) of neonates who received corticosteroids and the control group (n = 221) of patients who did not receive treatment. There was no statistically significant difference in the incidence of any adverse neonatal morbidity (47.3% vs to 40.7%) or in the percentage of neonatal morbidity composite (34.4% vs to 37.8%) between those two groups. Moreover, there was no statistically significant difference in the frequency of admitting newborns to the intensive care unit, and in the occurrence of acute respiratory distress syndrome, transient neonatal tachypnea, hypothermia, and the need for phototherapy. The presented studies clearly showed that administering corticosteroids before delivery to patients with late preterm labor does not reduce the incidence of short-term complications in newborns [14]. Porto et al. [11] also investigated the effect of corticosteroid treatment at 34–36 week of pregnancy. Their analysis included 143 treated patients and 130 of control group participants. Conclusions drawn from their research clearly indicated no reduction in the incidence of respiratory disorders in newborns whose mothers received corticosteroids [11].

The use of antenatal corticosteroids in LPP is supported by a retrospective cohort study of women conducted by Yinon et al. [12]. Women underwent amniocentesis to determine fetal lung maturity at 34–37 weeks of gestation [12]. Patients with negative results were divided into two groups: the test group treated with betamethasone (n = 83 women) and the control group in which the patients did not receive betamethasone therapy (n = 84 women). The study showed that the administration of steroids in the antenatal period after 34 weeks of pregnancy resulted in an improvement in neonatal results and should be considered, if the fetal lung immaturity is documented. The influence of prenatal steroids use was also investigated by Kamatkar S et al. [13]. Pregnant women were given two intramuscular injections containing 12 mg of betamethasone (equal parts of betamethasone sodium phosphate and betamethasone acetate) to the group after antenatal steroid therapy or its equivalent in form of placebo given 24 hours apart (placebo group). Researchers in their study showed that the use of noninvasive ventillation high-flow nasal cannula for at least two consecutive hours, or oxygen therapy of at least 0.30 for at least four uninterrupted hours, or mechanical ventilation was lower in the treatment group compared to placebo. Their studies show that the benefits of treating premature babies up to 34 weeks gestation clearly outweigh the risks of ACS. Still, this conclusion is less certain for premature babies between 34- and 37-weeks gestation due to the direct side effect of late steroid use, which was transient hypoglycaemia in the treatment group. Gyamfi-Bannerman C et al. [10] also observed a more frequent occurrence of hypoglycaemia in the newborns of the betamethasone group — hypoglycaemia occurred in 24.0% of newborns from the research group, while in the placebo group it was found in 15.0% [15].

Our study found a significantly higher incidence of respiratory disorders requiring treatment in the group of children after prenatal steroids when compared to the control group (83.8 vs 58.1%).

Respiratory disorders requiring the use of non-invasive methods of ventilation were more frequent in newborns from the steroid treatment group ($p < 0.05$). In this group, severe respiratory disorders requiring intubation and mechanical ventilation were also more frequent (5.4 vs 3.6%), taking that into consideration, the difference was also statistically significant $p < 0.05$).

CONCLUSIONS

If there is a risk of preterm labor in the 34–36 week of pregnancy, the use of steroid therapy should be considered. Steroidotherapy at this moment of gestation may not be such beneficial, like in the more premature delivery, before 34 weeks of pregnancy.

Conflict of interest

All authors declare no conflict of interest.

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Evaluation of the effectiveness of Ampicillin and *Lactobacillus casei rhamnosus* treatment in cases of preterm premature rupture of membranes remote from term

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ABSTRACT

Objectives: Preterm premature rupture of membranes (PPROM) remote from term is an important obstetric cause of maternal and fetal adverse outcomes. The aim of our study is to examine the efficacy of ampicillin and *Lactobacillus casei rhamnosus* treatment in cases of PPROM remote from term.

Material and methods: The study was carried out by examining the results of cases who were given Ampicillin and *Lactobacillus casei rhamnosus* treatment. The patients were divided into two groups. Group 1 who didn't develop clinical chorioamnionitis and Group 2 who developed clinical chorioamnionitis. Obstetric characteristics, neonatal outcomes, adverse events were recorded.

Results: A total of 46 pregnant women, 40 in Group 1 and six in Group 2, were included in the study. The frequency of clinical chorioamnionitis developing during the treatment was found to be 13.0%. Mean gestational age at diagnosis was 28.43 ± 2.38 and 28.17 ± 1.33 for Groups 1 and Group 2, respectively. Mean gestational age at the time of delivery was 32.38 ± 2.07 31.33 ± 1.63 for Group 1 and Group 2, respectively. The mean latency period for Group 1 and Group 2 was 27.45 ± 1.71 days, 23.66 ± 4.53, respectively. Sepsis developed in six newborns (15%) in Group 1, while it developed in three newborns (50%) in Group 2. While 90% of the babies in Group 1 were discharged from the hospital, this rate was 66.7% in Group 2.

Conclusions: Ampicillin + *Lactobacillus casei rhamnosus* is an effective treatment method in PPROM cases and positively affects perinatal outcomes.

Key words: preterm premature rupture of membranes; ampicillin; *L. casei rhamnosus*; clinical chorioamnionitis

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INTRODUCTION

Preterm premature rupture of membranes (PPROM) is the rupture of membranes developing without uterine activity prior to the 37th week of gestation. PPROM remote from term is a subtype of PPROM that occurs in 23–31 weeks and 6 days of pregnancy. Generally, PPROM has many maternal and fetal adverse effects. PPROM accounts for 30–40% of preterm births and is an independent risk factor for neonatal morbidity and mortality resulting from prematurity, respiratory distress syndrome (RDS), intraventricular hemorrhage, sepsis, and pulmonary hypoplasia [1]. In the long term, there is a risk of developing neurological sequelae (cerebral palsy) and lung disease (bronchopulmonary dysplasia) [2]. Since neonatal complications increase significantly in deliveries below 32 weeks, prolonging the gestational period is preferred in appropriate cases to decrease neonatal mortality and morbidity. Despite treatment, 50–60% of women with PPROM remote from term deliver within a week after the rupture of membrane [3].

Maternal risks also exist in the presence of PPROM and its subtype. The most important risk factor is clinical chorioamnionitis; the frequency of chorioamnionitis in PPROM

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or spontaneous preterm births has been reported to be 40–70% [4]. Clinical chorioamnionitis also causes bleeding secondary to uterine atony, uterine rupture, endometritis, pelvic abscess, maternal sepsis, and an increase in the need for intensive care [5–7].

The most common source of the development of chorioamnionitis is the formation of fetal vessels (choriovasculitis) and inflammation of the amnion membrane (amnionitis) as a result of the change of normal flora in the lower genital tract and the increase in the number of pathogenic bacteria. This leads to the formation of prostaglandin, matrix metalloprotease and reactive oxygen radicals in maternal tissues after a while [8]. Maternal and fetal systemic inflammation also occurs in chorioamnionitis [9, 10]. Cytokine increase in fetal blood initiates white matter necrosis in the brain. Fetal inflammatory response syndrome (FIRS) causes neurological sequelae in the long term [11]. It is thought that the main cause of neonatal morbidity is FIRS [12].

Antibiotic use in PPROM is associated with the prevention of clinical chorioamnionitis, prolongation of the latent phase, and reduction of neonatal and maternal morbidity [13, 14]. However, antibiotics used in the treatment of chorioamnionitis also have a detrimental effect on the normal flora of the lower genital tract. This is especially the case when broad-spectrum antibiotics are used in treatment [15, 16]. Normally, *Lactobacillus spp*. species in vaginal microflora constitute the most important barrier against the development of infection. Vaginal infections developing during pregnancy are successfully treated with locally applied probiotics [17]. A previous study showed that vaginal probiotics administered synchronously with antibiotic treatment prolong the latent phase significantly and positively affect neonatal outcomes in PPROM cases remote from term [18].

This study aims to examine the perinatal effects of the antibiotic + vaginal probiotic treatment used in PPROM cases remote from term.

MATERIAL AND METHODS

The retrospective study was conducted by evaluating the results of expectant treatment applied to patients hospitalized with the diagnosis of PPROM remote from term (cases with 23 weeks and 31 weeks and 6 days of pregnancy) in the Obstetrics Service of Firat University Faculty of Medicine, Department of Obstetrics and Gynecology between January 2019 and January 2021. The study was initiated after the approval of the local ethics committee (Ethics committee approval number: 2019–01/25). Patients with a pregnancy between 23 weeks and 31 weeks and six days at the time of diagnosis and those in whom the period between the date of hospitalization and the date of birth (latent phase) was 14 days or more were included in the study. Through the examination of the files, the age, obstetric history and characteristics of the pregnancy were recorded. Patients who were in active labor at the time of admission, who experienced clinical signs of chorioamnionitis [fever, uterine fundal tenderness, maternal tachycardia (> 100/min), fetal tachycardia (> 160/min) and purulent amniotic fluid], who had fetal distress and/or significant vaginal bleeding as well as those with other obstetric risk factors such as pregnancy-induced hypertension, gestational diabetes, fetal anomaly, and multiple pregnancies were excluded from the study.

The records regarding ultrasonography performed for the confirmation of gestational age and evaluation of amniotic fluid volume were examined and fetal results were recorded. In the treatment plan, the white blood cell and lymphocyte count and C reactive protein (CRP) values in the blood values obtained from the patients were recorded. The values at the time of delivery and the values at the time of admission were recorded.

As the standard treatment protocol, Ampicillin 1 g flc. 4 × 1/day (Ampisina 1 g. flc., Mustafa Nevzat Pharmaceuticals Istanbul, Turkey) and vaginal 1 × 1/day of *Lactobacillus casei rhamnosus* (> 40000 CFU) (Vagiflor vaginal capsule, Paris, France) were given to all patients until delivery. Antibiotic treatment was continued for three weeks and discontinued for one week. In this way, it was continued until birth. *Lactobacillus casei rhamnosus* treatment was continued until delivery. Magnesium sulphate IV was initiated for fetal neuroprotection in cases with a pregnancy between 23–31 weeks and six days among the cases decided to give birth [19]. As the clinical criteria of chorioamnionitis, the key clinical finding associated with clinical chorioamnionitis was accepted as having at least two of the following symptoms: fever, uterine fundal tenderness, maternal tachycardia (> 100/min), fetal tachycardia (> 160/min), and purulent or foul amniotic fluid [20]. In those who developed clinical chorioamnionitis, broad spectrum antibiotics that were effective against Gram-positive and Gram-negative microorganisms were initiated.

The patients were divided into two as Group 1 who did not develop chorioamnionitis during the treatment and Group 2 who developed clinical findings of chorioamnionitis during the treatment. In both groups, gestational age during delivery, the latent period, birth weight, and the 5-minute APGAR score after birth were obtained from the records. Neonatal complications such as neonatal sepsis, respiratory distress syndrome (RDS), pulmonary hypoplasia, pneumonia and necrotizing enterocolitis (NEC), retinopathy of prematurity, and perinatal mortality data were obtained from the records of the neonatal unit.

Statistical analysis

Statistical Package for the Social Sciences 21.0 statistics software was used for statistical analysis of the data. Within group evaluations, the normality tests of continuous variables were performed using the Kolmogorov Smirnov test. The Paired Samples t-test was used to compare normally distributed continuous variables, while the Related Sample Wilcoxon Signed Rank Test was used to compare continuous variables which were not normally distributed. While comparing the within-group mean measurement of continuous variables in the group with $n < 30$, the Related Sample Wilcoxon Sign Rank test was used again.

The Repeated Measures ANOVA method was used to test whether two different measurements of continuous variables belonging to the same group changed due to a factor. The Mann Whitney U test was used to compare continuous variables between the two groups. The Shapiro Wilk Test was applied to determine whether the data were normally distributed. $p < 0.05$ was considered statistically significant.

RESULTS

During the period, 2829 deliveries were conducted in the obstetrics service. Preterm PROM was detected in 321 cases (11.34%), and PPROM remote from term was diagnosed in 97 cases. The incidence of PROM remote from term was calculated as 3.42% (1/29). In 51 cases, the latent phase lasted less than 14 days. Twelve of these cases were in activation at the time of diagnosis. Nine showed clinical signs of chorioamnionitis. Thirty cases gave birth between 2 and 13 days after diagnosis. In the cases who received Ampicilin + *L. casei rhamnosus* treatment, the cases (46 cases) whose latent phase was 14 days, or more were found to be 60.5%.

Clinical chorioamnionitis developed in 6 (13.04%) of the 46 pregnant women included in the study. Accordingly, 40 cases without clinical chorioamnionitis were determined as Group 1 while six cases with clinical chorioamnionitis were accepted as Group 2. The patients were delivered in those who developed clinical findings of chorioamnionitis. Other cases were terminated in the gestational age of maximum 34 weeks 0 days depending on obstetric indications. In both groups, cesarean section (C/S) was performed with obstetric indications, and C/S ratio was 30% in Group 1 whereas it was 83.3% in Group 2. Additionally, in Group 2, two cases were taken to C/S due to previous C/S, one case due to breech presentation, one case due to cord prolapse, and one case due to fetal dysterosis. Surgical site infection developed in three cases (7.5%) who underwent C/S in Group 1, while it occurred in one case (16.6%) in Group 2. Maternal mortality and permanent morbidity were not seen in either group.

In Group 1 (n: 40), obstetric characteristics and laboratory data at the time of diagnosis and delivery are presented in Table 1. The mean gestational age at the time of diagnosis was 28.43 ± 2.38 while the mean gestational age at the time of delivery was 32.38 ± 2.07 (mean latent time: 27.45 ± 1.71 days). In this group, Hb and Htc values decreased significantly as the pregnancy progressed. There was no statistically significant difference between the time

Table 1. Obstetric and laboratory parameters of Group 1

Group 1	Parameters	Mean	SD	Difference	Proportional Difference	p correlation	p value
GW [week]	Admission	28.43	2.38	3.950	13.9%	0.000	0.000**
	Delivery	32.38	2.07				
WBC [10e^3/μL]	Admission	12332.00	3568.49	102.750	0.8%	0.706	0.883*
	Delivery	12434.75	2749.55				
Hb [g/dL]	Admission	11.55	1.37	–0.878	-7.6%	0.000	0.000*
	Delivery	10.67	1.48				
Htc [%]	Admission	34.96	4.32	–2.617	-7.5%	0.001	0.000*
	Delivery	32.34	4.37				
Plt [10e3/μL]	Admission	274.33	79.51	–11.125	-4.1%	0.000	0.221*
	Delivery	263.20	77.06				
Lymphocyte [10e3/μL]	Admission	1.57	0.51	0.076	4.9%	0.191	0.478*
	Delivery	1.64	0.56				
CRP [mg/L]	Admission	7.39	5.55	0.704	9.5%	0.002	0.657**
	Delivery	8.10	5.60				

* — paired t test; ** — related Sample Wilcoxon Signed Rank test; CRP — C reactive protein; Hb — hemoglobin; Htc — hematocrit; SD — standard deviation; Plt — platelet; WBC — white blood cell; GW — gestational weeks

Table 2. Obstetric and laboratory parameters of Group 2

Group 2	Parameters	Mean	SD	Difference	Proportional Difference	p correlation	p value**
GW [week]	Admission	28.17	1.33	3.167	11.2%	0.395	0.026
	Delivery	31.33	1.63				
WBC [10e^3/μL]	Admission	12066.67	3616.44	800.000	6.6%	0.097	0.345
	Delivery	12866.67	4175.00				
Hb [g/dL]	Admission	11.13	0.87	−1.283	−11.5%	0.064	0.043
	Delivery	9.85	1.14				
Htc [%]	Admission	33.65	2.54	−3.950	−11.7%	0.114	0.028
	Delivery	29.70	3.53				
Plt [10e3/μL]	Admission	299.17	111.72	60.333	20.2%	0.096	0.249
	Delivery	359.50	144.58				
Lymphocyte [10e3/μL]	Admission	1.65	0.74	0.217	13.1%	0.145	0.357
	Delivery	1.87	0.19				
CRP [mg/L]	Admission	8.00	5.54	110.167	1377.1%	0.445	0.028
	Delivery	118.17	54.80				

** — related Sample Wilcoxon Signed Rank test; CRP — C reactive protein; Hb — hemoglobin; Htc — hematocrit; SD — standard deviation; Plt — platelet; WBC — white blood cell; GW — gestational weeks

of diagnosis and the time of birth in lymphocyte (Paired t test) and CRP (Related Sample Wilcoxon Signed Rank test), levels ($p > 0.05$).

Obstetric characteristics and laboratory data of Group 2 (n: 6) at the time of diagnosis and delivery are given in Table 2, and the mean gestational age at the time of diagnosis was 28.17 ± 1.33 and the mean gestational age at the time of delivery was found to be 31.33 ± 1.63 (mean latent time: 23.66 ± 4.53 days). In this group, Hb (Related Sample Wilcoxon Signed Rank test) and Htc (Related Sample Wilcoxon Signed Rank test) values showed a significant decrease as the pregnancy progressed ($p < 0.05$). The patients were delivered in one case on the 40th day after admission to the hospital, two on the 27th day, one on the 20th day, and two on the 14th day as clinical chorioamnionitis developed. In Group 2, there was a 20.2% increase between Plt. (Related Sample Wilcoxon Signed Rank test) values at the time of diagnosis and at the time of delivery. This increase was not statistically significant ($p > 0.05$). While there was no significant difference between lymphocyte (Related Sample Wilcoxon Signed Rank test) levels in Group 2, when CRP (Related Sample Wilcoxon Signed Rank test) levels were examined, a statistically significant difference was found between the time of diagnosis and the moment of birth ($p < 0.05$).

When obstetric characteristics and neonatal parameters of the pregnant women were compared for Group 1 and Group 2, it was found that the results were similar. The 5-minute APGAR score was higher in Group 1 and that result was statistically significant in Group 1 ($p < 0.05$, Mann Whitney U test.). Values are given in Table 3.

Table 3. Obstetric characteristics and neonatal parameters of pregnant women

Parameters	Group 1 (n: 40) Mean ± SD	Group 2 (n: 6) Mean ± SD	p value*
Age [year]	29.27 ± 0.96	26.83 ± 1.37	NS
GW admission	28.42 ± 0.37	28.16 ± 0.54	NS
GW delivery	32.37±0.37	31.33 ± 0.66	NS
Latent phase [day]	27.45 ± 1.71	23.60 ± 4.53	NS
Newborn weight [gram]	1965.87 ± 86.46	1700 ± 145.27	NS
APGAR Score 5th minute	8.55 ± 0.17	5.83 ± 0.087	0.003

* — Mann Whitney U test; GA — gestational age; SD — standard deviation; GW — gestational weeks; NS— not significant

When neonatal parameters are examined

Sepsis developed in six newborns in Group 1 (15%, within group %). Two newborns who developed sepsis died while four newborns were discharged. When sepsis factors were examined, it was seen that Staph. *Aureus* grew in one newborn, *Staph. Epidermidis* in two newborns, *Strep. Viridans* in a newborn and although a newborn showed signs of sepsis, there was no reproduction in repeated cultures. Records of a newborn referred to another hospital with a pre-diagnosis of sepsis were not available. In Group 1, a total of four newborns died (10%, within group %). Two (5%, within group %) died due to sepsis. One of the two newborns who died due to sepsis was born at 27 weeks

and 1 day with abdominal bleeding due to placenta previa totalis, and the baby died on the 11th day due to sepsis. The second newborn was born at 30 weeks and 2 days (uterine anomaly, breech delivery could not be stopped), and died on the 63rd day due to sepsis. In the third newborn who died, the latent phase was determined as 26 days and was delivered at 32 weeks and 2 days upon the development of severe preeclampsia. The baby died on the second postnatal day due to the development of tension pneumothorax and gastrointestinal bleeding. The 4th newborn was born in the 30th week of gestation and died on the postnatal 2nd day due to prematurity and respiratory failure. Congenital hypothyroidism and amniotic band syndrome were diagnosed in a newborn who developed PPROM at the 28th week of gestation and gave birth at the 32nd week and 2nd day (latent phase 30 days). In this group, intrauterine growth retardation (IUGR) was diagnosed in five fetuses (12.5%, within the group). Prematurity retinopathy (ROP) developed in five newborns in Group 1 (12.5%, within group %). All newborns who developed ROP were discharged.

Six cases with clinical chorioamnionitis were detected in Group 2, three of the newborns developed sepsis (50%, within the group%) and two babies (33.3%, within the group %) died due to sepsis. Considering sepsis factors, it was seen that *Streptococcus spp*. grew in one newborn, *Acinetobacter* in one newborn, and *Staph. epidermidis* in one newborn. The birth week of one of the newborns who died was determined as 30 weeks and 2 days, and the baby died on the postnatal 2nd day. The birth week of the other newborn was determined as 29 weeks and 3 days and died from sepsis on the 36th day. While one of the babies who died was diagnosed with sepsis and pulmonary hypertension, there was no pathology other than sepsis in the others. A newborn with sepsis was successfully discharged. Amniotic band syndrome and pyloric stenosis were diagnosed in a newborn. Premature retinopathy (ROP) developed in two newborns (33.3%, within group%). All newborns who developed ROP were discharged. In the first group, five fetuses (12.5%) developed intrauterine growth retardation (IUGR), while there was no such diagnosis in the second group. Newborns are accepted as Small for gestational age (SGA). While respiratory distress syndrome developed in three cases (7.5%) in Group 1, it developed in two cases (33.3%) in Group 2. Amniotic band syndrome was diagnosed in one newborn in both groups (2.5% and 16.6%, respectively). Neonatal results of both groups are given in Table 4.

Table 4. Neonatal results of Group 1 and Group 2

Newborn Results	Group 1 (%) n: 40	Group 2 (%) n: 6
Discharged	36 (90)	4 (66.7)
Died	4 (10)	2 (33.3)
Sepsis developed	6 (15)	3 (50)
Death due to sepsis	2 (5)	2 (33.3)
ROP	5 (12.5)	2 (33.3)
ABS	1 (2.5)	1 (16.6)
SGA	5 (12.5)	–
RDS	7 (17.5)	3 (50.0)

ABS — amniotic band syndrome; n — number; RDS — respiratory distress syndrome; ROP — retinopathy of prematurity; SGA — small for gestational age

DISCUSSION

Etiology of PPROM is multifactorial. Expectant treatment is conventionally applied in cases of uncomplicated rupture of membranes that develop less than 34 weeks. For this purpose, antibiotics, corticosteroids, magnesium sulfate, and tocolytics are used. While antibiotics are given to prevent the development of morbidity due to chorioamnionitis and neonatal infection and to prolong the latent phase, the others are used to reduce adverse neonatal outcomes [21–23].

Chorioamnionitis is one of the main causes of maternal and neonatal morbidity. The incidence of chorioamnionitis is inversely proportional to gestational age. Its frequency is 41% in births before 27 weeks, while it is 15% in births between 28–36 weeks [24]. Chorioamnionitis can occur clinically, subclinically or histologically. Unlike histological chorioamnionitis, the negative effects of clinical chorioamnionitis on the newborn are more pronounced [25]. In a study conducted by Nasef et al. [26], it was shown that histological chorioamnionitis had no effect on neonatal morbidity and neurodevelopmental disorders.

Unfortunately, there is no objective diagnosis of clinical chorioamnionitis. The most important parameter in diagnosis is maternal fever (38°C and above) [20]. Maternal leukocytosis white blood cell (WBC) over 15,000 alone is not a definitive feature for diagnosis [27]. When clinical chorioamnionitis is suspected, other reasons explaining fever should be excluded [28]. When a clinical diagnosis of chorioamnionitis is made due to adverse maternal and fetal effects, delivery should be planned regardless of the gestational age [29]. In our study, the frequency of clinical chorioamnionitis was found to be 13.0% (6 cases). After the diagnosis, the pregnancies of these cases were terminated. The type of delivery was determined by obstetric indications, and permanent maternal morbidity did not develop.

Some recent studies examining PPROM cases remote from term have shown a significant improvement in perinatal outcomes with the use of vaginal probiotics in addition to standard antibiotic treatment [18, 30]. Vaginal probiotics containing lactobacilli are the most widely used probiotic group. Lactobacilli decrease vaginal pH by producing lactic acid, produce antibacterial agents and stimulate the immune system by producing anti-inflammatory cytokines

[31–33]. Probiotics can be used safely in any period of pregnancy [34].

Infection development is an important problem in PPROM cases. In a study, the frequency of intrauterine infection was found to be 60% in cases where antibiotics were not used after membrane rupture, due to ascending bacterial invasion [3]. In PROM cases remote from term, for whom Bendix et al. applied expectant treatment, 45% of the major complications developed due to chorioamnionitis [35]. In another study, 1153 PPROM cases with 24–34 weeks of gestation were examined retrospectively, and the frequency of clinical chorioamnionitis was found to be 29% [36]. In our study, the frequency of clinical chorioamnionitis was found to be 13.0%. The use of a probiotic agent as a treatment has been found to be effective in reducing clinical rates of chorioamnionitis.

In the study of Aziz et al. [36], newborns born to mothers with PPROM diagnosed with clinical chorioamnionitis were found to have higher (34.8% vs 22.9%) RDS, necrotizing enterocolitis, intracranial hemorrhage, pneumonia, and low 5-minute APGAR scores compared to newborns born to mothers without chorioamnionitis. In the study, the frequency of neonatal sepsis in the group developing chorioamnionitis was 7.1% while it was 5.6% for the other group. The low 5-minute APGAR score was found to be 34% versus 23%. In our study, the frequency of neonatal sepsis in the group developing chorioamnionitis was 50% versus 15%, the low 5-minute APGAR score was found to be 50% versus 5%, and the frequency of RDS was 33.3% vs 7.5%. Since our study evaluated cases with latent phase longer than 14 days, we think that sepsis rates were higher.

Approximately 75% of cases developing midtrimester PPROM give birth within 15 days [37]. Therefore, we examined cases in which the latent phase was at least 14 days. With the antibiotic + probiotic treatment applied during the expectant treatment, the mean latent phase was 27.4 days in Group 1, whereas it was 23.6 days in Group 2. We think that fetal weights were positively affected in both groups due to the positive contribution of the treatment on the latent phase. The mean weight of the babies in Group 1 was 1965.87 ± 86.46 g. and 1700 ± 145.27 g. in Group 2. Newborn weights were not statistically significant between both groups. However, SGA was detected in five newborns in Group 1.

In our study, 66.7% of the newborns in the group developing clinical chorioamnionitis were discharged healthily from the hospital, while this rate was found to be 90% in the group without chorioamnionitis. Considering Group 2 and Group 1, respectively, neonatal mortality was 33.3% versus 10%, ROP was 33.3% versus 12.5%, and amniotic band syndrome was 16.6% vs 2.5%. We think that the prolongation of the latent phase positively affects neonatal outcomes in both groups. In our study, no cases of intracranial hemorrhage and necrotizing enterocolitis were found in either group.

CONCLUSIONS

Ampicillin + *Lactobacillus casei rhamnosus* is an effective treatment method in PPROM cases and positively affects perinatal outcomes. The limitation of our study is that it is retrospective, and the number of cases is relatively low. In addition, long-term neurological results in newborns could not be examined. There is a need for larger scale studies on the issue.

Ethics committee approval

Firat University Faculty of Medicine Ethics Review Committee approved the trial (reference number 2019-01/25).

Financial disclosure

Author has any financial or commercial affiliation with this study.

Conflict of interest

There are no conflicts of interest to declare.

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Evaluation of the prevalence of folic acid supplementation before conception and through the first 12 weeks of pregnancy in Polish women at high risk of fetal anomalies

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ABSTRACT

Objectives: Local and international organizations recommend folic acid (FA) supplementation in the periconceptional period. This study aimed to analyse the prevalence of periconceptional supplementation with FA in women at high risk of fetal anomalies refferred for first trimester screening.

Material and methods: Our analysis involved 1,455 women at high risk of fetal anomalies refferred for first trimester screening. FA supplementation was assessed by face-to-face interviews conducted by doctors performing first trimester screening for aneuploidy.

Results: FA supplementation before pregnancy was reported by 46.8% of the women and during the first trimester by 57.2% of those studied. Women used FA supplementation more frequently if they had a history of at least one miscarriage (OR 2.2, 95% CI 1.70–2.83; $p < 0.001$), a history of assissted reproductive techniques (OR 2.25, 95% CI 1.18–4.31; $p = 0.014$), or were aged between 30 and 34 (OR 2.87, 95% CI 1.47–5.58; $p = 0.002$). Among 122 women with a history of fetal defects only 50% confirmed FA supplementation before pregnancy and 62.2% during pregnancy ($p = 0.488$). A similar frequency of FA supplementation was noted among women with epilepsy, diabetes, and hypertension. Less frequent taking of FA was noted among women at least third and subsequent pregnancies ($p < 0.001$). In the current pregnancy, neural tube defects (NTDs) were less frequent by 86% in the group of women with FA supplementation than in the non-supplementation group (1 case vs 6 cases, respectively) and for other fetal defects by 62.5% (24 vs 40 cases, respectively).

Conclusions: We found an unsatisfactory compliance with recommendations for the use of folic acid supplementation during periconceptional period among women at high risk of fetal defects and folate deficiency, that could have negative effects on the health of child and mother. The study results show the need to increase the awareness of FA supplementation during periconceptional period especially in women with high risk of fetal anomalies.

Key words: folic acid supplementation; pregnancy; fetal defects; epidemiology

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INTRODUCTION

During pregnancy, the need for basic nutrients, vitamins and minerals increases due to the development of the fetus, placenta and maternal tissues [1, 2]. One of the most important elements necessary for the synthesis of nucleic acids in rapidly dividing cells is folate. Folate is also essential in protein synthesis processes, reducing reactive oxygen species, epigenetic regulation, enzymatic processes, transcription pathways, and signal transduction [2–4]. It has been shown that folic acid (FA) alone, or in combination with other minerals and vitamins taken during periconception (the time preceding the woman's conception until the 12th week of gestation) prevents neural tube defects (NTDs) such as anencephaly, spina bifida or encephalocele

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in fetus [5–9]. Studies also indicate that folate deficiency may be associated with a higher risk of defects of the heart, urinary tract, limbs, cleft palate as well as being associated with a higher risk of preeclampsia [8–11]. The World Health Organization (WHO) [3, 4, 12] and most European countries [13] recommend that all women, during periconception, should take 400 µg of folic acid daily as a supplement. In Poland, in accordance with the 2017 [14] and 2020 [15] recommendations of the Polish Society of Gynecologists and Obstetricians, all women of reproductive age should take FA as a supplement to a natural, folate-rich diet and such supplementation should be continued through pregnancy and lactation. Moreover, the Polish reccomendations state that doses should depend on the woman's history of NTDs or other fetal defects in prior pregnancies and/or their risk of folate deficiency [14, 15]. Therefore, for those women with a low-risk of fetal defects and pregnancy complications, a dose of 400 µg/day is sufficient; compared with those in an increased-risk or high-risk group. In the increased-risk group, which includes women with fetal defects in their own or close family history, a history of IUGR/preeclampsia, pregestational diabetes, digestive diseases, hepatic failure, renal failure, bariatric surgery, obesity, smoking, using anti-epileptic drugs, metformin, methotrexate, cholestyramine, sulfasalazine or with reduced MTHFR activity, folate at a dose of 0.8 mg/day including active folate and vitamin B12 within 12 weeks before planned pregnancy, during pregnancy and lactation is advised.

In turn, in the high-risk group with a history of NTDs in the mother, father or their offspring, 5 mg/day including active folate and vitamin B12 within 12 weeks before planned pregnancy and in the first trimester of pregnancy, and subsequently, 0.8 mg/day during the second and third trimesters and the period of lactation are recommended [14, 15].

It is estimated that 70–98% of pregnant women in countries in Europe and the USA use dietary supplements [1, 2]. In Europe, where it is reported that as many as 45% of pregnancies may be unintended [16], FA supplementation is significantly lower; for instance, a recently published paper by Camier et al. [17] showed that only 26% of French women received folic acid supplementation during their periconceptional period. Hence, the aim of this study was to analyze the prevalence of supplementation with FA during the periconceptional period in women at high risk of fetal anomalies refferred for first trimester screening.

MATERIAL AND METHODS

We carried out a retrospective cohort study at one tertiary centre for the prenatal diagnosis and management of fetal and neonatal pathology (the Department of Obstetrics and Perinatology in Cracow, Poland). The study is a retrospective analysis of the medical records of 1,455 pregnant women referred for first trimester screening for fetal aneuploidy, who met criteria esthablished by the Polish National Health Fund (Fig. 1) [18]. Multiple pregnancies were excluded from the analysis. We also excluded patients whose records were incomplete and did not contain data on supplementation and the use of other drugs as well as patients under 18 years of age, with cancer, organ transplant or intellectual disabilities. Women were interviewed between January 2017 and December 2019 regarding their indications for the examination, accompanying diseases, use of supplements with FA before pregnancy and during the first 12 weeks of pregnancy. The interviews also collected information about the women's previous pregnancies, and family history of NTDs or any other structural or genetic anomalies.

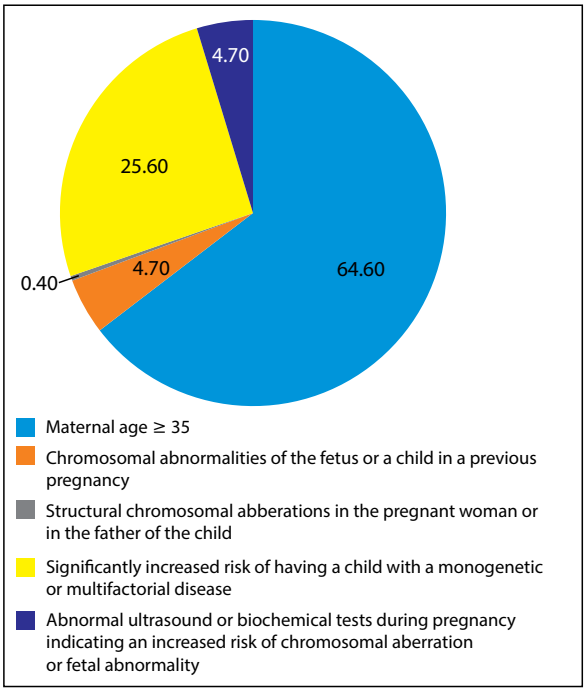

Figure 1. Distribution of indications expressed in percentages for pregnant women referred for first trimester screening for aneuploidy [18]

Data were collected through standardized face-to-face interviews conducted by trained physiscians and prior to the woman's ultrasound scan. Each woman was asked the following questions: 1. Have you taken FA before pregnancy? 2. Have you taken FA during pregnancy? 3. Have you taken multivitamin supplements during pregnancy? Have you taken any medications and if so, which ones?

In addition, we analysed the results of first trimester screening for aneuploidy. First trimester screening was performed following Fetal Medicine Foundation, UK, and Polish national guidelines [19, 20]. Nuchal translucency

(NT) above the 95th percentile was considered abnormal. Ultrasound examinations were carried out using a Voluson E6 (GE Healthcare Medical Systems, Milwaukee, WI, USA).

The institutional review board waived the requirement for a separate ethical approval for this analysis, since the interview and sonographic evaluations were both performed as integral parts of routine clinical care, for which informed consent had been previously given by the women. Data were anonymized.

Statistical analysis

Patient characteristics are described as means with standard deviation for normally distributed numerical data and as percentages for categorical variables. Differences were analyzed by the Student's t-test for normally distributed data and the Mann-Whitney U-test for non-normally distributed data. Chi-square and Fisher's exact tests were used for comparisons of categorical variables determined by whether the assumption of the expected values more than five was fullfilled or not. As a first step of analysis a comparison of selected maternal risk factors in groups of declared folic acid supplementation before pregnancy has been done. Next only those variables, which were identified as significant were put into multivariable binomial logistic regression. The model enabled to assess the association between identified factors and the presence of folic acid supplementation before pregnancy. The strength of the association has been measured by the odds ratios (ORs), and the multivariable logistic regression model provided information after the adjustement for all the others coviariates presented in the model. Additionally, to show the precision level for OR estimates, 95% confidence intervalls (CIs) were provided. In all analyses, p values < 0.05 were considered statistically significant.

RESULTS

Selected maternal risk factors for adverse pregnancy outcomes in the study cohort are listed in Table 1 and 2. Most of women (66%) had a normal body mass index (BMI). A quarter of women had a history of at least one miscarriage. For 73.7% of the women, it was their first or second pregnancy. The most common comorbidity was hypothyroidism which affected 18% of cases. FA supplementation before pregnancy was declared by 46.8% of the women, and that during first trimester by 57.2%. 88.2% of patients declared FA dose of 400 µg before pregnancy and 11.8% declared dose was 800 ug of activate folate or more. During first trimester 226 women (33.2%) have taken FA in multivitamin kits containing 800 µg of activate folate. In turn, in group of women who did not supplement FA before pregnancy, 157 (20.2%) started using multivitamin supplements during pregnancy. The main (64.7%) reason for screening was maternal age of 35 years or more, and of these women, 42.5% reported using FA supplementation before pregnancy. However, the highest incidence (59.4%) of supplementation was observed among women with a history of fetal chromosomal abnormalities or having a child by a previous pregnancy (Tab. 2). Considering the risk of fetal defects and pregnancy complications, 60% of the women were in the intermediate-risk group, and only 2% in the high-risk group; and it was in that latter group that FA supplementation was the most frequent (62%) (Tab. 2). Women reporting FA supplementation were more likely to have had a history of at least one miscarriage (OR 2.2, 95% CI 1.70–2.83; p < 0.001), a history of assissted reproductive techniques (ART) (OR 2.25, 95% CI 1.18–4.31; p = 0.014), or were aged between 30 and 34 (OR 2.87, 95CI 1.47–5.58; p = 0.002) (Tab. 3). Fewer instances of FA supplementation were noted among women in their ≥ 3rd pregnancy (p < 0.001) (Tab. 3). Among the 122 women with a history of fetal defects, only 50% confirmed their use of FA supplementation before pregnancy, and 62.2% during pregnancy (OR 1.16, 95% CI 0.76–1.76; p = 0.488). A similar frequency of FA supplementation before pregnancy was noted among women with epilepsy (50%), diabetes (56.5%), or hypertension (53.2%); and, similarly, for those during their first trimester (54.5%; 65.7%; or 59.6%, respectively) (Tab. 1).

Of the group of women with FA supplementation, 24 (3.5%) cases of fetal defects were detected during the first trimester screening; and in the group without FA supplementation 40 (5.1%) cases were found (Tab. 4), thus fetal defects were found 62.5% less frequent in those with FA supplementation. Among women who declared FA supplementation before pregnancy, a history of NTDs in previuos pregnancies was observed in 1.2% instances and in 1.1% of those women who did not supplement FA. In the current pregnancy, neural tube defects (NTDs) were less frequent by 86% in the group of women with FA supplementation than in the non-supplementation group (1 case vs. 6 cases, respectively) (Tab. 4).

DISCUSSION

To our knowledge this is the first study concerning FA supplementation before pregnancy and during the first trimester in a large cohort of Polish pregnant women with high risk of fetal anomalies reffered for first trimester screening. Our study showed a generally unsatisfactory frequency of FA supplementation during the periconceptional period, indicating the need for education in this field.

Studies carried out in recent years indicate that a 12--week precontraceptive period of supplementation is necessary to obtain the appropriate concentration of folate in blood cells [1, 17]. Bitzer et al. [22] showed that less than 40% of European women of child-bearing age had ever taken FA. In that study only 28% of women trying to conceive had taken FA compared with 55% of women during their

Table 1. The distribution of selected maternal risk factors for adverse pregnancy outcomes in 1,455 women with singleton pregnancy during first trimester screening for aneuploidy

	Total [n = 1455]	Folic acid supplementation declared before pregnancy		p-value
		Yes [n = 681]	No [n = 774]	
Maternal age < 35, n (%)	514 (35.3)	281 (54.7)	233 (45.3)	$p^{chi2} < 0.001$
Maternal age ≥ 35, n (%)	941 (64.7)	400 (42.5)	541 (57.5)	
BMI < 18.5, n (%)	44 (3.0)	18 (40.9)	26 (59.1)	$p^{chi2} = 0.267$
BMI 18.5–24.99, n (%)	960 (66.0)	458 (47.7)	502 (52.3)	
BMI 25–29.9, n (%)	321 (22.0)	150 (46.7)	171 (53.3)	
BMI 30–34.9, n (%)	95 (6.5)	45 (47.4)	50 (52.6)	
BMI 35–39.9, n (%)	22 (1.5)	5 (22.7)	17 (77.3)	
BMI > 40, n (%)	13 (1.0)	5 (38.5)	8 (61.5)	
Parity:				$p^{chi2} < 0.001$
First child, n (%)	491 (33.7)	273 (55.6)	218 (44.4)	
Second child, n (%)	582 (40.0)	307 (52.7)	275 (47.3)	
Third child, n (%)	280 (19.3)	88 (31.4)	192 (68.6)	
Fourth child and more, n (%)	101 (7.0)	13 (12.7)	89 (87.3)	
History of miscarriage				$p^{chi2} < 0.001$
Yes, n (%)	371 (25.5)	230 (62.0)	141 (38.1)	
No, n (%)	1084 (74.5)	451 (41.6)	633 (58.4)	
Known fetal defects in previous pregnancies n (%)	[n = 896]	[n = 384]	[n = 512]	$p^{chi2} = 0.104$
Yes, n (%)	123 (13.7)	61 (49.6)	62 (50.4)	
No, n (%)	773 (86.3)	323 (41.8)	450 (58.2)	
Smoking status — Never smoked, n (%) — Smoked only before pregnancy, n (%) — Smoked before pregnancy and during first trimester, n (%)	 1101 (75.7) 309 (21.2) 45 (3.1)	 556 (50.5) 118 (38.3) 7 (15.2)	 545 (49.5) 190 (61.7) 39 (84.8)	$p^{chi2} < 0.001$
Diabetes Mellitus				$p^{chi2} = 0.078$
Yes, n (%)	76 (5.2)	43 (56.6)	33 (43.4)	
No, n (%)	1378 (94.8)	637 (46.2)	741 (53.8)	
Hypertension				$p^{chi2} = 0.300$
Yes, n (%)	62 (4.2)	33 (53.2)	29 (46.8)	
No, n (%)	1393 (95.7)	648 (46.5)	745 (53.5)	
Hypothyroidism				$p^{chi2} < 0.001$
Yes, n (%)	263 (18.1)	164 (62.4)	99 (37.6)	
No, n (%)	1192 (81.9)	517 (43.4)	675 (56.6)	
Epilepsy				$p^{chi2} = 0.762$
Yes, n (%)	22 (1.5)	11 (50.0)	11 (50.0)	
No, n (%)	1433 (98.5)	670 (46.8)	763 (53.2)	
Assisted reproductive technology				$p^{chi2}<0.001$
Yes, n (%)	54 (3.7)	40 (74.1)	14 (25.9)	
No, n (%)	1401 (96.3)	641 (45.8)	760 (54.2)	

BMI — body mass index; p^{chi2} — the p-value from the chi-square test

pregnancy [22]. In the Bitzer study, which used a structured on-line questionnaire, the highest rates of awareness and knowledge of FA and its benefits were among women in Poland and the UK. However, in our Polish study only 46% of women reported using FA supplementation before their pregnancy compared with 57% during their first trimester. Thus, during the most important period of organogenesis, only about half of the women used FA supplementation.

Table 2. Folic acid supplementation by the main indication for first trimester screening [18] and by the risk score of fetal defects and pregnancy complications [21]

	Total [n = 1455]	Folic acid supplementation before pregnancy		p-value
		Yes [n = 681]	No [n = 774]	
The main indication for first trimester screening				
Maternal age > 35, n (%)	940 (64.6)	400 (58.7)	540 (69.8)	$p^{chi2} < 0.001$
Chromosomal abnormalities of the fetus or a child in a previous pregnancy, n (%)	69 (4.7)	41 (6.0)	28 (3.6)	$p^{chi2} < 0.05$
Structural chromosomal aberrations in the pregnant woman or in the father of the child, n (%)	6 (0.4)	3 (0.4)	3 (0.3)	$p^{chi2} = 0.760$
Significantly increased risk of having a child with a monogenetic or multifactorial disease, n (%)	373 (25.6)	207 (39.6)	166 (21.4)	$p^{chi2} < 0.001$
Abnormal ultrasound or biochemical tests during pregnancy indicating an increased risk of chromosomal aberration or fetal abnormality, n (%)	67 (4.6)	30 (4.4)	37 (4.8)	$p^{chi2} = 0.768$
The risk score of fetal defects and pregnancy complications				
Low-risk group, n (%)	552 (37.9)	245 (44.4)	307 (55.6)	$p^{chi2} = 0.149$
Intermediate-risk group, n (%)	873 (60.0)	418 (47.9)	455 (52.1)	$p^{chi2} = 0.762$
High-risk group, n (%)	30 (2.1)	18 (60.0)	12 (40.0)	$p^{chi2} = 0.267$

p^{chi2} — the p-value from the chi-square test

Table 3. Odds ratios for folic acid supplementation during periconceptional period associated with selected characteristics in 1,455 pregnant women at a high risk of fetal anomalies

	OR	95% CI	p
Maternal age, years			
17–24	1 (ref)		
25–29	2.31	1.18–4.53	p = 0.014
30–34	2.87	1.47–5.58	p = 0.002
35–39	1.79	0.95–3.37	p = 0.072
≥ 40	1.34	0.66–2.75	p = 0.411
Parity			
First	1 (ref)		
Second	0.83	0.62–1.11	p = 0.212
Third	0.37	0.26–0.53	p < 0.001
≥ Fourth	0.23	0.15–0.37	p < 0.001
History of miscarriage (at least one)	2.2	1.70–2.83	p < 0.001
Smoking status			
Never smoked	1 (ref)		
Smoked only before pregnancy	0.53	0.41–0.71	p < 0.001
Smoked before pregnancy and during first trimester	0.18	0.08–0.43	p < 0.001
Hypothyroidism	1.80	1.34–2.42	p < 0.001
Assisted reproductive technology	2.25	1.18–4.31	p = 0.014

Multivariable logistic regression. All variables presented in a table were put into one model. CI — confidence interval; OR — odds ratio

Similar results were obtained in a study by Medawar et al. [23], among Lebanese women where FA supplementation was used by 48% of women before pregnancy. Other studies undertaken in developed countries where women seem to pay more attention to pregnancy planning, have shown that less than half take FA supplements before pregnancy [24–28]. What is concerning is that only one in every two women with a history of any fetal defects, including NTDs,

Table 4. Fetal anomalies detected during the first trimester in a cohort of 1,455 pregnant women according to folic acid supplementation declared before pregnancy and without supplementation before pregnancy

	Folic acid supplementation declared before pregnancy n = 681	Without folic acid supplementation declared before pregnancy n = 774	p-value
NTDs in a previuos pregnancy, n (%)	8 (1.2)	9 (1.1)	$p^{chi2} = 0.950$
NT > 95th centile, n (%)	46 (6.7)	52 (6.7)	$p^{chi2} = 0.891$
Chromosomal anomaly, n (%)	10 (1.4)	20 (2.5)	$p^{chi2} = 0.135$
NTDs, n (%)	1 (0.1)	6 (0.7)	$p^{chi2} = 0.417$
Omphalocele, n (%)	2 (0.2)	3 (0.3)	$p^{chi2} = 0.760$
Heart defects, n (%)	8 (1.2)	6 (0.7)	$p^{chi2} = 0.436$
Other defects, n (%)	3 (0.4)	5 (0.6)	$p^{chi2} = 0.597$
Total, n (%)	24 (3.5)	40 (5.1)	$p^{chi2} = 0.759$

NT — nuchal translucency; NTDs — neural tube defects; p^{chi2} — the p-value from the chi-square test

used FA supplementation. Studies conducted over the past fourty years found that supplementation with FA significantly reduces the risk of neural tube defects by 32–72% [5–9, 21, 28, 29]. In our study the prevalence of NTDs was 86% lower in the group of women who used FA supplementation compared with those who did not. Other recent studies also indicate the effect of supplementation on reducing the incidence of heart defects, urinary tract defects, limb defects, cleft lip and palate, and preeclampsia [9–17]. In our cohort we also noted a 62.5% lower prevalence of fetal defects other than NTDs in women who used FA supplementation.

Food fortification with FA may be the solution to the problem of inadequate FA supplementation. The United States of America (USA) was the first country to implement a national folic acid food fortification program in 1998 to prevent NTDs, and nowadays over 80 countries, but not Poland, fortify food with folic acid [21]. However, questions remain about the impact of food fortification in reducing the occurence of NTDs [21]. Some authors indicate that there is a very weak correlation between the incidence of NTDs and FA fortification levels, and that a woman's socioeconomic status may be more influential [21]. Our study did not analyze socioeconomic factors as these were the subject of previous studies [17, 30]. On the other hand, some fetal defects may be related to chromosomal anomalies and other factors not related to FA deficiency.

Our study has some limitations. First, it was a retrospective study conducted in a single national referral centre. The incidence and levels of folic acid supplementation were declarative, and we did not measure actual FA intake against declared intake. The best way to check folate status is by measuring maternal red blood cell folate concentrations, because as it was published ≥ 906 nmol/L (400 ng/mL) is associated with a significantly low risk of NTDs [31]. We believe that the obtained results indicate the need to organize a prospective study in which the reliability and validity of the applied survey will be determined.

CONCLUSIONS

Despite these limitations our study highlights the need for better health education among women of child-bearing age, during the periconceptional period, especially among those women with risk factors of folate deficiency and/or NTDs. As our research and data from the literature have shown, FA supplementation levels are still insufficient, even in developed countries. Our study provides solid basis for well planned larger cohort study wich would enable investigation of dietary and supplementary sources of FA, with folate blood concentration analyses giving the opportunity to analyse associated fetal risks.

Conflict of interest

All authors declare no conflict of interest.

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Role of adipokines in ovarian cancer epidemiology and prognosis

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ABSTRACT

Ovarian cancer is one of the most serious problems in modern oncological gynecology. The link between obesity (expressed in BMI, WHR, waist circumference, body weight) and ovarian cancer has been poorly studied. Obesity is defined as an excessive accumulation of bodily fat, exceeding its physiological needs and adaptability. Study results suggest a link between specific histological types of ovarian cancer with increased patients' BMI. Adipose tissue is hormonally active and secretes biologically active proteins called adipokines. Resistin and leptin may show proliferative and anti-apoptotic effects. There is currently increasing attention to adipokine levels in ovarian cancer research. The influence of adiponectin on the secretion of angiogenic factors by ovarian cancer cells has been shown. It has been proven that leptin is associated with a worse prognosis for patients treated with platinum compounds combined with paclitaxel/docetaxel. The relation has been observed between the level of resistin and the growth of neoplastic cells, their spread and the resistance to chemotherapy. The level of AdipoR1 may be independent prognostic factor in the case of epithelial ovarian cancer. The role of adipokine in the neoplasm development requires further investigation, in the view of fact that results of current research are still inconclusive. Considering increasing number of people suffering from obesity as well as the current analysis results, it is necessary to extend experimentation on the influence of obesity on the development and prognosis of ovarian cancer.

Key words: ovarian cancer; adiponectin; leptin; resistin; visfatin; adipokines

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INTRODUCTION

Ovarian cancer poses a significant problem in modern oncological gynecology. Globally, it is the eighth most diagnosed cancer among women. A total of 312,800 new diagnoses and 206,800 deaths were recorded in 2020 worldwide [1].

Due to the growing number of scientific reports concerning the link between obesity and metabolic disorders with the risk of cancer, it has become necessary to determine the molecular and metabolic factors involved in the process of creating neoplasms including ovarian cancer.

OVARIAN CANCER

The American Cancer Society estimates that in 2021 in the United States, 21,410 women will be diagnosed with ovarian cancer, and 13,770 will die there from [2]. In Poland, ovarian cancer is the fifth most common cancer among women and the fourth in terms of mortality [3]. The high mortality rate concerning ovarian cancer is primarily caused by late diagnosis (at the time of diagnosis approx. 75% of patients are already in clinical stage III or IV) [4].

In population studies, an increased risk of ovarian cancer is observed among women experiencing early puberty, entering menopause late, among nulliparous women, as well as those taking advantage of ovulation-stimulating therapy. The link between obesity (expressed in BMI, WHR, waist circumference, body weight) and the risk of ovarian cancer remains much less studied [5]. At the same time, there is an indicated relation between metabolic changes concerning glucose management in the entire body and in the tumor's surrounding, including the expression of glucose transporters (mainly GLUT-1) as a marker of malignancy, invasiveness, and advancement, as well as a prognostic factor concerning many malignant neoplasms, including ovarian cancer [6].

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OBESITY DEVELOPMENT MECHANISMS

Obesity is defined as an excessive accumulation of bodily fat, exceeding its physiological needs and adaptability, carrying the risk of adverse effects on health [7].

There is a genetic predisposition for developing obesity with a hereditary tendency to obesity whose level is 40–70% [8].

The arcuate nucleus of the hypothalamus is the center for integrating signals that regulate appetite.

In it, there are two opposing systems that regulate energy consumption. The first one — the orexigenic system reduces the use of energy in conditions of hunger and stimulates the intake of meals. The second one consists in the anorexigenic system that suppresses appetite and increases the use of energy in the event of its excess [9].

Currently, it is known that white adipose tissue is hormonally active and secretes numerous biologically active proteins with multidirectional action, called adipokines. So far, approx. 50 active substances produced by adipose tissue cells have been described, many of whom have the properties of hormones, for example: leptin, adiponectin, resistin, visfatin, apelin, chemerin, and omentin. The relation with ovarian cancer has been studied in terms of the above, and proven mainly for leptin, adiponectin, resistin, and visfatin.

Leptin is one of the most important proteins secreted by adipocytes. It is created mainly in mature cells of white adipose tissue (WAT) of mammals, and its biosynthesis and secretion depend on adipose tissue mass and constitutes a reflection of the energy reservoir in this tissue [10]. It turns out that leptin also affects fetal development, puberty, lactation, hematopoiesis, and the body's immune response.

Adiponectin is a peptide secreted by adipose cells. Adiponectin acts through a membrane receptor (two receptor isoforms differing in gene and organ location). It plays an important role in regulating the metabolism of glucose, lipids, has an impact on appetite control, and has a strong vasoprotective effect by acting directly on the vascular endothelium. Adiponectin leads to vasodilation, inhibition of adhesion molecule expression, inhibition of inflammatory cytokine (TNFα) inflammation, increasing the production of nitric oxide (NO), stimulation of angiogenesis, inhibition of proliferation and migration of endothelial cells and smooth muscle cells. Obesity, type 2 diabetes, hypertension, coronary artery disease, and stroke are accompanied by a decrease in adiponectin levels, while its high values have been recorded among long-lived people [11]. At the same time, lower adiponectin concentrations and higher leptin concentrations are observed among patients with polycystic ovary syndrome [12].

Resistin is an adipokine that reduces tissue sensitivity to insulin, and in case of high insulin concentrations, a factor for developing insulin resistance. It has been proven that, in addition to modulating insulin sensitivity, resistin participates in the development of inflammation, regulates carbohydrate and lipid metabolism, and stimulates endothelial cell proliferation. Additionally, it directly affects the adipose tissue through proliferation and differentiation of adipocytes. By controlling food intake, it participates in establishing energy balance. Furthermore, resistin stimulates and facilitates angiogenesis. Resistin has also been shown to affect endothelial cells of blood vessels — both in terms of proliferation and endothelial cell migration. It has also been established that resistin modulates the activity of female gonads by participating in the regulation of steroidogenesis, folliculogenesis, and cellular proliferation of follicular layer cells in some animal species. Resistin has also been proven to regulate the synthesis and secretion of sex hormones — progesterone and estradiol [13].

Visfatin is a protein produced by visceral adipose tissue. An experiment confirming the origin of visfatin consisted in a demonstration of a correlation between the concentration of this protein and the amount of visceral adipose tissue and the lack of such a relation with the amount of subcutaneous adipose tissue. Summarizing the research concerning visfatin conducted so far, it should be stated that it shows some similarities in action with insulin (hypoglycemic effect, activation of the insulin pathway by an insulin receptor). A low concentration of visfatin compared with insulin — as well as the lack of change in concentration after a meal — results in a relatively low hypoglycemic effect of this protein under physiological conditions. However, it seems that in conditions of excessive amount of visceral adipose tissue, and thus with higher production of pro-inflammatory cytokines, the participation of visfatin in glycemic-lipemic homeostasis increases. Visfatin constitutes one of the elements of the relation between adipose tissue and an inflammatory response, although this mechanism constitutes a challenge for further research [14].

THE RELATION OF OBESITY WITH CANCER

In a study published in "Lancet", Bhaskaran K., Douglas I. et al. [15] showed a link between obesity (increased BMI) and 17 out of 22 examined cancers, including primarily endometrial, gallbladder, kidney, cervical, and thyroid cancer, as well as leukemias. They also associated elevated BMI with cancer of the liver, colon, ovary, and breast in the postmenopausal period.

Epidemiological and clinical data point to the key role of hormones, cytokines, and other mediators as metabolic markers of obesity, expressed in pro-proliferative and pro-inflammatory activity, linking the activity of adipose tissue cells (adipocytes, macrophages etc.) with the appearance and expansion of cancer cells [16].

Resistin and leptin may show proliferative, anti-apoptotic, pro-inflammatory effects, stimulate angiogenesis, which makes them a potential diagnostic and prognostic biomarker of cancer. At the same time, attention is drawn to the protective nature of adiponectin, which possesses anti-inflammatory, anti-atherosclerotic, anti-diabetic, and anti-cancer properties. Studies have shown low levels of adiponectin in breast, liver, pancreatic, prostate, colon, and ovarian cancer [17].

LINK BETWEEN OBESITY AND OVARIAN CANCER

The link between obesity and the risk of ovarian cancer remains much less studied.

In UK 512 in 7011 new cases of ovarian cancer per year are considered attributable to overweight and obesity, while 125 extra cases per year are projected with concomitant 1 kg/m^2 population wide increase in BMI [15].

Study results suggest a link between specific histological types of ovarian cancer — serous with low malignancy potential and invasive mucous tumors with increased parients' BMI [18].

Studies have been carried out concerning the simultaneous use of quantification of osteopontin, IGF-II, leptin, prolactin, and Ca 125 as markers of early ovarian cancer — not giving any positive results [19].

For patients suffering from ovarian cancer with elevated levels of leptin in the serum and excessive receptor expression (Ob-R), this was related with an aggressive course of the disease [20]. It was possible to prove the stimulating effect of leptin on the growth of OVCAR-3-line ovarian cancer cells with simultaneous inhibition of apoptosis by increasing the share of cyclin D1 and Mcl-1 expression by activating the PI3K/Akt and MEK/ERK1/2 pathways [21]. Studies concerning the expression of leptin receptors in ovarian cancer cell lines and its impact on proliferation, activating the JAK2/STAT3, IRS1/2-PI3K/AKT, SHP2/ERK, and COX-2 pathways, as well as the inhibition of apoptosis, suggest that leptin may be a regulating factor for ovarian cancer [22].

Adiponectin stimulates the secretion of CXCL1 from cancer cells in ovarian cancer, leading to VEGF-independent angiogenesis. Studies suggest that it is a key factor initiating angiogenesis in ovarian cancer. At the same time, it may become a new therapeutic target in the treatment of ovarian cancer. However, the role of adiponectin in angiogenesis, tumor development, and metastasis formation, requires further research as the current results are often inconclusive or even contradictory [23].

The levels of adiponectin and leptin among patients with ovarian cancer were lower compared to the control group. However, no significant differences have been found in terms of the stage of the disease. The decreased level of adiponectin and leptin in ovarian cancer compared to other gynecological neoplasms may be of diagnostic importance [24].

In a study with AdipoRon — a synthetic agonist of AdipoR1 and AdipoR2 receptors, an anti-proliferative and pro-apoptotic impact on cells was demonstrated in high grade serum ovarian cancer. AdipoRon activates AMPK, disrupts the cell cycle and activates caspase 3. This suggests that the same pathways may be activated with the use of exogenous adiponectin, which plays a significant role in the survival of tumor cells [25].

It has been determined that adiponectin reduces cell proliferation in epithelial ovarian cancer and is a phenomenon independent of apoptosis. At the same time, it reverses the stimulating effect of estradiol and IGF-1 on cell proliferation. Progesterone increases the sensitivity of cancer cells to adiponectin by increasing the expression of its receptors. These dependencies suggest that there is a link between adiponectin and ovarian steroid hormones and growth factor pathways in ovarian cancer cells [26].

IMPACT OF OBESITY ON SURVIVAL PARAMETERS AMONG PATIENTS WITH OVARIAN CANCER

It has been proven that leptin is associated with a worse prognosis for patients treated with platinum compounds combined with paclitaxel/docetaxel. Leptin reduces the sensitivity of ovarian cancer cells to paclitaxel/docetaxel. Flow cytometry showed that the administration of exogenous leptin reduced the proportion of ovarian cancer cells in the G2/M phase, the titre of which was increased as a result of treatment with paclitaxel/docetaxel [27].

The studies explained the relation on the leptin/OB-Rb axis and the role of the estrogen receptor α in tumor growth and confirmed the estrogen-dependent effect of ERα on leptin-induced cell growth in ovarian cancer, which may contribute to discovering a new mechanism of leptin-dependent progression in ovarian cancer [28].

Serum leptin levels, although, according to most researchers, decreased among patients with ovarian cancer, has not become a prognostic marker. Higher leptin levels were found among obese patients, which was associated with shorter survival times. The concentration of leptin in ascites in combination with the Ca 125 marker has been considered an important prognostic factor in terms of resistance to first-line chemotherapy [29].

Research has been carried out concerning the OB3 protein, which could play a metabolic role similar to leptin, without its oncogenic potential. The OB3 protein in ovarian cancer could prevent neoplasm initiation and progression by disrupting leptin-dependent proliferative signals through STAT3 phosphorylation and ERα activation.

Taking advantage of OB3 protein in case of obese individuals should be taken into consideration as a prophylaxis of leptin-induced cancers [30].

Studies have revealed that blocking the action of leptin as a factor activating the epithelial-mesenchymal transformation of ovarian cancer cells by activating the PI3K/Akt/mTOR pathway is related to a significant reduction in peritoneal metastasis, which provides new therapeutic possibilities [31].

It has also been determined that leptin plays a key role in expressing urokinase plasminogen activator via the OB.-Rb, RhoA/ROCK, PI3K/AKT, JAK/STAT, and NF-kB pathways, which constitute a new mechanism of ovarian cancer expansion [32].

In ovarian cancer, the inductive effect of resistin on the growth of cancer cells, their spread, resistance to cisplatin through the transformation of epithelial into mesenchymal stem cells (EMT) is indicated, which with the simultaneous suppression of miRNA, let-7a, miR-200c, and miR-186 lies at the base of producing chemoresistance [33].

CONCLUSIONS

Taking into consideration the global increase in the number of obese people as well as the current research results, it is necessary to deepen the research concerning the mechanisms linking obesity with the increased risk of ovarian cancer development and its impact on the prognosis and course of the disease among female patients.

Conflict of interest

All authors declare no conflict of interest.

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Uretero-vaginal fistulas — clinical presentation, treatment and literature overview

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ABSTRACT

A uretero-vaginal fistula (UVF) describes an abnormal connection between the ureter and vagina causing urinary incontinence, frequent infection, and discomfort. Although UVF might be diagnosed after vaginal delivery, infertility treatment or pelvic radiation therapy, gynecological operations, especially total abdominal hysterectomy, remain the leading cause of ureteral injury and formation of UVF. Traditional ureteroneocystostomy was usually the treatment of choice in patients with UVF. Nevertheless, it is now frequently replaced by less invasive endoscopic and percutaneous procedures which are also highly effective and feasible. That is why, ureteral stenting became the first-line treatment in uncomplicated UVF.

The aim of this review is to present clinical presentation of UVF and to assess the current state of knowledge about the diagnosis and management of uretero-vaginal fistula with special interest on minimally-invasive methods.

Key words: uretero-vaginal fistula; post-operative; complication; minimally-invasive

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INTRODUCTION

A uretero-vaginal fistula (UVF) describes an abnormal connection between the ureter and vagina causing urinary incontinence, frequent infection, and discomfort [1]. Although UVF might be diagnosed after vaginal delivery, infertility treatment or pelvic radiation therapy, gynecological operations, especially total abdominal hysterectomy, remain the leading cause of ureteral injury and formation of UVF [2–6]. Apart from mechanical injury of the ureter, thermal effects of electrocoagulation of the ovarian vessels may result in UVF [7]. Authors also report an increase of ureteric injuries resulting in creation of UVF since the introduction of laparoscopic surgery. According to Parpala-Spårman et al. [8], gynecological laparoscopic procedures account for more than half of the ureteric injuries, especially its lower part. Traditional ureteroneocystostomy was usually the treatment of choice in patients with UVF [9]. Nevertheless, it is now frequently replaced by less invasive endoscopic and percutaneous procedures which are also highly effective and feasible [10]. Selzman et al. [10] who described his 20 years of experience with management of patients with UVF concluded that every effort should be made to avoid an open operation. That is why, ureteral stenting became the first-line treatment in uncomplicated UVF.

Objectives

The aim of this review is to present clinical presentation of UVF and to assess the current state of knowledge about

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the diagnosis and management of uretero-vaginal fistula with special interest on minimally-invasive methods.

CLINICAL PRESENTATION

Case 1

A 70-year-old patient was admitted to the Department of Gynecology with diagnosis of cervical cancer in early stage (FIGO IIA). She underwent Wertheim-Meigs radical hysterectomy. After six days of uneventful hospitalization, she was discharged in good clinical condition and no abnormalities in lab results. Unfortunately, seven days after the operation the patient started to complain about flank pain and constant dribbling with normal urine evacuation. A Foley catheter was placed. CT-urography disclosed a formation of a UVF. The patient was qualified for implantation of DJ-stent and nephrostomy. With patient in a prone position the right flank region was cleansed with povidone iodine and draped. In local anesthesia and under ultrasound guidance the upper pelvis calyx was punctured. Afterwards, under fluoroscopy guidance right ureter was catheterized. Contrast injection confirmed the presence of UFV (Fig. 1A). A 6 French sheath was introduced and catheterization of urinary bladder with microcatheter was attempted. Multiple attempts were futile. Therefore, cystoscope was inserted and with use of the loop the wire was passed from the urinary bladder to the puncture site (Fig. 1B). Afterwards, DJ catheter and nephrostomy were placed. She also received oral antibiotics. Initial hematuria subsided after two days. A double-dye tampon test which was conducted six days after stent implantation showed incomplete resolution of UVF. The test was repeated after two weeks and showed complete resolution of UVF.

Case 2

A 39-year-old patient was admitted to the Department of Gynecology with diagnosis of multiple fibroids. She reported long history of excessive bleeding, anemia and painful cramps. She was therefore qualified for laparoscopic hysterectomy. After four days of uneventful hospitalization, she was discharged in good clinical condition and no abnormalities in lab results. Three weeks after the procedure she was admitted with right flank pain and constant dripping. Intravenous urography disclosed hydronephrosis at the right side (30 mm) with dilatated right ureter (20 mm) (Fig. 2A). Based on clinical symptoms and imaging findings the patient was referred for DJ-implantation. Despite multiple attempts and use of microcatheter DJ-implantation was futile. The decision about nephrostomy implantation was made. Control intravenous pyelography was performed five weeks after the procedure. It showed proper position of the nephrostomy and persistent dilatation of the right ureter (Fig. 2B). That is why, second DJ-stent implantation

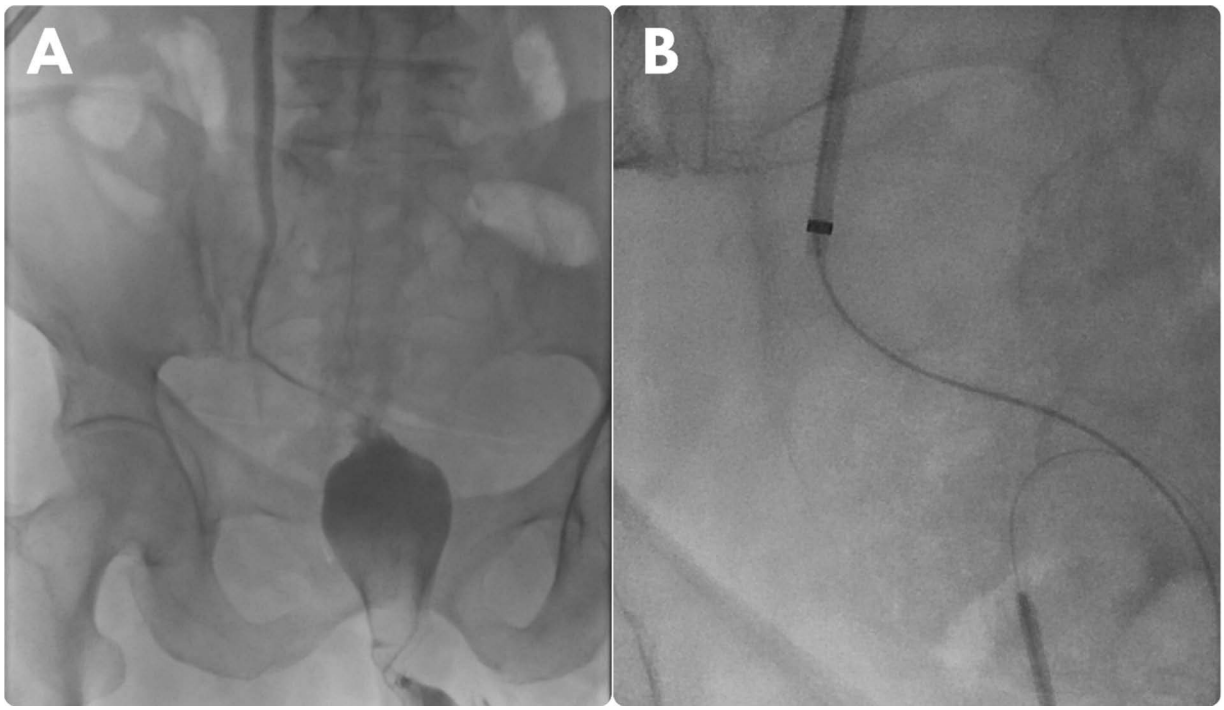

Figure 1. A. Initial contrast injection confirmed the presence of utero-vaginal fistula; **B.** After insertion of the cystoscope the guiding wire was successfully passed and DJ catheter was placed

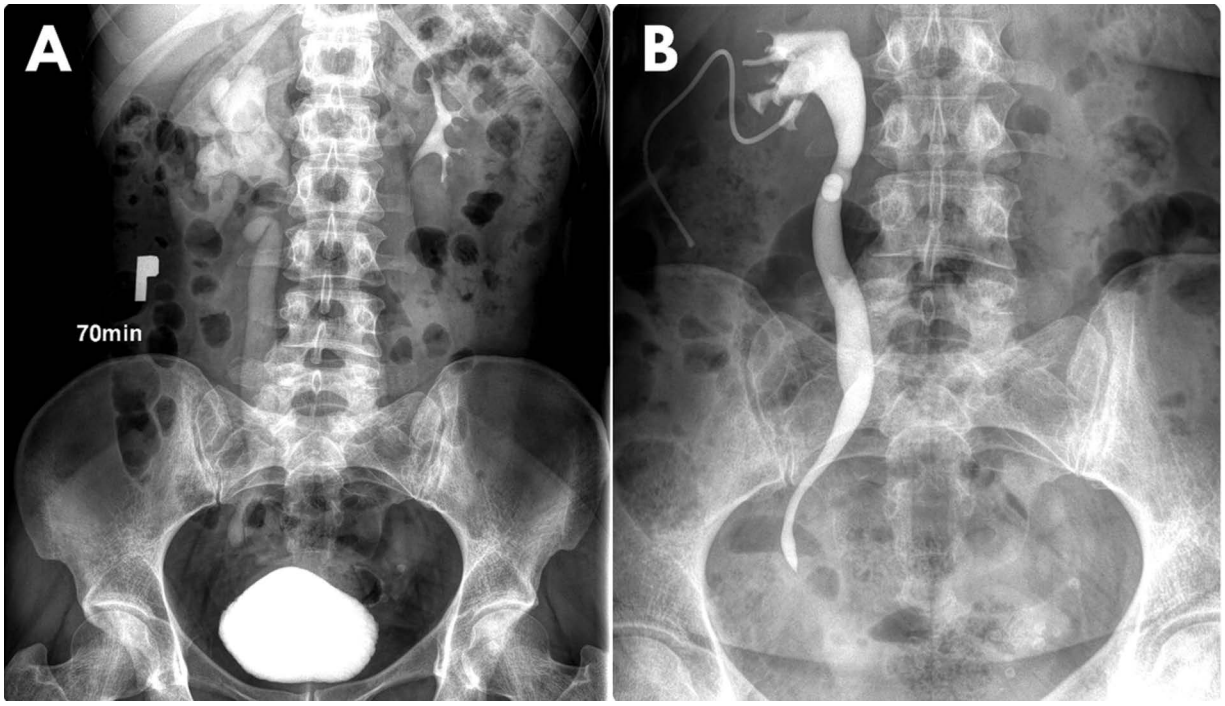

Figure 2. A. Initial intravenous urography showing significant hydronephrosis and ureter dilatation at the right side; **B.** Control intravenous pyelography performed 5 weeks after nephrostomy placement confirming the persistence of right ureter dilatation

was attempted. Again, the procedure was futile. The patient underwent urological examination and complete occlusion of the right ureter was confirmed. Based on these findings, she was referred for open ureter reimplantation. The operation was successful and the patient was discharged in good clinical condition 10 days after the procedure.

In case of UVF suspicion, all patients should undergo thorough history and physical examination. Most common clinical presentation of UVF include continuous vaginal leak of urine with or without ipsilateral flank, fever and urinary tract infection which typically occur up to four weeks after the ureteral injury [11]. It is crucial to obtain an accurate medical history as some symptoms may be very helpful in differentiation of uretero-vaginal fistulas from other types of fistulas without radiological imaging (*e.g.*, the sensation to void and hold a normal bladder capacity would not be present in case of vesicovaginal fistula) [12].

DIAGNOSIS

The diagnostic method of choice to diagnose various types of vaginal fistulas, including UVF is a double-dye tampon test during which one dye is injected to the patient's bladder and the second dye of different color is injected intravenously [13]. The staining on the packs removed from patient's vagina indicate the localization of the fistula. Its main advantages are low costs, simplicity and high accuracy.

As far as the imaging examinations are concerned, CT-urography is the most commonly used diagnostic modality and is considered to be the gold standard for the detection of ureteral injury, including fistula [14]. In addition to this, intravenous pyelography and retrograde pyelography are also very useful and should be considered as part of a UVF diagnosis and evaluation [15].

Despite all methods mentioned above, some authors state that overall rate of ureteral injury during gynecological surgery, which may lead to creation of UVF is much higher than reported [16]. That is why, they suggest that the routine intraoperative cystoscopy during major gynecologic and especially urogynecologic surgery might prevent sequelae from lower urinary tract injuries. On the other hand, routine intraoperative cystoscopy does not guarantee recognition of all lower urinary tract injuries, especially UVF which may develop over time [17]. Hence, the role of routine intraoperative cystoscopy remains debatable.

Treatment

Traditional treatment of UVF included reimplantation of the ureter into the bladder (ureteroneocystostomy). Although the reported were satisfactory, the procedure had all drawback of an open surgery [8, 18]. Recent laparoscopic and robotic techniques are promising alternatives to open surgery with comparable rate of clinical success [19, 20].

In addition to that, reports on successful repair of UVF performed exclusively through the vaginal approach are also available in the literature [21, 22]

Nonetheless, according to Chen et al. [12] who proposed a ureterovaginal fistula management algorithm, the first step in management of UVF should to assess if a patient is candidate for placement of ureteral stent. Placement of nephrostomy alone is contraindicated as it is associated with relatively high rate of clinical failure [5, 23]. Contraindication for primary ureteral stenting include presence of concurrent vesicovaginal fistula and/or history of ureteral injury. These patients should be considered as candidates for ureteral reimplantation surgery.

Over last decades the success rate of stent placement increased from < 40% to > 70% [5, 24, 25]. Chen et al. [12] even reported success rate of 92% which was attributed to use of innovative techniques (which included multi-stage procedures) and multidisciplinary approach . As far as the optimal timing for ureteral stent placement is concerned, no clear indications are available. Although delayed treatment increases the risk of procedural failure, cases of patients treated successfully over two years after initial surgery are described [14]. Similarly, no guidelines on safe time frame of stent maintenance can be found in the literature. Based on authors' experience, Chen et al. [12] recommended to keep stents for at least three months and perform retrograde pyelogram upon stent removal.

Another minimally-invasive procedure in treatment of UVF is retrograde ureteroscopic stenting. In their paper Rajamaheswari et al. [26] described 17 patients with UVF of which 13 (77%) was successfully managed with ureteroscopic DJ stenting. All 13 patients were followed-up and no leakage, stricture or obstruction was reported. Remaining four patients underwent ureteral reimplantation due to near-total ureteral occlusion precluding safe stent implantation. However, authors suggest that even in subtotal ureteral occlusion open surgery could be replaced by less invasive alternatives (*e.g.*, simultaneous antegrade and retrograde ureteroscopy) [27].

Complications

Most common complications of UVF treatment are persistent fistula and ureter stricture. These complications appear to be especially frequent after placing a percutaneous nephrostomy only. Schmeller et al. [23] who described 11 patients with UVFs treated only by percutaneous nephrostomy, reported 55% rate of persistent fistula and 18% of stricture. Similarly, Al-Otaibi observed high rate of ureter stricture after placing a percutaneous nephrostomy [5]. That is why, in case of failure of either conservative or minimally-invasive treatment, surgical intervention is necessary [14].

CONCLUSIONS

Ureterovaginal fistula is rare yet important post-operative complication and should therefore be included in the differential diagnosis in patients reporting post-operative urinary incontinence. Early and correct diagnosis is crucial and can be made in the clinical setting with a simple dual-dye tampon test. Proper treatment selection is of great importance as minimally invasive ureteral stenting is associated with high cure rates and low morbidity compared with surgery in eligible patients. In case of contraindications or treatment failure, ureteral reimplantation may be necessary.

Ethical approval

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

Informed consent

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

Contributions

All authors contributed significantly to the paper: MSZ, KP, TR, HSZ and SW evaluated the data and prepared the manuscript. KP, MSZ, SW, TJ and TR participated in described procedures. All authors approved the final version of the manuscript.

Conflict of interest

All authors declare that they have no conflict of interest.

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Contact thermography — a modern method and its role in breast cancer prevention

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ABSTRACT

Breast cancer is one of the most common oncological conditions among Polish women and is a serious health, social, as well as economic problem. Knowledge of early cancer detection methods, risk factors and prevention methods are key issues in the fight against breast cancer in women. Introduction of modern technologies using contact thermography can be both practical and complementary diagnostic method in relation to mammography or ultrasonography of mammary gland.

Key words: breast cancer; prevention; contact thermography; Braster

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INTRODUCTION

Malignant tumors in Poland are a growing health, social and economic problem. Malignant tumors are the second leading cause of death in Poland, causing about 26.3% of deaths among men and 23.1% among women. It constitutes a significant health problem mainly in young and middle-aged people. This phenomenon is particularly evident in the population of women under the age of 65 and is the most common cause of death among young (33% of deaths) and middle-aged women (49% of deaths). The most common malignant neoplasm in women is malignant breast cancer, which accounts for approximately 22.5% of the incidence of all cancers. The incidence of this cancer is systematically increasing. Annually, more than 20,000 Polish women face a diagnosis of breast cancer, of which one third dies. In the last thirty years there has been a twofold increase in the incidence of malignant breast cancer in women between 20 and 65 years of age. It is projected that in the next seven years there will be an increase in the incidence of malignant breast cancer in all age groups, especially in women aged between 50 and 69 years. Projections to 2025 indicate that further increases in the incidence of this type of cancer will be observed during this period, with the most pronounced increase in incidence in women over 50 years of age [1–5].

A significant problem in the fight against breast cancer is the low participation in screening and ineffective health care system in Poland. According to the data of the Main Coordination Center of the Breast Cancer Early Detection Program, only 35% of eligible women aged 50–69 participate in screening programs in Poland. It should be emphasized that early detection of breast cancer increases survival in women to 98.6%, but if the cancer is detected at a later stage with metastases to regional lymph nodes or is disseminated, the survival decreases to 83.8% and 23.3%, respectively. The dysfunctionality of the health care system in the area of screening — mammography, lies in recommending it only for women over 50 years of age. Diagnostic tests in the form of ultrasound and magnetic resonance imaging are recommended for women under 50. In the Polish population of young and middle-aged women, the incidence rate of malignant neoplasms is higher than in men, and epidemiological data indicate that approximately 7% of all breast cancer cases are diagnosed in women under 40 years of age [1, 5–8].

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BREAST CANCER DIAGNOSIS

The key issue in the fight against breast malignancy in women is knowledge of prevention methods and knowledge of methods and possibilities of cancer detection and diagnosis. In modern cancer prevention, activities are aimed at detecting the disease at the earliest possible stage. A factor that significantly affects the results of treatment is the detection of cancer at the earliest possible stage of development. Breast cancer diagnosis is based on palpation and physical examination. Mammography, ultrasound, magnetic resonance imaging, and microscopic examination, which are always performed when changes are found on palpation, play an important role in the diagnosis [8].

Breast palpation is the simplest clinical examination of the breast that allows early diagnosis of lesions. More than 90% of breast cancers are detected by women during breast self-examination [7]. Therefore, both palpation in the doctor's office and breast self-examination should be performed by every woman. Although breast self-examination is easy to perform, it should be kept in mind that incorrect technique and errors made while performing breast self-examination can lead to misinterpretation of the result, which consequently may result in failure to detect alarming changes [6, 7]. Thus, palpation examination, seems to be ineffective in detecting the early stage of the disease and is recommended mainly to increase breast cancer awareness in the female population. According to the recommendations of the American Cancer Society and the Polish Cancer Union, the best method for early detection of breast cancer in women without clinical symptoms is screening mammography (MMG). Mammography is a method that can significantly identify pathological changes in the breast tissue. Its sensitivity is the highest and is estimated to be 90–95% for postmenopausal women. Randomized clinical trials have shown a 25–30% reduction in breast cancer mortality among women aged 50–69 who had mammography annually or every two years. Ultrasound (US) is safe and widely used to evaluate palpable breast defects in young women. However, the false-negative rate for clinically latent lesions can be up to 47%, resulting in diagnostic and therapeutic delays. Ultrasound also has a relatively high false positive rate, i.e., as high as 8.1% when used without an adjunctive method. False-positive results are also a problem with MRI, which, combined with the high cost and requirement for contrast, means that MRI is not suitable as an early diagnostic tool. Therefore, a cost-effective method for early diagnosis of breast cancer in younger women is a necessity [8–12].

Consequently, the use of innovative technologies such as contact thermography, complementary to other diagnostic modalities points to a very interesting direction for the application of this method to improve the efficiency of lesion detection in young and middle-aged women as an important element in the diagnostic pathway.

CONTACT THERMOGRAPHY

Thermography is an imaging technique that involves recording the surface distribution of body temperature. The technique has been known since the 1960s, where Lawson noted in 1956 that the skin temperature above breast lumps was elevated. Thermographic breast imaging using infrared cameras has been used and tested as a tool for cancer detection. Despite promising results, this research was challenged in the early 1970s by a large research project called the Breast Cancer Detection and Demonstration Project (BCDDP) in the US. However, the technique was not validated for the early detection of breast cancer and the use of thermography in medical applications was virtually abandoned for an extended period, mainly due to the lack of standardized testing protocols and equipment, poor reproducibility, lack of authoritative guidelines for the interpretation of thermographic images, and poor quality of scientific articles. The end of the standstill in thermography research was initiated by the military, which in the late 1980s made available for public use the so-called Focal Plane Arrays (FPAs), which revolutionized the thermal imaging market. They replaced the single detectors or lines of detectors used in earlier versions of thermographs and the accompanying complex optomechanical signal recording systems. Another breakthrough was the use of uncooled thermal detectors in FPA arrays, which significantly reduced the price of thermal imaging arrays. Currently, we notice a great interest of researchers in the area of medical thermography. The modern use of non-contact methods of measuring body temperature is due to rapid advances in computer and information technology, particularly methods of digital image data analysis and processing. Thanks to technological advances, more advanced active dynamic thermography (ADT) began to be used, carrying information about the three-dimensional heat transfer over time that occurs in tissues under the influence of an external thermal stimulus. The measurement methods used in thermography have been widely applied in the last few decades not only in medicine and physiotherapy, but also in biomedical engineering in its broadest sense [13–17].

Thermography is the process of imaging, detecting and recording the temperature of the body under test, the organ under test. There is a distinction between remote thermography, in which the image is obtained without contact by recording heat exchange by radiation, and contact thermography, in which the image is generated on the basis of conduction heat exchange when in contact with the surface under test. Contact thermography is a fully non-invasive method of functional imaging of organ function. It uses

the so-called dermothermic effect, which consists in recording from the skin surface the biothermic processes occurring in the observed organs inside the body. Tumor cells, including breast cancer cells, are characterized by a higher metabolic rate, additionally within the tumor a dense network of capillaries is formed, this leads to the formation of hyperthermia foci (elevated temperature), which can be recorded on the surface of the examined organ as the so-called thermal marker. Pathological changes within the breast suspected of malignancy have a higher temperature than healthy areas and are visible on thermograms as colored areas, which allows to observe the pathomorphological change in the examined organ by registering the temperature increase in each area on the thermographic image. A multitude of relevant and worldwide reference studies indicate that the method of breast thermography examination is characterized by high sensitivity and specificity (80–90%) [15–17].

Braster is a Polish device employing contact thermography, which can be used as a supplement to standard diagnostic examinations. This device was patented by Polish scientists who developed a breakthrough way to use liquid crystals in diagnostics, creating a unique device in the world for breast examination. The Braster is a Class IIa certified medical device that uses liquid crystal thermography (LC) to produce high resolution contact thermographic images of the breast. It provides color images (thermograms) indicating temperature changes on the surface of the breast in direct contact with the LC film, the effect is to image the temperature distribution in three colors: red, green, and blue (RGB) [12]. The images are captured using a digital camera built into the device. Breast tumors appear on thermograms as areas of elevated temperature or thermal asymmetry. The Braster device consists of a camera, a light-absorbing dome, a light source, and removable LC films. Once the device is applied to the subject's breast, a series of images are taken, with the film held against the breast for 15 seconds before being removed and moved to another area of the breast, clockwise. Because a single application usually does not cover the entire breast, the test procedure includes several such application sequences covering each breast area (3 or 5 applications per breast, depending on breast size). The thermal images of the breast recorded by Braster are transmitted to an analysis system that interprets them and distinguishes between images of heat released, for example, by blood vessels and heat caused by the activity of tumor-forming cancer cells. Additionally, the interpretation system configured with Braster remembers the image of a given woman's breast and periodically compares all subsequent thermal images made by Braster, creating a kind of unique "fingerprint" of the organ [12, 18, 19].

Braster S.A. offers its product for consumer use as well as for medical offices — Braster Pro. The Braster device for consumer use offers the possibility of performing a reliable, monthly self-examination at home and receiving the results online. The consumer, through the Braster Device and the Braster Care mobile application installed on a smartphone or tablet, connects wirelessly to the device, and is intuitively guided through the entire examination process, and then sends the data to the Braster Telemedical Center for analysis. The user, via the mobile app, receives the results of the test within 48 hours. The Braster Pro system was introduced in 2018 and is used by professionals in the doctor's office. The Braster Pro system uses artificial intelligence algorithms that analyze the thermographic images of the breast, collected during the examination, which are then subjected to automatic interpretation through the mobile application. The result of the examination is the information transmitted to the doctor to what extent the standards for thermal asymmetry, both structural and superficial, of the examined breasts have been exceeded. On this basis, the doctor refers the patient for in-depth diagnostic tests [12, 20].

Between 2013 and 2016, three formal observational studies, ThermaCRAC, ThermaRAK, and ThermaALG, were conducted to compare the effectiveness of the Braster device with standard diagnostic procedures. The studies were conducted on women with diagnosed breast lesions who were referred for further diagnosis (over 1350 women in total). During the ThermaCRAC study (n = 736), the sensitivity of thermography was 72% and its specificity was 58% for the whole population, which allows us to conclude on the effectiveness and usefulness of the tested device; when thermography was combined with mammography, an increased efficiency of breast cancer detection was also found. Another study aimed at the development of an algorithm for the interpretation of thermographic images was the ThermaRAK project (n = 318), the clinical material obtained during the study was the basis for the development of supporting tools, such as an atlas of pathological thermographic images, which is a scientific aid for medical personnel performing and interpreting the obtained thermographic images obtained using the Braster [21, 22].

The ThermaALG study was a prospective study evaluating the method of contact thermography in relation to current diagnostic standards for breast disease. The study included 274 women aged 25–83 years, who were divided into two groups: under 50 years of age (50–) and over 50 years of age (50+). The results of this study showed a higher sensitivity of the Braster method in detecting potential breast lesions in women in the 50– group compared to the older 50+ group. Women under 50 years of age who had an abnormal breast ultrasound result, and a positive thermographic finding (presence of areas of hyperthermia) had a two-fold increased risk of breast cancer compared to the group of

patients with an abnormal ultrasound result and a negative thermographic finding (no foci of hyperthermia) [8, 12].

Based on the results of the Therma-ALG study and our own research, the Polish Society of Gynecologists and Obstetricians (PTGiP) issued an opinion on the usefulness of the medical device, the Braster System for Homeoprophylaxis of Breast Cancer. The authors of the opinion concluded that contact thermography is a complementary examination, supplementary to such methods as X-ray mammography or ultrasonography of the breast. It was indicated that in the future this technique may be a complementary diagnostic tool in the protocol of preventive examinations of breast cancer. At the same time, the experts emphasized that for this to happen, further studies should be conducted in sufficiently large populations to unambiguously determine the possibility of using the system in a breast cancer screening program [12].

A positive opinion on the usability of the Braster Pro system was also issued in 2018 by the Polish Society of Gynecologic Oncology (PTGO). This opinion was based on the manufacturer's research findings and data, as well as on their own tests of the device. Using the Braster Pro system, 169 patients were tested, with 134 negative results, 28 positive results (for in-depth diagnostics), and in the case of 7 patients, incorrect performance of the test prevented the result. In its conclusions, the PTGO assessed the device as useful, easy to use, and able to complement basic examination and breast ultrasound in gynecological offices. It was also indicated that research is still needed to evaluate the sensitivity and specificity of breast assessment by thermography [23].

In the economic perspective, the huge potential of the device was pointed out, in addition, Braster S.A. investigating ways to detect breast lesions could also plan to expand the use of thermographic diagnostics in the field of other organs [24].

In 2017, the European Society of Breast Imaging (EUSOBI) issued a statement advising against screening with thermography and other optical tools if they were to be an alternative to mammography, the use of which was considered a priority [25].

In February 2019, a U.S. Food and Drug Administration (U.S. FDA) opinion was released that also emphasized that thermography is not an effective alternative and should not replace mammography for screening and diagnosis of breast cancer. The opinion also indicated that there is insufficient scientific evidence to conclude that thermographic devices are an effective screening tool for breast cancer detection. At the same time, the agency emphasizes that thermography-based devices are approved by the FDA for marketing only for use with other tests such as mammography, not as stand-alone diagnostic tools. In the released document, the authors noted that in various types of health-related settings (e.g., health spas, homeopathic clinics) where thermography-based services have been offered, there has been misinformation convincing patients of the superiority of thermography over mammography, which could induce people who have had a thermography scan not to have a mammography test [26].

Not long after, in March 2019, a group of Polish oncologists issued a statement on the use of thermography in breast cancer diagnostics. The authors emphasized that there is no evidence to support the value of thermography in the detection and diagnosis of breast cancer, and no evidence for its value as a preventive screening test. Experts concluded that the use of thermographic methods instead of tests with proven efficacy may deprive patients of the chance of successful treatment because it carries a high risk of overlooking cancer [27].

Braster S.A. responded to the above opinions by emphasizing that their devices are not intended for independent diagnostics of breast cancer and cannot be used as an independent diagnostic method; the response also emphasized that Braster is an additional supplementary method to mammography and ultrasound of the breast. It was underlined that the Board of Directors of Braster S.A. does not feel that it is the addressee of the March 2019 opinion of Polish oncologists [28, 29].

Regarding the media publications in March 2019, the Polish Society of Gynecologic Oncology confirmed its opinion. The document emphasizes that despite its low sensitivity (21–41%), self-examination is an important element of breast cancer prevention, but it is not performed correctly or at all by most patients; it also points out that there is a lack of screening among young, healthy women, and mammography has limited effectiveness in this group. Experts see the Braster Pro as a helpful tool in the office of GP or gynecologist [30].

CONCLUSIONS

The introduction of modern technologies using contact thermography can provide a safe, practical as well as complementary method to mammography or breast ultrasound. The inclusion of the described method in the diagnostic algorithm of breast cancer and reliable health education on breast cancer prevention with the use of modern technologies, bring hope for increased health awareness among women. At the same time, there is a need for education related to the place of thermography in preventive measures — it should be emphasized that it is not a method that can be treated as sufficient for the prevention of breast cancer and it does not replace standard diagnostic procedures (breast ultrasound, mammography), it should be treated as a complement in the diagnosis of breast pathology.

Conflict of interest

All authors declare no conflict of interest.

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Visceral therapy in disorders of the female reproductive organs

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ABSTRACT

Dyspareunia is genital pain during sexual intercourse without constriction of the vulva or vagina. This is one of the most significant issues that lies at the border of gynaecology and sexology. Dyspareunia can be caused by endometriosis. Many women can also experience premenstrual syndrome, which can occur as a separate problem. All three of these can result from an imbalance between the female genital organs and their surrounding tissues with other structures of the skeletal or visceral system, with impaired mobility and motility of organs, intra-organ movement, vascular drainage, a pressure gradient between the urogenital and diaphragmatic cylinders, dysfunctions in the area of the broad ligament of the uterus, and fascial bonding. Apart from standard treatment methods used in gynaecology and sexology, physiotherapy (e.g., visceral therapy) is of great value. Visceral therapy aims at restoring intra-organ movement, reducing tension, focusing on the area of the two cylinders of the trunk, and supporting the functioning of the vascular system in the vicinity of the uterus. All these activities reduce pain and substantially change the functioning of the uterus and ovaries.

Key words: visceral therapy; woman; reproductive organ

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INTRODUCTION

The current fashion of healthy lifestyles translates into healthy eating, eco-living, and using a variety of non-pharmaceutical treatment methods that improve health. A good thing is that contemporary women are paying a lot of attention to the proper functioning of their bodies, wishing to stay healthy as long as possible, and also taking care of their sexual health. Dyspareunia (genital pain during sexual intercourse), which can be caused by endometriosis, is a very significant issue that lies at the border of gynaecology and sexology [1]. Dyspareunia is a form of female sexual dysfunction (FSD) that can involve hypoactive sexual desire disorder, aversion disorder, sexual arousal disorder, orgasmic disorder and vaginism. Many women can also experience premenstrual syndrome, which can occur as a separate problem [2].

All these issues can result from an imbalance between the female genital organs and their surrounding tissues with other structures of the skeletal or visceral system, such as impaired mobility and motility of organs, intra-organ movement, vascular drainage, a pressure gradient between the urogenital and diaphragmatic cylinders, dysfunctions in the area of the broad ligament of the uterus, and fascial bonding. Dyspareunia is a sexual dysfunction that manifests itself as pain in the reproductive organs before, during or immediately after sexual intercourse [3]. It should be emphasised that dyspareunia is pain during sexual activity, and it is not accompanied by constriction of the vulva or vagina, which is why it should be distinguished from vaginism, where penetration of the penis is not possible. Considering the issues outlined in this article, holistic care over patients experiencing these dysfunctions needs to be highlighted [1–3]. The structure and function of the body are interdependent. It is often the case that symptoms occur in the body in places very far from their causes. A holistic view on the body can significantly eliminate disorders.

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The influence on premenstrual syndrome and the above-mentioned lifestyle issues (physical activity, diet), personality disorders, addiction to psychoactive substances, and high body mass index (BMI) is pointed out.

Modifications to the diet can be an effective complementary treatment. For instance, as far as premenstrual syndrome is concerned, it is recommended to reduce salt and salty food intake. Similarly, caffeine (found mostly in coffee) can exacerbate emotional symptoms. It is also reasonably necessary to avoid drinking alcohol, as well as limit the consumption of simple carbohydrates and replace them with complex carbohydrates. Vitamin and mineral deficiencies can be a risk factor for the symptoms of the above presented issues. For example, B-group vitamins and folic acid are essential for the synthesis of neurotransmitters (potentially implicated in the pathogenesis of premenstrual syndrome). The importance of vitamin D has also been pointed out – a dose of above 2.5 µg lowers the risk of premenstrual syndrome. Between ovulation and menstruation, it is suggested to take a daily amount of 1200 mg of calcium and 6 g of tryptophan, as well as an increase in magnesium and vitamin D intake. Gingko, saffron, soya, vitamin E, as well as herbal preparations (vitex agnus-castus, St John's-wort and black cohosh) are effective in preventing the issues in question. It is crucial to recommend a balanced diet, tailored to the patient's personal needs by a dietician. Based on a dietary history, dieticians can identify mistakes made by patients and determine the necessity and scope of a diet modification [4].

Femininity, which manifests itself in good reproductive health, is of key importance for women. Dysfunctions in the female reproductive organs may take a variety of often clinically equivocal forms that in many cases feature similar aetiology. The reasons for that can lie in disorders of the fascia-muscle-organ axis, which qualifies for visceral therapy targeted to the causes of gynaecological disorders. Paying attention to the anatomical relationships of the uterus and ovaries through the ligament system with the sacral bone, or through the fascia with the surrounding muscle sheaths and organs, can give a clearer picture of the reasons of excessive tension resulting in pain in this area. An important factor causing discomfort in patients may be unbalanced pressure between the abdominal cylinders formed by the respiratory diaphragm and the urogenital diaphragm of the pelvic floor [5–7]. Disorder within the core stability can lead to diastasis recti, which is often observed in late pregnancy or in the postpartum period and affects the bowels. Visceral therapy significantly improves bowel function and help with constipation [8, 9]. Abnormal pressure between the respiratory diaphragm and the urogenital diaphragm can cause urinary incontinence. Randomised double-blind studies carried out among women suffering from urinary incontinence have shown that the groups which had undergone pelvic floor training and visceral therapy recorded significantly better results and improved quality of life [10].

Considering the system of connections between the reproductive organs and the bony components of the spine, the sacral bone can be pointed to as a source of pain in women visiting therapists. For that reason, differential diagnosis should be an indispensable element in the search for the source of the problem. The resulting conclusions, combined with history including information about dysmenorrhea, sexual activity, ovulation and other conditions indicating gynaecological pathologies, should suggest the implementation of visceral therapy in the treatments.

Amongst the lesions in the female genital tract, we can distinguish endometriosis, dyspareunia and premenstrual syndrome [11–13] that are characterised by pain within the abdominal cavity. It can be said that a common denominator of these disorders is increased muscle tone. Visceral therapy focuses on regaining the mobility and motility of internal organs, myofascial release, regulating pressure between the chambers of the abdominal cavity, and relieving the negative consequences of dysfunctions of the female reproductive organs [14, 15]. Visceral therapy can also support infertility treatment [16]. Due to the fact that women often consider their disorders as shameful, some techniques require an extensive trust in therapists.

Objective

the objective of this paper is to present visceral therapy — a non-pharmacological and non-invasive complementary method — in the treatment of gynaecological dysfunctions.

ANATOMICAL RELATIONSHIPS BETWEEN THE STRUCTURES OF THE REPRODUCTIVE SYSTEM

The uterus lies in the small pelvis, between the rectum and the bladder, in the intraperitoneal (and partially in the subperitoneal) space. The cervix is to some extent situated in the retroperitoneal space and can change its position depending on expansion in the rectum and bladder.

The vagina lies in the caudal direction, and the sigmoid colon and the ileum lie in the cranial direction. Dorsally, the small intestine enters from the top, and the rectum from the bottom. Ventrally, in the vicinity of the organs is the urinary bladder, and laterally, the wide ligament of the uterus [17]. The uterine suspension system relies on elements of the skeletal system and consists of the following structures: the peritoneum, the round ligament of the uterus, the broad ligament of the uterus, and the sacro-recto-genito-pubic lamina. Adhesions or other restrictions in the peritoneum area have a significant impact on the mobility of the uterus. The round ligaments of the uterus run through the inguinal canal to the litter of the labia majora, laterally on both sides

of the uterus. The broad ligament of the uterus is very important for the functioning of the entire reproductive system as most of the structures supplying the uterus with blood (veins, arteries, lymphatic vessels and venous plexuses) are located in this region. It provides support and stabilises this organ. Delbet's lamina (sacro-recto-genito-pubic) stabilises this organ in the sagittal plane using the sacro-uterine ligament, which when pulled and irritated restricts mobility in the area of the sacrum and hips [18]. Sensory information from the uterus travels through axons via the hypogastric plexus to the thoracolumbar segments of the spine via the minor visceral nerve (T10-L2) [19]. In the other direction, impulses from the parasympathetic system are transported. The sacro-recto-genito-pubic lamina is connected with the hypogastric plexus, which acts as a locating connective tissue structure [18]. The axons carrying the sensory sensations from the vagina reach the spinal cord through the pelvic nerves and run to the sacral segments (S2-S4). The area surrounding the cervix creates a transitional zone for the nervous system, and impulses from this area can reach the spine using both types of the above-mentioned pathways [19]. The organs supplied by the hypogastric plexus are connected to it by integration located along the strands constituting the stabilising structures. Any abnormal tension may lead to stress asymmetry on either side of the pelvis, or irritation of the particular tissues [20]. Autonomic control resulting from dual sympathetic and parasympathetic innervation in the genitals is very advanced and complex. Feedback processes take place and are reflected in pain impulses from internal organs, and in centripetal connections carrying tension information, and are connected with local feedback loops [21].

RELATIONSHIPS BETWEEN DYSFUNCTIONS OF THE REPRODUCTIVE ORGANS AND PAIN IN THE SPINE

In the abdominal-pelvic cavity there are somatic structures of the pelvic floor and the abdominal cavity, whose synergistic movement between the individual organs supports the maintenance of the body's midline in a proper relation to its anatomy. The fascial planes along with the organs surrounding and connecting the abdominal-pelvic cavity are the starting point for assessment of the slide and its dynamic, position in relation to other organs, and the decision to undertake visceral therapy [22]. The thoracolumbar fascia has a great influence on intra-abdominal pressure and contributes to the proper functioning of the lumbar and pelvic areas [23]. Other important elements of the fascial system in the context of the reproductive system are the diaphragm, the iliopsoas muscle, the iliac fascia, the superficial abdominal fascia, the transversalis fascia, the pelvic fascia, the urogenital fascia, and the presacral fascia [12].

Gynaecological diseases can cause pain in the pelvic area and in the lower spine. If the examination excludes musculoskeletal causes, dysfunctions in the reproductive system should be considered, and a more detailed medical history regarding the genital organs should be taken. Back pain can be caused by pregnancy, ovarian cysts, uterine retroversion, endometriosis, uterine fibroids, or inflammation of the upper genital tract [24, 25]. An increased tension in the abdominal cavity caused for example by hypertonia of the pelvic urogenital diaphragm can also shorten the iliopsoas muscle and, consequently, cause dysfunction of the lower spine. Each disease process in this area manifests itself in increased protective tissue tension [26]. Similar causes can be seen in pelvic pain: misalignment of the uterus, (ectopic) pregnancy, uterine fibroids and ovarian cysts, the use of an intrauterine device, endometriosis, pelvic prolapse, vulvodynia, premenstrual syndrome, adhesions, polyps, or varicose veins. In the case of pain in the sacrum and sacroiliac joint, the causes may be neoplasms of the reproductive system, prolapse of the uterus, pelvic inflammatory disease, uterine retroversion, pregnancy, ovarian cysts, the use of an intrauterine device, or endometriosis [27]. Pain in the lower spine, pelvis, sacrum and sacroiliac joint may also be caused by sexual abuse or incestuous intercourse [24]. Santos et al. showed that visceral manipulations combined with a physiotherapeutic programme improve mobility in the lumbar spine [28]. Visceral therapy can successfully be used for non-specific pain in the cervical spine. In the case of the liver and spleen, these techniques significantly reduced pain in the cervical spine and improved EMG [29]. A considerable improvement in functional status was observed following the use of visceral treatment for non-specific low back pain [30, 31].

VISCERAL THERAPY — PRINCIPLES AND OBJECTIVES

The objective of visceral therapy for selected dysfunctions is to support movement, articulation and tissue rhythm. Movement is a physiological phenomenon and a fundamental aspect of life. This also applies to micromovements. There is no body activity that is not expressed in the rhythm of pulsations, peristalsis and vibrations. The membranes and the fluids they contain vibrate and transmit mobility to the surrounding structures, which is explained by the tensegration phenomenon [32]. The anatomical structures in the human body (*e.g.*, muscles and internal organs) are not isolated tissue forms. Each of them is surrounded by bands of connective tissue and a system of blood and lymphatic vessels. Treatment of dysfunctions in these structures needs to include the structure of the entire cavity [14, 15]. In the case of dysfunctions in the reproductive system, this involves an assessment of the abdominal and pelvic cavity. For the cavity to be

able to maintain its physiological movement, the organs must move in relation to each other, and in relation to the surrounding sheaths. There are three pathomechanisms that disturb the sliding motion between organs and the surrounding myofascial structures that can lead to pain and other dysfunctions. These are referred pain, changes in the local tissue dynamics, and central sensitisation [22]. Dysfunction within an organ irritates C-fibre nerve endings, causing diffuse pain accompanied by an increased tension of the skeletal muscles within this organ that can radiate to areas on the surface of the skin innervated by a particular segment of the spinal cord supplying the organ in question [33]. Pain can occur in any structure connected to the nerve running from that particular spinal segment. This is due to the existence of ganglia transmitting and receiving information to and from the spinal cord through the plexuses [24]. Somatic dysfunctions can lead to disproportionate pressure gradients in the pelvic cylinder, which may result in stasis, inflammation processes, retentions, visceral disorders and vasomotor restrictions. Visceral pathologies can manifest themselves in abnormalities related to mobility, motility and the position of organs [20]. Mobility refers to the movement of organs in relation to each other, the diaphragm, the musculoskeletal system, and the cylinder. Organs can cause movement of the intestinal passage, fallopian tubes and ureters, the rhythmic pumping of the heart, as well as lung expansion and deflation. Movement is the determinant of health and life. Motility is the movement of an organ within its area caused by the breathing rhythm, which is why it can change morphologically and shape in a natural way [14, 15]. It is a sign of an organ vitality. Motility of the uterus, ovaries and fallopian tubes shows an upward and dorsal tendency, *i.e.*, upward and backward during the phase of inhalation [17]. The diaphragm, which does not show a propensity for tension, allows the organs to correlate with the movement of inhalation and exhalation, and conditions their physiological sliding motion between each other, the fascias and the cavities [26]. The pelvic urogenital diaphragm should also show similar movement characteristics. If intra-abdominal pressure is disturbed, the viscera will also yield to compression, and their mobility and motility will be disturbed [26]. According to Andrew Taylor Still, the founder of osteopathy, multiple dysfunctions of the reproductive organs are due to the retention of body fluids. Venous vessels that do not drain the arterial blood cause pelvic congestion that results in inflammation, considered by physiotherapists and osteopaths as a functional disorder. For this reason, the objective of treatment is to improve venous drainage within the pelvis [20]. In terms of physiology, the myometrium exhibits contractions that increase during the menstrual cycle and then subsequently decrease. This is a cyclical phenomenon. During the diastole phase, blood rich in oxygen and nutrients enters the tissues and the relaxation phase takes place. If this process is disturbed, the amount of oxygen decreases, and pain occurs. Improper drainage within the small pelvis can lead to extensive tension of the uterus [18]. General procedures for dysfunctions of the reproductive system involve restoration of the postural balance, breathing, pelvic activity, and balancing the pressures between particular diaphragms in the body. It is also essential to pay attention to tension in the muscles within the pelvis and the thoracolumbar fascia, centralisation of the hip joint and the area of the sacral bone, and pubic symphysis [23]. An assessment of the spine (particularly at the Th12-L1 and L5-S1 segments) and the sacrococcygeal joint is also important. Restrictions resulting from sympathetic innervation at the thoraco-lumbar junction of the spine can lead to vasodilation within the small pelvis. Blood pressure decreases, and the supply with oxygen and nutrients deteriorates significantly [26]. We cannot rule out external reasons for dysfunctions of the uterus and the reproductive organs, such as surgical treatments that cause intraperitoneal adhesions within scars, which can also result from the inflammation process [26]. Visceral therapy should begin with a postural analysis, as mobility disorders in the lumbar spine, hip joints and pubic symphysis have a key influence on the dissonance of myofascial tensions. A correct posture is characterised by a symmetry of weight distribution and a vertical line of projection of the centre of gravity passing through the acoustic meatus, the acromion, the L3 vertebral body, the greater trochanter and the lateral malleolus. In the anterior projection, the internal organs tend to descend through the inspiratory position of the diaphragm. It is also characterised by extensive tension within the trunk, which results in an inappropriate pressure gradient. The pelvis is tilted forward. The posterior projection features the expiratory position of the Figure 1, a backward tilted pelvis, as well as tension at the level of the sacroiliac joints and the cervicothoracic junction [26].

SELECTED VISCERAL THERAPY

When striving to balance pressures in the abdominal cavity, it is worth beginning by examining the diaphragm, the superior thoracic aperture, and the pelvic floor. A basic examination is by palpation of the uterus and the ovaries and is very important not just as an element of diagnosis, but also in therapy.

Palpation of the uterus

We palpate the uterus to assess any adhesions, pathological location (Fig. 2), shape, mobility and location. We can evaluate the physiological condition of this organ when we do not encounter strong resistance or pain in the lower

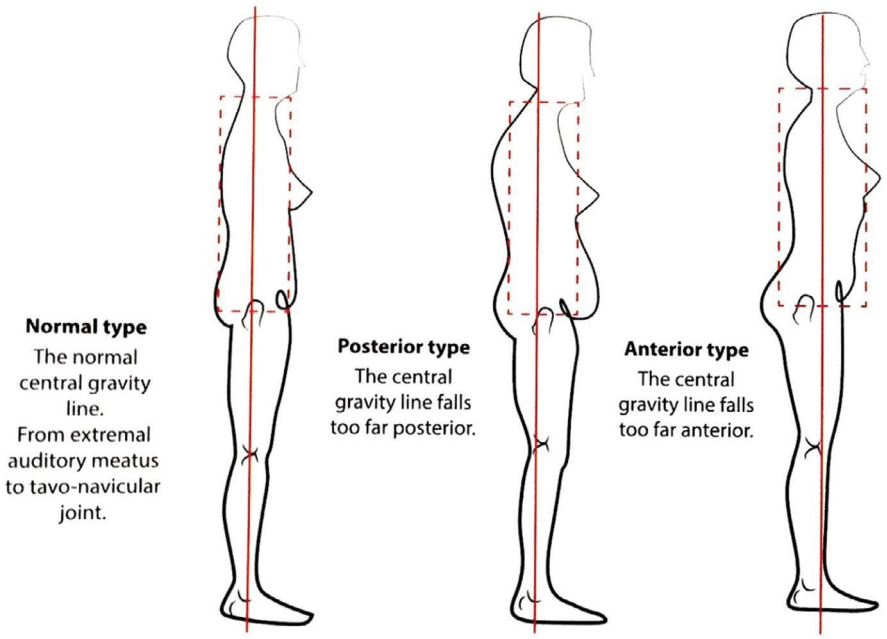

Figure 1. Projection types [18]

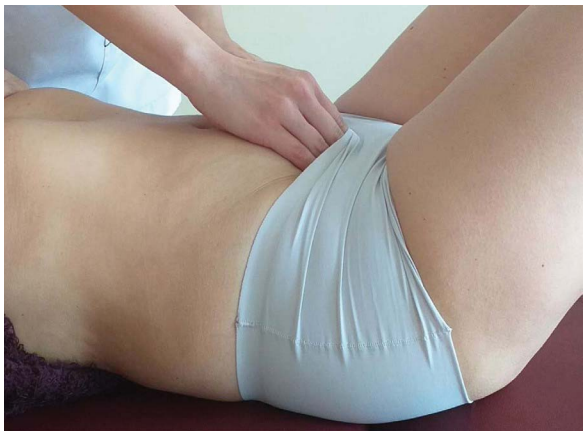

Figure 2. Palpation of the uterus (source: own elaboration)

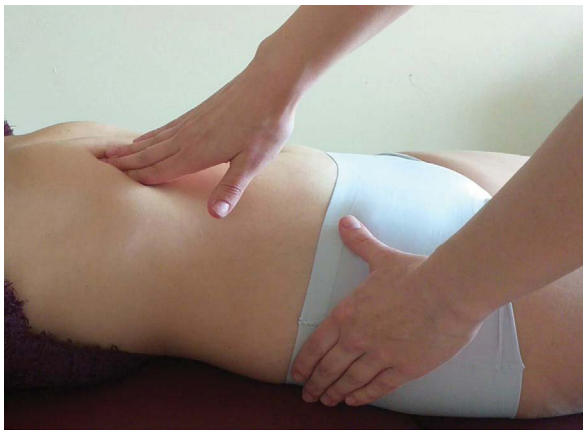

Figure 3. Unilateral therapy with the diaphragm (source: own elaboration)

abdomen area. The uterus should show features of flexible shaping. A strong reaction to pressure may be a sign of adhesions. The complete absence of resistance may result from a retroversion of the uterus. The patient should be placed in a supine position with lower limbs bent, the therapist places their hands over the pubic symphysis on the side of the rectus abdominis muscle and palpates in the dorsal direction with a medial tendency. During localisation, one should focus on a sense of the organ's mobility by performing mobilisation movements [14, 15, 17].

Therapy with the respiratory diaphragm

Normalisation of the diaphragm can be carried out in several ways: by releasing the diaphragm ligaments, as well as working with the central tendon and the diaphragm cruses. Normalisation can be achieved by a unilateral or reciprocal action. With unilateral therapy, the patient lies on her side or back, the therapist places a hand under the costal arch and depresses as far as the tissue restrictions allow, then waits for their release (Fig. 3). With bilateral action, the therapist works with the respiratory rhythm in a cycle of several breaths (Fig. 4). While inhaling, the therapist holds the costal arches of the supine the patient with both hands, and while exhaling, prevents them from returning to their original position. The central tendon is mobilised in the backward position, the hand is placed above the navel and when exhaling, depressing deeper into the tissues and rotating them like clock hands (Fig. 5). The work with the

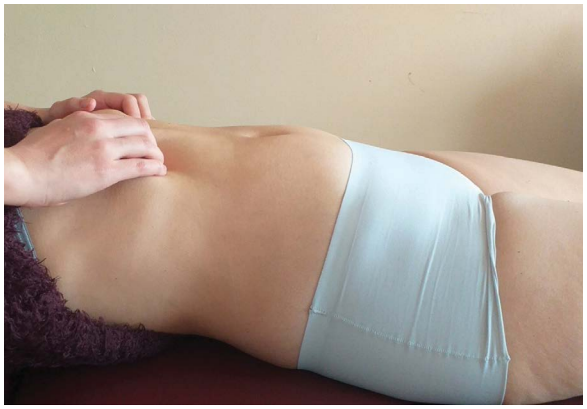

Figure 4. Bilateral therapy with the diaphragm (source: own elaboration)

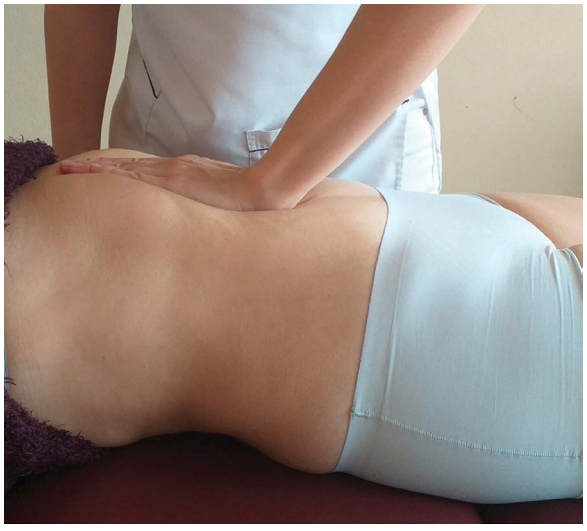

Figure 5. Therapy with the central tendon (source: own elaboration)

diaphragm cruses is performed when the patient is lying face down. The therapist places one hand at the height of L1, and the other near the popliteal fossa of the extended leg (Fig. 6). The patient should be asked to breathe in and relax the entire body as much as possible during exhalation. The therapist's hands should move away from each other, more and more with each respiratory rhythm [26].

The visceral therapy in somatic dysfunctions

Supporting the mobility and motility of the uterus also helps recover the mobility of the fallopian tubes and ovaries. The presented techniques are important in the case of genital dysfunctions, as the restoration of vascular circulation, elimination of adhesions (fascial bonds within the organs), and coordination of organ movement with the respiratory rhythm are helpful for the organ to work. In the event of loss of uterine mobility, a general technique that relaxes the uterus is useful (Fig. 7). It supports the drainage of blood vessels supplying this organ. The patient is lying on her back and the therapist is standing at the level of the patient's knee joints. The therapist places one hand on the sacrum of the woman and the other on her stomach, so that the wrist is above the pubic bone and the fingers are placed caudally. The tissues should be stretched up to the limit of resistance by moving both hands in opposite directions – with the hand upside down and forward, and the hand down at the bottom, up and backward. Another way to counteract adhesions in the genital area is a two-handed mobilisation of the uterus (Fig. 8). The patient is lying on her back with her legs extended. It is a deep technique which involves inserting a finger into the patient's vagina until the cervix is palpated, with the other hand feeling the bottom

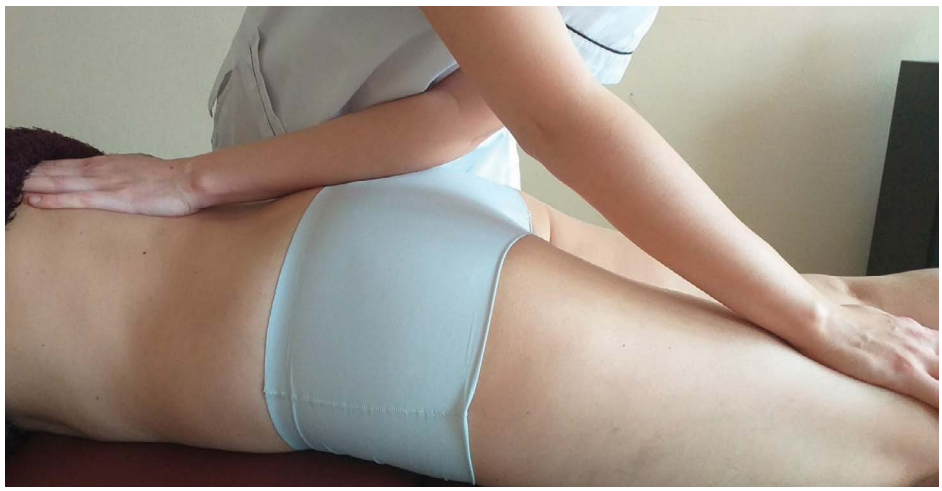

Figure 6. Therapy with the diaphragm cruses (source: own elaboration)

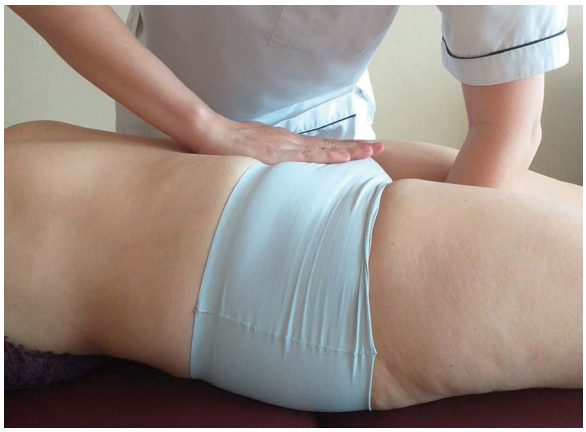

Figure 7. General therapy for releasing the uterus (source: own elaboration)

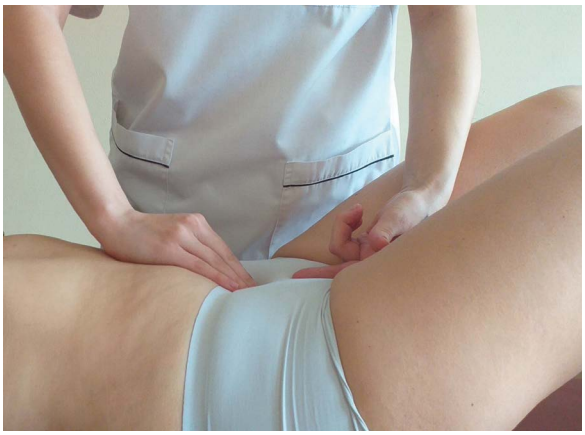

Figure 8. Two-handed uterine mobilisation therapy (source: own elaboration)

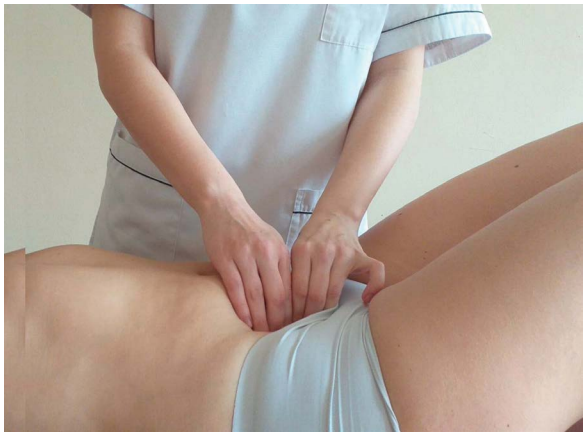

Figure 9. Mobilisation therapy of the broad ligament of the uterus (source: own elaboration)

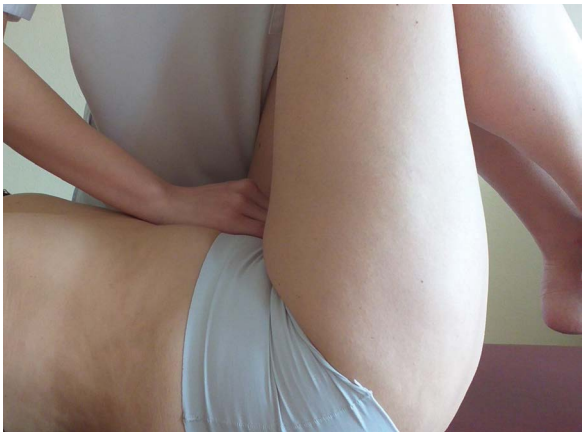

Figure 10. Another variant of the broad ligament mobilisation therapy of the uterus (source: own elaboration)

of the uterus through the skin on the abdomen and holding the hands close until the fingers are felt through the abdominal wall. With the finger placed inside the body, any adhesions are mobilised, and the hand placed outside moves the tissues in different directions. The treatment is continued until the effect of elastic resistance between the epithelia is obtained. Another option is indicated in the case of painful intercourse, premenstrual syndrome and painful periods. The procedure is based on regaining lost mobility in the area of the broad ligament of the uterus and consists of the patient lying down on her back placing her bent lower limbs on a couch and placing the therapist's hands close together on the patient's abdomen above the pubic symphysis (Fig. 9 and 10). Delving into the tissues and displacement of the small intestine loop laterally allows a good contact with the uterus. It should be mobilised in this grip in order to obtain the best tissue relaxation possible. Another possibility is to hold the pelvic floor in a similar grasp with one hand and obtain relaxation by supporting and mobilising the lower limbs with the other hand [14, 16].

CONCLUSIONS

Visceral therapy can be an effective complementary method in the treatment of gynaecological dysfunctions.

Visceral therapy can improve reproductive health in women.

Maintaining the mobility and motility of internal organs by means of visceral therapy can regulate anatomical relations and physiological processes within the urogenital diaphragm.

Conflict of interest

None.

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VIA MEDICA

CLINICAL VIGNETTE

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Non-obvious diagnosis and breast development in pure gonadal dysgenesis

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ABSTRACT

Pure gonadal dysgenesis is a situation when the karyotype is 46, XY, but for various reasons there is a disorder of differentiation of Wolffian and Mullerian structures and in consequence the phenotype is female. It is known that abdominal gonads and the presence of Y chromosome allow to qualify this condition as a high risk of tumor. In most cases breast development is limited because of lack or low level of estrogen. A 27-year-old patient with differences of sexual development (DSD), was admitted to the Department of Endocrinological Gynecology for a control examination. In the history: dysgerminoma, primary amenorrhea and ambiguous karyotype. The patient has not taken hormonal replacement therapy. The breast development is Tanner stage V.

Key words: pure gonadal dysgenesis; breast development; differences of sexual development

Ginekologia Polska 2022; 93, 6: 519–520

We present a 27-year-old patient with differences of sexual development (DSD), who was admitted to the Department of Endocrinological Gynecology for a control examination. The medical documentation showed that at the age of 13 the patient went through a laparotomy due to an accidentally detected tumor with dimensions 16.5 x 12 x 11 cm that filled the entire pelvis minor. The tumor was completely removed including the left ovary. Histopathology revealed dysgerminoma. 1.5 year later the patient reported to the Department of Pediatric Endocrinology due to primary amenorrhea. On physical examination the patient was of tall stature, female phenotype, female external genitalia and Tanner stage III pubertal development. Patient was reared as female. Hormonal tests showed hypergonadotropic hypogonadism and normal level of testosterone. Ultrasound examination demonstrated prepubertal uterus. The cytogenetic examination was administered with result 46, X, +mar. Because of clinical picture, dysgerminoma in the past and ambiguous karyotype it was decided to verify cytogenetic results in another genetic laboratory. Finally, the karyotype: ish Yp11.3 (SRY+),Xp11.1q11.1(DXZ1+) was confirmed by fluorescence in situ hybridization (FISH) using peripheral blood samples. The Magnetic resonance imaging (MRI) demonstrated structure corresponding to dysgenetic gonad on the right, without follicles typical to ovaries. In line with indications, the structure was removed by surgery. Despite the recommendations, the patient has not taken hormonal replacement therapy. The patient's breast development is Tanner stage V. Uterus ultrasound picture is shown in Figure 1. The patient's hormone levels are shown in Table 1. Patient complains of hot flushes and mood swings. The psychological condition is good.

According to the Consensus Statement from 2006 the definition of DSDs is "congenital conditions within which the development of chromosomal, gonadal, and anatomic sex is atypical" [1]. The situation when the karyotype is 46, XY, but for different reasons there is a disorder of differentiation of Wolffian and Mullerian structures and in consequence phenotype is female, is called pure gonadal dysgenesis. Frequency of this condition is approximately 5 of 100,000 newborns [2].

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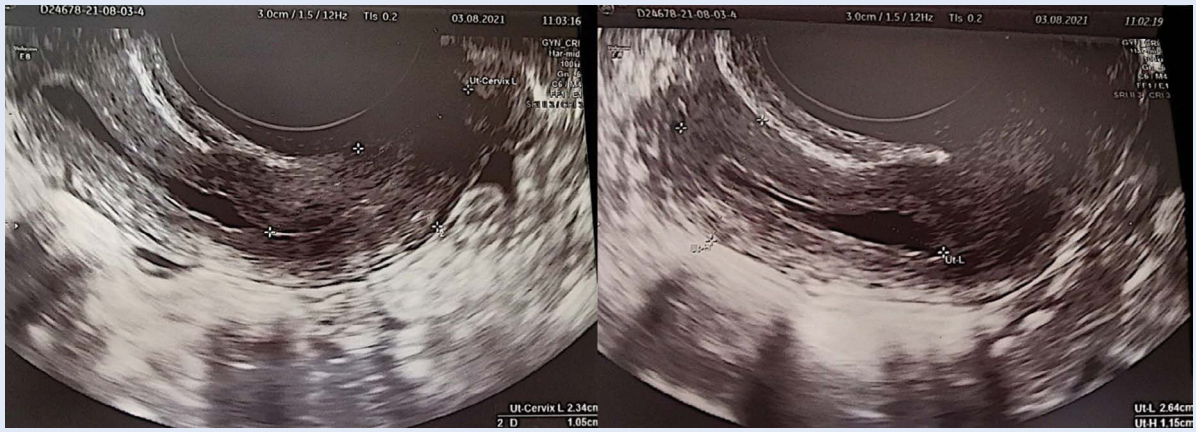

Figure 1. Current uterus ultrasound picture

Table 1. Patient's hormone results during adolescence and adulthood

	01.2010	08.2021
FSH (IU/L)	119	58.6
LH (IU/L)	29.3	10.6
Estradiol (pg/mL)	21.30	< 5.0

FSH — follicle-stimulating hormone; LH — luteinizing hormone

Estimating the risk of cancer is difficult because this DSD is rare and according to the recommendations in these cases gonadectomy should be performed as soon as possible after diagnosis, but it is known that abdominal gonads and presence of Y chromosome allow to qualify this condition as high risk of tumor [3]. In this case the situation is atypical because the first symptom of the disease was dysgerminoma which is additionally less common than gonadoblastoma [3]. Moreover, histopathology results did not raise suspicions of DSD. In most cases breast development is limited because of a lack or low level of estrogen [4]. The main aim of hormonal replacement therapy is to support development of secondary sex characteristics, including breast development, prevent osteoporosis and cardiovascular diseases [2]. It is interesting that our patient resigned from this therapy and despite that the breast development was proper. It's worth mentioning that nowadays DSDs are still being learned and the diagnosis is easier than a few years ago when the treatment of the patient started. In this case despite typical malignancy and clinical picture, diagnosis was delayed, and genetic tests results were ambiguous. The important finding is that the patient affected by the pure gonadal dysgenesis can develop proper secondary sex characteristics, even without pharmacological support. It shows how unknown DSDs still are.

Conflict of interest

All authors declare no conflict of interest.

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Fatigue fracture of the sacrum related to pregnancy

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ABSTRACT

Pregnancy is the period when, due to hormonal and structural changes connected with fetal growth, temporary musculoskeletal dysfunctions occur. Pregnancy-related fatigue fractures may be a rare cause of persistent or increasing pain in the sacrum region.

Key words: lumbopelvic pain; fatigue fracture; sacrum; pregnancy

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CASE REPORT

Lumbar and pelvic pain is often reported by pregnant and postpartum women. Persistent, severe pain may be a result of pregnancy-related fatigue fracture of the sacral bone. These types of fractures occur more frequently after childbirth than during pregnancy, and they are usually unilaterally. Their cause may be pregnancy-induced osteoporosis, heparin-intake that secondary induces osteopenia, significant weight gain or increased lumbar lordosis. However, more frequently, it is a fracture induced by forceps delivery, and a rapid vaginal delivery, especially of a child with a high birth weight. It inconveniences diagnostic difficulties due to the similarity of the symptoms, which concern typical spinal pain as well as due to frequent lack of radiological symptoms. Diagnosis is difficult due to similarity of symptoms with spinal pain syndromes and frequent false negative results of classical X-ray images, especially in early fracture stage [1–5].

A 30-year-old patient after the first vaginal delivery came to a gynecological consultation two weeks after delivery because of exacerbation of pain located in the posterior part of the pelvis. In the gynecological examination, no abnormalities were found. Before pregnancy she had sporadic pain in the cervical and thoracic spine. No chronic diseases, metabolic diseases, eating disorders, or previous injuries of the spine and pelvis were found. The birth weight of the child was 3800 g. The patient began breastfeeding after delivery. Pain ailments appeared from the 24th week of pregnancy during prolonged sitting position and lasted until the delivery. The highest pain intensity appeared after delivery. The pain appeared in the area of the left sacroiliac joint and radiated to the gluteal region. The imaging study revealed no changes in the lumbar spine and the presence of a fatigue fracture in the lateral mass of the sacral bone and near the lower part of the sacroiliac joint on the left (Fig. 1). A package of studies evaluating calcium-phosphate metabolism was recommended. Only decreased concentration of 25-hydroxywitamin D was found. The patient was recommended to take Osteogenone, vitamin D supplementation, use varied diet, self-sparing lifestyle and have minimum 3 months break from work, do unweighing exercises in water environment. The physiotherapist recommended partial unweighting of the lower left limb during walking, using of the sacroiliac belt, applying electrotherapy and magneto therapy procedures.

In the period of up to three months after delivery, the pain was gradually getting decreased. However, it got intensified with prolonged physical activity, or a prolonged sitting position. Six months after delivery, the pain subsided or occurs sporadically at low intensity.

CONCLUSIONS

As to the pain located in the sacral bone area and in the gluteal area, which significantly limits daily functioning, persisting or increasing over time, the presence of a fatigue fracture of the sacrum should be considered. Treatment of

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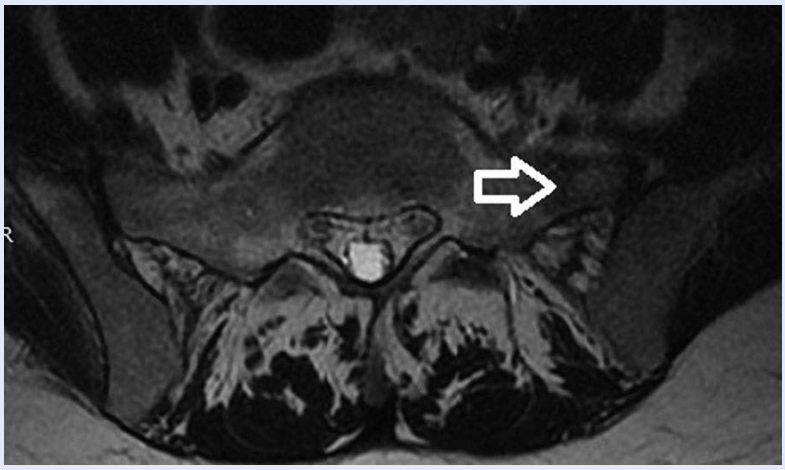

Figure 1. Pelvic MRIs showing bone marrow edema and the fracture line in the left sacral ala

fracture includes non-invasive methods including analgesic therapy with the use of pharmacotherapy, vitamin D supplementation, lower limb unweighting and physiotherapy [1, 2].

Conflict of interest

All authors declare no conflict of interest.

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