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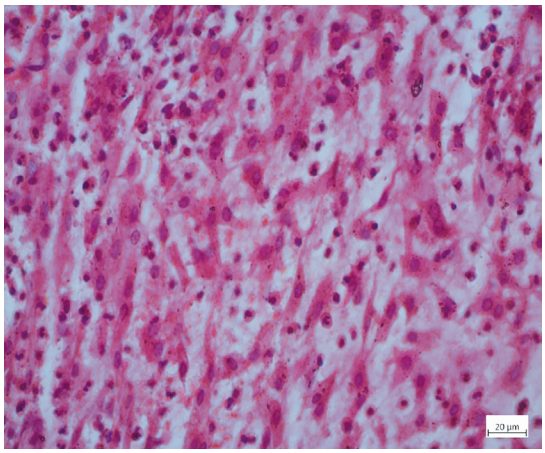

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EDITORIAL

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Diagnostic imaging of ovarian masses and not only — beyond ultrasound

Monika Bekiesinska-Figatowska

Department of Diagnostic Imaging, Institute of Mother and Child, Warsaw, Poland

Dear Sir,

following the editorial in one of the issues of *Ginekologia Polska* in which it was stated that "the primary goal of ovarian tumor diagnosis is to determine the nature of the lesion (benign, malignant) and to assess the possibility of sparing surgical treatment and to verify the need for surgery in the case of a non-malignant lesion" [1], I read detailed guidelines for the diagnostic and therapeutic algorithm for ovarian tumors in children that were published earlier last year [2]. Although I was pleased to find that radiologists representing Pediatric Section of the Polish Medical Society of Radiology (PLTR) were involved in their preparation, the issue of ovarian lesions imaging was only included in the Supplementary/ /additional files, and magnetic resonance imaging (MRI) was not included in the "Algorithms without acute symptoms", while in the "Observation choice criteria" it was recorded on a par with computed tomography (CT) under "preparation for elective surgery" as: "in case of diagnostic uncertainty, consider CT and MRI".

I fully agree that MRI (and not CT!) should be used in cases that are diagnostically unclear — this is the position of the European Society of Urogenital Radiology (ESUR), among others, and applies to any age group: [ultrasound (US)] "US is the first diagnostic tool to detect an ovarian mass. If the mass is indeterminate at US, an MRI should be performed… For women with indeterminate adnexal masses MR imaging is the method of choice. In these women MR imaging can reduce the number of unnecessary surgeries for benign lesions and the risk of missing malignant lesions… CT may be used in emergency situations, i.e., acute pelvic pain… Contrast enhanced CT, MRI and PET/CT are used for staging and follow-up" [3], the latter concerns ovarian cancer in adult women mainly.

Ultrasound strongly depends on the operator's skills, knowledge and experience. The use of the recently developed Ovarian-Adnexal Reporting and Data System (O-RADS; originally applied to US [4], later also to MRI [5]) by an experienced operator certainly increases the chances of correctly diagnosing the nature of an ovarian lesion (once it has been established that it is an adnexal lesion at all). If this does not happen, then no CT, at any age of the patient, is a problem-solving tool, as it 1) has too limited tissue resolution, 2) burdens the patient — particularly important in the pediatric population — with a dose of ionizing radiation and iodine contrast agent, 3) is incompatible with the ALARA principle (As Low As Reasonably Achievable) and with 4) the "Image gently" campaign [6]. The same, by the way, applies to any local evaluation of the reproductive organs in any age group. On CT one cannot assess the extent of endometrial or cervical cancer infiltration and this exam should neither be ordered nor performed for such indications.

Magnetic resonance imaging is a problem-solving tool as it has already been stated above and in the author's own experience as well as in that of the team of radiologists at the Department of Diagnostic Imaging of the Institute of Mother and Child in Warsaw [7]. Let me illustrate it with a clinical case of a 34-year-old woman who was referred to CT with a clinical question whether her adnexal cysts are endometrial or not. After CT the answer was that they might be endometrial or not (Fig. 1). And another example: a 12-year-old girl with intellectual disability and constipation, a patient of the Neurology Clinic, was diagnosed with a giant adnexal cyst on US and offered surgery, but the neurologists referred the child beforehand to MRI, which showed a giant rectum and sigmoid colon bloated with fecal masses and misinterpreted as "adnexal cyst" (Fig. 2), thus saving the child from unnecessary surgery.

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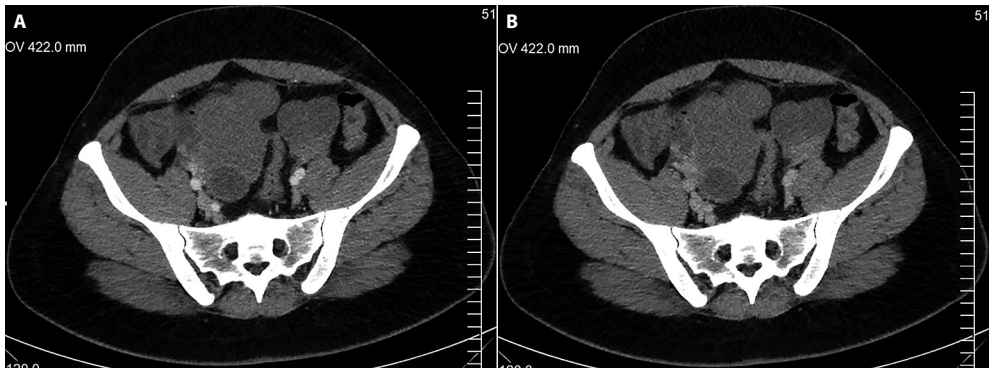

Figure 1. Computed tomography (CT) in the arterial (**A**) and venous (**B**) phase. Bilateral multilocular dense cystic adnexal lesions that may represent endometriosis. The clinical problem is not solved after CT

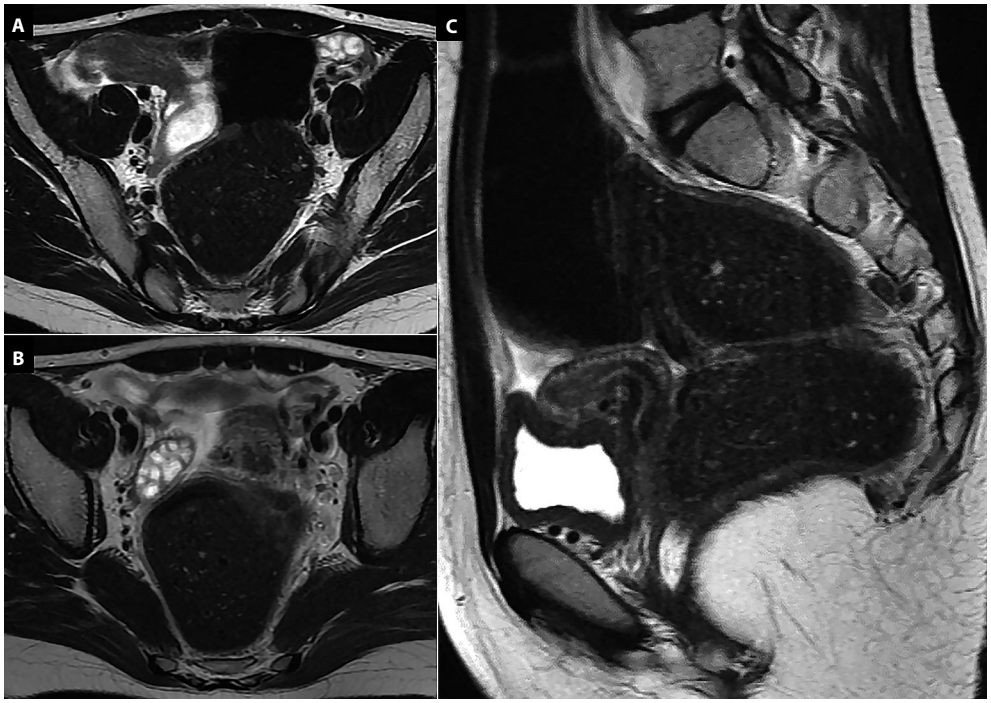

Figure 2. Magnetic resonance imaging (MRI) in T2-weighted images; **A.** Axial plane, sigmoid colon distended by feces and gas, normal left ovary; **B.** Axial plane, sigmoid colon distended by feces, normal right ovary; **C.** Sagittal plane, giant sigmoid colon distended by feces and gas, normal uterus

It has been postulated for years to incorporate MRI in diagnostic algorithms in gynecology and obstetrics before laparoscopy, not only in girls but in all age groups, not only in case of adnexal masses but in other clinical situations, *e.g.*, endometriosis, not only by radiologists but also by gynecologists-obstetricians [*e.g.*, 8].

I hope to achieve this goal together.

Article information and declarations

Author contributions

The only author.

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Conflict of interest

The author have no conflict of interest.

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Recurrent cervical adenofibroma progressing to adenosarcoma: a rare case report

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ABSTRACT

Objectives: Cervical adenofibroma is a rare form of mixed mesodermal tumor that can present as cervical polyps with a tendency for local recurrence and progression. Few cases progressing to adenosarcoma have previously been reported. We report a case of cervical adenofibroma progressing to adenosarcoma, and we seek to remind clinicians of the method and importance of the differential diagnosis of this disease.

Material and methods: A fertile woman was admitted in our department for the eighth recurrence of a cervical polypoidal mass which for the past 10 years. Recurrence of cervical adenofibroma was confirmed by ultrasound and MRI. A wide local excision under hysteroscopy was performed due to her strong desire to preserve the uterus.

Results: Surgical pathology and immunohistochemical interpretation revealed cervical adenosarcoma. A hysterectomy with conservation of the ovaries was recommended, with regular follow-ups for evidence of disease recurrence.

Conclusions: Differential diagnoses of cervical adenofibroma are hard to prove. Adenosarcoma should be ruled out, especially in women presenting with recurrent cervical polypoidal masses. A combined histological/immunohistochemical investigation is mandatory.

Keywords: cervical adenofibroma; adenosarcoma; recurrence; histological/immunohistochemical investigation

Ginekologia Polska 2024; 95, 1: 4–7

INTRODUCTION

Uterine cervical adenofibroma was first reported by Abell in 1971 as a form of mixed mesodermal tumour which is composed of benign stromal and epithelial components [1]. Benign cervical adenofibroma is rare and has a strong proclivity for local recurrence and potential for developing to adenosarcoma, which is characterized by benign epithelial glands and malignant stromal elements [2, 3]. Adenosarcoma is a low-grade malignancy which is often described as a midway point between benign adenofibroma and malignant carcinosarcoma [4]. Cervical adenosarcoma is extremely unusual and presents as cervical polyps which can be confused with benign cervical polyps both clinically and pathologically [5]. In this report, we describe the case of a young woman with recurrent cervical adenofibroma presenting as cervical polyps and progressing to adenosarcoma.

MATERIAL AND METHODS

A 40-year-old woman was referred to Women and Children's Hospital of Chongqing Medical University in July 2021 with a history of a recurrent cervical polypoid mass over the last 10 years. She had her first cervical polypoid mass, which presented with no symptoms, excised in July 2011. A cervical polyp was confirmed by postoperative pathological examination. Over the next 4 years, she had recurrent cervical polypoid masses roughly every year and underwent local hysteroscopic removal of the mass. Routine histological examination of the polypoidal tissue showed cervical polyps, but no immunohistochemical tests were performed. Although fertile, she underwent an embryo transfer in September 2016 and successfully conceived twins. She delivered two healthy boys by cesarean section at 34 weeks of gestation in May 2017. During her pregnancy and lactation, the cervical polypoid mass did not recurrence

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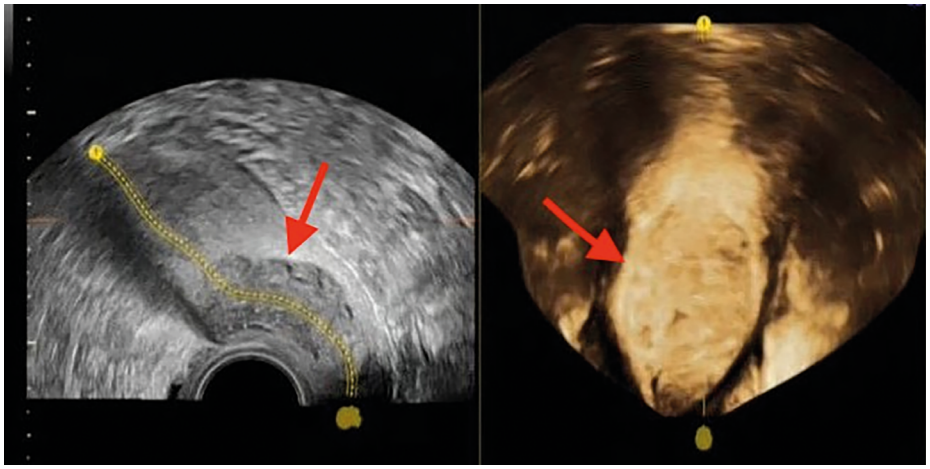

Figure 1. The polypoidal mass of the cervical canal under 3D Ultrasound (measuring 3.73 × 1.71 cm, arrow)

and there was no history of discomfort during this period. In July 2020, however, the cervical polypoid mass recurred again and was treated by hysteroscopic surgery. Postoperative pathological examination and immunohistochemistry indicated cervical adenofibroma. She had recurrence again in 2021, but she refused the hysterectomy due to a strong desire to retain her uterus, and she underwent hysteroscopic surgery again for recurrence of the disease. During this last hospital visit, her ultrasound examination showed a normal sized uterine body but a 3.73 × 1.71 cm polypoidal mass in the region of the cervical canal (Fig. 1). On examination, she was found to have a normal appearing cervix and her cervical cytology and human papilloma virus (HPV) tests were both negative. Magnetic resonance imaging (MRI) showed a heterogeneously enhancing lesion of 2.8 × 3.9 × 2.6 cm in the region of the cervix canal, and the uterine body and ovaries appeared normal (Fig. 2). There was no lymphadenopathy. Sex hormones and tumor markers were all within the normal range. Histology of the polyp confirmed adenofibroma. Hysterectomy was recommended as the primary treatment option considering the number of recurrences, however she again refused. To excise the lesion completely, we performed hysteroscopy under laparoscopic supervision. The polypoidal mass was seen to be arising from the cervix canal and decomposed clearly into the muscular layer, but the endometrial cavity was normal (Fig. 3).

RESULTS

The lesion was completely resected by hysteroscopy and was sent for pathological examination. Unfortunately, the histology showed a tumor having benign glandular epithelium with fusiform stromal tumor components. The interstitial ingredients were dense with "sleeve collar hair belt" locally. The mitotic figures were > 4/10 high-power field. Immunohistochemistry showed CK (epithelial +), CD10 (+),

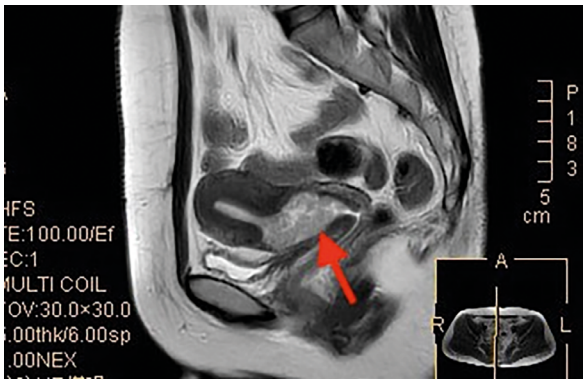

Figure 2. The polypoidal mass under magnetic resonance imaging (MRI) scan (measuring 2.8 × 3.9 × 2.6 cm, arrow)

SMA (–), CD34 (vascular +), Ki67 (about 5-10%), WT-1 (+), ER (about 70% medium intensity +), PR (about 70% strong +), Caldesmon (–), S-100 (–), p53 (–), Des (focal +) (Fig. 4). Given these results, a diagnosis of cervical adenosarcoma was decided. Hysterectomy with conservation of ovaries was again recommended along with regular follow-ups for evidence of recurrent disease.

DISCUSSION

Cervical adenofibroma is rare and usually presents as cervical polyps, and can be confused with benign cervical polyps and malignant adenosarcoma both clinically and pathologically [6, 7]. The possibility of more serious lesions such as adenosarcoma must be considered in patients with recurrent cervical polyps. Histopathological examination combined with immunohistochemistry can be more effective in differential diagnosis.

The patient in this case was only 30 years old when she was first diagnosed with cervical polyps. Her cervical lesions took 10 years to progress from benign polyps to

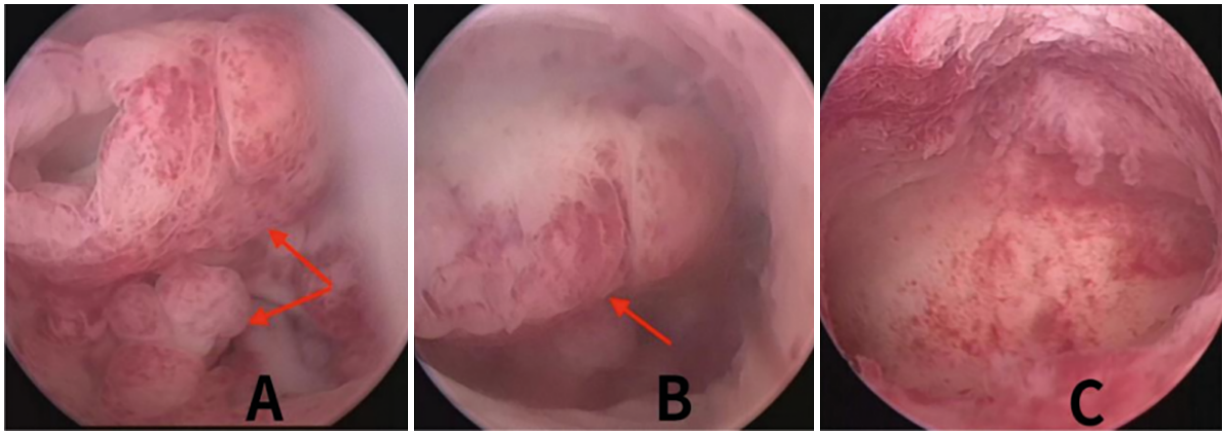

Figure 3. The polypoidal mass under hysteroscopy

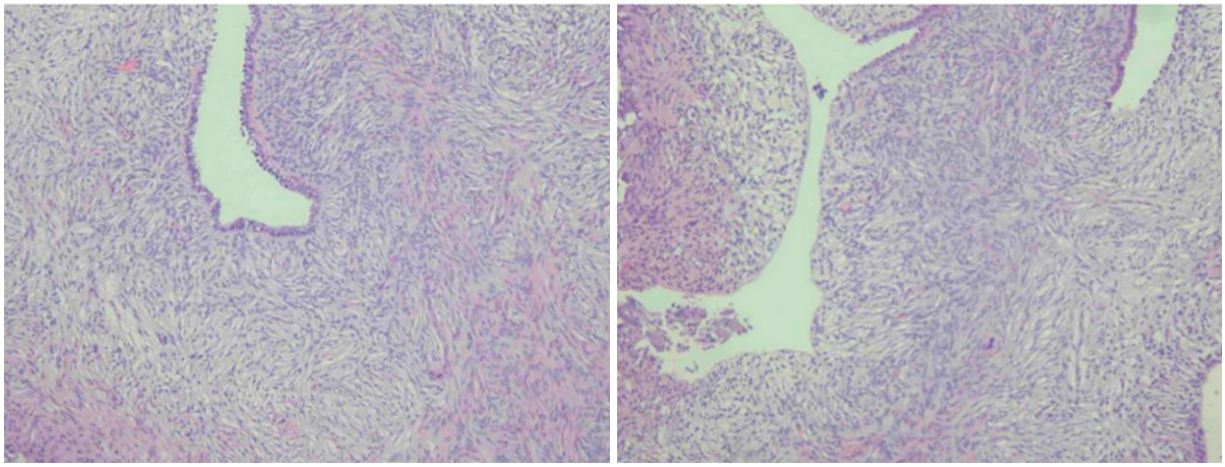

Figure 4. Histologic findings of the polypoidal mass (20× magnification)

adenosarcoma with 8 instances of recurrence, and the average recurrence time was roughly one year. After 10 years, she was diagnosed with adenosarcoma at 40 years old, which is consistent with a previous case report [8]. Benign recurrent endocervical polyps are unusual in women of reproductive age, hence the possibility of adenosarcoma in patients with a history of recurrent polyps must be considered. Some scholars often describe Mullerian adenosarcoma as a midway point between benign adenofibroma and malignant carcinosarcomas [4]. These lesions appear to represent a continuum of these diseases. Our patient's disease progression seems to confirm these views.

It is clinically difficult to distinguish adenofibroma from benign polyps and adenosarcomas, and histopathological examination seems to be a useful method. Polyps generally lack papillary processes, have more glands, and are less cellular than adenofibromas [9]. Adenofibromas contain a mixture of histologically bland epithelium and mesenchyme. They have no peripheral coagulation and no mitotic activity in the stromal compartment. Mitotic figures (MFs) are rare or invariably less than 4 MF/10 high power field (4MF/10HPF) in adenofibroma, which is a criterion to distinguish adenofibroma from adenosarcoma. Due to an insufficient understanding of adenofibroma by our clinicians and pathologists, the patient only received a general pathological examination without immunohistochemical examination during the previous pathology review. Her cervical polypoid mass was treated as benign cervical polyps many times and she continued to experience obvious recurrence. After the fifth conservative operation, the pathological and immunohistochemical examinations confirmed that the cervical polypoid mass was a cervical adenofibroma. Therefore, a careful evaluation of mitotic activity and nuclear atypia under histopathological examination combined with immunohistochemistry should always be performed in reproductive aged women with a history of recurrent endocervical polyps.

Adenofibroma is a benign lesion, but typically recurs. Recurrent tumors are prone to infiltrate the muscle layer and

blood vessels and adequate sampling is needed to exclude adenosarcoma [10, 11]. The main reasons for recurrence could be due to incomplete tumor resection or missed diagnosis of borderline tumors with recurrent adenofibroma [10, 12]. Our patient underwent cervical lesion resection 8 times for local recurrence. The fact is that the signs of cervical adenofibroma are similar to polyps and are often misdiagnosed as common benign cervical polyps for simple polypectomy. The incomplete excision of lesions from previous conservative operations was a potential reason for recurrence in this case. Another possibility is that her recurring adenofibroma itself may have potentially been malignant.

The main treatment method of cervical adenofibroma is surgical treatment including local tumor resection and total hysterectomy. Hysterectomy seems to be the preferred treatment method because the neoplasm may recur if incompletely curetted [10]. Therefore, for postmenopausal women, the standard treatment has been hysterectomy, but for young and fertile patients with limited early lesions, hysteroscopy may be considered for extensive lesion resection. Our patient was 30 at the time that her adenofibroma was diagnosed and she had a strong desire to preserve her uterus to remain fertile, so the option of conservative treatment by hysteroscopy was considered. As predicted, she experienced multiple relapses and repeated operations. At the eighth instance of recurrence, a total hysterectomy was recommended as the first treatment option, which she again refused due to her strong desire to preserve her uterus. Because of this, extensive lesion resection under hysteroscopy was the chosen method of treatment. On the one hand, there is no consensus on the optimal therapy for adenofibroma of the uterine cervix, and in rare cases, local excision has been curative. On the other hand, both MRI and 3D ultrasound indicated that the lesions were confined to the cervical canal and did not invade the muscle layer or have distant metastases. Unfortunately, postoperative pathological examination revealed adenosarcoma. For adenosarcoma, most doctors recommend total hysterectomy, usually accompanied by bilateral salpingo-oopherectomy [9]. In the latest research on adenosarcoma, investigators found that patients undergoing radical surgery have a higher overall survival rate, and early surgical resection can extend the survival time of patients [13]. Therefore, hysterectomy accompanied with salpingo-oopherectomy is generally recommended for older patients with no fertility requirements, but there is insufficient evidence to support or discourage ovarian conservation in young women [14]. Our patient is now 40 years old, has completed childbirth, and has no fertility requirements. We again recommended radical surgery, and her prognosis will be followed up on.

CONCLUSIONS

Cervical adenofibroma is highly recurrent and may have a potential malignant tendency. It is difficult to differentiate between benign polyps and malignant adenosarcoma.

Article information and declarations

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Conflict of interest

All authors declare no conflict of interest.

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Therapeutic effect of the temperature-controlled radio frequency technology in female sexual dysfunction

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ABSTRACT

Objectives: To explore the therapeutic effect of the temperature-controlled radiofrequency technology in female sexual dysfunction (FSD).

Material and methods: From July 2020 to June 2021, patients with FSD who visited the Gynecology Clinic of Peking University Shenzhen Hospital were treated with the temperature-controlled radiofrequency technology once every two weeks, for a total of five times. The therapeutic effect was objectively evaluated with pelvic floor dysfunction (PFD) indicators (FSFI score, pelvic floor muscles surface electromyography, sexual function test). The pre- and post-treatment (2 weeks)/follow-up (3 months) results were compared to evaluate the feasibility of this technology for treating FSD, as well as using PFD-related indicators in objective evaluation of FSD patients.

Results: Fifty patients completed treatment; 31 patients completed follow-up. The mean FSFI score for post-treatment/follow-up was significantly higher than pre-treatment ($p < 0.05$). There were no significant changes in the mean pelvic floor resting surface myoelectric potential and its variability and mean myoelectric potential of sexual function test between pre- and post-treatment/follow-up. The mean surface myoelectric potential of the patients' type I and II muscle fibers of the pelvic floor for post-treatment/follow-up was significantly higher than pre-treatment ($p < 0.05$). The mean peak myoelectric potential for post-treatment was significantly higher than pre-treatment ($p < 0.05$).

Conclusions: Temperature-controlled radiofrequency technology has a certain therapeutic effect on FSD. Pelvic floor surface electromyography and sexual function test can be used as an objective indicator for PFD in FSD patients. Subsequent studies may involve a larger size sample and evaluate the effect over a consecutive time-point, to develop a better therapeutic approach.

Keywords: female sexual dysfunction; radio frequency; female sexual function index questionnaire; pelvic floor dysfunction

Ginekologia Polska 2024; 95, 1: 8–14

INTRODUCTION

With the improvement in the living standards, women's requirements for their own life experience and quality continue to rise, and issues related to female sexual dysfunction (FSD) have received more and more attention. FSD refers to the occurrence of obstacles in the female normal sexual response cycle, such as sexual desire disorder, sexual arousal disorder, orgasm disorder or sexual intercourse pain. The main pathogenic factors and risk factors are relatively complex, and are closely related to the underlying diseases, age factors, physical conditions, as well as psychological and spiritual factors [1].

About 43% of women have experienced sexual dysfunction, of which 12% of them have anxiety and depression [2], which seriously affect their quality of life and emotional state. Therefore, research on the diagnosis and treatment of FSD has gradually increased. It is worth noting that damage and degeneration of the pelvic floor tissue in women can lead to the decrease in pelvic floor support function, resulting in pelvic floor dysfunction (PFD) diseases, such as stress urinary incontinence (SUI), chronic pelvic pain (CPP), overactive bladder (OAB), pelvic organ prolapse (POP), and difficulty defecation, and are often complicated by FSD. Female sexual dysfunction is present in 50% to 83% of women with PFD symptoms [3].

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Based on the traditional and new effective methods for treating PFD, it is desirable to explore effective treatment methods for FSD and make up for the current deficiencies.

Previous study found that radiofrequency is safe for treating PFD [4]. Radiofrequency is a promising treatment option for SUI [5]. Numerous studies showed tissue contraction and determined a therapeutically optimal temperature ranged 40–45°C. This temperature can promote fibroblasts to produce collagen de novo, resulting in clinical tightening. Temperature-controlled radiofrequency have been found to improve SUI in postmenopausal women [6].

In this study, we evaluate the efficacy of the newly developed temperature-controlled radiofrequency technology in the treatment of PFD for patients in our hospital. The Chinese version of the widely used female sexual function index (FSFI) questionnaire was used. The therapeutic effect was objectively evaluated through the changes in the pelvic floor tissue of patients detected by pelvic floor surface electromyography (EMG), and sexual function test.

MATERIAL AND METHODS

Research object

From July 2020 to June 2021, patients who visited the Gynecology Clinic of Peking University Shenzhen Hospital and were diagnosed as FSD by senior physicians after evaluating the medical history, chief complaints and symptoms, and at the same time completed the treatment course of the temperature-controlled radiofrequency technology and related follow-up were recruited. A total of 50 patients completed the two weeks treatment, and 31 patients completed three months follow-up. All patients signed the informed consent, and this study was approved by the Hospital Ethics Committee.

Study criteria

Inclusion criteria: 1. Women with sexual dysfunction; 2. other treatment effects were unsatisfactory or ineffective; 3. if there was treatment for other diseases, the minimum window between previous treatment and this treatment must be more than 12 months.

Exclusion criteria: 1. Congenital malformations of the reproductive tract; 2. history of previous vaginal surgery; 3. acute reproductive tract infections (such as genital herpes, Candida, trichomonas, bacterial infections, etc.); 4. patients with acute or recurrent urinary tract infection; 5. patients with pelvic organ prolapse ≥ stage II; 6. patients with previous pelvic floor reconstruction surgery with mesh; 7. patients with metal birth control rings or metal implants (such as cardiac pacemakers, etc.); 8. suffering from other malignant tumors, serious heart, brain, kidney or other systemic and mental diseases, and other chronic diseases that affect research compliance; 9. having mental and psychological disorders or diseases that affect assessment; 10. oral drugs that affect sexual function, etc.

Treatment process and therapeutic effect evaluation

Pre-treatment preparation

Basic examination: full physical examination, gynecological examination, routine vaginal secretion examination, cervical liquid-based cytology examination, blood examination (hepatitis B, hepatitis C, HIV, syphilis, etc.), three sex hormones (estradiol, follicle stimulating hormone, luteinizing hormone).

Observation index: Using the online questionnaire "Wenjuanxing" (Sojump Professional site survey, Shandong, P.R. China) platform, the general information (age, marital status, occupation, education level, birth history, etc.) and the FSFI questionnaire in Chinese version [7] was made into webpage questionnaires, and the patients were asked to filled in. The questionnaires were filled in before treatment. The Chinese version of FSFI has been developed through translation, back translation, revision by research team and pilot study. It is reliable and valid[8]. This technology has already been used abroad, and this system may be available outside China in the second half of the year.

The MEDLANDER (Nanjing, P.R. China) pelvic floor surface EMG analysis, the Glazer scheme of biofeedback training system, and PHENIX USB 8 (France) neuromuscular stimulation therapy devices were used to perform pelvic floor surface electromyography and sexual function testing, respectively. The measurements were performed by a qualified rehabilitation therapist in the Pelvic Floor Diagnosis and Treatment Center of Peking University Shenzhen Hospital.

Treatment method

FemeTite (Shenzhen Peninsula Medical Co., Ltd., Guangdong, PR. China) vaginal rejuvenation system was used for treatment.

The treatment scheme module for the inner vagina

Specific operation: unipolar treatment for 15 min: the three indication points A, B, and C of the applicator was aligned at 12 o'clock direction in turn, and each area was treated for about 5 min. When changing the area for treatment, the applicator was turned clockwise. Bipolar treatment for 10 min: It was divided into two areas for treatment. First, point A was aligned at 12 o'clock direction for treatment, then rotate 90° for treatment, and each area was treated for 5 min. When changing areas for treatment, the applicator was turned clockwise.

Parameters: power 35–40 W, temperature 40–45°C, 25 min each time.

Treatment plan module for vulva

Specific operation: The applicator was installed, the vulva module was selected, and the medical sterile gel was applied evenly on one side of the labia, clitoris, and perineum. The applicator was placed flat on the vulva, the pedal was stepped on, and the treatment started. The labia majora was operated in an inward circle for 5 min; the labia minora and clitoris were operated by sliding upwards and downwards for 2 min, and the perineal body was operated by sliding horizontally for 3 min. During the operation, the applicator should be kept close to the skin, and the power and temperature at the labia minora and clitoris should be appropriately reduced.

Parameters: Power 10–15 w, temperature 38 °C–45 °C, each side for 10 min each time.

Treatment time

The treatment time was once every two weeks, for a total of five times.

Post-treatment precautions

After each treatment, the patient was explained regarding the post-treatment precautions as follows: 1. keep the vulva clean; 2. prohibit bathing for 24 h after treatment; 3. avoid hot water baths, 4. avoid strenuous exercise and heavy physical activities for 3–4 d after treatment; 5. avoid wearing tight underwear; 6. strict contraception during treatment.

Post-treatment and follow-up

Between 1–2 weeks after completing the five treatments, a gynecological examination was performed, and the post-treatment FSFI questionnaire, pelvic floor surface EMG test and sexual function test were completed. The patients were reassessed after three months of follow-up.

Measures to ensure safety of the implementation

Before treatment: the treatment parameters were set based on the safety of the treatment, after certain basic experimental validation and pre-experimental exploration.

During treatment: the rehabilitation therapists took up their positions after training and interacted with patients in real-time to ensure their safety during the treatment process.

After treatment: ensured there was regular phone calls and outpatient followed up one week after treatment to understand whether there were any adverse reactions after treatment.

Statistical analysis

The Wenjuanxing questionnaire data were exported, and the observation index results were collected. Microsoft Office Excel 2019 was used for data entry. The Statistical Program for Social Science (SPSS) 25.0 statistical software (IBM Corp., Armonk, NY, USA) was used for data analysis. The data were expressed using mean ± standard deviation. Comparison between two groups was analyzed by t-test. $P < 0.05$ indicated that the difference was statistically significant.

Results

General information

The age of the 50 patients ranged from 25 to 55 years, with a mean of (35.60 ± 6.31) years; their height ranged from 148 to 174 cm, with a mean of (159.46 ± 5.59) cm; their weight ranged from 35 to 73 kg, with a mean of (54.02 ± 8.06) kg; and their BMI ranged from 15 to 30.39, with a mean of (21.24 ± 3.08). None of the patients received systematic treatment for FSD before enrollment. Some patients have received physical therapy for PFD more than 12 months prior to enrollment.

FSFI scores for pre- and post-treatment/follow-up

The mean FSFI scores of patients for post-treatment/follow-up were significantly higher than pre-treatment (26.20 ± 3.69 vs 22.67 ± 4.55 and 27.19 ± 1.83 vs 22.99 ± 5.0, respectively; $p < 0.05$) (Tab. 1).

Surface EMG of pelvic floor muscles pre- and post-treatment/follow-up

There were no significant changes in the mean pelvic floor resting surface myoelectric potential and its variability for pre- and post-treatment [(4.78 ± 3.04) μv vs (5.10 ± 4.02) μv and (0.21 ± 0.01) vs (0.35 ± 0.08), respectively; $p > 0.05$]. The mean surface myoelectric potential of the patients' type I and II muscle fibers of the pelvic floor for post-treatment was significantly higher than pre-treatment [(28.99 ± 1.58) μv vs (20.29 ± 1.33) μv and (40.86 ± 1.76) μv vs (29.74 ± 1.77) μv, respectively; $p < 0.05$] (Tab. 2).

There were no significant changes in the mean pelvic floor resting surface myoelectric potential and its variability

Table 1. Female sexual function index (FSFI) score pre- and post-treatment after 2 weeks (completed treatment) and 3 months (follow-up)

Group	Mean FSFI	
	2 weeks (n = 50)	3 months (n = 31)
Pre-treatment	22.67 ± 4.55	22.99 ± 5.0
Post-treatment/follow-up	26.20 ± 3.69	27.19 ± 1.83
p value	0.000	0.000
t value	–6.372	–4.360

n — number of patients

Table 2. Surface electromyography (EMG) of pelvic floor muscles pre- and post-treatment after 2 weeks (completed treatment) and 3 months (follow-up)

Group	Mean resting surface myoelectric potential [μv]		Mean resting surface myoelectric potential variability		Mean myoelectric potential of type I muscle fibers of the pelvic floor [μv]		Mean myoelectric potential of type II muscle fibers of the pelvic floor [μv]	
	2 weeks	3 months	2 weeks	3 months	2 weeks	3 months	2 weeks	3 months
Pre-treatment	4.78 ± 3.04	5.08 ± 3.35	0.21 ± 0.01	0.20 ± 0.11	20.29 ± 1.33	20.56 ± 8.66	29.74 ± 1.77	30.47 ± 12.06
Post-treatment/ /follow-up	5.10 ± 4.02	5.54 ± 3.46	0.35 ± 0.08	0.23 ± 0.35	28.99 ± 1.58	28.16 ± 10.37	40.86 ± 1.76	39.52 ± 10.37
p value	0.608	0.545	0.116	0.647	0.000	0.000	0.000	0.000
t value	–0.517	–0.612	–1.599	–0.463	–5.932	–4.292	–6.275	–4.297

Number of patients (n) = 50 for 2 weeks, n = 31 for 3 months

Table 3A. Sexual function test for pre- and post-treatment; A. After 2 weeks (completed treatment)

Group	Mean myoelectric potential [μv]	Mean peak myoelectric potential [μv]
Pre-treatment	18.42 ± 0.92	39.46 ± 1.89
Post-treatment	19.78 ± 1.02	44.34 ± 2.03
p value	0.229	0.001
t value	–1.217	–3.704

Table 3B. Sexual function test for pre- and post-treatment; B. After 3 months (follow-up)

Group	Mean myoelectric potential [μv]	Mean peak myoelectric potential of type I muscle fibers of the pelvic floor [μv]	Mean peak myoelectric potential of type II muscle fibers of the pelvic floor [μv]
Pre-treatment	19.00 ± 7.21	38.81 ± 13.67	37.03 ± 13.39
Post-follow-up	18.48 ± 6.37	36.71 ± 8.25	39.59 ± 8.13
p value	0.694	0.380	0.268
t value	0.397	0.890	–1.128

Number of patients (n) = 50 for 2 weeks, n = 31 for 3 months

for pre-treatment and post-follow-up [(5.08 ± 3.35) μv vs (5.54 ± 3.46) μv and (0.20 ± 0.11) vs (0.23 ± 0.35), respectively; $p > 0.05$]. The mean surface myoelectric potential of the patients' type I and II muscle fibers of the pelvic floor for post-follow-up was significantly higher than pre-treatment [28.16 ± 10.37) μv vs (20.56 ± 8.66) μv and (39.52 ± 10.37) μv vs (30.47 ± 12.06) μv, respectively; $p < 0.05$] (Tab. 2).

Sexual function test for pre- and post-treatment/ /follow-up

There were no significant changes in the mean myoelectric potential of patients for pre- and post-treatment [(18.42 ± 0.92) μv vs (19.78 ± 1.02) μv; $p > 0.05$]. However, the mean peak of myoelectric potential of patients for post-treatment was significantly higher than pre-treatment [(44.34 ± 2.03) μv vs (39.46 ± 1.89) μv; $p < 0.05$] (Tab. 3A).

There were no significant changes in the mean myoelectric potential, and the peak myoelectric potential of the patients' type I and II muscle fibers of the pelvic floor for pre-treatment and post-follow-up [(19.00 ± 7.21) μv vs (18.48 ± 6.37) μv, (38.81 ± 13.67) μv vs (36.71 ± 8.25) μv and (37.03 ± 13.39) μv (39.59 ± 8.13) μv, respectively; $p > 0.05$] (Tab. 3B).

DISCUSSION

The results of this study showed that the mean FSFI scores of patients after completed two weeks treatment and three months follow-up were significantly higher than pre-treatment. The mean pelvic floor resting surface myoelectric potential and its variability for pre- and post-treatment/follow-up did not show significant changes. The mean surface myoelectric potential of the patients' type I and II muscle fibers of the pelvic floor for post-treatment/follow-up was significantly higher than pre-treatment. There were no significant changes in the mean myoelectric potential for sexual function test of patients for pre- and

post-treatment/follow-up. The mean peak of myoelectric potential of patients for post-treatment was significantly higher than pre-treatment. Our study is consistent with the research by Dayan et al which found no significant changes in resting pelvic muscle tone but an improvement in the maximal pelvic floor contraction [4]. However, the mean peak of myoelectric potential of patients after three months follow-up was not significantly different from pre-treatment. This may probably be due to some patients were unable to turn up for follow-up, and thus the therapeutic outcome could not be assessed. Subsequent studies may involve a larger size sample and evaluate the effect over a consecutive time-point to view the pattern of the therapeutic outcome, to develop a better therapeutic approach.

Current situation of female sexual dysfunction

With the development of society and rise of women's consciousness, women's sexual health has gradually received more attention, and clinical research on the diagnosis, classification and treatment of FSD has also gradually increased. The incidence of FSD in Asian women ranges from 30% to 52%, and more than 50% of women in China are reported to suffer from sexual dysfunction [9]. According to the American College of Obstetricians and Gynecologists on guidelines for the management of female sexual dysfunction, the current American Psychiatric Association Diagnostic and Statistical Manual of Mental Disorders (Fifth Edition, DSM-5) classified FSD into 5 categories: sexual interest or arousal disorders, orgasmic disorder, genito-pelvic pain or penetration disorder, substance or drug-induced sexual dysfunction, and other unspecified sexual dysfunction [1]. There are many pathogenic factors of FSD, including psychological aspects, social factors, physiological changes, pathological damage and other factors [10]. Therefore, there are various treatment methods for FSD, including psychological and behavioral therapy, drug therapy, physical rehabilitation, and surgical treatment. However, due to the influence of tradition and education level, some Chinese women have weak perception about sexual health and lack of relevant physiological knowledge, so they are unable to realize the occurrence of FSD and its harm to the quality of life, as well as physical and mental health. Only 22.7% of the patients sought medical attention, 28.5% of the patients searched for information on their own, and 30% of the patients had never gone to the hospital for medical treatment [11]. Therefore, it is necessary to spread the relevant knowledge of FSD, and explore more objective diagnostic methods and new treatment methods.

Relationship between FSD and PFD

The damage to the pelvic floor tissue during pregnancy and childbirth often leads to female PFD and various clinical symptoms. However, the pelvic floor tissue is composed of a variety of muscles and fascia, and there are many muscles directly related to sexual function, such as the bulbocavernosus muscle, the deep transverse perineal muscle, and the levator ani muscle [12]. Studies have shown that pregnancy and childbirth can lead to various abnormal conditions such as perineal pain, urinary incontinence, depression and changes in sexual function in women. Therefore, pelvic floor tissue damage will also have adverse effects on the female sexual function. As for the exact relationship between FSD and PDF, there is no conclusion yet. Some studies believe that PFD and FSD have no obvious correlation. Other studies have shown that women suffering from PFD affect the quality of life and cause anxiety and other adverse emotional states, thereby increasing the occurrence of FSD. It is closely related [13–15].

In summary, both FSD and PFD have a certain correlation with changes in the female pelvic floor structure. Many treatment methods for PFD, while improving the relaxation and injury of pelvic floor structure, promote the blood supply of tissues near the clitoris, improve female vaginal relaxation, and stimulate glandular secretion, and thus improve their quality of sexual life [16]. Therefore, the occurrence of FSD and PFD are closely related to a certain pathogenic mechanism, and the research on PFD is relatively mature. Based on clear principle and safe application, we can explore whether PFD treatment method can achieve ideal therapeutic effect when applied to FSD treatment.

Feasibility of the application of the temperature-controlled radiofrequency technology in FSD

The temperature-controlled radio frequency technology uses high-frequency alternating electromagnetic waves generated by radio frequency to act on the electrons and ions in the target tissue of the human body, causing them to move in a directional manner and produce a thermal effect. Through constant temperature control, it can promote the regeneration of collagen and elastic fibers in the human body and improve blood circulation without causing tissue damage, to achieve the purpose of non-invasive physical therapy for the treatment of diseases. When applied to FSD, it can promote the regeneration of vaginal collagen and elastic fibers and promote the overall blood circulation of the pelvic cavity, so as to reduce the symptoms of vaginal relaxation, vaginal dryness, and sexual pain in FSD. Relevant basic research shows that after percutaneous temperature-controlled radiofrequency treatment of the vulvovagina, vaginal mucosal sections showed that the treatment promoted the regeneration of collagen, and regeneration of blood vessels and small nerve fibers [17]. The temperature-controlled radiofrequency technology has been gradually applied to the treatment of PFD, and it

has achieved good results in the treatment of vaginal relaxation and urinary incontinence [18, 19]. Previous study found that radiofrequency can improve the maximal pelvic muscle contraction [4]. Some European and American countries have applied the temperature-controlled radiofrequency technology to the treatment of FSD in a small scale and achieved certain results [20]. Therefore, applying the temperature-controlled radio frequency technology to the treatment of FSD has certain rationality and considerable exploration value. At the same time, with its non-invasive treatment characteristics, it can relieve the pain of patients, improve the treatment experience, and relieve the psychological burden of FSD patients.

CONCLUSIONS

In this study, the mean FSFI score, mean surface myoelectric potential of the patients' type I and II muscle fibers of the pelvic floor and mean peak myoelectric potential of the sexual function test were improved after treatment, indicating that the application of temperature-controlled radio frequency technology has a certain therapeutic effect on FSD. Applying the objective evaluation index of PFD to the assessment of the condition of the FSD patients can reflect the treatment effect to a certain extent and improve the patients' subjective feelings.

Article information and declarations

Data availability statement

The datasets used or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics statement

This study is approved by the Ethics Committee of Peking University Shenzhen Hospital, NO. [2020](001A). Signed informed consent were also obtained from all participants.

Author contributions

We declare that all the listed authors have participated actively in the study and all meet the requirements of the authorship. Dr. NW designed the study and wrote the paper, Dr. HL managed the literature searches and analyses, contributed to the correspondence. All authors reviewed the manuscript.

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None.

Conflict of interest

The authors declare that they have no conflict of interest.

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The role of PET/CT with fluorine-18-deoxyglucose in the detection of relapsed serous ovarian cancer in patients with normal serum CA125 levels

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ABSTRACT

Objectives: To assess the role of the positron emission tomography with fluorine-18-deoxyglucose (PET/CT) in the detection of recurrent serous ovarian cancer in patients with normal serum CA125 level.

Material and methods: Thirty-one patients with suspected recurrent serous ovarian cancer with normal (< 35 IU/mL) serum CA125 level and no prior recurrence underwent PET/CT imaging. The results of the PET/CT were analyzed considering clinical data of the patients, histological diagnosis and 6 months follow-up.

Results: The patients were referred to the PET/CT due to suspected relapse in imaging tests (CT — 11 cases, US — 3 cases, MRI — 2 cases; n = 16; 51.6%), clinical examination (n = 4; 12.9%) and clinical symptoms (n = 11; 35.5%). The recurrent serous ovarian cancer was present in 16 patients (51.6%). In 9 these cases (56.3%) the recurrences were diagnosed in patients aged 51–70 years. In 15 cases (93.8%) the recurrences were diagnosed within 24 months after treatment. There were 15 true positive (48.4%), 12 true negative (38.7%), 3 false positive (9.7%) and 1 false negative (3.2%) PET/CT results. Sensitivity, specificity, positive and negative predictive value of the PET/CT were calculated as 93.8% (95% CI, 86.1–97.4%), 80.0% (95% CI, 69.7–88.9%), 83.3% (95% CI, 74.3–90.4%) and 92.3% (95% CI, 84.2–98.3%), respectively.

Conclusions: In patients with a diagnosis of complete remission after treatment for serous ovarian cancer, even a multifocal recurrence may occur during follow up despite normal serum CA125 levels. Our results showed a usefulness of the PET/CT in detecting and differentiating malignant from benign lesions in patients with normal serum CA125 levels but inconclusive results in other imaging tests. We observed false results of the PET/CT for lesions in parotid gland, mesorectal adipose tissue and mediastinal lymph nodes.

Keywords: [^{18}F]FDG PET/CT; ovarian cancer; relapse; normal CA125 level

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INTRODUCTION

Ovarian cancer is characterized by the highest mortality rate of all gynecologic malignant tumors. Serous ovarian cancer is its most frequent histological subtype [1]. Despite successful initial treatment, relapse occurs in most patients with a median time of 18–24 months [2, 3]. For this reason, it is important to accurately assess ovarian cancer patients during follow-up to determine whether a relapse has occurred.

Imaging methods focused on detecting abnormalities in morphological structure of the organs, such as ultrasonography (US) and computed tomography (CT) lack the accuracy to detect asymptomatic peritoneal dissemination with small volume lesions, metastases to lymph nodes without changes in their structure and size, or with postoperatively changed anatomical conditions [4]. When the diagnosis of recurrent ovarian cancer is unclear, positron emission tomography with fluorine-18-deoxyglucose (PET/CT) may play an important role. The PET/CT identifies both structural and metabolic abnormalities of the tissue and it can diagnose relapse up to 6 months earlier than compared to the

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CT [5]. The resolution of the method is currently 4–5 mm, therefore even small lesions can be detected. In cases of lesions < 5 mm in diameter, the PET/CT false negative result rate increases by 5–10% [6].

In 1983, a cancer antigen 125 (CA125) radioimmunoassay was introduced, with the specific aim to monitor treatment of non-mucinous ovarian cancer patients. CA125 is a glycoprotein produced by epithelial cells and the test could reliably, and at an early stage, detect recurrences after initial successful treatment of ovarian cancer. It is known, that CA125 has relatively high specificity and 80% accuracy in detection recurrence of the ovarian cancer [2, 4, 7]. However, sensitivity of the marker remains insufficient, especially for small-volume disease. As the effect, normal serum CA125 concentration can coexist with relapsed cancer [8, 9]. The optimal cutting point for the CA125 level (17.6–18 U/mL) was established that helps determine for which patients the PET/CT scan is the most justified [5].

The appearance of disturbing symptoms and inconclusive results in imaging tests, despite normal serum CA125 level, can be an indication to perform the PET/CT. The questions about the sensitivity and specificity of the PET/CT in this group of patients and about the anatomical location of false positive and negative results are still valid.

Objective

The aim of the study was to assess the role of the PET/CT in the detection of recurrent serous ovarian cancer in patients with normal CA125 levels.

MATERIAL AND METHODS

The prospective study included 31 consecutive patients aged > 18 years with normal (< 35 IU/mL) serous CA125 concentration, who were referred with suspected recurrent ovarian cancer of the serous type to the Nuclear Medicine Unit of the Copernicus Memorial Provincial Multidisciplinary Center of Oncology and Traumatology of Lodz between 2017–2021. The suspicion of the relapse was based on results of imaging tests (CT — 11 cases, US — 3 cases, MRI — 2 cases), clinical examination (n = 4) and clinical symptoms (n = 11). The patients with the follow-up period < 6 months were excluded from the study.

In the treatment of primary cancer, 29 patients (93.6%) underwent complete or optimal tumor cytoreduction (residual less than 1 cm) and the remaining 2 patients (6.4%) — suboptimal cytoreductive surgery. Chemotherapy was given in all cases, including neoadjuvant chemotherapy in 3 cases. In all patients a clinical complete remission was diagnosed. nTreatment was completed 2–44 months before the PET/CT. Characteristics of the study group are presented in Table 1.

A research survey containing clinical data and treatment history of the patients was designed. It was filled by patients on medical consultation preceding the PET/CT. The data collected from the questionnaires, results of the PET/CT, histological diagnosis and clinical follow-up findings were analyzed. The follow-up period was at least 6 months.

Table 1. Characteristics of the study group

Selected clinical and pathological data	n	[%]
Age of patients [years]		
≤ 50	6	19.3
51–70	18 5	8.1
> 70	7	22.6
FIGO staging of the cancer		
I	4	12.9
II	7	22.6
III	18	58.1
IV	2	6.4
WHO grading of the cancer		
G1	1	3.2
G2	3	9.7
G3	27	87.1
Time from completion of treatment to the [^{18}F] FDG PET/CT [months]		
2–12	12	38.7
13–24	14	45.2
25–36	3	9.7
> 36	2	6.4
Total	31	100.0

FIGO — International Federation of Gynecology and Obstetrics; WHO — World Health Organization; FDG PET/CT — positron emission tomography with fluorine-18-deoxyglucose

PET/CT procedure

All patients had at least six hours fasting, and their fasting blood sugar levels were less than 180 mg/dL. Oral contrast was given to all the patients. Intravenous injection of 240–380 MBq of the [18F]FDG was performed and followed by a 60 min interval, during which patients rested in quiet room. After this period PET/CT examination was performed. Scanning, from the patient's skull base to the mid-thigh level was done using Biograph mCT 128 scanner. Unenhanced low-dose CT was used for anatomical localization and attenuation correction.

Image interpretation

In all cases the PET/CT were evaluated by a medical team consisting of a specialist in nuclear medicine and a specialist in radiology. For semi quantitative evaluation, the maximum standardized uptake value (SUV_{max}) was used, which was determined within the detected pathological lesions. The SUV_{max} > 2.5 was accepted as a criterium of malignancy.

Data analysis

Results of the PET/CT were qualified to four groups: true positive (TP), false positive (FP), true negative (TN) and false negative (FN). In cases diagnosed with relapse in the PET/CT, the results were verified based on histological diagnosis after biopsy taken from detected lesions (relapse: confirmed n = 6; not confirmed n = 3). If the lesions were not histologically examined, cases were qualified to the TP group when:

- the lesions were observed in other imaging tests — including progression in control PET/CT,
- disease regression in control PET/CT after applied systemic treatment was observed,
- disease progression despite treatment was observed.

When the PET/CT result was negative and relapse was not detected during 6 months of the follow-up, the case was classified to the TN group. When the PET/CT result was negative, but the relapse was detected during 3 months of the follow-up, the result was considered as FN. Metabolically active lesions (SUVmax > 2.5) in the PET/CT, which during further diagnostics within 6 months turned out to be benign lesions, were classified as the FP.

Statistical analysis

The data were statistically elaborated using the Statistica 10.0 PL program (Statsoft Inc., Tulsa, OK, USA). Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) in the diagnosis of relapsed serous ovarian cancer were calculated. The p value below 0.05 was considered statistically significant.

The study was approved by the Bioethics Commission of the Medical University of Lodz No. RNN/64/16/KE.

RESULTS

The patients were referred to the PET/CT due to suspected relapse in imaging tests (51.6%), clinical examination (2.9%) and clinical symptoms (35.5%). The recurrent serous ovarian cancer was finally confirmed in 16 patients (51.6%). In 15 cases (93.8%) the recurrences were diagnosed within 24 months after treatment and only in 1 patient (6.2%) later ($p < 0.001$).

The median age of patients in the study group was 60.6 ± 10.0 years. The median age of patients diagnosed with relapsed ovarian cancer was 61.8 ± 10.5 years. In patients with no relapse, it was 57.3 ± 9.5 years ($p = 0.222$). The recurrences were diagnosed in 4 of 6 patients ≤ 50 years (25%), in 8 of 18 patients aged 51–70 years (50%) and 4 of 7 patients aged ≥ 71 years (25%). Characteristics of the group with recurrent serous ovarian cancer is presented in Figure 1.

There were 15 TP (48.4%), 12 TN (38.7%), 3 FP (9.7%) and 1 FN (3.2%) PET/CT results. Sensitivity, specificity, positive and negative predictive value of the PET/CT were calculated as 93.8% (95% CI, 86.1–97.4%), 80.0% (95% CI, 69.7–88.9%), 83.3% (95% CI, 74.3–90.4%) and 92.3% (95% CI, 84.2–98.3%), respectively.

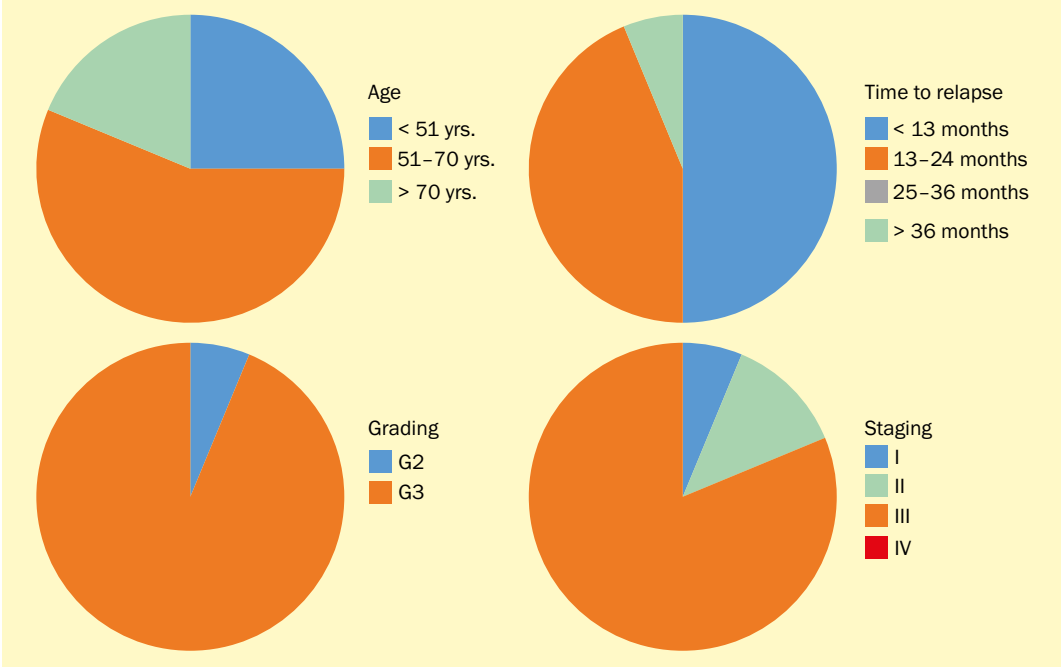

Figure 1. Characteristics of the group with recurrent serous ovarian cancer

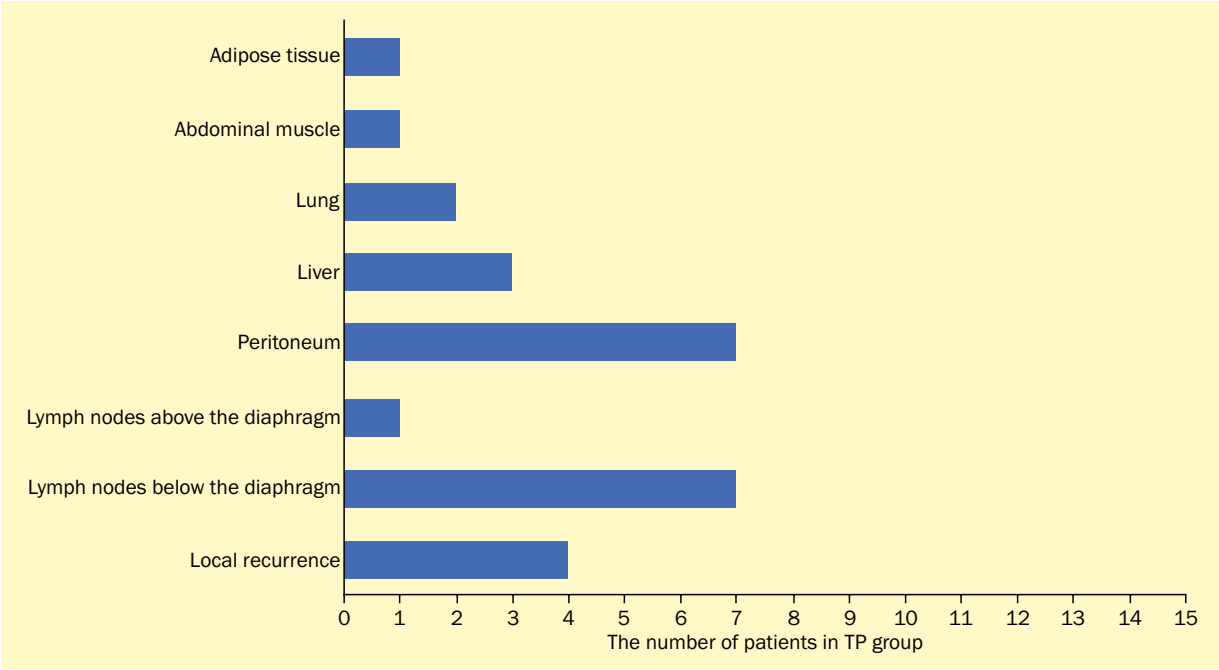

Figure 2. Frequency of abnormal FDG PET findings by the site of involvement in true positive (TP) patients

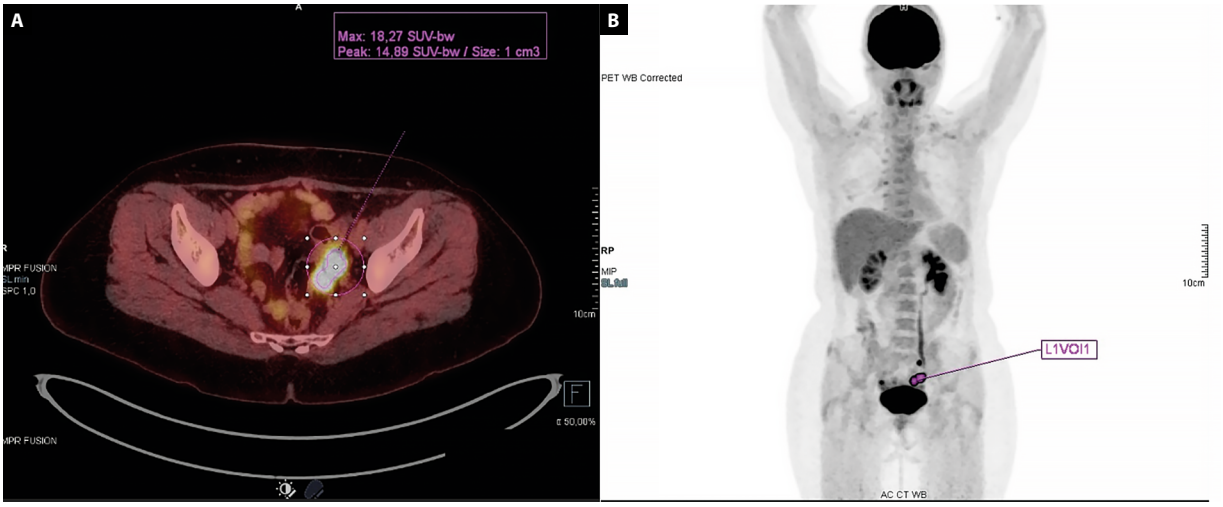

Figure 3. Example of TP findings of positron emission tomography (PET/CT) scan; **A.** Transaxial slice; **B.** 3D maximum intensity projection (MIP)

The locations of the relapsed serous ovarian cancer in the TP group are presented in Figure 2. In the TP group 3 unifocal and 12 multifocal recurrences were diagnosed ($p = 0.043$) (Fig. 3). In the FP group metabolically, active lesions were located in the parotid gland (n = 1), mesorectal adipose tissue (n = 1) (Fig. 4) and mediastinal lymph nodes (n = 1), but in these cases relapse was excluded after biopsy. In one FN case, the PET/CT showed no abnormal findings, but lung metastases were detected 2 months after the PET/CT.

DISCUSSION

In about 70% of patients with ovarian cancer, an increase in the level of the CA125 is the first sign of recurrence, that anticipates clinical recurrence by about 3–4.5 months [7, 10]. Our study confirmed the observation of Bhosale et al. [9], that normal CA125 levels can coexist with even a multifocal recurrence. In our study, patients with relapsed disease had multifocal lesions and the recurrence appeared within 24 months after end of treatment. According to the literature,

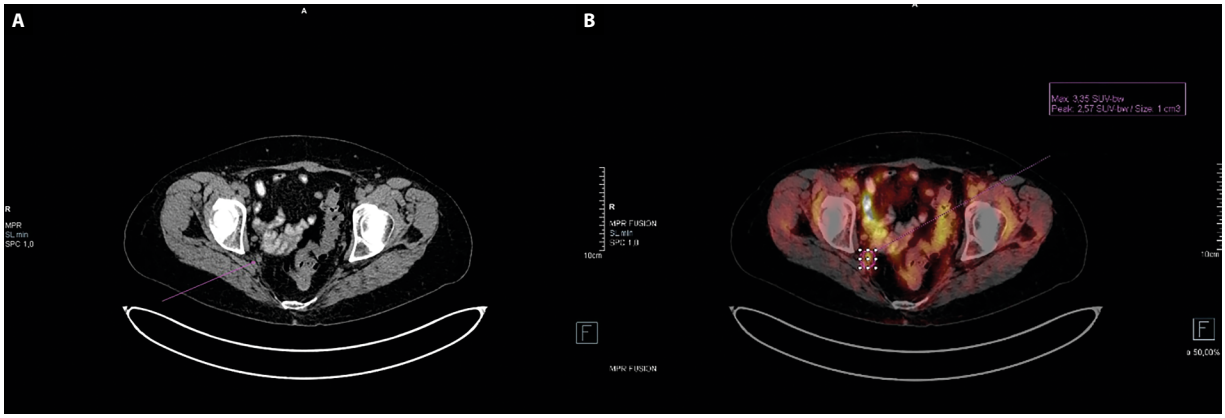

Figure 4. Hypermetabolic lesion suspected of recurrence located in mesorectal adipose tissue; **A.** Computed tomography (CT) presentation; **B.** Positron emission tomography (PET/CT) presentation

the median interval to first recurrence in ovarian cancer is 18 to 24 months [3]. The data from the literature show that relapsed ovarian cancer in most cases is multifocal [11–13]. In our patients only in 3 cases (20.00%) the relapses detected in the PET/CT were unifocal. These patients were qualified for surgery.

Among 31 patients in our study group, we achieved 93.75% sensitivity and 80.00% specificity in diagnosing the recurrence of ovarian cancer. The high sensitivity of the method is similar to studies [4, 5, 8, 11, 14–19]. Superiority of the PET/CT over conventional imaging methods, like US, CT and MRI was demonstrated in the literature [9, 18–20]. Risum et al. [17], reported sensitivity and specificity of US and CT to detect recurrence in ovarian cancer patients as 66% and 90% for US and 81% and 90% for CT [17]. In another studies, sensitivity and specificity of these methods in the diagnosis of recurrent ovarian cancer ranged between 40–93% and 50–98% for CT, 62–91% and 40–100% for MRI [21]. The sensitivity of the CT drops to 25–50%, when metastatic lesions in the peritoneum are smaller than 1 cm [22, 23]. The presence of postoperative anatomical alterations in the abdominal cavity reduces specificity of the MRI in detecting recurrence [4, 24]. In the PET/CT these anatomical conditions are less important for the diagnosis [11, 15, 16], but non-specific nature of the [18F]FDG tracer uptake, which accumulates at any site with increased glucose metabolism, *e.g.* areas of inflammation and infection or in muscles on contraction, is however a limitation of the method and like in our study can cause false positive results [6, 25]. The normal physiological uptake in loops of bowel or urinary bladder activity are considered pitfalls of PET/CT and may be difficult to interpret [26].

Relapsed ovarian cancer in near 75% is diagnosed in peritoneal cavity and retroperitoneal space [11–13]. The high incidence of both peritoneal implants and retroperitoneal lymph nodes involvement in recurrent serous ovarian cancer was confirmed in our study. According to the data from the literature, the sensitivity and the specificity of the PET/CT in detecting peritoneal implants in recurrent ovarian cancer are very high [8, 15, 16, 27]. Rubini et al. [14] described an advantage of the PET/CT over another imaging methods in this indication (85% sensitivity and 92.3% specificity) [14, 18].

The lymph nodes, especially of retroperitoneal location, are common site of relapse in ovarian cancer [13, 28]. The PET/CT can detect metastases even in non-enlarged lymph bnodes. In a meta-analysis of patients from 18 centers, which examined the diagnostic value of various imaging methods in detecting recurrence in lymph nodes, the sensitivity and specificity of the PET/CT were 73.2% and 96.7%, respectively.

These values were higher when compared to CT (sensitivity 42.6%, specificity 95%) and MRI (sensitivity 54.7%, specificity 88.3%) [29]. On the other hand, small and necrotic lymph nodes may not be detected on the PET/CT scans, leading to false negative results [30].

The limitations of our study were lack of histological verification of the relapses in most cases and a small number of patients. For this reason, the results cannot be generalized to whole population. In our opinion, further prospective studies in larger populations of patients with serous ovarian cancer are required to better characterize the group of patients, who get the most benefit from PET/CT examination. Identification of these patients will facilitate optimal individualization of diagnosis and treatment for each patient.

Although the role of PET/CT in the diagnosis of recurrent ovarian cancer was discussed in the literature, our study was valuable because it was prospective, the study group was homogeneous composed only from patients with serous ovarian cancer with no prior recurrence and normal CA125 levels. Additionally, the patients were observed within 6 months following the PET/CT, that increased reliability of bthe results.

CONCLUSIONS

In patients with a diagnosis of complete remission after treatment for serous ovarian cancer, even a multifocal recurrence may occur during follow up despite normal serum CA125 levels. Our results showed the usefulness of the PET/CT in detecting and differentiating malignant from benign lesions in patients with normal serum CA125 levels but inconclusive results in other imaging tests. We observed false positive results of the PET/CT in parotid gland, mesorectal adipose tissue and mediastinal lymph nodes.

Article information and declarations

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None

Ethics approval statement

The study was approved by the Bioethics Commission of the Medical University of Lodz No. RNN/64/16/KE.

Conflict of interest

All authors declare no conflict of interest.

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Supplementary material

None.

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Basic hope, level of stress and strategies used to cope with stress after miscarriage during hospitalization and 3 months after its completion

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ABSTRACT

Objectives: Basic hope is important for successfully coping with, and adapting to, difficult situations. The aim of the study was to determine the level of stress and basic hope and identify the associated coping processes in women after miscarriage during hospitalization and three months after discharge.

Material and methods: A total of 161 women hospitalized due to miscarriage were included. To evaluate the level of stress, basic hope and coping strategies, the following standardized questionnaires were used: the Perceived Stress Scale (PSS-10), the Inventory to Measure Coping Strategies with Stress (Mini-COPE) and the Basic Hope Inventory (BHI-12).

Results: 110 patients declared high levels of stress during hospitalization and 80 claimed the same three months after discharge. The level of stress decreased after three months ($p < 0.001$). Adaptive stress-coping strategies were employed more frequently than maladaptive stress-coping strategies. During hospitalization, the most frequently used strategies were acceptance and seeking emotional support; with planning, acceptance, seeking emotional and instrumental support being used three months after discharge. The sense of basic hope increased after three months ($p < 0.001$). The level of the sense of basic hope correlates significantly ($p < 0.001$) and negatively ($r < 0$) with the severity of stress symptoms during and after the hospital stay.

Conclusions: The sense of basic hope increased significantly after three months in relation to the level experienced during the hospitalization period, and the intensity of stress decreased. Preventive women-oriented interventions are needed to minimize the risk of post-traumatic stress disorder.

Keywords: miscarriage; stress; coping strategies; basic hope; hospitalization

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INTRODUCTION

Miscarriage is the most encountered failure of procreation [1]. In Poland, miscarriage is defined as the loss of pregnancy before the 22nd week of pregnancy or when the weight of the dead foetus does not exceed 500 g. As many as 80% of miscarriages occur in the first trimester of pregnancy. Recurrent miscarriages account for 1–2% of cases [2].

Pregnancy loss may cause considerable psychological stress in women [3–5]. It has been demonstrated that the stress rates after miscarriage range from 28% to 45% both immediately after the event and even six months afterwards [6]. The women who have experienced a miscarriage have a seven-fold higher risk of developing post-traumatic stress disorder (PTSD) symptoms compared to the women who have not been pregnant before [4], and the prevalence of PTSD in this group reaches up to 39% [5]. Women who had experienced miscarriages for the second and third time showed a significant degree of severity of PTSD symptoms, while a moderate degree was noted by 64.29% of women for whom it was the first reproductive failure [7].

Understanding the nature of pregnancy loss is therefore extremely important in order to provide appropriate

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support, thereby minimizing mental health morbidity and long-term health care costs. One form of work in this area might be to inspire hope. Hope is important for dealing effectively with difficult situations, making decisions, adapting psychosocially, or improving the quality of life. It is also considered to be an important factor in the recovery process [8]. Higher levels of hope have been associated with reduced anxiety and depression and improved quality of life in patients treated for chronic somatic illnesses, including oncological ones [9, 10]. Hope is therefore defined as a positive phenomenon, which is crucial for the development of adaptive and constructive coping strategies.

There also exists a stance whereby hope is a specific disposition of the individual. This is related to the paradigm of basic hope by Erikson [11], who defined basic hope as a psychological structure which is formed in early childhood and plays a key motivational role in regulating an individual's behaviour. Its development is the result of an appropriate relationship between the caregiver and the child, which provides a sense of security, satisfies the need for closeness, love and bonding. Therefore, the basic hope is the inner conviction that the world is well organised and benevolent to people. It is, then, associated with a belief in orderliness, meaningfulness and the purposefulness of events in the surrounding world. Thus, the function of basic hope is to be convinced that it is possible to re-establish order when it is disrupted, despite confusion, chaos or doubts about the meaning of life and objective justice. In this sense, the level and meaning of basic hope is a key component for the functioning of a person, acting as a buffer protecting them from fear, confusion, a sense of loneliness and at the same time fulfilling the function of integration, regulation in addition to facilitating the course and process of growth. As a result, basic hope triggers efforts to improve circumstances, solve a problem, or seek constructive remedial strategies. It is understood as a person's generalized and complex conviction that the surrounding world is well ordered and is generally favourable to people. This particular concept was used in this work.

The aim of the study was to determine the level of stress intensity, basic hope and analysis of coping strategies in difficult situations amongst women who had experienced a miscarriage both during and three months after hospitalization.

MATERIAL AND METHODS

The study was approved by the Bioethics Committee of the Jan Kochanowski University (25/2020). The study was divided into two stages. The first stage of the study took place on day 2 or 3 of hospitalization, and the second one, three months after its completion. The study included 161 patients who were admitted to the Department of Obstetrics and Gynaecology of the Provincial Combined Hospital in Kielce due to miscarriage between September 2019 and August 2021. The rate of returned and completed questionnaires was 77.8%.

The qualification of the respondents included the following inclusion and exclusion criteria:

— inclusion criteria:
  - patients hospitalized due to miscarriage,
  - the absence of traumatic events within one month before hospitalization following the miscarriage,
  - returning completed questionnaires three months after the end of hospitalization,
  - being over 18 years of age,
  - a consent to participate in the study;

— exclusion criteria:
  - patients hospitalized for reason other than miscarriage;
  - the experience of a traumatic event within one month before hospitalization following the miscarriage;
  - the lack of completed questionnaires three months after the end of hospitalization;
  - a history of a psychological dysfunction that prevents the examination or diagnosis of a mental illness (*e.g.*, depression, anxiety disorder, content — thought disorder);
  - intellectual disability;
  - being under 18 years of age;
  - a lack of consent to participate in the study.

The study assumed that the level of stress intensity of the women surveyed was not related to any other traumatic factor (*e.g.*, death of a loved one, catastrophic event), which the respondent may have experienced during the month prior to hospitalization. For this reason, the sociometric survey included a question about whether such a situation had occurred in the previous month, and upon receiving a positive answer, such patients were excluded from the study. The period of one month was adopted for the following reason. According to The American Psychiatric Association Classification of Mental Disorders (Edition 5; DSM-5) [12], exposure to a stressor may result in acute stress disorder (ASD) or PTSD. The symptoms defining ASD and PTSD basically overlap. The most important difference, however, is that the acute stress disorder is characterised by acute stress responses which can occur in the first month after a person's exposure to a traumatic event. These events are, *e.g.*, the death of a loved one, a serious life and health threat, or the experience of physical violence). Post-traumatic stress disorder, on the other hand, refers to the long-term consequences of the injury.

An original survey was used to collect sociometric data. The assessment of the severity of stress levels, coping strategies,

and the level of basic hope was performed through standardized questionnaires.

The Perceived Stress Scale (PSS-10) by Cohen et al. [13] in the Polish adaptation of Juczyński and Ogińska-Bulik [14] was employed to assess the level of perceived stress. The scale assesses the intensity of stress related to the respondent's own life situation over the last month. According to the adopted assumption, the intensity of stress is determined not by the number of stressful events, but by their subjective assessment. The scale consists of 10 questions, of which six have a negative construction (1, 2, 3, 6, 9 and 10), and four have a positive construction (4, 5, 7 and 8). Each question begins with the phrase, "How often in the last month …", where 0 means never, 1 — almost never, 2 — sometimes, 3 — quite often, 4 — very often. The score for each question ranges from 0 to 4 points, and the overall score reaches from 0 to 40 points. The higher the score, the higher the stress level.

The strategy of coping with difficult situations was analysed thanks to the application of the Inventory to Measure Coping Strategies with Stress (Mini-COPE) questionnaire — Stress Management Inventory by Carver [15] in the Polish adaptation of Juczyński and Ogińska-Bulik [14]. The structure of the questionnaire is based on a theoretical model according to which the remedial actions taken by a person in stressful situations are the result of the interaction between the coping style characteristic of a given person and the characteristics of the situation. Mini-COPE contains 28 sentences specific to a given way of coping with stress. The strategies are divided into four categories: active coping (including: active coping, planning, positive reappraisal), helplessness (including: taking psychoactive substances, cessation of activities, blaming oneself), seeking support (including: seeking emotional support and instrumental support), avoidance behaviours (including: keeping oneself occupied with something else, denial, venting feelings). Three of these strategies create independent factors (turning towards religion, acceptance, sense of humour). The surveyed women evaluate the statements regarding their behaviour in a stressful situation scaling them from 0 to 3, where 0 means: I almost never do so, 1 — I rarely do so, 2 — I often do so, 3 — I almost always do so.

The Basic Hope Inventory (BHI-12) Questionnaire by Trzebiński and Zięba [16] was used to assess the sense of basic hope. According to the authors, hope is understood as the belief of an individual in the order and meaningfulness of the world and its favour towards people. This belief is the determining factor in the human being's constructive response to changes and disruptive events. The questionnaire is intended to assess the way a person responds to stress and trauma, as well as the speed and constructiveness of adaptation to new situations. It consists of 12 statements. A participant determines the extent to which they agree with each statement, using the scale from 1 ("strongly disagree") to 5 ("strongly agree"). The total score is the result of the overall level of basic hope. The maximum score on the scale is 45 points. The higher it is, the greater basic hope is.

Statistical analysis

Quantitative variables were analysed by calculating the mean, standard deviation, median and quartiles. The analysis of the qualitative variables was conducted by calculating the number and percentage of the occurrences of each value. A comparison of the values of quantitative variables in two repeated surveys was made using the Wilcoxon test for bound pairs.

The correlations between quantitative variables were analysed using the Spearman rank correlation coefficient.

A comparison of the values of quantitative variables in two groups was made using the Mann-Whitney test. A comparison of the values of quantitative variables in three or more groups was made using the Kruskal-Wallis test. Once statistically significant differences were detected, a post-hoc Dunn's test analysis was conducted in order to identify groups that differ with statistical significance.

A multivariate analysis of the impact of many variables on the quantitative variable was performed using the linear regression method. The results are presented as regression model parameter values with a 95 percent confidence interval.

The analysis of the returned questionnaires in the second stage of the study was carried out in accordance with the standards proposed by the American Association for Public Opinion Research (AAPOR) [17].

In the statistical analysis, a significance level of 0.05 was adopted. The analysis was performed in the program R, version 4.1.2 [18].

RESULTS

The study involved the participation of 161 women hospitalized due to miscarriage. Most of them were women aged 31 to 35 (36.02%), married (82.61%), living with the husband and/or partner (96.27%), in a provincial city (47.20%), with higher education (64.60%), employed (73.91%) and planning their lost pregnancy (72.67%). The shortest duration of procreative efforts was one month, and the longest one 180 months. The average duration of procreative efforts was ± 14.62 ± 25.02. Most of the women had one child (42.86%) and had miscarried for the first time (59.01%). The week of pregnancy loss ranged from 6th to 21st. Of all the women surveyed, most of them lost their pregnancy between the 9th and 10th (36.65%) and 6th and 8th week of pregnancy (35.40%). Most of them did not undergo any treatment at a Procreative Health Centre (83.85%). The characteristics of the study group are presented in Table 1.

Table 1. Participants' characteristics

Participants' characteristics	n	[%]
Age [years]		
15–25	12	7.45
26–30	45	27.95
31–35	58	36.02
36–40	30	18.63
41–50	16	9.94
Marital status		
Married	133	82.61
In relationship	26	16.15
Not in relationship	2	1.24
Education		
College	29	18.01
University	104	64.60
Other	28	17.4
Employment		
Employed	119	73.91
Self-employed	6	3.73
Annuitant	1	0.62
Unemployed	35	21.74
Residence		
Urban-province capital	76	47.20
Urban-other	32	19.88
Rural	53	32.92
Way of residence		
With husband/partner	155	96.27
By oneself	6	3.73
History of pregnancy loss		
First pregnancy loss	95	59.01
1 previous pregnancy loss	34	21.12
≥ 2 previous pregnancy losses	32	19.87
Week of pregnancy loss		
6–8	57	35.40
9–10	59	36.65
11–12	22	13.66
≥ 13	23	14.30
Having children		
No children	63	39.13
One child	69	42.86
Two and more children	29	18.01
Pregnancy planning		
Yes	117	72.67
No	44	27.33
Length of procreation for a lost pregnancy [months]		
0–50	110	94.02
≥ 50	7	4.34
Infertility treatment		
Yes	26	16.15
No	135	83.35

In the first stage of the study, the patients were also asked to indicate what was subjectively the most important to them during hospitalization because of miscarriage. In the group of women surveyed, it was found that the most important thing during the hospital stay due to a miscarriage is to be informed about each procedure, drug administration and other activities, to give informed consent to each intervention (78.26%) and to provide information about the miscarriage with respect and without third parties (77.64%) and/or available psychological help (70.81%). According to the women surveyed, the least important thing turned out to be a conversation with a chaplain or another clergyman representing their denomination (1.86%).

During the hospital stay, the patients were also asked to select the most subjectively stressful factors concerning their hospitalization. It was demonstrated that the most stressful factors include: the sudden occurrence of miscarriage (62.73%), fear of another pregnancy (62.73%) and the lack of knowledge about the cause of miscarriage (50.31%). Excessive bureaucracy during hospital admission turned out to be the least stressful (3.73%). The above results are presented in Table 2.

Of the 161 women surveyed, 110 (68.32%) declared high levels of stress, 33 (20.50%) average levels, and 18 (11.18%) low levels of stress. After the completion of hospitalization, 80 respondents (49.69%) faced high levels of stress, 45 (27.95%) low, and 36 respondents (22.36%) experienced average levels of stress. Stress levels significantly decreased after three months compared to the levels reached during the hospital stay (Tab. 3).

When assessing coping strategies during the hospitalization, the ones which were the most frequently used were Acceptance and Search for Emotional Support, and the least often used were strategies such as: Denial, Cessation of Activities, Sense of Humour and Taking Psychoactive Substances. three months after the hospitalization ended, the most used strategies were: Planning, Acceptance, Search for Emotional Support and Search for Instrumental Support; and the least frequently used strategies were: Cessation of Activities, Taking Psychoactive Substances and Sense of Humour. The frequency of the Denial strategy decreased significantly after three months as compared to the level reached during the stay ($p = 0.002$), and the frequency of the Planning strategy ($p = 0.023$), Acceptance ($p = 0.019$) and Seeking Instrumental Support ($p < 0.001$) increased significantly after 3 months as compared to the level reached during the hospital stay (Tab. 4).

When assessing the level of basic hope during the hospitalization, 69 (42.86%) women had a low level, 58 (36.02%) had a high level, and 34 (21.12%) reached an average level of basic hope. In turn, three months after the hospitalization ended, 65 respondents (40.37%) had a high level of basic hope, 53 (32.92%) had a low level, and 43 (26.71%) reached an average level. The level of hope increased significantly after 3 months as compared to the level reached during the hospitalization (Tab. 5).

During the hospital stay, BHI-12 correlated significantly ($p < 0.05$) and positively ($r < 0$) with the frequency of using the Positive revaluation strategy ($r = 0.219$; $p = 0.005$), and significantly ($p < 0.05$) and negatively ($r < 0$) with the level of stress intensity ($r = –0.364$, $p < 0.001$), the frequency of using the Denial strategy ($r = –0.267$; $p = 0.001$), Venting emotions ($r = –0.193$; $p = 0.014$), Cessation of activities ($r = –0.318$, $p < 0.001$) and Blaming oneself strategy ($r = –0.374$, $p < 0.001$). On the other hand, three months after the end of hospitalization, BHI-12 correlates significantly ($p < 0.05$) and positively ($r < 0$) with the frequency of using the Positive revaluation strategy ($r = 0.207$, $p = 0.008$); significantly ($p < 0.05$) and negatively ($r < 0$) with the level of stress intensity ($r = –0.652$, $p < 0.001$), the frequency of using the Denial strategy ($r = –0.308$, $p < 0.001$), Venting feelings ($r = –0.167$, $p = 0.035$), Taking psychoactive substances ($r = –0.175$, $p = 0.026$), Cessation of activities ($r = –0.286$, $p < 0.001$) and Blaming oneself ($r = –0.385$, $p < 0.001$).

Table 2. Subjectively most stressful factors during hospitalization due to miscarriage

What is the most stressful thing for you about miscarriage?	n	[%]*
a) The suddenness of the miscarriage	101	62.73
b) Fear of getting pregnant again	101	62.73
c) Lack of knowledge about the possible cause of the miscarriage	81	50.31
d) Uterine curettage treatment	70	43.48
e) Pharmacological induction of abortion	64	39.75
f) Fear of engaging in sexual activity in the future	63	39.13
g) Physical pain	56	34.78
h) The sight of a miscarried child	39	24.22
i) Decision of the possible burial of the child	31	19.25
j) Providing information about miscarriage to the relatives	23	14.29
k) The method providing information about the miscarriage by the physician	19	11.80
l) Lack of support from loved ones	8	4.97
ł) Bureaucracy in the hospital	6	3.73
m) Other	6	3.73

*percentage of the study group

The multivariate linear regression model demonstrated that the following strategies are important ($p < 0.05$) independent predictors of the level of a sense of basic hope: Return to religion (the regression parameter is 0.972); Search for instrumental support (the regression parameter is –2.466); Cessation of activities (the regression parameter is –1.927).

The increase in the level of a sense of basic hope correlates significantly ($p < 0.05$) and positively ($r < 0$) with the level of stress intensity ($r = 0.226$, $p = 0.004$) and with the use of coping strategies such as Denial ($r = 0.245$, $p = 0.002$), Cessation of activities ($r = 0.169$, $p = 0.032$) and blaming oneself ($r = 0.218$, $p = 0.005$). Thus, the higher the level of stress intensity and the more frequent the use of these strategies during the hospital stay, the more positive the change in the level of a sense of basic hope. The increase in the level of a sense of basic hope correlates significantly (p 0.05) and negatively (r0) with the use of the Sense of humour strategy ($r = –0.21$, $p = 0.008$).

The multivariate linear regression model demonstrated that the following independent predictors of the increase in the level of a sense of basic hope are significant (p 0.05): a decrease in the intensity of stress (the regression parameter is 0.175, so a decrease in the intensity of stress by each additional point boosts the rise in the level of hope by an average of 0.175 points.

DISCUSSION

In the literature on the subject related to the process of recovery, the concept of hope is becoming increasingly important in the context of treating patients. Hope is important for coping effectively with difficult situations, making decisions or adaptation [8]. It contributes to greater therapeutic effectiveness, and its loss increases the feeling of loneliness and lack of adaptation to a new situation [19]. It was also found that the level of hope was associated with personal immunity or variability in symptomatology after traumatization [20]. Studies have shown that a level of hope is associated with lower stress, anxiety, and depression [9]. This is consistent with the results obtained in this work. However, the research on basic hope is very limited and so far, has been left without corresponding studies in the context of miscarriage. Despite numerous analyses in foreign

Table 3. Level of stress during hospitalization and 3 months after — analysis of changes

PSS-10 [points]	During hospitalization	After 3 months	p
Mean ± SD	21.82 ± 6.54	18.17 ± 6.29	< 0.001
Median	23	19	
Guartiles	18–27	13–23	

PSS-10 — Perceived Stress Scale; SD — standard deviation

Table 4. Coping strategies during hospitalization and 3 months after its completion — analysis of changes

Mini-COPE		During hospitalization	After 3 months	p
Acting coping	Mean ± SD	2.22 ± 0.72	2.25 ± 0.72	0.332
	Median	2	2.5	
	Quartiles	2–3	2–3	
Planning	Śr ± SD	2.21 ± 0.73	2.27 ± 0.7	0.023
	Median	2	2.5	
	Quartiles	2–3	2–3	
Positive reappraisal	Śr ± SD	1.77 ± 0.7	1.82 ± 0.74	0.096
	Median	2	2	
	Quartiles	1.5–2	1.5–2.5	
Acceptance	Śr ± SD	2.32 ± 0.54	2.36 ± 0.58	0.019
	Median	2.5	2.5	
	Quartiles	2–2.5	2–3	
Sense of humor	Śr ± SD	0.26 ± 0.49	0.24 ± 0.45	0.511
	Median	0	0	
	Quartiles	0–0.5	0–0.5	
Turning to religion	Śr ± SD	1.81 ± 1.16	1.81 ± 1.14	0.875
	Median	2	2	
	Quartiles	0.5–3	1–3	
Seeking emotional support	Śr ± SD	2.27 ± 0.68	2.31 ± 0.69	0.109
	Median	2.5	2.5	
	Quartiles	2–3	2–3	
Seeking instrumental support	Śr ± SD	2.2 ± 0.64	2.31 ± 0.62	P<0.001
	Median	2	2.5	
	Quartiles	2–2.5	2–3	
Dealing with something else	Śr ± SD	2.19 ± 0.78	2.21 ± 0.75	0.344
	Median	2.5	2.5	
	Quartiles	2–3	2–3	
Denial	Śr ± SD	1.62 ± 1.13	1.48 ± 1.07	0.002
	Median	1.5	1.5	
	Quartiles	0.5–3	0.5 -2.5	
Venting of emotions	Śr ± SD	1.94 ± 0.78	1.97 ± 0.75	0.289
	Median	2	2	
	Quartiles	1.5–2.5	1.5–2.5	
Use of psychoactive substances	Śr ± SD	0.25 ± 0.48	0.29 ± 0.52	0.193
	Median	0	0	
	Quartiles	0–0.5	0–0.5	
Supression of activites	Śr ± SD	0.91 ± 0.64	0.9 ± 0.64	0.425
	Median	1	1	
	Quartiles	0.5–1.5	0.5–1.5	
Self-blamr	Śr ± SD	1.88 ± 1.03	1.82 ± 1	0.174
	Median	2	2	
	Quartiles	1–3	1–3	

Mini-COPE — Inventory to Measure Coping Strategies with Stress; SD — standard deviation

Table 5. Basic hope during hospitalization and 3 months after its completion — analysis of changes

BHI-12 [points]	During hospitalization	After 3 months	p
Mean ± SD	27.79 ± 7	29.17 ± 6.37	0.001
Median	28	29	
Quartiles	23–33	25–35	

BHI-12 — Basic Hope Inventory; SD — standard deviation

literature assessing the psychological reactions of women after miscarriage, the small number of Polish publications makes it extremely difficult to refer to the results presented in our own work, as well as to draw broader conclusions in this context. There is also something left to be desired regarding the inability to compare the results on the level of basic hope after miscarriage with the results of other centres.

The level of hope is related to the preferred style of coping. People with high levels of hope may be more likely to see stressors as a challenge and use more constructive strategies [21]. Therefore, how well a woman can adapt to the emotionally demanding situation of pregnancy loss depends to a large extent on her personal resources, precisely including the level of basic hope, defined as the belief in two traits of the world: a higher order and a general positive attitude towards human beings [22].

Although women experienced high levels of stress, they adopted constructive strategies such as active counselling, planning, positive reappraisal, acceptance, and seeking emotional and instrumental support. This is consistent with the research of other authors [22, 23]. The women who adopt more constructive coping strategies were shown to be more socially active, have a greater tendency to share their feelings about pregnancy loss, and set more realistic goals for the future. On the other hand, those who do not do well often develop unhealthy convictions (for example, that their only hope is a miracle) and behaviours (inability to share feelings, avoiding mothers with children). This assumption agrees with the results of the work. The analysis of regression demonstrated that the using the strategy of the cessation of activities lowers the level of a sense of basic hope.

This issue is worth discussing more broadly. It is interesting that immediately after the miscarriage, while still in the hospital, active coping, planning and seeking instrumental support were of particular importance for the women surveyed, and three months after this event, women were more inclined to accept, seek support not only instrumental, but also emotional. Moreover, after three months, the frequency of using denial strategies also decreased significantly compared to their level during the hospital stay.

Another observed strategy of coping with the situation of miscarriage was to turn to religion. It was noted that in people looking for some meaning in difficult experiences, as well as among women after experiencing the loss of pregnancy and infertility treatment, the return to religion turned out to be a factor reducing despair [22, 24, 25]. This is also consistent with the results obtained in this work. The analysis of the regression showed that the use of this strategy raised the level of basic hope.

An equally important factor in coping with the experience of miscarriage is to overcome a sense of guilt. It is a condition in which one believes or finds out how they contributed to the loss of pregnancy through something they could have done, or vice versa - something they did not do to prevent it. A study by Barr and Cacciatore [26] on the issue of grief after experiencing a miscarriage found that guilt is one of the four important factors contributing to the intensity of its course. This data is basically consistent with the results obtained by the authors of this work. It was noted that the more often the blaming strategy is used, the lower the level of basic hope is. Conversely, the lower one's level of hope is, the more often they blame themselves. An explanation of the cause of foetal death may be helpful in coping with a sense of guilt [27]. Moreover, the certainty that it was independent of the measures undertaken by the mother increased her psychological well-being [28]. Receiving information about the cause of the miscarriage in the light of the results obtained in this work also turned out to be one of the most important factors during hospitalization.

However, the strategies for coping with infertility treatment derived from the literature worldwide are different from those determined in this study [29, 30]. Withdrawal from social life and the use of avoidance turned out to be among the most widespread strategies in other studies. Women in particular avoided interacting with those who were expecting or already had children. Indeed, from a psychological point of view, a treatment for infertility may cause isolation. After all, such actions intensify a sense of loneliness and exclusion, and above all, increase the instances of not sharing emotions and, as a consequence, not taking actions aimed at seeking support. In addition, it has been noted that isolation as a coping strategy may lead to the onset and/or worsening of the symptoms of depression [31].

Therefore, emotional support proved to be an important factor in the process of coping with miscarriage. This strategy was chosen by the respondents as the most

preferred one. This is confirmed by the results of Taşçı et al. [32], which demonstrated that almost 50% of women needed support in connection with pregnancy loss. Most often, the supporters turned out to be partners/husbands and closest relatives [29, 33]. The analysis of women treated for infertility also showed that the support they received had a positive effect on them [33]. This observation was also supported by the results obtained in this work. It was noted that a conversation with a psychologist was declared as one of the most important needs of women during the hospitalisation caused by miscarriage, as was the chance to express their emotions, not suppress their own feelings and being allowed to experience grief. Moreover, sharing one's emotions was a healing factor in the process of grief after miscarriage [34].

This may correspond to the next issue. It was demonstrated that using the strategy of seeking instrumental support was a factor lowering the level of a sense of basic hope during hospitalisation. However, it can be assumed that seeking information about miscarriage, and at the same time the lack of a clear cause thereof, may intensify the feeling of sadness, frustration and misunderstanding of the situation. This is probably also because three months after the end of hospitalisation, the women ceased to deny the occurrence of miscarriage (the frequency of denial significantly decreased after three months compared to the level during the hospital stay) and began to accept this experience (acceptance strategies were at that time used between often and almost always). This may mean that the women adopted the stance of acknowledging the loss and recognised the fact that statistically about 25% of early pregnancies end in spontaneous miscarriage, most of which remain without an understood aetiology [1]. Therefore, seeking instrumental support and sharing one's emotions might no longer be a healing factor and may lead to experiencing a corrective emotional experience, thus offering an opportunity to distance oneself, gradually release oneself from experiences and thoughts about the miscarriage, which until then had disrupted or prevented optimal functioning.

Some note that the emotional impact of pregnancy loss is underestimated by health care professionals [28, 35]. The women reported dissatisfaction especially when an early stage miscarriage was considered an insignificant or minor medical event [36], when they did not receive adequate information on the course of the miscarriage [37] and an explanation for why it had occurred (although it should be admitted that an explanation is not always possible) [36–38], and the curettage of the uterine cavity was treated as a routine procedure ignoring the aspect of the woman's experience [36]. It was also important for the women not to be separated from the ones who gave birth to a healthy child [37–39]. It was also noted that the women who had experienced miscarriage were less satisfied with the provided care than those who gave birth to a stillborn [40]. They thought that their experience in the face of loss in the third trimester was marginalised, diminished and lacked information support. This kind of patient treatment after losing a child seemed to suggest that the miscarriage was a trivial event, inconsistent with the woman's own interpretation of the experience. These observations are in line with the women's opinions obtained in this work. Being informed about each procedure, administration of a drug and other activities undertaken, as well as being able to freely and consciously agree to each medical intervention, receiving information from the doctor about the cause of the miscarriage and instructions on how to proceed and return to sexual activity after leaving the hospital proved to be the most important aspects during hospitalisation. Importance was also attached to the fact that doctors used a language that was understandable and provided information about miscarriage with respect and without bystanders, to the availability of a separate room during hospitalisation and the medical staff's empathy expressed in the tone of voice, eye contact or a handshake.

CONCLUSIONS

The conducted study has several limitations. First, the sample of the surveyed women was collected in only one clinical unit and in one time perspective. The unquestionable strength of this study lies in its objective. There are few studies in Poland assessing the level of stress intensity in women after experiencing a miscarriage, and the conclusions from international studies cannot be fully extrapolated due to cultural differences. Neither are there any studies in the available literature that assess the level of perceived basic hope in the studied group. Understanding the functioning of women in this situation should therefore become a valuable guide in therapeutic proceedings.

Article information and declarations

Data availability statement

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Ethics statement

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee (The Bioethics Committee of the Jan Kochanowski University of Kielce (25/2020) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Author contributions

BK: study design, analyzed the research material, wrote the paper, data collection, interpreted the data.
SM: analyzed the research material, prepared the manuscript, performed the manuscript review.
AGO: analyzed the research material, prepared the manuscript, wrote the paper.
MJ: statistical analysis, interpreted the data.
SG: study design, performed the manuscript review.
All authors read and approved the final manuscript.

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Conflict of interest

The authors declare that they have no competing interests.

Supplementary material

None.

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Rhabdomyosarcoma of the genitourinary system in girls — the role of magnetic resonance imaging in diagnosis, treatment monitoring, and follow-up

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ABSTRACT

Objectives: Rhabdomyosarcoma of the genitourinary system in girls is a rare neoplasm, especially in non-dedicated centers. Our work aimed to sum up and present genitourinary rhabdomyosarcomas in girls from the radiological point of view.

Material and methods: We retrospectively reviewed all girls with genitourinary RMS who underwent treatment at the Institute of Mother and Child in Warsaw between 2009 and 2022. We evaluated the demographic, clinical, and pathological patient data and imaging studies.

Results: During the study period, ten patients presented with genitourinary RMS and underwent magnetic resonance imaging (MRI). The median age at the time of diagnosis was 2.8 years, six patients were younger than three years, and four patients were older than ten years. The most common clinical symptoms were tumor fragments protruding from the vagina/falling out of the vagina and vaginal bleeding or discharge, and the most common original location was the vagina. One hundred percent of patients had the embryonal subtype of RMS, and 100% of cases where molecular tests for PAX3/FOXO1 fusion gen status were performed had negative status. At presentation, the median tumor volume was 114 cm^3. Eight patients (80%) were classified as clinical group III according to the IRS Group, and most patients (70%) were in a standard-risk group. All patients received multimodal treatment, including surgery and chemotherapy; 60% received radiotherapy. Neoadjuvant chemotherapy was the primary treatment for all our patients. In six patients (60%) with a measurable tumor mass after a biopsy, a gradual tumor volume reduction was observed after induction chemotherapy (approximately ten weeks of treatment) — all of which had a partial response (PR). All our patients (100%) responded completely to treatment.

Conclusions: MRI was performed at every stage of diagnosis and treatment as well as during follow-up. It allowed for staging, monitoring of chemotherapy, and guided surgery.

Keywords: genitourinary system; rhabdomyosarcoma; magnetic resonance imaging (MRI)

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INTRODUCTION

Rhabdomyosarcoma (RMS) represents the most common soft tissue sarcoma in infants and children (50% of pediatric soft tissue sarcomas, 3% of all childhood tumors) and the third most common pediatric solid tumor (after brain tumors and neuroblastoma), accounting for 5% to 15% of all childhood solid tumors. Of these, 15% to 20% arise from the genitourinary tract, with the most common sites of origin being the prostate, bladder, and paratesticular regions, followed by the vagina and uterus [1, 2]. In contrast to the prostate and bladder, the vagina and uterus are favorable sites of rhabdomyosarcoma. Almost 60% of RMS cases are recognized in children younger than six years of age. However, embryonal RMS of the vagina mostly occurs in infants and very young girls, unlike that of the cervix which occurs in older patients [3]. The most common symptoms of urogenital RMS are vaginal bleeding or hematuria, visible introital mass or pathological masses that may protrude from the vagina and undergo autoamputation. Other symptoms include abdominal pain or discomfort in the abdominal or pelvic area, a mass or swelling in the genital area, increased abdominal circumference, urinary or/and stool incontinence, and abdominal pathological mass on palpation. The diagnosis requires, except physical

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Table 1. Intergroup Rhabdomyosarcoma Study group clinical classification system

Group	Definition
I	Localized tumor, completely removed with pathologically clear margins and no regional lymph node involvement
II	Localized tumor, grossly removed with (a) microscopically involved margins, (b) involved grossly resected regional lymph nodes, or (c) both
III	Localized tumor, with gross residual disease after grossly incomplete removal, or biopsy only
IV	Distant metastases present at diagnosis

Table 2. Risk stratification for rhabdomyosarcoma

Risk group	Subgroup	Pathology	IRS group	Site	Node stage	Size & Age
Low	A	Favorable	I	Any	N0	Favorable
Standard	B	Favorable	I	Any	N0	Unfavorable
	C	Favorable	II, III	Favorable	N0	Any
	D	Favorable	II, III	Unfavorable	N0	Favorable
High	E	Favorable	II, III	Unfavorable	N0	Unfavorable
	F	Favorable	II, III	Any	N1	Any
	G	Unfavorable	I, II, III	Any	N0	Any
Very High	H	Unfavorable	II, III	Any	N1	Any

Pathology: *Favorable* = all embryonal, spindle cell, botryoid RMS; *Unfavorable = all alveolar RMS*
Site: *Favorable* = orbit, genitourinary non bladder/prostate, non parameningeal head&neck; *Unfavorable = all other sites (parameningeal, extremities, genitourinary bladder/prostate and "other site");*
Node stage: *N0* = no clinical and pathological node involvement; *N1 = clinical or pathological node involvement;*
Size & Age: *Favorable* = tumor size (maximum dimension) ≤ 5 cm **and** age < 10 years; *Unfavorable = all others*
IRS — Intergroup Rhabdomyosarcoma Study; RMS — rhabdomyosarcoma

examination, imaging studies [ultrasound (US), magnetic resonance imaging (MRI)], and is based on pathological examination of pathological tissue. Treatment for RMS of the vagina and uterus may include surgery to remove the cancerous tissue, chemotherapy, and radiation therapy [4]. The treatment plan depends on the stage and location of the cancer, as well as the child's overall health. The prognosis is generally good with early diagnosis and treatment. However, the individual outcome depends on cancer biology and the child's response to treatment.

We encounter rhabdomyosarcoma quite often at the Institute of Mother and Child in Warsaw, a tertiary referral center for bone and soft tissue sarcomas in children and adolescents, whereas in non-dedicated centers it is an outstandingly rare pathology, especially in genitourinary location, and reported as rare case descriptions [5]. This prompted us to choose this topic.

Objective

The purpose of this study is to sum up and present genitourinary rhabdomyosarcomas in girls from the radiological point of view: diagnostics, treatment decisions and monitoring, and follow-up.

MATERIAL AND METHODS

Our material consists of 10 girls aged between 8 months and 17 years at the time of diagnosis who underwent treatment for RMS of the genitourinary system at the Department of Oncology and Surgical Oncology for Children and Youth in cooperation with the Department of Obstetrics and Gynecology of the Institute of Mother and Child in Warsaw in the years 2009–2022.

We retrospectively evaluated the patients' data and imaging studies. The analysis included age at diagnosis, clinical picture and tumor characteristics — origin, histological subtype, and genetic evaluation. The stage was determined according to the Intergroup Rhabdomyosarcoma Study (IRS) Group clinical classification system which groups patients based on the extent of the tumor, resectability, and microscopic assessment of surgical margins (Tab. 1) [6]. Risk stratification was performed based on the classification mentioned above, other tumor features (site, size, pathology), nodal stage and age at diagnosis (Tab. 2) [7].

Initial tumor volume (at diagnosis), response to treatment, and status at end-of-treatment were reviewed retrospectively based on magnetic resonance imaging (MRI) studies. In each case, a formula for the ellipsoid and round

Table 3. Response evaluation

Complete response (CR)	Complete disappearance of all visible disease
Very good partial response (VGPR)	≥ 90% reduction of tumor volume or persistence of unclear residuals upon imaging
Partial response (PR > 2/3)	≥ 66% reduction of tumor volume
Minor partial response (PR < 2/3)	< 66% but ≥ 33% reduction of tumor volume
Stable disease (SD)	< 33% reduction of tumor volume
Progressive disease (PD)	≥ 33% increase of tumor volume or appearance of new lesions

tumors was used to calculate tumor volume: $V = a \times b \times c \times \times 0.52$ in cm^3. Response to treatment was assessed based on the percentage reduction of tumor volume compared to the initial volume, which then allowed to qualify patients for the appropriate group: complete response (CR), partial response (PR), stable disease (SD), progressive disease (PD) (Tab. 3) [8].

In addition, regional lymph nodes were evaluated on the initial MRI study — shape, size and presence of hilum were assessed.

In our center, the standard follow-up examinations consist of local assessment on imaging studies (MRI or US) and gynecological examinations — vaginoscopy or hysteroscopy with biopsy of suspicious lesions if needed. Chest X-ray/chest CT (every 3 months) and PET-CT (if applicable) are used to check for distant metastases.

RESULTS

Between 2009 and 2022, ten girls with genitourinary RMS were examined and treated at the Institute of Mother and Child. The median age at the time of diagnosis was 2.8 years, six patients (60%) were younger than three years at diagnosis, and four patients (40%) were older than ten years. The clinical symptoms included: tumor fragments protruding from the vagina/falling out of the vagina (60%) (Fig. 1), vaginal bleeding or discharge (40%), or enlargement of the abdominal circumference (20%). The original locations of the genitourinary RMS were the vagina (40%), cervix (30%), and uterine body (10%); in 2 cases (20%) the origin of the tumor was unclear. All patients had the embryonal subtype of RMS, of which there was botryoid variant in three girls and one spindle cell variant. In 60% of cases, molecular tests for PAX3/FOXO1 fusion gen status were performed; in this group all patients had negative status.

At presentation, the median tumor volume was 114 cm^3 (5.3–807.0 cm^3). In two patients there were suspicious regional lymph nodes. No patient had distant metastases at diagnosis, but one developed lung metastases during treatment.

According to the IRS Group, eight patients (80%) were classified as clinical group III. 70% of patients were in a standard-risk group, and 30% were in the high-risk group.

All patients received multimodal treatment, including surgery (Fig. 2) and chemotherapy; 60% received radiotherapy. Neoadjuvant chemotherapy was the primary treatment for all our patients. In six patients (60%) with a measurable tumor mass after a biopsy, a gradual tumor volume reduction was observed after induction chemotherapy (approximately ten weeks of treatment) (Fig. 3) — all of which had a PR. Finally, all our patients (100%) responded completely to treatment and are still in follow-up. One patient (10%) had lung recurrence one year after the first line of chemotherapy and brachytherapy. Still, she finally achieved a complete response after second-line chemotherapy and whole lung radiation.

A summary of patients' data and results of their examinations is shown in Table 4.

DISCUSSION

Although it may seem that the material of a single center collected in this study is not large, when comparing it with large databases one must change one's mind: in the Surveillance, Epidemiology, and End Results (SEER) Program providing information on cancer statistics in the USA, 67 cases of pediatric rhabdomyosarcoma of the female genitourinary tract were identified over the course of 33 years [9]. Knowledge of this neoplasm is essential, not least so that treatment is not delayed by looking for evidence of sexual misconduct, as was the case in one of our patients.

Not all patients came to our institute immediately, hence we do not have imaging studies performed on all of them from the very beginning of the diagnosis, but they were all followed up with US and MRI studies performed at the Department of Diagnostic Imaging of our Institute.

The most common location of RMS of the genitourinary system in girls is vagina [10] and this was confirmed in our material - including the case of an unclear point of origin, but most likely originating in the vagina, half of our patients had vaginal RMS. It is often a pedunculated tumor that protrudes outside the vagina and can undergo autoamputation, as in half of our patients with a clear tumor origin. In such cases, the first diagnosis is based on the clinical picture — visual. Only 0.5% of the RMS of the genitourinary system is located in the cervix, usually in older patients [10] — in our study,

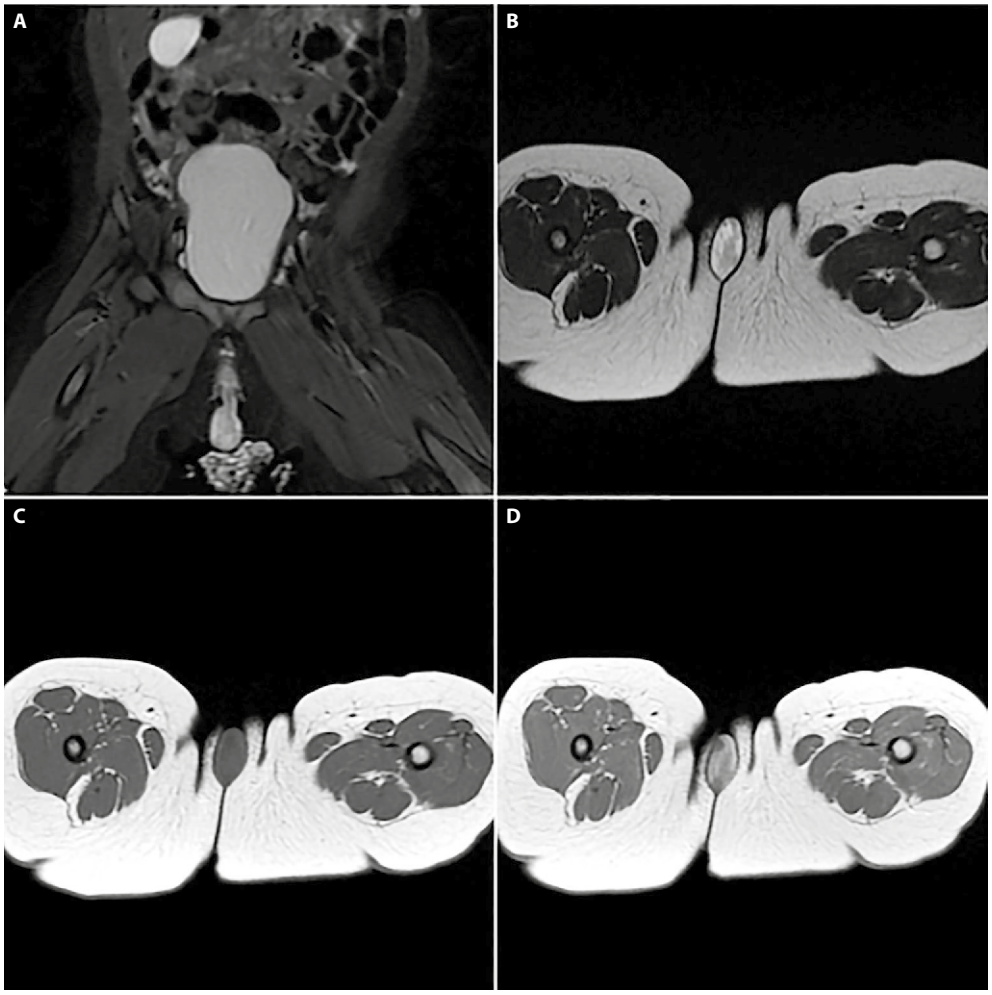

Figure 1. Initial magnetic resonance imagining (MRI) of an 8-month-old girl with vaginal rhabdomyosarcoma (RMS). Visible tumor protruding from the vagina between the labia majora; **A.** STIR, coronal plane; **B.** FSE/T2, axial plane; **C.** FSE/T1, axial plane; **D.** FSE/T1 post-Gd, axial plane

we have three patients with this tumor origin. Two of them at the time of diagnosis were in the second decade of life (one aged 11.1 years, the other aged 17.5 years) and the tumor was an incidental pathological finding after resection of the cervical polyp in these cases. In both above clinical situations, imaging studies are used to search for signs of possible involvement of the reproductive organ beyond the protruding/resected lesion.

In the other, less obvious cases, such as two of our patients, in which enlarged abdominal circumference was the only clinical symptom, imaging methods play a leading role in diagnosis from the beginning. Ultrasonography is usually the first method of imaging soft tissue tumors in children as it is non-invasive, easily accessible, has a high resolution, allows for a quick assessment of tumor size and vascularity, and enables the evaluation of regional lymph nodes. However, imaging is never limited to ultrasound, and MRI is performed which is a method of choice. It allows for precise determination of tumor location, its possible spread outside the affected organ, its relation to the surrounding structures, and for the assessment of regional lymph nodes and metastases in the examination area (*e.g.*, to the bones).

Computed tomography is not currently used to assess local tumor staging due to too low tissue resolution in relation to needs and therefore the pros and cons tilt decisively to the negative side: too little information in relation to the burden of ionizing radiation and iodine contrast agent. Only chest CT is performed to look for lung metastases in patients with genitourinary RMS.

To complete staging and follow-up in RMS the whole bone examination is mandatory; in our center, positron-emission tomography — computed tomography (PET-CT) is usually performed.

The appearance of RMS on US is non-specific with typically well-defined mass that is inhomogeneous and slightly hypoechoic and can show significant increase of blood flow on Doppler examination. The MRI appearance of RMS is non-specific as well, with intermediate signal intensity

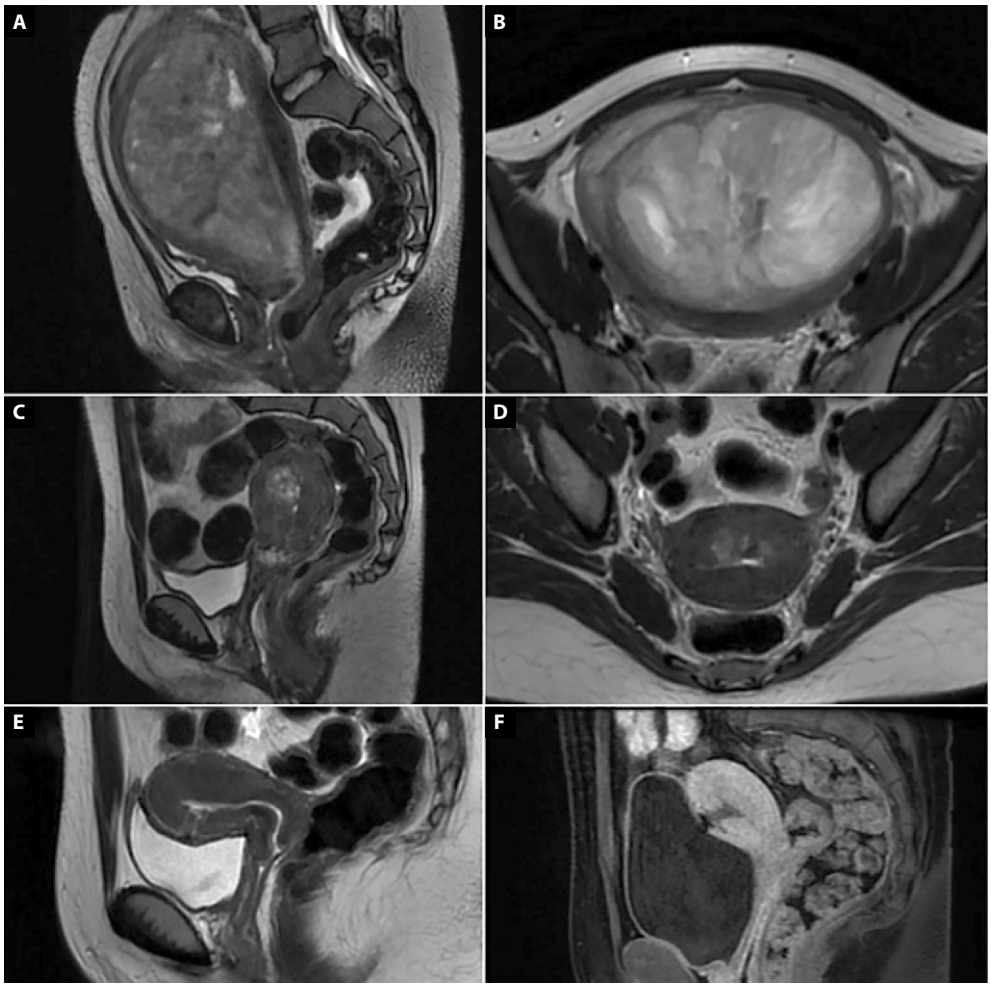

Figure 2. Three magnetic resonance imagining (MRI) studies of a 13-year-old female patient with rhabdomyosarcoma (RMS) of the uterine body. **1.** Initial examination. A giant tumor fills the uterine cavity; **A.** CUBE/3D/T2, sagittal plane; **B.** FSE/T2, axial plane; **2.** Examination after the first cycle of chemotherapy (after 14 weeks). Significant reduction in tumor volume; **C.** CUBE/3D/T2, sagittal plane; **D.** FSE/T2, axial plane; **3.** Examination after fertility-sparing resection. Non-enhancing scar and hemosiderin deposits in the anterior/inferior uterine wall; **E.** FSE/T2, sagittal plane; **F.** WATER/T1 post-Gd, sagittal plane

(SI) on T1-weighted images and intermediate to high SI on T2-weighted images, diffusion restriction, and strong contrast enhancement of solid parts (as the tumors may show multicystic architecture). It may also be solid, with a lobulated contour [11].

In our study, all patients (100%) had the embryonal subtype of rhabdomyosarcoma, which accounts for approximately 90% of genitourinary RMS [10] and is associated with a significantly better prognosis than the other subtypes. Genetic evaluation of the tumor for the presence of PAX3/FOXO1 or PAX7/FOXO1 fusions is currently performed to distinguish between subtypes. Eighty percent of the alveolar subtype has a positive status, which means they express the oncogenic genes fusing PAX3 or PAX7 with FOXO1; this expression is not present in any other cancer [12]. In 60% of our patients, genetic tests were performed — all of them had a negative PAX3/FOXO1 status, which clearly indicates the embryonic subtype. Moreover, localization in non-bladder/non-prostate sites is favorable, like in 80% of our patients (girls with clear tumor origin) [13].

Chemotherapy is the base of multimodal RMS treatment [14]. In 60% of our patients (who had a measurable tumor mass after biopsy), chemotherapy was the main treatment, and in most cases, a partial response to subsequent cycles of systemic therapy was observed, manifested by a reduction in tumor volume on follow-up MR examinations. Local treatment includes surgery and radiotherapy. All our patients underwent surgery at some stage of treatment — at the beginning (in 40%) and, in other cases, to remove residual tumor mass after chemotherapy or recurrence. Postoperative chemotherapy was mandatory and received by all our patients. Radiotherapy was realized as teleradiotherapy or

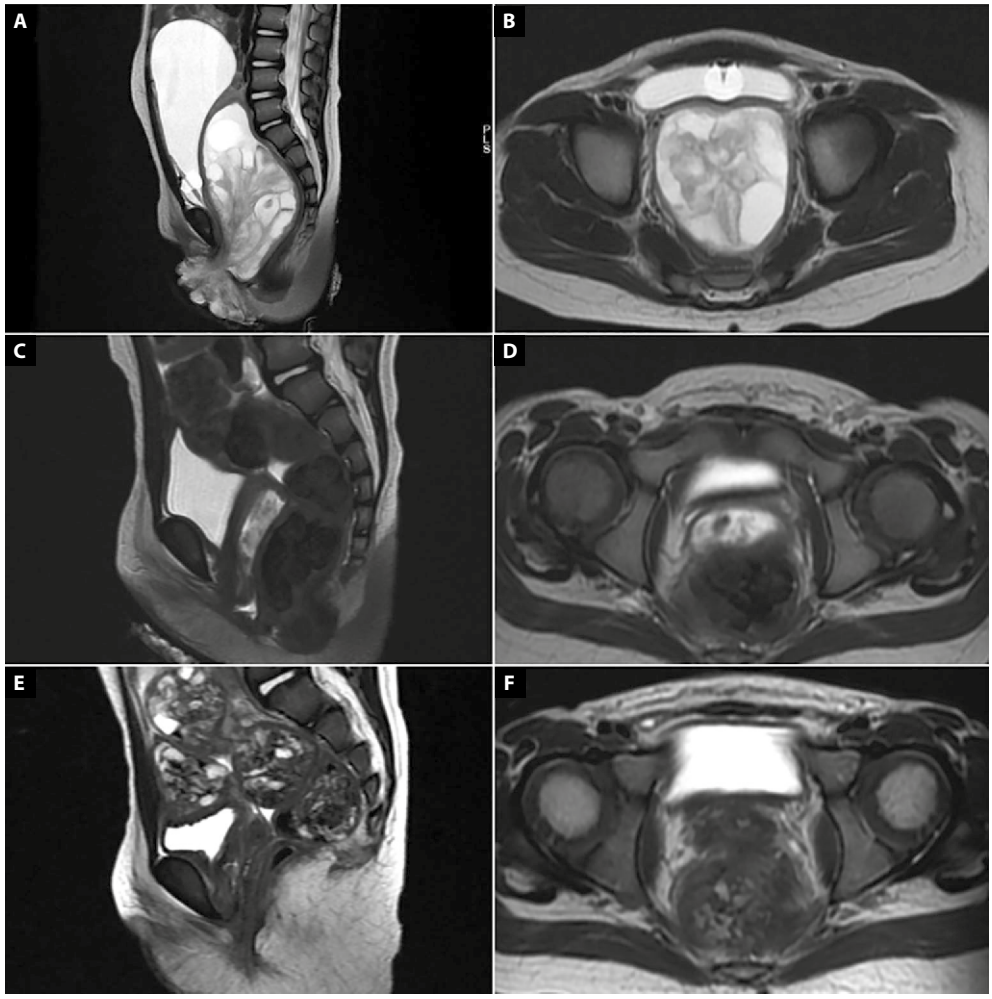

Figure 3. Three consecutive magnetic resonance imagining (MRI) studies of a 2-year-old patient with vaginal rhabdomyosarcoma (RMS) show a very good response to chemotherapy; **1.** Initial study. A large tumor fills the vagina and protrudes outwards; **A.** FSE/T2, sagittal plane; **B.** FSE/T2, axial plane; **2.** Examination after ten weeks of chemotherapy. Reduction of tumor volume, no protruding part; **C.** FSE/T2, sagittal plane; **D.** FSE/T2, axial plane; **3.** Follow-up examination after 20 weeks of chemotherapy. There is no visible tumor in the vagina **E.** FSE/T2, sagittal plane, **F.** FSE/T2, axial plane

brachytherapy. Postoperative radiotherapy was performed in 6 girls (60%) and in 3 cases it was brachytherapy.

Magnetic resonance imagining is a modality of choice to show the potential residual mass and to plan the fertility-sparing resection which is an issue of utmost importance in girls and requires close radiological-gynecological co-operation. In one case of uterine body sarcoma, which almost reached the diaphragm before chemotherapy, the first step after oncological treatment was an operative hysteroscopy. The main goal was to detect any neoplastic tissue in the anterior uterine wall. Hysteroscopy was performed in the operative room under general anesthesia with a 10 mm resectoscope (Gynecare Hysteroscope, Johnson and Johnson, New Jersey) with bipolar energy. The samples were taken from the anterior wall from a place that was identified on MRI as a possible residual sarcoma. Pathomorphological samples revealed no neoplasia. As hysteroscopy can only remove tissue from the uterine cavity and from the cavity side of the uterus wall, the next step was to perform laparoscopy to remove all other uterine tissue that was identified as suspicious on MRI, from the anterior uterine wall. The surgery was performed in patient in a 30° Trendelenburg position under general anesthesia, using a carbon dioxide insufflation laparoscopy system (Karl Storz, Munich, Germany). The intra-peritoneal laparoscopic view was obtained *via pneumoperitoneum*, and laparoscopic instruments were introduced through the abdominal wall *via* 0.5–1-cm valveless trocars. Both monopolar cautery and scissors were used, and a suspicious part of the front uterine wall was removed. The uterus cavity was exposed. Then, the anterior wall was closed with intracorporeal absorbable sutures. Because the patient was qualified — according to the oncological protocol — for the small pelvis radiotherapy in the next step of treatment, during the same operation transposition of the

Table 4. Patients' data and results of their examinations

No.	Age at diagnosis (years + months)	Clinical picture	Localization	Pathology subtype and variant	Genetics (PAX3/ /FOXO1 fusion status)	Initial volume [cm^3]	Suspicious regional lymph nodes	Distant metastates	IRS group	Risk stratification	Treatment	Response	Time of observation (years + months)
1	17 + 6	Vaginal bleeding	Cervical polyp	Embryonal, variant unknown	Negative	Initial study not available	No	Yes	III	SR C	Surgical, cht, rtx	CR	2 + 0
2	1 + 0	Vaginal bleeding + tumor protruding from the vagina	Vagina	Embryonal, botryoid	Negative	81	No	No	III	SR C	Cht, surgical	CR	2 + 6
3	11 + 1	Vaginal bleeding	Cervical polyp	Embryonal, spindle cell	Negative	Initial study not available	No	No	I	SR B/C	Surgical, cht	CR	2 + 6
4	13 + 5	Abdominal circumference enlargement (mass in the lower abdomen)	Uterine body	Embryonal, variant unknown	Negative	807	Yes	No	III	HR F/H	Cht, surgical, rtx	CR	2 + 3
5	0 + 8	Tumor protruding from the vagina	Vagina	Embryonal, variant unknown	Data not available	5.3	No	No	II	SR C	Surgical, cht, rtx	CR	7 + 8
6	2 + 9	Vaginal discharge + masses falling out of the vagina	Cervix	Embryonal, variant unknown	Negative	6,7	Yes	No	III	HR E	Cht, surgical	CR	3 + 0
7	17 + 3	Menstrual disturbance + tumor protruding from the vagina	Vagina	Embryonal, botryoid	Data not available	582	No	No	III	SR C	Cht, surgical, rtx	CR	3 + 6
8	1 + 7	Data not available	Unclear origin — vagina?	Data not available	Data not available	Initial study not available	Data not available	No	data not available	data not available	Cht, surgical, rtx	CR	13 + 6
9	2 + 3	Tumor protruding from the vagina	Vagina	Embryonal, botryoid	Data not available	147	No	No	III	SR C	Cht, surgical	no end-of-treatment examination	0 + 5
10	2 + 10	Data not available	Unclear origin	Rhabdomyo-fibrosarcoma infantile	Negative	Initial study not available	Data not available	No	II/III	HR E/F	Surgical, cht, rtx	CR	3 + 4

IRS — Intergroup Rhabdomyosarcoma Study; SR — standard risk group; HR — high risk group; B/C, F/H, E/F — subgroups; Cht — chemotherapy; Rtx — radiotherapy; CR — complete response

ovaries outside the pelvis and outside the potential radiotherapy field was performed. During this part of the procedure the ovaries were mobilized and grasped. The ureters were identified through the peritoneum. The utero-ovarian ligament was cauterized and severed using bipolar forceps for coagulation and scissors alternatively. The fallopian tubes were separated from the ovaries through the mesovarium. The peritoneum then was incised along the infundibulopelvic ligament to mobilize the ovaries completely. Dissection of the ovarian vessels was performed up to the level of the aortic bifurcation. The ovaries were transposed laterally to the paracolic gutters and fixed securely with use of two sutures. Two metal clips were applied to each transposed ovary to guide subsequent roentgenographic localization. Pathomorphological samples revealed no neoplasia.

As in case of adnexal masses that have indeterminate appearance on US, MRI is a modality of choice in the diagnosis of unclear pathological masses in the transposed ovaries which – depending on the site of transposition — may be difficult to reach with US.

Only two patients (20%) had a local relapse during treatment, diagnosed on follow-up MRI. One of these patients had unfavorable prognostic factors, such as age > 10 years and initial maximum tumor dimension > 5 cm. Magnetic resonance imagining examinations at the end of treatment showed no abnormalities or only scars and hemosiderin deposits after surgical procedures were visible.

CONCLUSIONS

In conclusion, magnetic resonance imaging was performed at every stage of diagnosis and treatment of our patients as well as during follow-up. It allowed for staging, monitoring of chemotherapy, and guided surgery.

Article information and declarations

Data availability statement

Additional data is available from the corresponding author on a reasonable request.

Ethics statement

The study was conducted in accordance with the Declaration of Helsinki. Written informed consent for clinical imaging was obtained from the patients/patients' guardians.

Author contributions

PS collected and analyzed the imaging data, analyzed the literature, and wrote the text; ZM and AR completed the oncological part of the text; TI completed the gynecological part of the text; MBF conceptualized and supervised the study, reviewed the text. All authors read and approved the final manuscript.

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None.

Conflict of interest

All authors declare no conflict of interest.

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Ductus venosus opens in high-risk pregnancies without signs of increased central venous pressure

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ABSTRACT

Objectives: It has been belived that changes in diastolic blood velocities in the fetal ductus venosus were due to increased central venous pressure secondary to increased fetal heart strain during hypoxia or heart failure. There have been recent reports of changes in ductus venosus blood velocity without signs of increased fetal heart strain. The aim of this evaluation was to compare blood velocity in the right hepatic vein as a marker of increased central venous pressure in relationship to changes in ductus venosus blood velocity.

Material and methods: Fifty pregnancies suspected of fetal growth resitriction were evaluated by Doppler ultrasound. Blood velocity was recorded in the right hepatic vein, ducus venosus and in the umbilical vein. Placental blood flow was also recorded in the uterine and umbilical arteries as well as the fetal middle cerebral artery.

Results: Increased umbilical artery pulsatility index was recorded in 19 fetuses and 20 has signes of brain sparing according to recordings in the middle cerebral artery. Abnormal blood velocity in the ductus venosus was recorded in 5 fetuses, none of these fetuses had an abnormal pulsatility in the right hepatic vein.

Conclusions: Opening of the ductus venosus is not only related to fetal cardiac strain. This might indicate that the ductus venosus does not primarily open due to increased central venous pressure in moderate fetal hypoxia. Increased fetal cardiac strain might be a late event in the process of chronic fetal hypoxia.

Keywords: ultrasound; Velocity vector imaging; fetal heart; strain; Doppler; ductus venosus; umbilical vein; pulsations; hypoxia; pregnancy

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INTRODUCTION

About 20 to 30% of umbilical venous blood flow passes the fetal ductus venosus (DV). The main part of the blood stream from the DV passes through the oval foramen for the left heart atrium [1]. During fetal hypoxemia the DV opens giving away more of the oxygenated blood from the umbilical vein towards the left part of the heart and thus for the coronaries and brain as a part of a redistribution regulation. As much as 70% of the umbilical venous blood flow has been reported to pass the DV in severe fetal hypoxia [2].

Fetal central venous blood flow and flow in the DV has a pulsating pattern, which reflects pressure within the right atrium. Increased reversal of blood flow during diastole has been demonstrated during fetal heart failure [3]. Blood flow in the umbilical vein is normally without pulsations. A pulsating blood flow pattern has been demonstrated in severe fetal hypoxia and heart failure presumably because of opening of the ductus venosus due to increased central venous pressure, which has been believed to be secondary to increased strain on the fetal heart [3, 4].

Studies of fetal heart function have not given signs of strain during moderate chronic hypoxia using analysis of speckle tracking of the heart walls or during analysis of waveforms in the hepatic veins or inferior vena cava

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entering the right atrium which might indicated increased central venous pressure. Fetal heart function has been shown normal even during abnormal blood flow pattern in the ductus venosus [5–8]. Ductus venosus might thus open without an increase in fetal central venous pressure. The ductus might thus react by opening due to hypoxia, as a part of redistribution of oxygenated blood to the vital organs heart and brain. This redistribution of oxygenated blood from the placenta might maintain fetal heart function for some time during moderate chronic hypoxia.

The aim of this study was to examine blood flow in the DV and hepatic veins in pregnancies suspected of chronic hypoxia. Signs of DV opening without changes in hepatic venous blood velocity should proof that opening of the ductus during moderate chronic hypoxia might occur without an increased in central venous pressure due to increased fetal heart strain.

MATERIAL AND METHODS

Singleton pregnancies suspected fetal growth restriction and at risk of developing chronic hypoxia were examined. Fetal size was evaluated by ultrasound and related to normal reference levels [9]. The amount of amniotic fluid was also evaluated. Fetal condition was evaluated by cardiotocography and by ultrasound Doppler recording of the umbilical, uterine and middle cerebral arteries. Blood velocity was also recorded by Doppler ultrasound in the right hepatic vein, in the DV and in the umbilical vein in the cord and intra-abdominally. Blood velocity waveforms recorded were analysed for pulsatility index (PI) and related to normal reference values.

The umbilical artery blood flow velocity was recorded from a free-floating central part of the umbilical cord at a zero-degree angle. Pulsatility index was analysed during three consecutive cardiac cycles and compared with normal reference values [10]. The uterine artery blood velocity was recorded from both uterine arteries after the vessels have been located by color flow mapping in an oblique scan with the sample volume placed in the artery just cranial to the crossing of the external iliac vessels. Three even blood velocity waveforms were analysed for pulsatility index. Increased uterine artery vascular impedance was defined as PI > 1.20. A pattern of an early diastolic notch in the uterine blood velocity spectrum was also documented. Umbilical venous blood flow was recorded in the central intra-abdominal part of the vein and in a free-floating part of the vein in the cord. The DV blood velocity was recorded in either a midsagittal or transverse view, positioning the Doppler gate at the isthmic portion. The DV blood velocity pattern was analysed for pulsatility index for veins (PIV) related to normal reference levels [11]. Blood flow velocity was also be recorded in the right hepatic vein before its entrance into the inferior vena cava. The blood velocity pattern was evaluated for PIV and related to normal reference levels as a marker of increased central venous pressure [12]. Blood flow in the middle cerebral artery (MCA) was also be recorded about 1 cm from the circle of Willis and analysed for PI and related to normal reference limits for signs of brain sparing [13].

Outcome of pregnancy was evaluated as interventions during labor such as: Caesarean section; operative delivery for fetal distress (ODFD) indicated by abnormal cardiotocography tracing and/or fetal scalp blood pH. The gestational age at birth was noted as well as birthweight. A small-for-gestational-age (SGA) infant were defined as having a birthweight below 10th percentile for the corresponding gestational age [9].

The neonatal condition was evaluated by the Apgar score at 1, 5 and 10 minutes, umbilical artery and venous cord blood gases at birth, the frequency of admission to a neonatal intensive care unit (NICU), the need for artificial ventilation and perinatal mortality was also be noted.

RESULTS

Fifty pregnancies were included in the study suspected of fetal growth restriction. The mean gestational age at admission was 33.9 weeks (range 24–39) and the mean growth percentily deviation was 3.22 ± 22.7 %.

Nineteen of the pregnancies had an increased PI in the umbilical artery, one having absent flow in diastole. There were 9 cases with abnormal PI in the right uterine artery and 14 in the left artery. There were 20 fetuses with signs of brain sparing in the middle cerebral artery. Increased PIV in the DV was recorded in 5 fetuses, none having absent or reversed flow in end-diastole. None of the fetuses had signs of pulsations the umbilical vein. Blood flow veliocity in the right hepatic vein was normal in all these cases.

Gestational age at birth was 35.5 weeks (range 25––39). There were 23 abdominal deliveries, 6 due to breech presentation and 17 due to suspected fetal distress. Umbilical cord pH was normal in all the newborns. There were 13 admissions for neonatal intensive care. The avarage gestational age at birth in these cases was 30.5 weeks (range 25–37), the avarage birth weight was 1164 g (range 490–1870), the avarage number of days on NICU was 23 days (range 2–80). Twelf of the newborns needed respiratory support. Seven newborns needed mechanical ventilation first and then continuous positive airway pressure (CPAP). The avarage gestational age at bith in that group was 28.5 weeks (range 25–31) and the avarage birth weight was 844 g (range 490–1300). The avarage time on mechanical ventilation was 13 days (range 5–41) and on CPAP 26 days (range 2–56). One newborn born in 25 weeks' gestation with birth weight of 490 g died after 5 days of mechanical ventilation. Five newborns needed only CPAP after being

admitted to NICU. The avarage gestation age at birth in that group was 32 (range 30–35) and the avarage birth weigt was 1470 g (range 1100–1770). The avarage time on CPAP was 7.6 days (range 3–14). There was no correlation between any blood velocity or PIV recorded by Doppler ultrasound in the hepatic vein or in the DV and the need of any respiratory support in newborn infants.

DISCUSSION

These resulsts support the theory that the ductus venosus can open in moderate chronic hypoxia without there being signs of increased central venours pressure due to increased cardiac strain.

Increased venous pulsatility has been demonstrated in fetal heart failure and severe hypoxia as a sign of increased central venous pressure [3, 4]. The increase in fetal heart failure and severe hypoxia has been show to be transmitted to the ductus venosus and even to the umbilical vein where the steady flow becomes pulsating due to opening of the ductus venosus. We belived based on this knowledge, that changes in ducus venosus PIV was a reflection of increased cardiac strain during chronic fetal hypoxia. However, Doppler research on blood flow in the central fetal veins like the hepatic veins and inferior vena cava have not been able to demonstrate changes in pulsatility in the central venous pulsatility in cases suggested in moderate chronic hypoxia [5, 6]. The same applies for evaluation of fetal heart wall motility. Increased blood flow pulsatilify in the ductus venousus could not be demonstraited by using spectral tracking of fetal ventricel walls and the right atrial wall movements where reduced motility would be a sign of increased cardiac strain [7, 8]. These findings might suggest that the ductus venosus functions as a redistributional organ facilitating increased flow of oxygenated blood to the left side of the heart and thus the coronaries and brain without there being an increase in central venous pressure in moderated fetal hypoxia.

The DV Doppler is presently increasingly being used for fetal surveillance in early onset fetal growth restriction before 30–32 weeks of gestation. The results indicate that DV PIV measurement is a good predictor of perinatal outcome and may be useful in determining the timing of the delivery in of early FGR fetuses [14].

CONCLUSIONS

The use of DV Doppler in conbination with computerized CTG on deciding on delivery because of worsening fetal condition has given reasuring results with a surveival rate of about 90% without major neurology handicap [15, 16]. The results suggest that the optimal timing of delivery of fetuses with early intrauterine growth restriction may be best determined by monitoring them longitudinally, with both DV and CTG monitoring [17]. Admission to NICU and the need of respiratory support was seen in the preterm infants group without any correlation with any blood velocity or PI recorded by Doppler ultrasound in the hepatic vein and in the DV. This tends to confirm the fact that respiratory condictions are the most common reason for admissions tu NICU [18, 19] and are mostly related to the gastational age of the newborn infant [20].

Article information and declarations

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Conflict of interest

All authors declare no conflict of interest.

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Comparison of dydrogesterone plus progesterone gel with subcutaneous aqueous progesterone plus progesterone gel for luteal phase supplementation of subsequent *in vitro* cycle in women after previous cycle failure

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ABSTRACT

Objectives: The luteal phase supplementation (LPS) of the *in vitro* fertilization (IVF) cycle is crucial to increase the chance of a live birth. There is no preferred progestogen for use in the general population. The optimal progestogen regimen in the event of prior IVF failure is unknown. The aim was to compare the live birth rate for dydrogesterone plus progesterone gel versus aqueous progesterone plus progesterone gel in LPS of the IVF cycle in women with at least one previous IVF failure.

Material and methods: A prospective randomized single-center study enrolled women with at least one previous IVF failure undergoing another IVF cycle. Women were randomly assigned in a 1:1 ratio to 2 arms depending on LPS protocol: dydrogesterone (Duphaston®) + progesterone in vaginal gel (Crinone®) vs aqueous progesterone solution in subcutaneous injection (Prolutex®) + progesterone in vaginal gel (Crinone®). All women underwent fresh embryo transfer.

Results: The live birth rate with one prior IVF failure was 26.9% for D + PG vs 21.2% for AP + PG (p = 0.54), and with at least two IVF failures: 16% for D + PG vs 31.1% for AP + PG (p = 0.16). There were no significant differences in live birth rates between protocols, regardless of the number of prior IVF failures.

Conclusions: In light of the evidence from this study that neither of the two LPS protocols is more effective in women with prior IVF failure, other factors, such as potential side effects, dosing convenience and patient preference, should be considered when choosing a treatment.

Keywords: luteal phase support; *in vitro* fertilization; fresh embryo transfer; progestogens; live birth rate

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INTRODUCTION

In *in vitro* fertilization (IVF) cycles the course of luteal phase is deficient due to premature luteolysis caused by supra-physiological levels of estradiol and progesterone in human chorionic gonadotropin (hCG)-induced early luteal phase, aspiration of granular cells from follicles during oocyte retrieval, and suppression of luteinizing hormone (LH) in agonist and antagonist protocols [1]. In particular, progesterone significantly reduces LH production through negative feedback mechanisms in the hypothalamus and pituitary gland. Since LH activity is crucial for the function of the corpus luteum, a significant decrease in the concentration of this gonadotropin after triggering ovulation causes relative damage to the luteal phase [2]. Furthermore, the disturbed course of the luteal phase leads to impaired development of the endometrium

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and asynchrony between endometrial receptivity and the maturity of the transferred embryo [3]. The above phenomena adversely affect implantation and early pregnancy development, reducing the chance of establishing and maintaining the pregnancy. The luteal phase in IVF cycles must therefore be medically assisted using progestogens or hCG, and an optional addition of gonadotropin releasing hormone (GnRH) analogues [4, 5], at least until a positive pregnancy test. Due to the increased relative risk of ovarian hyperstimulation syndrome (OHSS) associated with the use of hCG, progesterone has become the drug of choice in the luteal phase supplementation (LPS) [6]. Much scientific research has been carried out to date to compare the efficacy and safety of progesterone preparations administered in different regimens and routes. Except for the oral administration of dydrogesterone [7], oral administration of progesterone to supplement IVF cycles is less effective compared to other routes of administration [6], *i.e.*, vaginal, rectal, subcutaneous, and intramuscular. However, no advantage of any of the above-mentioned routes of progesterone administration over the other has been identified in the systematic reviews and meta-analyzes [6]. It is worth noting that the studies conducted so far have not focused on women who are additionally burdened with factors reducing the chance of IVF success, such as previous IVF failure. Therefore, a study was designed to compare two protocols of LPS, i.e., dydrogesterone oral tablet with progesterone vaginal gel versus subcutaneous aqueous progesterone with progesterone vaginal gel in a population of women with the history of at least one IVF failure, approaching another IVF cycle. Due to the lack of a recommended administration route and dose of LPS, the addition of an oral or subcutaneous route to vaginal application in women with previous IVF failure, resulted from a cautious approach to possible issues related to progesterone bioavailability [8–11].

Objectives

Comparison of obstetric outcomes for dydrogesterone + + progesterone in vaginal gel protocol (D + PG) versus progesterone in subcutaneous injection + progesterone in vaginal gel protocol (AP + PG) in LPS in IVF cycles in women with previous IVF failure.

Specific aims

1. Comparison of the rates of obtained biochemical pregnancies with the use of D + PG vs AP + PG protocols in LPS.
2. Comparison of the rates of achieved clinical pregnancies with the use of D + PG vs AP + PG protocols in LPS.
3. Comparison of the rates of achieved live births with the use of D + PG vs AP + PG protocols in LPS.

MATERIAL AND METHODS

A prospective single-center study was conducted among women undergoing government-funded IVF in the years 2015–2016. The research was approved by the Bioethics Committee of the Jagiellonian University. Inclusion criteria were: i) at least one failed IVF cycle preceding the current cycle, ii) fresh embryo transfer (ET) strategy, iii) age 18–43 years, iv) FSH between days 2 and 4 of the cycle ≤ 10 IU/L. The exclusion criteria were: i) failure to obtain an embryo, ii) deferred ET strategy. A specialist in obstetrics and gynecology was responsible for qualification for IVF procedure, selection of ovarian stimulation protocol and qualification for transvaginal oocyte retrieval. A couple was qualified for the next consecutive IVF cycle only if all frozen embryos were used in subsequent transfers of thawed embryos. The women included in the study gave informed consent to the proposed management. Women underwent controlled ovarian hyperstimulation (COH) with a short GnRH-antagonist (cetrorelix; Cetrotide®) protocol or long GnRH-agonist (triptorelin; Gonapeptyl Daily®) protocol. The ovarian stimulation protocol, the dose and type of gonadotropins were selected individually, considering the ovarian reserve, age and weight, comorbidities and the doctor's experience [12–15]. Recombinant human chorionic gonadotropin (Ovitrelle®) was administered subcutaneously at a dose of 6,500 IU approximately 36 hours prior to oocyte pick-up to induce final oocyte maturation in all women, provided that at least 3 follicles greater than 17 mm in diameter were confirmed on transvaginal ultrasound (TVS). Women at an increased risk of OHSS, who received a trigger with 0.2 mg of triptorelin administered subcutaneously, were qualified for deferred ET [14] and were excluded from the study. Collecting oocytes by transvaginal ultrasound-guided aspiration from ovaries, laboratory embryo culture and ET were performed in accordance with current medical knowledge and appropriate guidelines [16]. *In vitro* fertilization was performed by intracytoplasmic sperm injection (ICSI) in all women. On the day of oocyte retrieval, women were randomly assigned to one of the two study arms. Random assignment to the two study arms was performed by coin toss. The first arm included women receiving oral dydrogesterone (Duphaston® 10 mg every 8 hours) combined with progesterone in vaginal gel (Crinone® 90 mg in a daily single dose) (D + PG protocol), and the second arm included women receiving progesterone in subcutaneous injection (Prolutex® 25 mg in a single dose) combined with progesterone vaginal gel (Crinone® 90 mg in a daily single dose) (AP + PG protocol). Progestogen supplementation was started within 24 hours of oocyte retrieval and continued until 12 weeks of gestation, unless spontaneous abortion occurred. ET was performed on the 5th day after fertilization of the collected oocytes. The number of transferred embryos

Table 1. Characteristics of the study population compared to the population in the first-time in vitro fertilization (IVF) cycle in terms of the nature of infertility, IVF indications, stimulation protocols, luteal phase supplementation protocols

Variable	First IVF cycle (1st ET transfer) (n = 80)	≥ One failed IVF (≥ 2nd ET transfers) (n = 170)	p
Primary infertility [%] (n)	73.8% (59)	74.1% (126)	0.95
Idiopathic infertility [%] (n)	27.5% (18)	12.9% (22)	0.057
Tubal factor [%] (n)	18.8% (15)	25.9% (44)	0.2
Male factor [%] (n)	46.3% (37)	50.6% (86)	0.49
Low ovarian reserve [%] (n)	10% (8)	19.4% (33)	0.058
Endometriosis [%] (n)	23.8% (19)	25.9% (44)	0.69
Ovulatory dysfunction [%] (n)	5% (4)	5.9% (10)	0.76
Short GnRh-antagonist protocol [%] (n)	78.8% (63)	58.8% (100)	0.002
Long agonist protocol [%] (n)	21.3% (17)	41.2% (70)	0.002
D + PG [%] (n)	80% (64)	54.1% (92)	< 0.001
AP + PG [%] (n)	20% (16)	45.9% (78)	< 0.001

ET — embryo transfer; D + PG — dydrogesterone + progesterone in vaginal gel; AP + PG — progesterone in subcutaneous injection + progesterone in vaginal gel

was at the discretion of the physician and patient. The pregnancy test (blood serum B-hCG detection) was performed on the 12th day after ET. Treatment was discontinued if the pregnancy test was negative. In the case of a positive result, the treatment was continued and 4 weeks after ET, TVS was performed to confirm a viable pregnancy (the presence of a fetal heartbeat in M-mode). In the absence of the fetal heartbeat at that time, appropriate diagnostic and therapeutic procedures were implemented. Blood progesterone levels were not measured in the post-oocyte retrieval course of treatment. The women whose medical data was used in the study were subjected to routine medical procedures commonly used in reference centers for infertility treatment. The study population was characterized by age, duration and the nature of infertility (primary or secondary), indications for IVF, number of previously failed IVF cycles, ovarian reserve test result expressed as Anti-Müllerian Hormone (AMH) concentration, progesterone concentration the day before oocyte aspiration, type of ovarian stimulation protocol, number of metaphase II oocytes retrieved, number of transferred embryos. Then, the percentages of biochemical pregnancies (no gestational sac on TVS and falling B-hCG concentrations), clinical pregnancies (loss of pregnancy before the fetus is viable after visualization of gestational sac in the uterine cavity) and live births (birth of a live fetus after 24 weeks of gestation) in both study arms were calculated and compared, taking into account the number of previously failed IVF cycles.

Statistical analysis

Data were analyzed according to their distribution which was confirmed with the Kolmogorov-Smirnov test. In order to compare selected variables in both subpopulations, the Mann-Whitney test was used as a non-parametric test, and the Student's t-test was used for variables with a normal distribution. Chi-square test was used to assess the categorical variable. The results were expressed as mean for continuous variable and as number of cases (N, n) and percentage (%) for categorical variable. A p value < 0.05 was considered statistically significant. Statistical analysis was performed using StatSoft STATISTICA v 13.3 software.

RESULTS

During the study period, 250 fresh embryo transfers were performed, of which 170 were effectuated in women with at least one previous IVF failure (the study population) and another 80 in women in first-time IVF cycle. The characteristics of the study population in terms of the nature of infertility, IVF indications, stimulation protocol and progestogen regimen compared to the first-cycle IVF population are presented in Table 1, while mean values of selected variables (age, AMH and progesterone concentration, number of transferred embryos, endometrium width, duration of infertility) are presented in Table 2. Of the significant differences, in the study population of women with at least one IVF failure, the long GnRh-agonist protocol was used more often compared to women in the first cycle of IVF (70/170 women, 41.2% vs 17/80 women, 21.3%, p = = 0.002), and the short GnRH-antagonist protocol was used less frequently (100/170 women, 58.8% vs 63/80 women, 78.8%; p = 0.002). Moreover, in the study population compared to women in the first IVF cycle, the percentage of women who received the AP + PG protocol was significantly higher (78/170 women, 54.9% vs 16/80 women, 20%, p < 0.001), and the proportion of those who received the D + PG protocol was significantly lower (92/170 women, 54.1% vs

Table 2. Mean values of selected variables in the study population compared to the population in the first-time *in vitro* fertilization (IVF) cycle

Variable	First IVF cycle (1st ET transfer)	≥ One failed IVF (≥ 2nd ET transfers)	P
Mean age [years]	32.7	33.3	0.21
Mean AMH concentration [ng/dL]	3.5	3.45	0.82
Mean progesterone concentration [ng/dL]	0.86	0.72	0.2
Number of transferred embryos [n]	1.1	1.4	0.02
Mean endometrium thickness on the day of embryo transfer [mm]	11.1	11.1	0.94
Duration of infertility [years]	3.9	4.01	0.75

ET — embryo transfer; AMH — Anti-Müllerian Hormone

64/80 women, 80%; p < 0.001). In the study population the number of transferred embryos was also significantly higher than in the first IVF cycle (1.4 vs 1.1, p = 0.02). Mean number of metaphase II oocytes obtained in the short GnRH-antagonist protocol vs in the long GnRH-agonist protocol in the study population was 6.04 vs 6.01 (p = 0.96). The analogous values among women in the first IVF cycle also did not differ significantly and amounted to 6.23 vs 5.9 (p = 0.74). No other significant differences were found between the study population and the population in the first IVF cycle.

Of 170 women from the study population, 100 (100/170; 58.8%) had a history of one failed IVF cycle, and 70 (70/170; 41.2%) had at least two consecutive IVF failures. The characteristics of the subpopulations of women subjected to fresh ET with a history of 1 IVF failure and at least two failures compared to women in the first IVF cycle are presented in Table 3, while mean values of selected variables are presented in Table 4. The long GnRH-agonist protocol was used significantly more often in women with one IVF failure than in the subpopulation with at least two failures (43/100, 43% vs 27/70, 38.6%, p = 0.02) in which the short GnRH-antagonist protocol was used more often (43/70, 61.4% vs 57/100, 57%, p = 0.02). In women with one IVF failure, the D + PG protocol was used significantly more often than in the subpopulation with at least two failures (67/100, 67% vs 27/70, 35.7%, p < 0.001), in which the AP + PG protocol was used more often (45/70, 64.3% vs 33/100, 33%, p < 0.001). With the increasing number of failed IVF cycles, the percentage of reduced ovarian reserve as an indication for IVF increased (transfer 1: 10% vs transfer 2: 17% vs transfer ≥3: 22.9%, p = 0.02), and the percentage of idiopathic infertility decreased (transfer 1: 22.5% vs transfer 2: 17% vs transfer ≥ 3: 7.1%, p = 0.01) (Tab. 3). With the increasing number of unsuccessful IVF cycles, the number of embryos transferred (n) in subsequent cycles increased (transfer 1: n = 1.1, transfer 2: n = 1.3, transfer ≥ 3: n = 1.5; p < 0.001) (Tab. 4). The average length of time from the last thawed ET to the fresh ET in the studied IVF cycle in the subpopulation of women with one IVF failure vs in the subpopulation with more than one IVF failure did not differ significantly and equaled to 17 vs 19 weeks, respectively.

The percentage of pregnancies achieved in the study population compared to the population in the first IVF cycle in relation to LPS protocol used is presented in Table 5. The percentage of achieved pregnancies and live births did not depend on the LPS protocol used in any of the studied populations. Moreover, there were no significant differences in the rates of achieved pregnancies and live births within the subpopulation with one IVF failure vs with ≥ 2 failures depending on LPS protocol used. In women with one failed IVF cycle, the frequency of using the D + PG protocol vs AP + PG was 67% vs 33% (p = 0.22), in women with at least two failed IVF failures, 35.7% vs 64.3% (p < 0.001), and in the first IVF cycle these values were 80% vs 20% (p < 0.001). In the population in the first IVF cycle, there was a trend of a significantly higher percentage of live births with tubal factor than in other indications (46.7% vs 23.1%, p = 0.06). However, in the population with at least two failures, the percentage of live births with tubal factor was significantly lower than in the other indications (5% vs 34%, p = 0.01) (Tab. 6).

There were no adverse effects of the progestogens used in the studied population.

DISCUSSION

The live birth rate for IVF-ET depends on many factors, such as the cause of infertility, the type of ovarian stimulation protocol, the quality of the embryo, the woman's age, endometrial thickness and receptivity, progestogens used, and many others [17–21]. Most of these factors are difficult or even impossible to modify. Among the modifiable factors affecting the outcome of IVF-ET, the implementation of LPS is of crucial significance [6]. Although there is no doubt that LPS is essential in IVF cycles, the preferred timing of the start and end of therapy, as well as the type and route of drug administration in the general population of women undergoing IVF, have not been established [22]. In women with prior IVF failure, the possibility of implementing a more effective

Table 3. Population characteristics in terms of the nature of infertility, indications for *in vitro* fertilization (IVF) and stimulation protocols applied in the subpopulations of women subjected to fresh embryo transfer: in the first IVF cycle (transfer 1), with a history of 1 IVF cycle failure (transfer 2), with a history of at least IVF 2 failures (transfer ≥ 3)

Variable	First IVF cycle (1st ET transfer)	One failed IVF cycle (2nd ET transfer)	≥ 2 failed IVF cycles (≥ 3rd ET transfer)	p
Primary infertility [%] (n)	73.8% (59)	74% (74)	74.3% (52)	0.9
Idiopathic infertility [%] (n)	22.5% (18)	17% (17)	7.1% (5)	0.01
Tubal factor [%] (n)	18.8% (15)	24% (24)	28.6% (20)	0.14
Male factor [%] (n)	46.3% (37)	49% (49)	52.9% (37)	0.4
Low ovarian reserve [%] (n)	10% (8)	17% (17)	22.9% (16)	0.02
Endometriosis [%] (n)	23.8% (19)	25% (25)	27.1% (19)	0.6
Ovulatory dysfunction [%] (n)	5% (4)	6% (6)	5.7% (4)	0.93
Short GnRh-antagonist protocol [%] (n)	78.8% (63)	57% (57)	61.4% (43)	0.02
Long agonist protocol [%] (n)	21.3% (17)	43% (43)	38.6% (27)	0.02
D + PG [%] (n)	80% (64)	67% (67)	35.7% (25)	< 0.001
P + PG [%] (n)	20% (16)	33% (33)	64.3% (45)	< 0.001

ET — embryo transfer; D + PG — dydrogesterone + progesterone in vaginal gel; AP + PG — progesterone in subcutaneous injection + progesterone in vaginal gel

Table 4. Mean values of selected variables in the subpopulations of women subjected to fresh embryo transfer: in the first cycle of *in vitro* fertilization (IVF) (transfer 1), with a history of 1 failure of the IVF cycle (transfer 2), with a history of at least 2 failures of the IVF cycle (transfer ≥ 3)

Variable	First IVF cycle (1st ET transfer)	One failed IVF cycle (2nd ET transfer)	≥ 2 failed IVF cycles (≥ 3rd ET transfer)	p
Mean age [years]	32.7	33.3	33.5	0.24
Mean AMH concentration [ng/dL]	3.5	3.48	3.40	0.78
Mean progesterone concentration [ng/dL]	0.86	0.76	0.66	0.2
Number of transferred embryos [n]	1.1	1.3	1.5	< 0.001
Mean endometrium thickness on the day of embryo transfer [mm]	11.1	11.1	11.1	0.99
Duration of infertility [years]	3.9	3.9	4.2	0.47

ET — embryo transfer; AMH — Anti-Müllerian Hormone

LPS protocol in the next cycle would be of key therapeutic importance. Our study evaluated the effectiveness of two LPS protocols, using two different routes of administration, in women with at least one IVF failure undergoing another IVF cycle. The results showed no significant differences in the rates of biochemical pregnancies, clinical pregnancies and live births between the subpopulations using the D + + PG and AP + PG protocols for LPS, regardless of the number of previous IVF cycles. The obtained obstetrics results were in line with the average IVF results in the national population at that time [23]. The results of the study indicated no superiority of any of the two tested progestogen protocols in LPS of the IVF cycle in women with previous IVF failure, irrespective of the number of failed cycles. The study included women of different age, with different diagnoses and types of infertility. Moreover, no exclusion criteria based on the woman's body mass index or comorbidities were used, allowing the two LPS protocols to be compared in real clinical practice. Similarly, the type of progestogen protocol used was not found to have a significant impact on the outcome of the first cycle of IVF. Thus, the results can be extrapolated to the general population of women undergoing IVF, *i.e.*, women approaching the first and subsequent IVF cycles. With the increase in the number of completed IVF cycles, the frequency of using the AP + PG protocol increased in consecutive cycles due to the implementation of the study inclusion criteria. The preference of dydrogesterone for luteal supplementation over aqueous progesterone injections in the first cycle resulted from its proven non-inferior efficacy to progesterone and the convenience of oral administration [24]. It could be therefore concluded that dydrogesterone in combination with progesterone gel was no less effective than aqueous progesterone in combination with progesterone gel in supplementing the luteal phase of the IVF cycle. It is worth emphasizing that the nature of infertility (primary/secondary) and indications

Table 5. Percentage of pregnancies achieved in the study population compared to the population in the first *in vitro* fertilization (IVF) cycle depending on the luteal phase supplementation protocol used

Study population (≥ 1 failed IVF cycle) (170)	**Variable**	**D + PG (92)**	**AP + PG (78)**	**p**
Biochemical pregnancy	6.5% (6)	10.3% (8)	0.37	
Clinical pregnancy	7.6% (7)	3.8% (3)	0.29	
Biochemical and clinical pregnancy	14.1% (13)	14.1% (11)	0.99	
Live birth	23.9% (22)	26.9% (21)	0.65	
One failed IVF cycle (2^{nd} ET transfer) (100)	**Variable**	**D + PG (67)**	**AP + PG (33)**	**p**
	Biochemical pregnancy	6% (4)	12.1% (4)	0.28
	Clinical pregnancy	9% (6)	6.1% (2)	0.61
	Biochemical and clinical pregnancy	14.9% (10)	18.2% (6)	0.67
	Live birth	26.9% (18)	21.2% (7)	0.54
≥ 2 failed IVF cycles (≥ 3^{rd} ET transfer) (70)	**Variable**	**D + PG (25)**	**AP + PG (45)**	**p**
	Biochemical pregnancy	8% (2)	8.9% (4)	0.89
	Clinical pregnancy	4% (1)	2.2% (1)	0.67
	Biochemical and clinical pregnancy	12% (3)	11.1% (5)	0.91
	Live birth	16% (4)	31.1% (14)	0.16
First IVF cycle (1^{st} ET transfer) (80)	**Variable**	**D + PG (64)**	**AP + PG (16)**	**p**
Biochemical pregnancy	6.3% (n = 4)	0 (n = 0)	0.3	
Clinical pregnancy	10.9% (n = 7)	25% (n = 4)	0.14	
Biochemical and clinical pregnancy	17.2% (n = 11)	25% (n = 4)	0.47	
Live birth	26.6% (n = 17)	31.3% (n = 5)	0.7	

D + PG — dydrogesterone + progesterone in vaginal gel; AP + PG — progesterone in subcutaneous injection + progesterone in vaginal gel

for IVF (idiopathic infertility, tubal factor, male factor, reduced ovarian reserve, endometriosis, anovulation) did not differ significantly between the studied subpopulations of women, both in the study population and in women in the first IVF cycle, and their impact on the results in terms of evaluating the effectiveness of progestogen protocols could be considered negligible. The more frequent use of the short GnRH-antagonist protocol than long GnRH-agonist protocol in women approaching the first cycle of IVF, compared to the study population, resulted from its recognition as the protocol of first choice in most IVF indications thanks to the lower risk of OHSS [12]. The effectiveness of both COH protocols, expressed as the number of MII oocytes retrieved [25], did not differ significantly between women in the first IVF cycle and the study population. Therefore, it could be concluded that the effect of the selected protocol on the live birth rate was insignificant. The increasing number of embryos transferred per cycle in consecutive IVF cycles resulted from the desire to increase the individual success of IVF-ET although, so far, it has not been proven that transferring more than one embryo improves the live birth rate [26]. This goal was not achieved in the study population either, which confirmed the results of previous studies. The decreasing percentage of idiopathic infertility as an indication for IVF with each successive cycle was probably caused by the effect of the number of IVF attempts made. The opposite trend was observed for reduced ovarian reserve, for which its increasing percentage among IVF indications with each subsequent IVF attempt was probably because of its significant impact limiting the couple's fertility. The chance of a live birth in the classic indication of tubal factor infertility, if unsuccessful in the first IVF cycle, decreased significantly in subsequent cycles, which could indicate the presence of an additional hidden factor reducing fertility. In the remaining indications, there was no significant difference in the percentage of live births depending on the number of previously unsuccessful IVF cycles.

CONCLUSIONS

It could be concluded that the most important factor determining the success of the IVF cycle is the nature of the factor impairing fertility. Pharmacotherapy, including the type of LPS protocol, is of secondary importance. Considering the lack of evidence that either of the two LPS protocols of the IVF cycle is more effective in women with prior IVF failure, other considerations should be taken into account when choosing treatment, i.e., potential side effects, dosing convenience, and patient preference. It seems

Table 6. Live birth rate in subsequent *in vitro* fertilization (IVF) cycles depending on the cause of infertility

	IVF indication	Live birth rate (%, n)	Live birth rate (%, N-n)	p
Study population (≥ 1 failed IVF) (170)	Idiopathic infertility	40.9% (9/22)	23% (34)	0.07
	Tubal factor	18.2% (8/44)	27.8% (35)	0.19
	Male factor	24.4% (21/86)	26.2% (22)	0.75
	Low ovarian reserve	15.2% (5/33)	27.8% (38/137)	0.46
	Endometriosis	20.5% (9/44)	27% (34)	0.37
	Ovulation disorders	20% (2)	26% (41)	0.68
One failed IVF cycle (2nd ET transfer) (100)	Idiopathic infertility	41.2% (7/17)	21.7% (18/83)	0.09
	Tubal factor	29.2% (7/24)	23.7% (18)	0.61
	Male factor	22.4% (11/49)	27.5% (14/51)	0.52
	Low ovarian reserve	11.8% (2/17)	27.7% (23/83)	0.13
	Endometriosis	20 % (5/25)	26.7 % (20/75)	0.48
	Ovulation disorders	16.7% (1/6)	25.5% (24/94)	0.61
> 2 failed IVF cycles (≥3rd ET transfer) (70)	Idiopathic infertility	40% (2/5)	24.6% (16)	0.45
	Tubal factor	5% (1/20)	34% (17)	0.01
	Male factor	27% (10) 10/37	24.2% (8)	0.79
	Low ovarian reserve	18.8% (3) 3/16	27.8% (15)	0.46
	Endometriosis	21.1% (4) 4/19	27.5% (14)	0.58
	Ovulation disorders	25% (1) 1/4	25.8% (17)	0.97
First IVF cycle (1st ET transfer) (80)	Idiopathic infertility	16.7% (3)	30.6% (19)	0.24
	Tubal factor	46.7% (7)	23.1% (15)	0.06
	Male factor	21.6% (8)	32.6% (14)	0.27
	Low ovarian reserve	37.5% (3)	26.4% (19)	0.5
	Endometriosis	31.6% (6)	26.2% (16)	0.64
	Ovulation disorders	50% (2)	26.3% (20)	0.3

reasonable to give the woman a choice of the route of drug administration if a decision is made to additionally support the vaginal LPS route.

Limitations of the study

The limitations of the study are the small sample size, its single-center character and heterogeneity of indications for IVF.

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Conflict of interests

The authors declare no conflict of interest.

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Expression of microRNA (miR126*, miR155, miR21, miR29a) in breast milk cell fraction in women with hypertension: a comparative analysis with women without hypertension

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ABSTRACT

Objectives: The ideal option of food for a newborn's nourishment has traditionally been human breast milk (HBM). Previous studies have demonstrated a connection between the length of exclusively breastfeeding and its preventive effects on several conditions in neonates. Considering the significance of HBM, the study aimed at detecting the expression of microRNA (miR126*, miR155, miR21, and miR29a) in the breast milk cell fraction of women with hypertension. This was a cohort study of 35 postpartum women.

Material and methods: Five ml of milk was collected into a sterile container from patients in the morning on the second and third days after the labor. The collected milk has been centrifuged, total cellular RNA has been isolated from cell fraction from the collected milk, isolated RNA has been subject to qualitative and quantitative analysis, next reverse transcription has been conducted, followed by that, evaluation of the expression of the selected microRNA has been conducted using the synthesized cDNA. Finally, the tested microRNA's relative expression level has been calculated.

Results: Among patients with hypertension, the analysis of cell fraction of breast milk reported lower mean expression of miR126*, miR155, miR21, and miR29a as compared to patients without hypertension. Strong and very strong positive correlation between the expression of miR126* and miR155, miR126* and miR21, miR155 and miR21, miR 155 and miR29a, and miR 21 and miR29a have been noted.

Conclusions: Comparing patients with and without hypertension, it has been noted that patients with hypertension had lower mean expression of miR126*, miR155, miR21, and miR29a.

Keywords: microRNAs; breast feeding; mil; human; hypertension

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INTRODUCTION

Human breast milk (HBM) has always been regarded as the best choice of food for the nutrition of newborns [1]. The process of feeding a young child, specifically under the age of two years, directly from the breast of a woman at the time of lactation is considered breastfeeding. It has been reported by World Health Organization (WHO) that feeding a newborn with the own milk of the mother during the first six months without any additional external supplements provides the optimum nutrition for the infants, which provides them with the benefits associated with health outcomes and immunity [2]. It has also been recommended

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in this context that children continue breastfeeding in addition to supplemental food till the age of two years. Studies have revealed that there is an association between exclusive breastfeeding duration and associated protective impacts against various diseases among newborns, for instance, type 1 diabetes (T1D), neurocognitive behavior changes and intelligence, malocclusions, cardiorespiratory disorders, pediatric sleep-disordered breathing, among others. Various studies have been conducted on understanding how HBM provides the mentioned protective effects. It has been revealed in these studies that HBM is a complex integration of various bioactive molecules and the contribution of all the components is not yet clear [3]. The presence of miRNAs in HBM was only not identified until 2010 [4]. It was suspected by the researchers that the molecules play a role in the regulation of significant aspects of the development of infants for instance the immune function. Considering the mentioned role of the molecules in HBM, it was also hypnotized that miRNAs can be incorporated in infant formula for ascertaining that infants receive the required benefits and do not miss out on the associated health benefits. Studies have also put forward the fact that HBM is highly rich in circulating RNA molecules, unlike other body fluids. In recent years studies have identified a wide range of circulating miRNAs in HBM, approximately 1400 miRNAs have been identified in HBM [5]. Based on the above-discussed aspects, it can be inferred that the studies on the expression of microRNA are at a considerably elementary stage. In addition to that, no major studies have been conducted on the impact of "Pregnancy-induced hypertension, or peripartum hypertension or hypertensive disorders of pregnancy" on the expression of microRNA in HBM, which affects 15% of women [6]. The reason for considering the expression of microRNA (miR126*, miR155, miR21, miR29a) in the current study is because of the metabolic significance that these microRNAs hold in the functioning of the human body. MiR 126 has been identified to play a pivotal role in the regulation of the metabolism of blood glucose and the development of T2DM. Similarly, MiR-21 has been identified to be associated with the metabolic alteration of cancer-associated fibroblasts (CAFs) along with the development of cancer cells. MiR-155, under usual physiological conditions has been identified to be associated with maintaining standard glucose levels through its association with the regulation of insulin sensitivity and blood glucose homeostasis. MiR-29 family is associated with altered substrate oxidation and insulin resistance and overexpression of miR-29a in adipocytes has been reported to cause insulin resistance. Thus, considering the above-mentioned aspects, the focus of the current study would be on identifying the expression of microRNA (miR126*, miR155, miR21, miR29a) in breast milk cell fraction in women with hypertension.

The most prevalent class of extremely short regulatory non-coding RNA molecules, miRNAs, comprises 20 to 24 nucleotides and can regulate 40% to 60% of post-transcriptional gene expression [7, 8]. The miRNAs can be created endogenously, supplied exogenously by neighboring cells as cell-cell communication, provided from foods like plants and human HBM as cell-free miRNAs, or given via milk exosome. All milk fractions, including lipids, cells, and skim, have been discovered to contain greater levels of miRNAs than other bodily fluids, such as plasma. While skim milk contains the lowest concentration and diversity of miRNAs, milk cells have the highest concentration and variety [9]. According to the study conducted by Alsaweed et al. [10], in milk cells, there be 1467 known miRNAs, 1996 unique miRNAs, and 308 miRNAs have been detected in milk lipids. MiRNAs extracted from HBM fat globules are affected by a maternal high-fat diet, and these miRNAs can alter the metabolic pathways in babies who are given HBM. Because HBM has the greatest concentration of miRNAs (47,240 g/L compared to 308 g/L in plasma and 94 g/L in urine), which is due to the presence of stem cells and miRNAs produced from HBM exosomes, the miRNA is an essential component of HBM [11].

According to another study conducted by Alsaweed et al. [12], it has been observed that HBM miRNA expression varies according to the stage of lactation, as seen by the significant decline in miR-181a and miR-155 expression levels after six months of breastfeeding. The total miRNA concentration in the proportion of colostrum whey was 87.78 ng/L in the study conducted by Xi et al. [13], which included 33 matched samples, wherein it was reported to be considerably higher than the total miRNA concentration in the proportion of mature milk whey (33.15 ng/L)" (445–449). Colostrum (4.64, 4.05, and 2.58, respectively) and mature milk both had high expression levels of miRNA-378, miRNA-30B, and Let-7a (3.62, 4.92, and 2.39, respectively). While levels of miRNA-30B in mature milk were greater as compared to colostrum, levels of miRNA-378 and let-7a dramatically reduced with lactation. The difference in miRNA composition between pre- and post-feeding results from the change in milk composition during breastfeeding (such as an increase in the cells and fat content), with post-feeding showing a high content and composition of miRNAs, suggesting that breastfeeding increases the content of miRNAs in HBM. More miRNAs are found in the fat and milk cells [13]. Associated with cell turnover during breast sucking, epithelial cell migration into milk channels, and the process of milk production, those components are enhanced in post-feeding. Elevated miRNAs associated with milk fat are substantially connected with newborn milk volume consumption, in contrast to miRNAs related to cell content.

A distinctive profile of HBM miRNA with adaptive metabolic targets and roles for growth in premature newborns was reported in premature infant delivery. Given that they have different dietary requirements than fully developed newborns, premature infants may experience a variety of physiological difficulties. 113 miRNAs' expression in skim and lipid samples from mothers of preterm infants (pMBM) and term infants (tMBM) have demonstrated some noticeable variances [14]. MiRNA expression is changed during pregnancy by a high-fat diet. According to target pathway analysis, changes in food consumption-related miRNA expression may have an impact on either mothers' or babies' metabolic processes [15]. High glucose and galactose diets showed no discernible impact on the miRNA species found in the mother's milk.

In addition to the above-mentioned aspects of miRNAs expression in breast milk, in various studies, miRNAs have also been reported to play a significant role in regulating endothelial function, which is an integral aspect of hypertension. In the study conducted by [16], the researchers opined that miR-126 is endothelial cell-enriched. In the study, circulating miR-126 was measured in rats with NTN [nephrotoxic nephritis] and among humans with acute endothelial and renal injury. The findings have been compared with patients with CKD (chronic kidney disease) and ESRD (end-stage renal disease) wherein the association between miR-126 and vascular dysfunction has been studied. The findings of the study revealed that in the case of NTN miR-126 was reported to be reduced. In the case of ANCA vasculitis, the findings revealed that pre-treatment miR-126 was reduced compared to health. A 3.4-fold increase in miR-126 was recorded post-treatment. The researchers concluded that between CKD and health, miR-126 did not differ, however, with endothelial dysfunction the concentration of miR-126 has been reported to be correlated. In ESRD miR-126 has been observed to be reduced ~350 fold and the researchers believe that for vascular inflammation miR-126 can be considered a marker. In this alignment, in the study conducted by [17], the findings of the study demonstrated high-density lipoprotein (HDL) when isolated from CHF [chronic heart failure] patients reduce the expression of pro-angiogenic miRs, for instance, miR-21 and miR-126, which the researchers considered to be contributing factor to endothelial dysfunction and atherogenesis. The study conducted by [18] which focused on understanding the role of miR-19b as an influencing factor in Atherosclerosis (AS) revealed that the inflammation associated with the condition is prevented by HDAC3 upregulation for inhibiting it by inactivating NF-κB/p65 through upregulation of miR-19b which is mediated by PPARγ.

Objectives

The study aims to analyze the expression of microRNA (miR126*, miR155, miR21, miR29a) in breast milk cell fraction in women with hypertension and compare the findings with women without hypertension.

MATERIAL AND METHODS

Study design

This was a cohort study. The study group comprised of two groups, one group comprised of patients with hypertension, and the second group comprised of patients without hypertension. 5 mL of milk was collected into a sterile container from patients in the morning (up to two hours after the meal) on the second and third day after the labour. The samples were collected from June to October 2022. The collected milk has been centrifuged, total cellular RNA has been isolated from cell fraction from the collected milk, isolated RNA has been subject to qualitative and quantitative analysis, next reverse transcription has been conducted, followed by that, evaluation of the expression of the selected microRNA has been conducted using the synthesized cDNA. Finally, the tested microRNA's relative expression level has been calculated.

Setting

The milk samples collected from patients hospitalized in The Department of Obstetrics and Pathology of Pregnancy SPSK no.1 in Lublin were transported to the Department of Clinical Genetics, Medical University of Lublin. Directly after the collection of the samples, they were transformed to the university, where further analyses were conducted.

Participants

In this study, a total of 35 postpartum patients have been considered. The participants selected for the study are within the age range of 22–43 years. The selected patients were divided into two groups based on the presence of gestational hypertension in patients. 29 out of 35 patients were without hypertension which formed one group of the participants, while only 6 out of 35 patients qualified for the group with hypertension (the patients were taking medications for hypertension; hypertension in these patients occurred between 18 and 36 weeks of gestation, with a mean of 29 weeks of gestation). One of the mentionable inclusion criteria for the participants for the study was patients free of addiction, who were considered eligible for the trial group. The adaption was effective since all the patients who were looked at gave birth to healthy babies who obtained an Apgar score of 10/10. Additionally, some individuals with hypertension also had hypothyroidism.

Variables

The variables for the study were the status of gestational hypertension among the patients [that is the presence or absence of the condition], the mode of delivery [cesarean section (CS) vs normal delivery (ND)], the number of pregnancies, previous miscarriages, the age of the patient, week of gestation at delivery, the weight of the newborn and gender of the newborn.

Data sources/Measurement

Milk samples were collected from the participants to collect data associated between the expression of microRNA in HBM and the impact of hypertension on it. To collect data related to the relative expression level of the tested microRNAs, the Livak method was used for the analysis of relative gene expression. The approach assumes that both the target and reference genes are amplified with rates close to 100% and within 5% of one another.

Study size

The sample size selected for the study is based on clinical parameters, which include hypothyroidism in pregnancy, number of pregnancies, gender of newborn, previous miscarriages, and the mode of delivery. In addition to that, to calculate the sample size for the study, the researcher has used a sample size calculator, wherein the margin of error has been considered to be 95%, with a 5% margin of error. Considering the mentioned parameters, the researcher selected the sample size for the current study.

Methodology for analyzing miRNAs in breast milk

Using an 805 g speed and 15°C temperature, 5 mL of collected milk has been centrifuged for 20 minutes (5810R Eppendorf centrifuge). The cell fraction has been washed using double centrifugation and buffered saline after centrifugation, with the supernatant and fat phase being collected. The whole cellular RNA has been extracted from the cell fraction using the miRVanaTM miRNA isolation Kit (Invitrogen by ThermoFisherScientific, Vilnius, Lithuania). The procedure for the isolation followed the manufacturer's instructions for the reagent. ThermoScientific's NanoDrop 2000c and an electrophoretic technique were used to perform qualitative and quantitative analysis on isolated RNA. In the following step, reverse transcription has been conducted using commercial reagent kits (High-Capacity cDNA Reverse Transcription Kit with RNase Inhibitor and TaqMan MicroRNA Reverse Transcription Kit, AppliedBiosystems by ThermoFisherScientificVilnius, Lithuania). Ready-to use primer kitsHuman Pool A and B (AppliedBiosystems by ThermoFisher Scientific, CA, USA), MegaplexTM RT Primers have been used in the process, wherein the amount of RNA recommended by the manufacturer has been used. In the following step, to evaluate the expression of the chosen microRNA synthetized cDNA has been used, wherein the qPCR method has been implemented. In the StepOnePlus system (AppliedBiosystems) the reaction has been conducted, in which, commercial reagents including TaqMan probes (TaqMan MicroRNA Assays, Applied Biosystems by ThermofisherScientific, CA, USA: hsa-miR-126* (Assay ID: 000451); hsa-miR-155 (Assay ID: 002623); hsa-miR-21 (Assay ID: 000397); has-miR-29a (Assay ID: 002112) have been used. In this regard, an endogenous control 18S (Hs99999901_s1) (Applied Biosystems by ThermofisherScientific, CA, USA) has been used. By the recommendation of the manufacturer, the volume of the reagents used and the reaction protocol along with the test material, have been maintained. To calculate the relative expression level of the tested microRNAs the Livak method has been used in the study, for which, ExpressionSuiteSoftware Version 1.3 (LifeTechnologies) software has been expressed in the form of RQ value.

Statistical analysis

Statistica v.13 was used to statistically analyze the findings that were collected. Mann-Whitney the U Test was employed to evaluate the variations among the research subgroups. To determine and analyze the correlation between the expression of miR126* and miR155; miR126* and miR21, miR 126* and miR 29a, miR155 and miR21, miR 155 and miR29a, and miR 21 and miR29a Spearman rank correlation coefficient of the tested microRNAs in milk cells have been conducted. The significance level was $p < 0.05$.

Ethical consideration

The study was conducted based on the approval of the Bioethics Committee at the Medical University of Lublin (No. KE-0254/88/04/2022). Each patient provided written consent to collect the material and conduct tests.

RESULTS

Characteristics of the study group

The study comprised a total of 35 participants who were postpartum patients. The participants were within the age range of 22–43 years. 6 out of the 35 participants were having hypertension and taking drugs for hypertension; hypertension in these patients occurred between 18 and 36 weeks of gestation, with a mean of 29 weeks of gestation. The other group of participants which included the remaining 29 patients was not suffering from hypertension. For the group of patients with no gestational hypertension, the mean age of the patients, week of pregnancy (hbd), and weight of the newborn were 31.41, 39.27, and 3402.00 respectively, while for the group with gestational hypertension has been

recorded to be 30.667, 36.667, and 2820.00 respectively. The weight of newborns, among the group of patients with gestational hypertension, is significantly low as compared to the group without gestational hypertension. Furthermore, in regards to the mode of delivery [cesarean section (CS) vs normal delivery (ND)], it can be noted that among the group with gestational hypertension, the percentage of patients is significantly higher as compared to the group of patients with no gestational hypertension, which has been recorded to be 66.7% and 44.8% respectively. When both the subgroups are compared based on the clinical parameter of miscarriages, it can be observed that among the group with no gestational hypertension, the percentage of respondents having miscarriages is significantly less when compared to the group with gestational hypertension, which has been recorded to be 20.7% and as high as 50%, respectively. Regarding the clinical parameter of the number of pregnancies, it has been noted that for both subgroups, the majority of the respondents had two or three pregnancies. In context to the mentioned parameter, for the sub-group of patients with no gestational hypertension, for two pregnancies, it is slightly high as compared to the sub-group of patients with gestational hypertension, which has been recorded to be 38% and 33.3% respectively. For the clinical parameter of hypothyroidism in pregnancy, it has been noted that among the sub-group of patients with gestational hypertension, as high as 50% of the respondents had hypothyroidism, which was significantly low for the group of patients with no gestational hypertension, which has been recorded to be as low as 13.8% (Tab. 1 and 2).

Table 1. The characteristics of the study group based on the patient's age, week of gestation at delivery, and the weight of the newborn

Group of patients	Parameter	n	Mean	Median	Minimum	Maximum	SD
No gestational hypertension	Patient's age [years]	29	31.414	31.000	22.000	43.000	4.9463
	hbd		39.273	39.500	35.000	42.000	1.5486
	Weight of the newborn [g]		3402.000	3410.000	2530.000	4050.000	354.8356
With gestational hypertension	Patient's age [years]	6	30.667	31.000	28.000	33.000	1.862
	hbd		36.667	37.500	31.000	40.000	3.0768
	Weight of the newborn [g]		2820.000	2920.000	1150.000	3850.000	937.1873

SD — standard deviation; hbd — week of pregnancy

Table 2. The characteristics of the study group based on the mode of delivery, history of miscarriages, number of pregnancies, hypothyroidism in pregnancy, and gender of the newborn

Parameter	Group of patients	
	With gestational hypertension, n = 6	No gestational hypertension, n = 29
Delivery		
Cesarean section	4 (66.7%)	16 (44.8%)
Normal delivery	2 (33.3%)	13 (55.2%)
Miscarriages		
Yes	3 (50%)	6 (20.7%)
No	3 (50%)	23 (79.3%)
Number of pregnancies		
1	1 (16.7%)	9 (31%)
2	2 (33.3%)	11(38%)
3	2 (33.3%)	8 (27.7%)
4	1 (16.7%)	1 (0.3%)
Hypothyroidism in pregnancy		
Yes	3 (50%)	4 (13.8%)
No	3 (50%)	25 (86.3%)
Gender of newborn		
Male	3 (50%)	15 (52%)
Female	3 (50%)	14 (48%)

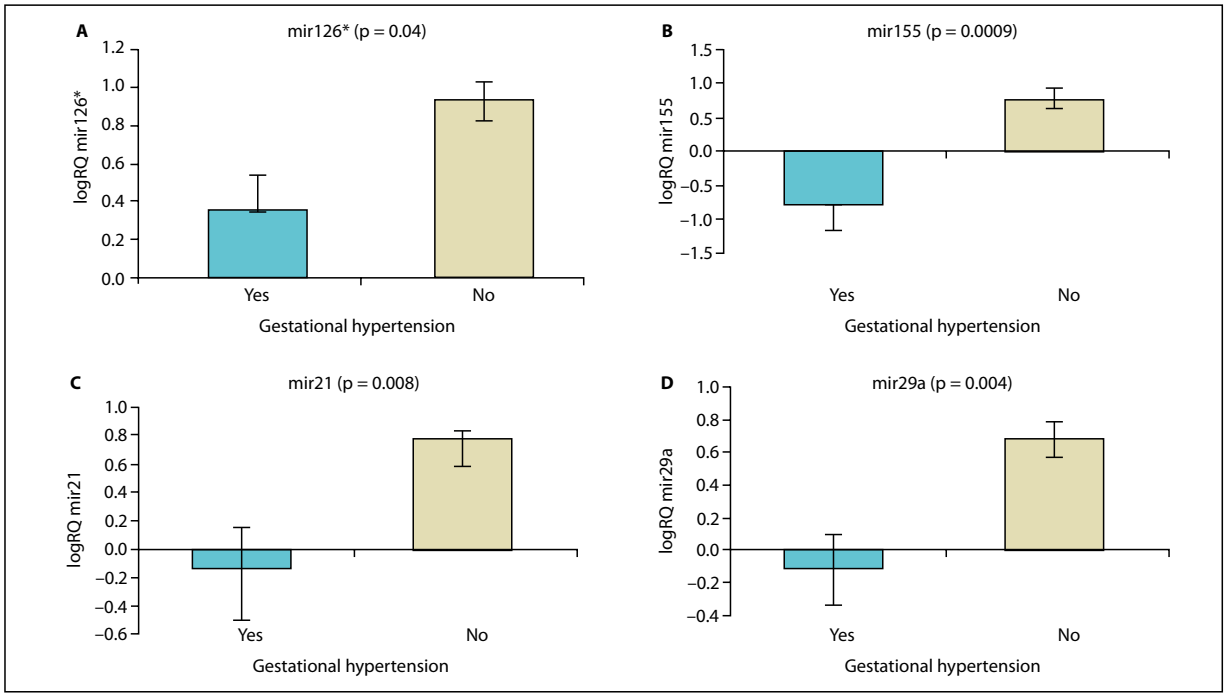

Figure 1. The mean expression level of miR126* (**A**), miR155 (**B**), miR21 (**C**), and miR29a (**D**) (logRQ ± SE) in breast milk cell fraction depends on the presence of gestational hypertension. Mann-Whitney U Test

Main results

The results of the experiments demonstrated that the miR126, miR155, miR21, and miR 29a genes are expressed in the cell fraction of the breast milk that was collected on the second and third day after delivery. In patients with gestational hypertension, the expression of the tested microRNAs was significantly different from the expression in patients without hypertension, according to a statistical analysis of the obtained expression results of the tested microRNA along with clinical data regarding the patients, such as the course of gestation and delivery, and data regarding the newborn. The mean expression of miR126* was reported to be 3 times lower ($p = 0.04$) in the cell fraction of breast milk from patients with hypertension, 10 times lower ($p = 0.0009$) in the cell fraction of miR155, 4 times lower ($p = 0.008$) in the cell fraction of miR21, and 7 times lower ($p = 0.004$) in the cell fraction of miR29, compared to patients without hypertension (Fig. 1).

No significant correlations between the expression level of miR126*, miR155, miR21, and miR29a in breast milk cell fraction and the mode of delivery (CC vs ND), the number of pregnancies, prior miscarriages, the age of the patient, week of gestation at delivery, the weight of the newborn, and gender of the newborn were found after statistical analysis of the obtained results of the expression of microRNAs along with the available clinical data.

Based on the analysis of the Spearman rank correlation coefficient of the tested microRNAs in milk cells and the selected clinical characteristics in the whole study group ($n = 36$) it has been noted that there is a significantly strong and positive correlation between the expression of miR126* and miR155 ($r = 0.775$, $p < 0.05$); miR126* and miR21 ($r = 0.776$, $p < 0.05$), miR126* and miR29a ($r = 0.775$, $p < 0.05$), miR155 and miR21 ($r = 0.938$, $p < 0.05$), miR155 and miR29a ($r = 0.947$, $p < 0.05$), miR 21 and miR29a ($r = 0.955$, $p < 0.05$) (Tab. 1). It has been further noted in this regard that there exists a moderate positive correlation between miR126* expression and milk cells and week of gestation at delivery ($r = 0.501$, $p < 0.05$) (Fig. 2, Tab. 3) and a weak positive correlation between the expression of miR155 in milk cells and the weight of the newborn ($r = 0.358$, $p < 0.05$) (Fig. 3, Tab. 3). On conducting a similar analysis in the group of patients with hypertension ($n = 6$) it has been noted that there are no significant correlations.

Outcome data

Based on the findings from the study, it can be inferred that lower mean expression of miR126*, miR155, miR21, and miR29a among patients with hypertension can be observed when compared to patients without hypertension. Strong and very strong positive correlation between the expression of miR126* and miR155, miR126* and miR21, miR155 and miR21, miR155 and miR29a, and miR21 and miR29a have been observed in this study.

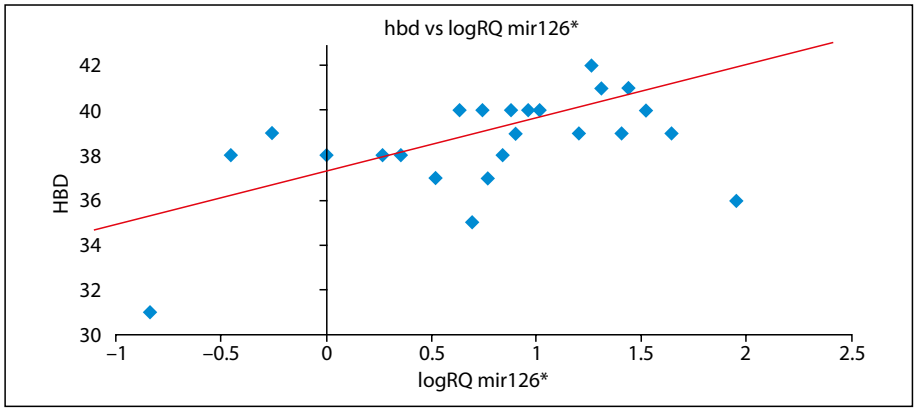

Figure 2. Scatter plot between the week of gestation at delivery and the expression of miR126* in breast milk cell fraction (r = 0.501 p < 0.05). Spearman rank correlation; hbd — week of pregnancy

Table 3. Spearman rank correlation coefficient between the tested microRNAs and selected clinical factors

Parameter	logRQ miR126*	logRQ miR155	logRQ miR21	logRQ miR29a
logRQ miR126*	1.000	0.775*	0.776*	0.775*
logRQ miR155	0.775*	1.000	0.938*	0.947*
logRQ miR21	0.776*	0.938*	1.000	0.955*
logRQ miR29a	0.775*	0.947*	0.955*	1.000
Number of pregnancies	–0.035	–0.082	0.035	0.022
hbd	0.501*	0.318	0.345	0.308
Patient's age	–0.213	–0.188	–0.173	–0.175
newborn weight	0.269	0.358*	0.326	0.300

*p < 0.05; hbd — week of pregnancy

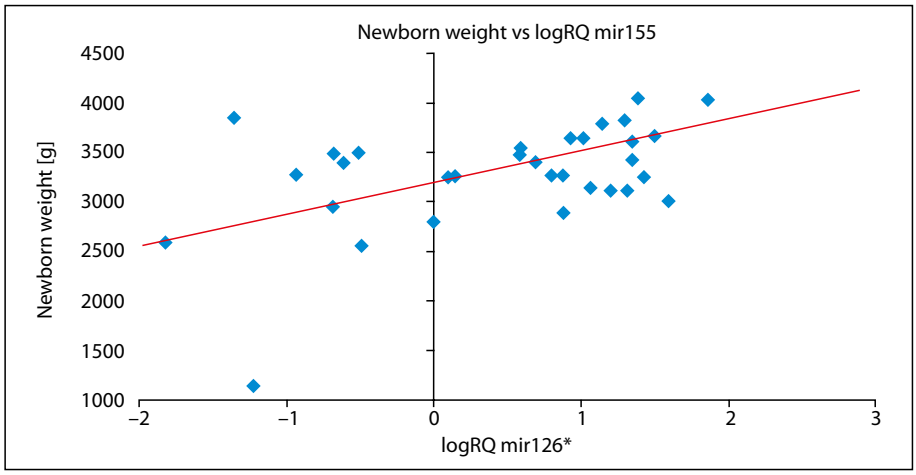

Figure 3. Scatter plot between the newborn weight and expression of miR155 in breast milk cell fraction (r = 0.358 p < 0.05). Spearman rank correlation

DISCUSSION

Interpretation of the literature

In the previous literature that has been considered for reviewing no major studies could be found that focused on analyzing the association between expressions of microRNA in breast milk cell fraction in women with hypertension. However, in endothelial dysfunction which plays an integral role in hypertension in various considered

studies in this paper, the significant role of miRNAs in regulating endothelial function has been identified. The study conducted by [19], which focused on determining the expression profiles of serum microRNAs significance in the function of ECs [Endothelial cells] revealed that miR-221-3p and miR-222-3p demonstrates a decreasing expression trend between the subclinical hypothyroidism (SCH) + + atherosclerosis (ATH) groups and the SCH group. For miR-126-3p and miR-150-5p a stepwise decrease was recorded from the normal control (NC) subjects to SCH groups, and SCH + ATH or ATH group. In the SCH, SCH + ATH, and ATH groups, miR-21-5p upregulation was recorded. Increased levels of miR-21-5p in the SCH + ATH group were recorded, which was observed to be higher as compared to SCH and ATH groups. The researchers, based on the findings concluded in the study that miR-21-5p can be associated with the atherosclerosis process among SCH patients and miR-150-5p can be considered to be sensitive risk markers to predict endothelial dysfunction in patients with ATH. According to the study conducted by [20], the findings of the researchers opined that human umbilical vein endothelial cells (HUVECs) highly expressed miR-155 which might co-target AT1R and Ets-1 and miR-221/222 targets Ets-1, which regulate the expression of various inflammatory molecules of ECs indirectly. In the study conducted by [20], the findings of the study demonstrated that among heart failure with preserved ejection fraction (HFpEF) patients, as compared to healthy controls miR-126, miR-342-3p, and miR-638 were significantly downregulated whereas miR-21 and miR-92 were observed to be upregulated. Followed by 3-month treatment with empagliflozin, among HFpEF patients, significant reduction in miR-21 and miR-92 was recorded. In the case of patients treated with metformin or insulin no major differences in the profile of endothelial miRs. The findings of the study [21] demonstrated circulating miRs associated with the regulation of endothelial function are highly regulated in frail HFpEF patients with diabetes mellitusas response to SGLT2 inhibition, indicating the association of novel microRNA signature with the regulation of endothelial function that is significantly regulated in patients with diabetes and HFpEF.

In addition to that, in recent studies, it has been revealed that HBM has many interconnected defensive elements that act as an "innate immune response" to defend against viruses [22]. Whey and casein are the two primary protein subgroups that have been identified to be present in HBM. These two groups are present in early and late lactation, respectively, with ratios changing from 70/30 to 80/20 and 50/50 [23]. Infants are protected against bacterial infections by lactoferrin, one of the primary proteins in the whey family. However, "cathelicidin-derived antimicrobial peptides", "folate-binding protein", and "α–lactalbumin" are some of the other proteins present in HBM. In the stomach, the main protein in HBM, "α-lactalbumin", is transformed into "human α-lactalbumin rendered deadly to tumor cells" (HAMLET). [23] HBM cells generate antimicrobial peptides derived from cathelicidin. They provide maternal protection against the risks associated with infection, BC, and allergy and newborn protection against autoimmune illnesses. Additionally, HBM controls inflammation by inhibiting the interleukins that regulate the production of "proinflammatory mediators" such as cytokine genes for instance IL-8 gene.

The previous studies have revealed that mature milk (3.62, 4.92, and 2.39, respectively) and colostrum (4.64, 4.05, and 2.58, respectively) both displayed high expression levels of miRNA-378, miRNA-30B, and Let-7a. While miRNA-30B levels in mature milk were higher than in colostrum, miRNA-378 and let-7a levels sharply decreased throughout lactation [13]. After six months of nursing, miR-181a and miR-155 expression levels significantly decreased, which demonstrated how HBM miRNA expression varies depending on the stage of lactation. In the current study among patients with hypertension, the analysis of cell fraction of breast milk has been observed to have the lower mean expression of miR126*, miR155, miR21, and miR29a as compared to patients without hypertension. Thus, based on the findings from the study, it can be inferred that the expression of miR126*, miR155, miR21, and miR29a in HBM is impacted if the mother is suffering from hypertension.

Strength and limitations

The major strength of the current study is the new finding associated with the expression of miRNA in HBM and the associated impact of hypertension on the expression level, which have not been studied in major studies conducted previously. The study is unique in its nature in identifying the association between the expression of miRNA in HBM and the impact of hypertension, wherein the finding of the current study can further contribute to the existing knowledge of the impact of the health conditions of the women on various aspects associated with pregnancy, along with its impact on the fetus, which leaves with new arenas of research. However, the small sample size and lack of literature associated with the research topic, for reviewing can be considered as two mentionable limitations. The consideration of a small sample size in this study may result in impacting the accuracy of the findings which can be considered as a major limitation of the existing study. The need to collect samples from the participants during the specific period of their pregnancy might have resulted in expedience bias in the current research. The consequence of this bias can be dependence of the researcher on one data point and

not taking the required time to receive clarity and understanding of the different aspects of the participants and the samples collected in this study.

CONCLUSIONS

Based on the findings from the study it has been noted that in context to clinical parameters, among patients with no gestational hypertension, the prevalence of miscarriages is significantly low as compared to patients with gestational hypertension. A similar pattern, with a significantly low rate of hypothyroidism during pregnancy, was observed among patients with no gestational hypertension. Regarding the delivery type, among patients with no gestational hypertension, normal delivery has been observed to be comparatively higher than patients with gestational hypertension. Among patients with hypertension, the analysis of cell fraction of breast milk reported lower mean expression of miR126*, miR155, miR21, and miR29a as compared to patients without hypertension. Strong and highly strong positive correlation between the expression of miR126* and miR155, miR126* and miR21, miR155 and miR21, miR 155 and miR29a, and miR 21 and miR29a have been noted.

Article Information and declarations

Data availability statement

The data presented in this study are available on request from the corresponding author.

Ethics statement

The study was conducted on the basis of the approval of the Bioethics Committee at the Medical University of Lublin. Each patient provided written consent to collect the material and conduct tests.

Author contributions

Conceptualization — A.K., M.W.-M., and B.K.; methodology — P.G.-K., A.P., and J.K.; validation — A.K.; formal analysis — P.G.-K., M.W.-M., A.K., and A.P.; writing — original draft preparation — A.K., M.W.-M., P.G.-K., A.P., and A.K.; writing — review and editing — B.K and J.K.; supervision — B.K. and J.K. All authors have read and agreed to the published version of the manuscript.

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None.

Conflict of interest

Authors declare no conflict of interest.

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The impact of the COVID-19 pandemic on the course of miscarriages

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ABSTRACT

Objectives: Miscarriage is the most common complication of pregnancy. Infections are well-known causes of pregnancy loss. It has been suggested that infection with SARS-CoV-2 virus may also have an adverse effect on the course of early pregnancy, causing miscarriage.

Aim: To assess the impact of the COVID-19 pandemic on pregnancy loss during the first half of pregnancy.

Material and methods: The clinical records of patients hospitalized at the Department of Fetal Medicine and Gynecology; Medical University of Lodz were retrospectively reviewed. The study was done during the pandemic (March 2020 to the end of March 2022) and the previous 2 years due to missed abortion, indicated by no fetal heartbeat and spontaneous (complete or incomplete) abortion with vaginal bleeding.

Results: While 682 women were hospitalized due to miscarriage in the first half of pregnancy in the period 2018–2020, there were 516 hospitalized during the pandemic. No differences in the proportion of missed and spontaneous abortions with bleeding were found between the group of patients before and during the epidemic SARS CoV-2. COVID-19 exposure appears to have an impact on earlier pregnancy loss.

Conclusions: There is no evidence that the COVID-19 pandemic predisposes to the abnormal course of pregnancy in its first half.

Keywords: COVID-19; pandemic; miscarriages

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INTRODUCTION

The COVID-19 outbreak was first detected in Wuhan, China in November 2019. The following epidemic, which began in the Chinese province of Hubei, eventually assumed the proportions of a pandemic. Its causative agent, the SARS-Cov-2 virus, is a single-stranded RNA member of the coronaviridae. It has been shown to be very similar to other highly pathogenic coronaviruses, such as Middle East respiratory syndrome coronavirus (MERS-CoV) and severe acute respiratory syndrome coronavirus (SARS-CoV) [1–3].

On 4 March, 2020, the first case of SARS-Cov-2 infection was detected in Poland, where COVID-19 infection has been confirmed in over six million inhabitants. The course of the infection is diverse and difficult to predict, ranging from completely asymptomatic to severe pneumonia with respiratory distress syndrome or multiple organ failure.

One of the risk factors for severe COVID-19 infection is pregnancy. Also, it has been proposed that infection with SARS-CoV-2 virus may have an adverse effect on the course of pregnancy, causing miscarriage.

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Miscarriage, or loss of pregnancy before week 22, is the most common complication of pregnancy. Loss of pregnancy is referred to as early miscarriage if occurring in the first trimester, and late miscarriage after 12 weeks of pregnancy. It is estimated that around 15% of clinically confirmed pregnancies are miscarried; however, the actual percentage may be higher. It is estimated that about 30% of embryos do not implant, and that another 30% are lost before the next menstrual period, in cases where pregnancy is confirmed only based on the concentration of human chorionic gonadotropin [4].

In most cases, the causes of miscarriage are difficult to identify; however, infections are known to result in pregnancy loss. To ensure the proper course of pregnancy, the immune system of the pregnant women maintains a balance between tolerance and rejection of the alloantigens (paternal) of the developing embryo, and later the fetus. Any infection can upset this balance, resulting in the loss of pregnancy [5, 6].

The SARS-Cov-2 virus binds to the angiotensin-converting enzyme 2 (ACE2) receptor, thus enabling its entry into target cells. Although ACE2 is particularly prevalent in type II pneumocytes, it has also been found in the upper respiratory tract, including the throat, and in the gastrointestinal tract, mainly in the small intestine [7]. In addition, ACE2 has been identified at different levels in the heart, liver, kidneys and the brain, as well as in endometrial cells, embryonic cells and placental cells (*e.g.*, syncytio- and cytotrophoblast) [8–11]. The expression of ACE2 is negatively correlated with gestational age: it is highest in trophoblast cells during the first trimester, and insignificant or undetectable in placenta cells during the third trimester [12].

Vertical transmission of the infection, especially during organogenesis, may have a very negative influence on the further course of pregnancy. In particular, the pathogens from the TORCH group (*Toxoplasma*, other, *Rubella*, cytomegalovirus, *Herpes*) have been associated with obstetric failures in pregnant woman [6, 13].

Key complications observed among patients with COVID-19 infection are coagulation disorders. Up to 46% of patients with laboratory-confirmed SARS-CoV-2 infection have abnormal high D-dimer values (≥ 0.5 mg/L). [14] Both congenital and acquired thrombophilia are known to result in *inter alia* miscarriage, premature placental abruption and preeclampsia [15, 16].

Thus, the question arises as to whether the SARS-CoV-2 virus may influence the risk of miscarriage.

The aim of the study was to determine whether the COVID-19 pandemic was associated with an increase in miscarriage rate.

MATERIAL AND METHODS

A review was performed of the clinical records of patients admitted to the Department of Fetal Medicine and Gynecology of the Medical University of Lodz in 2018–2022 for miscarriage. All patients had reported a spontaneous abortion with complete or incomplete vaginal bleeding or a missed abortion, in the first 22 weeks of pregnancy, confirmed by two ultrasound examinations. The case group comprised women aged 17–46 admitted to the Clinic during the SARS-CoV-2 coronavirus pandemic from March 2020 to the end of March 2022. The control group included patients aged 16–48 years admitted in the same period before the pandemic in 2018–2020. A total of 1,198 patients were enrolled in the study: 682 controls, *i.e.*, hospitalized before the pandemic, and 516 cases, *i.e.*, hospitalized during the pandemic.

Among the 516 women hospitalized for an abnormal course of early pregnancy during the early part of the COVID-19 pandemic, *i.e.*, between March and July 2020, 91 did not have a PCR test for COVID-19 infection.

Since July 2020, all patients admitted for elective or emergency procedures have received a routine PCR test for COVID-19. Among the study group, the result was positive in 26 patients, and negative in 399. In the infected patients, the course of infection was mild.

Ninety-one patients without the PCR test for COVID-19 were excluded from statistical analysis (Fig. 1).

Statistical analysis

For nominal variables, 2 × 2 tables with frequencies and percentages were used, and the Chi^2 test with appropriate corrections was used to assess differences between the study groups. Continuous variables with a non-normal

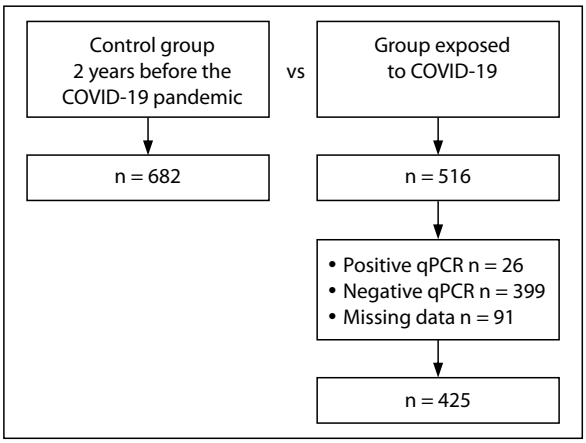

Figure 1. Flowchart of the two cohorts

Table 1. Differences between the women exposed to COVID-19 and the control group

	Median (Q1–Q3)/n%		
	Control group (n = 682)	**Group exposed to COVID-19 (n = 425)**	**p**
Age [years]	32 (28–37); min–max: 16–48	32 (28–37); min–max: 18–46	0.618
Number of pregnacies	2 (1–3); min–max: 1–7	2 (1–3); min–max: 1–8	0.197
Number offspring	1 (0–10); min–max: 0–6	1 (0–1); min–max: 0–6	0.500
Gestational week at pregnancy loss	9 (7–10); min–max: 5–20	8 (6–10); min–max: 5–22	**< 0.001**
Spontaneous abortion	254 (37.24%)	156 (36.71%)	0.857
Missed abortion	428 (62.76%)	269 (63.29%)	

distribution based on the Shapiro–Wilk W test result, as well as ordinal variables, were characterized using the median with 25% and 75% quartiles (Q1–Q3). The non-parametric Mann–Whitney U test was used to assess the differences between continuous and ordinal variables. Statistically significant results were presented using a box-whisker plot. Then, Kaplan–Meier curves together with the log-rank test were used to assess the time to the event. Statistical significance for all analyzes was $p < 0.05$.

Statistical tests were performed using the STATISTICA software version 13.3 (StatSoft TIBCO 2023).

RESULTS

Table 1 presents the most important differences between the groups. No statistically significant differences were found between the age of patients admitted with miscarriages in the groups before and during the SARS-CoV-2 pandemic. The median age in both groups was 32 years ($p = 0.62$).

In addition, no significant difference was found between the groups regarding the parity, previous abortion and the number of offspring (Supplemental Tab. S1).

Among the patients in the control, *i.e.*, pre-pandemic, group admitted to the clinic, 428 presented with a missed abortion, and 254 with complete or incomplete spontaneous abortion. In comparison, during the pandemic period, the respective values were 269 and 156. However, no differences were found in the proportion of missed to spontaneous abortions between the pre-pandemic and pandemic groups.

The survival analysis (Fig. 2) showed that patients exposed to COVID-19 were statistically significantly ($p < 0.002$) predisposed to miscarriage much earlier (8 weeks of gestation) compared to women admitted to the clinic in the same period before the pandemic (9 weeks of gestation).

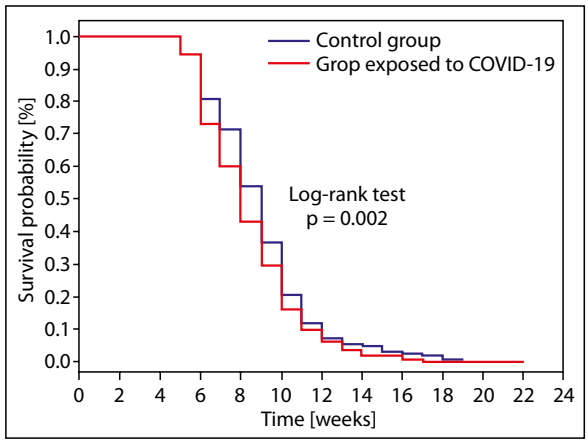

Figure 2. Survival analysis — Kaplan–Meier curves and log-rank test. Patients exposed to COVID-19 miscarry earlier than controls

DISCUSSION

COVID-19 follows a similar course of infection in pregnant women and non-pregnant adults. As many as 40–45% of cases are asymptomatic, and only 10–20% of those infected have a severe course of the disease [17]. In addition, there appears to be little difference during pneumonia arising in the course of SARS-CoV-2 infection in pregnant women and that observed in the general population [18]. Furthermore, a severe course of the infection does not appear to increase the risk of miscarriage or premature birth [19].

One study performed in a hospital in Turin, Italy compared cases of COVID-19 infection occurring among 100 women with spontaneous abortion during the first trimester of pregnancy, with 125 pregnant women with a normal pregnancy. Examination of nasopharyngeal swab samples, and COVID-19 IgG and IgM antibody levels in blood samples, found that SARS-CoV-2 virus infection does not seem to increase the risk of early pregnancy loss [20]. Similar results were obtained regarding SARS-CoV-2 seroprevalence among women with miscarriages in the first half of pregnancy and women with a proper course of pregnancy [21].

In a Danish study, la Cour Freiesleben et al. [22] assessed the effect of SARS-CoV-2 infection based on the presence of SARS-CoV-2 virus IgG and IgM antibodies, on the double test result and the course of the first trimester

of pregnancy. It was found that in pregnant women, the presence of antibodies was not related to any increase in nuchal translucency (NT) thickness, or the concentration of PAPP-A or beta-hCG protein. In addition, it did not increase the risk of miscarriage in the compared groups of pregnant women with and without SARS-CoV-2 virus IgG and IgM antibodies [22].

A study in Montreal investigated the impact of the pandemic environment as a stress-increasing factor on the risk of miscarriage in the first trimester of pregnancy [23]. Contrary to previous observations regarding conditions of increased stress, the pandemic environment did not seem to be an independent predictor of early pregnancy loss among the studied population of women [24, 25].

However, in a study of the Polish population, 22% of respondents admitted that the pandemic influenced their decisions to postpone having children. More specifically, they reported significant concerns about access to health care and the unstable economic situation resulting from the pandemic [26]. These findings are in line with preliminary data of the Polish Central Statistical Office indicating that there were approximately 15% fewer live births in in Poland in 2021 than in 2018.

Isolation intended to limit the spread of other infectious diseases was also an important factor influencing the total number of miscarriages related to infectious agents. Higher failure rates in early pregnancy are typically recorded during the flu season [27]. Limiting interpersonal contacts, wearing masks and ensuring proper hygiene appear to be advisable during early pregnancy.

However, the question of whether the pandemic influences reproduction and the course of early pregnancy remains ambiguous. Even so, it seems that neither COVID-19 infection nor the increased levels of stress associated with the pandemic environment increase the incidence of loss in the first half of pregnancy, and isolation may have a protective effect. However, a lower overall number of miscarriages was noted in the first half of pregnancy in the present study, but this could have resulted primarily from a lower total number of pregnancies, which was very likely related to postponing the decision to have children.

CONCLUSIONS

1. The data indicates that miscarriages in exposed to COVID-19 women are significant earlier than patients without COVID-19 exposure. However, no increase in the number of pregnancy loss in the first half of pregnancy was observed during the pandemic period from March 2020 to the end of March 2022.
2. Although COVID-19 infection was not found to have any effect on miscarriages in the first half of pregnancy, it was not possible to perform a statistical analysis on this data due to the small number of SARS-CoV-2 positive patients.
3. The COVID-19 pandemic had a negative impact on the reproductive decisions of couples due to concerns about possible complications during pregnancy for both mother and child.

Article information and declarations

Conflict of interest

All authors declare no conflict of interest.

Supplementary material

Table S1 and Figure S1.

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SUPPLEMENTARY MATERIALS

Table S1. Total number of miscarriages, after rejection of 91 patients with missing data

Variable		n (%)	
		Group exposed to COVID-19 (n = 425)	Control group (n = 682)
Total number of miscarriages	1	292 (68.71%)	494 (72.43%)
	2	85 (20.00%)	134 (19.65%)
	3	39 (9.18%)	42 (6.16%)
	4	7 (1.65%)	9 (1.32%)
	5	2 (0.47%)	3 (0.44%)

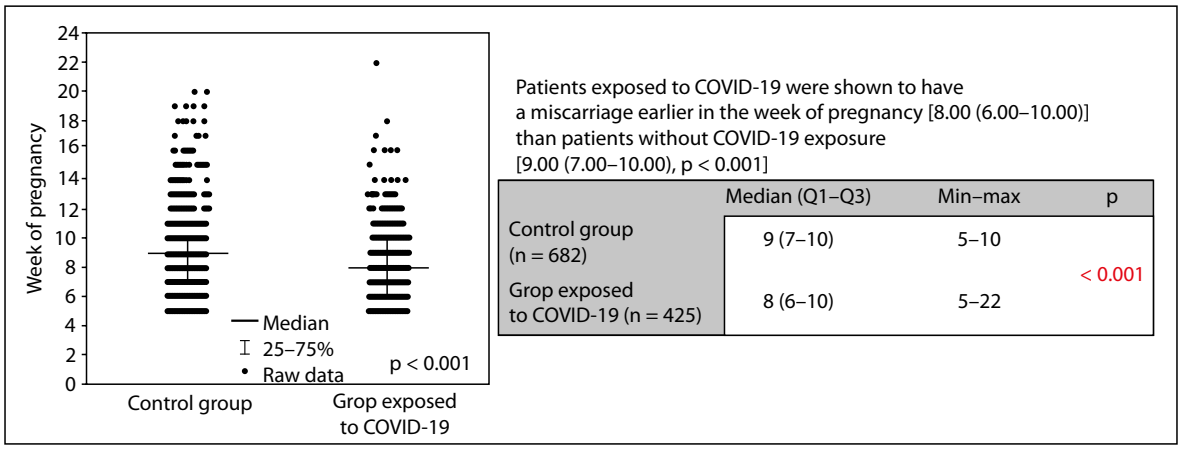

Figure S1. Exposure to COVID-19 and the week of miscarriage

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Evaluation of effectiveness of pharmacological treatment in pelvic congestion syndrome

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ABSTRACT

Pelvic congestion syndrome (PCS) is a pain syndrome characterized by positional pelvic pain and is associated with pelvic and vulvar varicosities as well as symptoms of dyspareunia and postcoital pain. Since the etiology of PCS is complex, the treatment should be individualized. Despite both pharmacological and interventional methods being used, there is significant predominance of minimally invasive therapies e.g. embolization. The study considers the answer to the question of whether pharmacological therapy is altogether effective. Using a combination of keywords, a PubMed search was performed for the years 1987–2022. The relevant articles were appointed and included in this narrative review. Despite the multitude of alternatives for pharmacological treatment, the systemic side effects of the medications used, as well as the interactions between drugs, affect patients' compliance and persistence. Furthermore, the quality of the currently existing evidence, considering the efficacy of the given substances, is low. Because of the adverse effects and thus the limited drug administration period, there is currently insufficient research on long-term effectiveness of the PCS pharmacological treatment. Therefore, prospective, comparative studies with larger patient population sizes are necessary to provide the possibility of efficient pharmacological therapy.

Keywords: pelvic congestion; chronic pelvic pain; sclero-embolization; pelvic varices

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INTRODUCTION

Pelvic congestion syndrome (PCS) is a pain syndrome characterized by positional pelvic pain and is associated with pelvic and vulvar varicosities as well as symptoms of dyspareunia and postcoital pain [1]. It is believed to be one of the causes of chronic pelvic pain (CPP) described as non-cyclical pain of greater than 6-month duration [1, 2]. Pelvic congestion syndrome is caused likely by failure or lack of the valve system in the periovarian and parametrial veins, which by causing reverse blood flow to the ovarian vessels results in visibly dilated veins and varices, as well as by mechanical vessel compression e.g., by the shifted uterus [2]. It can also be caused by a variety of other factors such as: genetic predisposition, anatomical abnormalities, hormonal factors, damage of the vein's wall and hypertension [3]. Since the term "PCS" does not characterize the full spectrum of the disease and that the International Union of Phlebology recommends using "PVD" — pelvic venous disorder, to describe this condition, the authors have decided to use the latter throughout the text [4].

The initial diagnosis of PVD is based on ultrasound imaging, as it has the advantage of allowing dynamic examination with provocative Valsalva maneuvers. Venography remains the gold standard for the final diagnosis [5, 6]. Nevertheless, computer tomography with contrast is becoming the predominant method for imaging vessels of the minor pelvis in many medical centers; magnetic resonance imaging (MRI) without contrast or with the use of gadolinium is an alternative as well. In certain cases, diagnostic laparoscopy is of great significance, as it enables visualization of the causes of PVD, *e.g.*, foci of endometriosis or adhesions [2].

Since the etiology of PVD is complex, therapy should be individualized based on the severity of pain and the patient's needs. Both pharmacological and interventional

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Table 1. The most frequent adverse effects of the medication used in the pelvic congestion syndrome (PVD) treatment

Medication		Side effects
Symptomatic pain relief treatment	Gabapentin, amitriptyline Nonsteroidal anti-inflammatory drugs Dihydroergotamine	Cognitive impairment, tolerance, car accidents/falls, abuse, dependence liability [8] Gastrointestinal disorders, gastrointestinal bleeding, suppression of hematopoiesis and agranulocytosis after long-term use [9] Gastric dyspepsia, headache, dizziness, arrhythmias, induction of angina [9]
Hormonal therapy	Danazol Medroxyprogesterone (MPA) Gonadotropin-releasing hormone (GnRH) agonists *e.g.*, goserelin Implanon (3-keto-desogestrel) Combined oral hormonal contraceptives	Weight gain, bloatedness [10] Hormonal imbalance, osteoarticular and vascular complications, thrombogenesis, amenorrhea, ovulation suppression [9] Osteoporosis, weight gain and mood swings [11, 12]
Venoactive drugs	Micronized purified flavonoid fraction (MPFF)	Upper abdominal pain, nausea, urticaria, diarrhea, gastralgia, flatulence, pain in the upper abdomen [9]

methods are used. Options for pharmacological treatment include progestin, medroxyprogesterone, danazol, combined oral hormonal contraceptives, phlebotonics, nonsteroidal anti-inflammatory drugs, psychotropic drugs (gabapentin, amitriptyline), dihydroergotamine, goserelin and gonadotropin-releasing hormone (GnRH) agonists as well as psychotropic drugs *e.g.*, gabapentin, amitriptyline. Patients whose symptoms are not manageable with medical therapy can be considered for ligation, embolization, or sclerotherapy of the ovarian veins. Currently one of the prevailing methods, that provide gratifying results, is embolization [2, 3]. Psychotherapy also plays a role in the treatment of this syndrome [4].

Objectives

The study considers the answer to the question of whether pharmacological therapy for PVD is altogether effective and should be used in a line of treatment.

MATERIAL AND METHODS

The available PubMed database was searched for articles published in English in the period of 1987-2022, using keywords "pelvic congestion syndrome", "pharmacological treatment", "embolization", "chronic pelvic pain". The search yielded 793 results, from which 22 met authors' criteria and were included in the analysis. Studies not available as a full text were excluded from the review. The authors explored data on etiology of PVD, the potential treatment, as well as the possible complications and side effects.

RESULTS

There are numerous alternatives for pharmacological treatment of PVD. Despite the multitude, available therapies do not seem to produce long term improvement [7]. The systemic side effects of the medications used, as well as the interactions between drugs, commonly affect patients' both compliance and persistence [3].

In the Table 1 [8–12] the authors gathered the most frequent adverse effects of the medication used in the PVD treatment.

Since, generally, the response to one drug alone is not sufficient, polypharmacy seems to be necessary. However, the administration of several medications, from different groups, causes their interactions. The most important interactions have been presented in the Table 2 [13].

DISCUSSION

As known, various medications, with different action mechanisms and diverse efficacy, are accessible for treatment of PVD. The choice of therapy depends on many aspects. There are multiple studies during which the authors attempted to test the effectiveness of pharmacological therapy of PVD. Past analysis showed the following:

1. Sator-Katzenschlager et al. [14] has shown that PVD may be treated sufficiently, although not completely, with gabapentin and amitriptyline. The research was conducted on 56 women (49 included in the final data analysis) with 24 months follow up with 300–3600 mg gabapentin and 25–150 mg amitriptyline. A significant reduction in CPP scores was achieved in all patients, however the pain relief was substantially greater in patients receiving gabapentin either alone or in combination with amitriptyline than in patients on amitriptyline alone. Long-term outcome was not reported [14]. Poterucha et al. [15] completed a retrospective review of medical records of 13 patients treated with topical amitriptyline 1–2% and ketamine 0.5%, which has shown reduction in CPP in 85% of the patients. One patient (8%) had complete relief, 6 (46%) had substantial relief, 4 (31%) had some relief, and 2 (15%) had no response.

Table 2. The most important interactions between the medications used in the pelvic congestion syndrome (PVD) treatment [13]

	Gabapentin	Amitriptyline	Dihydroergotamine	Danazol	MPA	Goserelin	Implanon	Combined oral hormonal contraceptives
Gabapentin		Increased side effects	–	–	–	–	–	–
Amitriptyline	Increased side effects		Risk of serotonin syndrome	–	–	QT interval prolongation	–	TCA toxicity and reduced effects; akathisia
Dihydroergo-tamine	–	Risk of serotonin syndrome		Increase of the plasma concentrations of ergot derivatives (leading to gangrene and myocardial infarction in severe cases)	–	–	–	–
Danazol	–	–	Increase of the plasma concentrations of ergot derivatives (leading to gangrene and myocardial infarction in severe cases)		–	–	–	–
MPA	–	–	–	–		–	–	Therapeutic duplication
Goserelin	–	QT interval prolongation	–	–	–		–	–
Implanon	–	–	–	–	–	–		Therapeutic duplication
Combined oral hormonal contraceptives	–	TCA toxicity and reduced effects; akathisia	–	–	Therapeutic duplication	–	Therapeutic duplication	

MPA — medroxyprogesterone; QT — as in QT interval in ECG; TCA — tricyclic antidepressants

Nonetheless neither the duration of treatment, nor long-term effects were reported [15].

2. There is limited data on effectiveness of intravenous dihydroergotamine (DHE). It has been shown that it may be effective in decreasing the size of parametrial veins and easing the pain. Reginald et al. [16] administered 1 mL of dihydroergotamine or 10 mL of placebo in 12 women with PVD. Dihydroergotamine administration resulted in constriction of the uterine and parametrial veins by 35% and a significant alleviation of pain in 95% of the patients. However, the effect was only sustained for two days after which the pain score between groups did not differ significantly [16]. Stones et al. [17] used 1 ml of DHE in 44 women with PVD and achieved reduction in pelvic veins diameter of 21%. Notwithstanding the results, the pain score was not assessed, and the duration of the treatment effects was not reported [17].
3. The hormonal treatment proves out well as the hormonal imbalance is considered one of the causes of PVD. Farquhar et al. [18] performed a study on 102 women using 50 mg medroxyprogesterone (MPA), placebo and psychotherapy. The duration of treatment was four months with a nine month follow up period. They reported that MPA in combination with psychotherapy was effective in 73% of PVD patients, however the cessation of pain was also noted in 33% of the women who used placebo. The follow up revealed persistent pain in 50% of female patients who underwent MPA and psychotherapy, and in 47% who used placebo [18]. Medroxyprogesterone has also been shown to be effective, by Cheong et al. [10], as it reduced the pain score in VAS (visual analogue scale) by more than 50% promptly after treatment and maintained the aftereffect up to nine months. The study

included 750 women — 406 women in the intervention groups and 344 in the control groups [10]. Soysal et al. [12] demonstrated the assets of 6-month therapy with 30 mg medroxyprogesterone and 3.6 mg goserelin. Medroxyprogesterone and goserelin have been used to suppress ovarian function, which diminishes varices by causing venous contraction. The study was performed on 47 women and was followed by a 12-month observation period. The authors reported reduction of symptoms in 65% of women and emphasized the superiority of goserelin to MPA in improving pelvic pain score. During follow-up, persistence of beneficial effects in all the female patients was reported, however the observation was limited to 12 months, thus long-term effects remain unknown [12]. The study by Shokeir et al. [11] has shown that Implanon (subcutaneous 3-keto-desogestrel) is efficient in alleviating symptoms of PVD. 23 women were included in the study which lasted for 12 months. Reduction of pain from 7.7 to 2.4 was reported in 85% of PVD patients. Long-term effects were not described [11].

4. Micronized purified flavonoid fraction (MPFF) has been shown to reduce the severity of pelvic symptoms. Serfaty et al. [19] performed a prospective observational study based on 1473 women with PMS with congestive components, administering 1000 mg MPFF per day. The study lasted for three months and the authors reported that symptoms of congestion gradually lessened in terms of both frequency and severity by about 60%. Long-term outcome was not reported [19]. Dissimilarly, in the study by Simsek et al. [20], that lasted for six months, included 20 women and compared usage of 1000 mg MPFF and placebo, it has been shown that reduction in pain in MPFF group is comparable to placebo group. Long-term outcome was not reported as well [20]. Tsukanov et al. [21] performed a study on 24 women, administering 1000 mg MPFF per day for one month. Cessation of pain and reduction in the diameter of the pelvic veins was observed in 75% of patients. Nevertheless, there was no follow-up period and long-term outcome remained unknown [21]. Gavrilov et al. [22] demonstrated that MPFF reduced the PVD symptoms, such as pain, heaviness and labia majora swelling, in all the observed patients. Women were administered 1000 mg once daily for two months (35 patients) or 1000 mg twice daily for one month followed by 1000 mg once daily for one month (30 patients) based on the intensity of pain. Both groups of patients reported reduction in pain severity. A considerable increase in linear blood flow velocity of internal iliac veins was also confirmed in phlebography (10–35%) [22]. Furthermore, it has been demonstrated, also by Gavrilov et al., that a double dose of MPFF (1000 mg twice a day) in the first month of treatment contributed to quicker symptoms decrease. The authors analyzed the efficacy of treatment in 125 women with PVD, administering 1000 mg MPFF once per day for two months in the first group of 65 patients and 1000 mg MPFF twice per day for one month followed by 1000 mg once daily for another month in the second group of 60 patients. The treatment was effective after 13.7 days in the first group and 3.1 days in the second one and the reduction in symptoms was significantly greater in the second group compared to the first group in the second month (46.6% vs 25%) [23].

Although pharmacological methods are- according to the aforementioned studies- effective, their systemic side effects, as well as the interactions between each other resulting from polypharmacy, commonly affect compliance and long-term acceptance. Due to the limited drug administration period, there is currently insufficient research on long-term effectiveness of the PVD pharmacological treatment. Furthermore, the quality of the currently existing evidence, considering the efficacy of the given substances, is low, as the majority of the studies was performed for an insufficient period of time, on groups of patients too small to draw more specific conclusions [10]. Moreover, no sufficient data is available on long-term consequences after suspension of treatment [3]. Therefore, prospective, comparative studies with larger patient population sizes are necessary to provide the possibility of efficient pharmacological therapy.

CONCLUSIONS

As a result of the complexity of PVD's etiology, therapy should be individualized based on the severity of pain and the needs of the particular patients. Both pharmacological and interventional methods can and should be used. Despite the lack of studies considering long-term effectiveness of pharmacotherapy and existence of various adverse effects, the authors believe that it should be used as the first line of PVD treatment and in the transitional period before embolization, as in some of the patients it allowed to achieve a significant improvement. Moreover, it cannot be forgotten that psychotherapy also plays an important role in the treatment of this syndrome [4]. In order not to waste resources or precious time, patients whose symptoms are not manageable with medical therapy can then be considered for surgical interventions. Pharmacotherapy should not be completely omitted in the treatment of PVD.

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Conflict of interest

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Female sexual functioning during pregnancy

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ABSTRACT

Sexuality is a fundamental, biological function of every human body, regardless of age, gender or race. However, the need for intimacy, closeness and sexual activity changes over time; it is influenced by the age, experience, physical and health condition. Sex is also one of the most important domains of the quality of life (QoL). However, this topic is still uneasy and rarely discussed, even though female sexual dysfunction (FSD) is a common problem, which affects 20% to 50% of women. Moreover, women experience processes that do not affect men, such as menstruation, pregnancy and menopause. In this review we focused on pregnancy, since sexual life of pregnant women alters during pregnancy due to the physiological, anatomical and hormonal changes in her body. Nonetheless, woman can keep having sex during a physiological pregnancy, but this issue is rarely addressed by physicians-gynecologists. Therefore, the aim of this manuscript was to discuss female sexuality during pregnancy.

Keywords: pregnancy; sexual functions; female sexual dysfunction

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INTRODUCTION

Sexuality is defined as "a basic necessary instinct needed to survive and to continue human species" [1]. Female sexual dysfunction (FSD) is a common healthy issue affecting from 20% to 50% of women and its prevalence increases with with age [2, 3]. Pregnancy is a state of carrying a developing embryo or fetus within the female body. This changes her anatomy, physiology, hormonal and emotional state altering sexual life of pregnant woman during pregnancy [4]. Although majority (86–100%) of couples declare they are sexually active during pregnancy period, majority of pregnant women feel the deterioration of their sexual life [5]. They experience decreased sexual intercourse and sexual desires during pregnancy that negatively affect their mood and well-being [6]. Whereas sexual health is one of the most important domains of the quality of life (QoL), sexual dysfunction (SD) is a serious problem [7]. Unfortunately, this issue is still uneasy and rarely discussed, as well as undervalued by the physicians-gynecologists who rarely address this problem. However, in order to better understand the needs of patients, and thus optimize the care for a pregnant woman, holistic approach in gynecological management is crucial. Even more so, that reduction of sexual activities during pregnancy very often results from fears and superstitions related to the potential risks to the health of the mother and child [8]. The most common ones are bleeding, induction of pre-term labor, infection, fetal damage, and the rupture of membranes [9].

Therefore, the aim of this review is to discuss sexual problems during pregnancy.

IMPACT OF PREGNANCY ON FEMALE SEXUAL FUNCTIONING

Female sexual functioning changes with the progression of her pregnancy. During the first trimester the female body must adapt to neurohormonal changes responsible for inducing drowsiness, mood swings, fatigue, nausea and vomiting, breast enlargement and tenderness, increased frequency of urination, abdominal bloating, shortness of breath and low back pain. These symptoms tend to develop abruptly as early as in 5–8 weeks of gestation and occur daily [10]. Such state has a clear negative impact on female's sexual desire and her QoL during preagnacy.

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First trimester is also the time of the greatest fluctuations in the frequency of sexual intercourse:

from normal pre-pregnancy activity to complete discontinuation of sexual contacts. In the study by Fok et al. [9], more than one-third of women stopped vaginal intercourse during pregnancy most probably because of the fear it may cause miscarriage, premature labor, or fetal damage [9]. Although there is no clear evidance of the negative impact of sexual activity during the first trimester bleeding, pregnant woman tends to avoid sexual intercourses and they are advised to do so by their physicians-gynecologists [11, 12].

On the other hand, Corbaciolgu et al. discovered a very interesting fact that women who were aware of their pregnancy had a significantly lower frequency of sexual intercourse than those who were unaware of their pregnancy in early gestation [13]. This observation may suggest that during pregnancy woman's sexual needs do not decrease but pregnant women may voluntarily resign from sexual intercourse because of the fears concerning both their and their child's health.

In the second trimester of pregnancy sexual intercourse are usually more frequent and of better quality compared to those during the 1st trimester [10, 14]. This may be explained by greater interest in sexuality and reduction in the physical symptoms of pregnancy, which makes woman feel better [15]. Due to the vascular changes in the vagina and vulva, satisfaction may be even greater than before pregnancy [16].

The last third trimester is the time of the lowest libido and lowest frequency of sexual compared with the previous trimesters of pregnancy [17]. Because of the fear of inducing labor or harming the child, many couples decide to stop sexual activity. Moreover, the changes in woman's body shape and in her anatomy may make it difficult to perform sexual intercourse.

However, sexual activity in late pregnancy is not associated with an increased risk of neither severe complications such as: low birthwaight, premature rupture of membranes or perinatal death, nor preterm birth [18, 19]. Sexual abstinence also has no clear role in prevention of prematurity [20].

This hypothesis is still controversial and needs further studies. Semen's prostaglandins released during orgasm can, in theory, increase activity of myometrial muscles [21].

On the other hand threatened preterm defined as the progression of cervical dilatation and ripening caused by regular uterine contractions occurring before 37 weeks of pregnancy is a serios perinatal complication. In this case restriction of sexual activity is routinely recommended, because of its still theoretical risk of inducing urterine contractions. However, data on that theory are contradictory and no firm conclusion can be drawn [22, 23].

Sexual activity that may lead to orgasm should be completely avoided in patients with placenta previa because of previously mentiond induction of uterine contractions, which in turn may provoke bleeding [24]. Additionally, insertion of penis or other„object" into the vagina may cause direct disruption of placental attachment to uterine wall. This recomendations are also not supported by objective published studies but extrapolated from observations that gynaecologivcal examination can often cause serious bleeding from placenta previa. Avoidance of sexual intercourse is also recommended for patients with preterm prelabor rupture of membranes [24]. As long as it is comfortable, most sexual positions are allowed during pregnancy as well as oral sex.

FEMALE SEXUAL DYSFUNCTION DURING PREGNANCY

Aydin et al. [25] in their study comparing sexual functions of pregnant and non-pregnant women demonstrated that SD was experienced by 91.08% of pregnant women and 67.61% of control subjects. Their results show higher rates compared to other published reports; Bartellas et al. [26] for *e.g.*, found SD in 49% of pregnant women. The authors explained their findings by cultural habits — Turkish womens' attitude to abstain from sexual activities in their entire life may be caused by the general tendency taught by parents. Nonetheless, the rates show that the problem is relevant.

The authors also analyzed various parameters influencing sexual function in pregnant and non-pregnant women, and they found that trimester, gravidity, parity, and abortion were those domains that influenced sexuality most in different ways. Also, physiological and psychological changes experienced by a woman during pregnancy period had impact on her sexual life [18].

Additionally, Brazilian team demonstrated that the factors associated with SD were young age of pregnancy, low income and the type of health service (private vs public one) [27]. This finding is very important since physicians must bear in mind that economic and social situation of their patients have equal influence on their health condition as physical and physiological factors.

Khalesi et al. [28] performed a study to assess the effect of pregnancy on sexual function of couples, and they demonstrated that sexual interest in pregnant women was decreased in the first trimester, increased in the second trimester and decreased at the end of the third trimester but in male it was either variable or decreased. Similar observation had Daid et al. [29]. In their study there was a significant difference in the incidence of difficulties in desire, arousal, lubrication, satisfaction and pain between first and second

trimester combined, as compared to the third trimester of pregnancy [29].

Erol et al. [30] assessed sexual function scores and androgen blood levels of women during pregnancy. The authors observed lower sexual activity during the third trimester compared with the first two trimesters of pregnancy, although it was not associated with lower androgen levels.

These data are consistent with other authors' observations [31, 32].

A Turkish team studied effects of pregnancy on sexuality, and they reported that dyspareunia was common in this group and pregnancy had a negative impact on orgasmic quality. Both influenced coital frequency, which declined as the month of the pregnancy increased [33]. This outcome confirms observation that FSD during pregnancy is a relevant problem, and third trimester is the time of the lowest frequency of sexual activity [15].

While evidence show that sexual wellbeing is important for a better QoL, women with SD feel problems in self-esteem and emotional distress [34].

Moreover, pregnancy is a condition which has an important impact not only on woman's QoL, but also on the sexual relationship between the couples [35]. Sexual function for any couple is determined by several different psychological, cultural, ethical, sociological, organic, and neurological factors [36].

Discomfort of pregnancy can affect the satisfaction of both men and women [37]. Inability to satisfy partner's sexual expectation is usually thought-out as a faintness and leads to decrease in self-esteem and well-being [38]. However, data also demonstrate that partners with low educational level and women who experienced preconceptional SD have a higher risk of developing/experience SD during pregnancy [39]. Thus, pregnant women and their partners need professional counseling about healthy sexual functioning in pregnancy. Proper communication and education are crucial.

SEXUAL HEALTH DURING POSTPARTUM PERIOD

Data show that only 12–14% of couples deny sexual problems after the childbirth [40].

According to the literature, the most common disorder after delivery appears to be that of sexual pain as a consequence of perineal trauma [41].

The extent of a birth injury is the main postpartum risk factor for dyspareunia. Breastfeeding is associated with low vaginal intercourse, as well as low sexual desires and satisfaction, not only of women, but also their partners. During this period, females more often suffer from dyspareunia, and thus postpone returning to sexual activity. Moreover, episiotomy is associated with a higher prevalence of a postpartum dyspareunia [42].

A Turkish study examined the relation between females' sexual functions before conception, during pregnancy and the postpartum period. The authors observed that sexual life during pregnancy and the postpartum period correlated with prepregnancy sexuality. There was no relation between pregnancy and postpartum sexuality. All of the participants who had SD before conception continued to experience it during pregnancy, and the majority of them had a significant level of SD during postpartum period [43]. Theses results show that sexuality before conception plays an important role in maintaining sexuality during pregnancy and the postpartum period.

In a Tunisian study to evaluate sexual functions of women in postpartum using questionnaire, the authors identified relevant SD faced by the respondents. In their study the average time to re-start sex after delivery was nine weeks. In postpartum, a change in sexual behavior and lower frequency of sexual intercourse were observed in 73% of cases. Some factors such as instrumental vaginal delivery, breastfeeding, body image disturbances (37%), fatigue (24%) and lack of availability (60%) influenced the resumption of sexuality. The major SD reported during postpartum included desire disorders (31%), altered vaginal lubrication (31%), painful intercourse (14%) and decreased sexual satisfaction (33%) [44].

Serati et al. [45] have reviewed the articles on sexual function during pregnancy and after childbirth, published from 1960 up to date. The authors found that sexual function significantly declined during pregnancy, particularly in the third trimester and this persisted for 3–6 months following delivery. The lack of adequate information and education about sexual functioning in pregnancy and concerns about the possible fetus damage were the most relevant factors responsible for the decline/resignation from sexual intercourse during pregnancy. Breast-feeding, dyspareunia, and postpartum pelvic floor dysfunction were the causes for the delay in resuming sexual activity after childbirth [45].

Byrd at al. [46] conducted a study on couples' sexual behavior during pregnancy and postpartum period. They reported that approximately 90% of couples engaged in sexual intercourse at first and third trimester and during postpartum, but only approximately 19% did it at the second trimester.

On average, couples resumed intercourse at seven weeks postpartum which is also the time of the first postpartum gynecological check-up visit. The role of physician-gynecologist is to advise patient to resume sexual activity when she feels comfortable and experience no pain or fatigue. Breastfeeding women had significantly less sexual intercourses

and were less satisfied with their sexual life than those who were not. The way of delivery did not impact sexual functions in a very different way, however women who were delivered by cesarean section resumed vaginal intercourse earlier than those who gave birth vaginally [46].

CONCLUSIONS

Sexuality is an important function of human's life and in couple relationship, with a great impact on QoL. Female sexual functioning is affected during pregnancy and postpartum period with a relatively high prevalence of SD, especially in the first and third trimesters and after delivery. Education, preconceptional sexual functions and adequate counseling about sexuality during pregnancy may help to reduce concerns, fears and the rate of FSD.

Article information and declarations

Author contributions

E. Szymanska — contextualisation, writing, supervision; R. Kisielewski — data collection, draft preparation.

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Accidentally discovered adolescent botryoid rhabdomyosarcoma

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INTRODUCTION

Rhabdomyosarcoma (RMS) is a rare malignant tumor arises from the embryonic muscles of the female genital tract of children, and adolescents, and it accounts for 4-6% of all malignancies in childhood [1].

The botryoid RMS is a polypoid form of RMS with a "grape-like" appearance. The origin of botryoid RMS is closely related to the age; it's originated from the vagina in infancy, and childhood, from the cervix in reproductive-age, and from the uterine corpus in postmenopausal women [2].

The botryoid RMS of the vagina is more common than the cervical botryoid RMS, while the cervical botryoid RMS has better prognosis [2]. The botryoid RMS tends to recur locally after excision and invades the adjacent organs [2].

The management of botryoid RMS is challenging especially at a young age (*i.e.*, childhood, or adolescents), as the preserved reproductive and sexual functions are essential.

There are no uniform consensus and/or guidelines regarding the surgical, and/or the conservative treatment of botryoid RMS.

Therefore, this report represents an adolescent botryoid RMS, to highlight the management challenges of botryoid RMS.

CLINICAL VIGNETTE

A 13-years-old adolescent girl, admitted to the hospital because of iron deficiency anemia (IDA) caused by the abnormal uterine bleeding (AUB). She had a normal hormonal profile (TSH 2.5 mIU/mL, prolactin 195 mIU/mL, FSH 5.3 mIU/mL, and LH 3.7 mIU/mL), normal liver enzymes (ALT 22 U/L, and AST 19.5 U/L), normal APTT 28 Sec., normal bleeding 3.8. min., and clotting 4.8 min. times.

The trans-abdominal sonography (TAS) showed a normal uterus, without any intrauterine lesions, and normal both ovaries.

The patient hemoglobin was 9.2 g/dL, and she received intravenous iron saccharate/sucrose (Spimaco, Saudi Arabia) to correct the IDA (ferritin was < 15 µg/L), and intravenous tranexamic acid (Advanz pharm., United Kingdom) to control the AUB.

The PALM (defines structural AUB; polyp, adenomyosis, leiomyoma, and malignancy), and COEIN (defines functional AUB; coagulopathy, ovulatory, endometrial, iatrogenic, and non-classified) classification of AUB facilitates the AUB diagnosis, and management.

During admission, the patient`s passed a fleshy, reddish "Grapelike" polypoidal lesion through the external genitalia. The "Grapelike" lesion sent for histological examination, and unfortunately the diagnosis of botryoid RMS was confirmed by two senior pathologists. The histological examination showed a non-keratinizing squamous epithelium with an edematous stroma underlying, plump stromal cells with dense eosinophilic cytoplasm, and mitotic activity (Fig. 1).

After control of the AUB, a departmental imaging/metastatic work-up, including pelvic magnetic resonance imaging (MRI), computerized tomography (CT) of the thorax, and bone scan was done, followed by referral of the patient to the specialized oncology center. Departmental approval, and written consent were obtained from the studied adolescent`s parents to publish the studied adolescent`s data as a clinical vignette.

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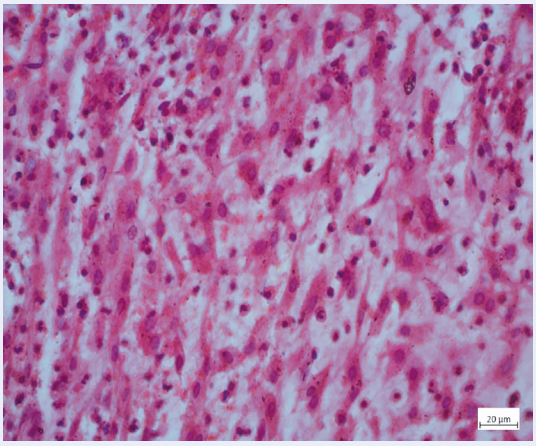

Figure 1. Botryoid (embryonic) rhabdomyosarcoma; embryonic myoblasts in myxoid stroma (staining with hematoxylin and eosin, magnification 400

DISCUSSION

This report represents a case of botryoid RMS presented with dysmenorrhea, and AUB, to highlight the management challenges of botryoid RMS.

The botryoid RMS is a rare malignant tumor, and the published data regarding the botryoid RMS are available from the published case-series, and case-reports [1].

The largest published series of botryoid RMS of the uterine cervix include 13 cases [3]. The botryoid RMS accounts for 10% of all RMSs. The botryoid RMS of the cervix tends to occur at older ages (i.e., children and adulthood), than those occur in the vagina [1].

Most of the botryoid RMS cases presented with either AUB and/or protruding mass from the introitus [2]. The differential diagnosis of botryoid RMS includes, adenosarcoma, cervical mesodermal polyp, and rhabdomyoma [1].

Complete surgical resection of botryoid RMS with a "safety margin" of normal tissue around is less applicable in metastatic botryoid RMS [1].

Daya and Scully [4], reported comparable results in 3 cases of botryoid RMS (out of 13 cases) treated using the fertility-sparing approach (*i.e.*, trachelectomy or polypectomy) with postoperative chemotherapy to those treated with radical surgery. This suggests that the cervical botryoid RMS may have a favourable outcome than those originated from the vagina [1].

Deletion of chromosome 1 short arm, and trisomies 13 and 18 were reported in RMS of uterine cervix [5].

CONCLUSIONS

Botryoid RMS is a polypoid form of RMS with a "grape-like" appearance. The botryoid RMS of the vagina is more common than the cervical botryoid RMS, while the cervical botryoid RMS has better prognosis. There are no uniform consensus and/or guidelines regarding the surgical, and/or the conservative treatment of botryoid RMS. Further studies evaluating the outcome of different management strategies of botryoid RMS are needed. An international guideline for the management of botryoid RMS are also needed.

Article informations and declarations

Ethics statement

Departmental approval, and written consent were obtained from the studied adolescent`s parents to publish the studied adolescent`s data as a clinical vignette.

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Conflict of interest

Authors declare no conflict of interest related to this clinical vignette.

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Uterus sarcoma in 26-year-old patient with multiple uterine fibroids

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INTRODUCTION

Uterine leiomyomas are one of the most common tumors in women. These tumors, commonly known as fibroids, affect women mainly during their reproductive years and are diagnosed in up to 70% of white women during their lifetime [1]. Other uterine tumors have similar clinical presentations and about 0.5% of resected tumors presumed to be fibroids in the preoperative diagnosis revealed as sarcomas in the final histopathological examination [2, 3].

This case presents 28-year-old-women with multiple fibroids, of whom one was diagnosed as leiomyosarcoma.

CASE STUDY

In February 2022 a nulligravid 28-years-old woman was admitted to the 3rd Chair and Department of Gynecology at Teaching Hospital No 4, Lublin, Poland due to heavy menstrual bleeding. Clinical examination showed stable vital signs and normal laboratory results. Pelvic ultrasound (Fig. 1A) showed anteflexed uterus with heterogeneous echostructure, thin endometrium, and multiple uterine fibroids: 4 International Federation of Gynecology and Obstetrics (FIGO) 4, and 1 FIGO 7 type with a diameter of 5 cm. There was no free fluid in the Douglas' pouch. A magnetic resonance was performed (Fig. 1B) which showed enlarged uterus with focal intramural lesions of the echostructure typical for fibroids: two within anterior wall with a diameter of 30 mm and 13 mm, two within posterior wall with a diameter of 21 mm and 8 mm, and one lesion (20 × 18 mm) on the left side. Furthermore, in front of the uterus, above the bladder, pedunculated fibroid was shown with measurements of 57 × 42 × 51 mm. The patient was offered scheduled fertility-preserving surgical treatment.

In June 2022, the patient was readmitted to the hospital to perform the operation. Pelvic ultrasound was performed, with results similar to the one performed in February. Patient was qualified for surgery. Laparotomy, with removal of uterine fibroids was chosen by the patient from the treatment options offered. The patient's postoperative course was

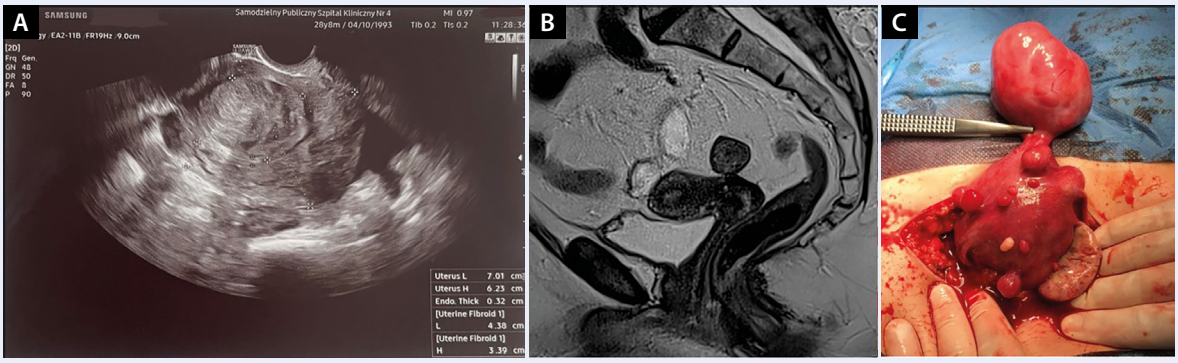

Figure 1. A. Ultrasound image of the uterus with fibroid; **B.** The magnetic resonance image of pelvis; **C.** Intraoperative view of uterus with fibroid

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complicated with mild postoperative wound infection. She was discharged twelve days after admission without further complications. The definitive histological diagnosis was leiomyosarcoma with bizarre nuclei within the pedunculated tumor, and leiomyoma for the remaining five tumors. Six weeks after the surgery, an ultrasound re-evaluation showed the normal sonographic appearance of uterus.

COMMENT

This is a rare case of single malignant tumor among multiple fibroids in young patient. It serves a reminder to maintain oncological vigilance in all patients with uterine tumors.

Article information and declarations

Conflicts of interest

The authors declare no conflict of interest.

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Pandemia COVID-19, która targnęła całym światem pokazała jak bardzo problem zakażeń pozostaje aktualny i nieprzewidywalny. Dotyczy to też zakażeń bakteryjnych i wirusowych, które mimo ogromnego postępu wiedzy, szeroko prowadzonej profilaktyki, znajomości zasad aseptyki i antyseptyki nadal stanowią prawdziwe wyzwanie w położnictwie, ginekologii i neonatologii. Wiele nauczyliśmy się na temat mechanizmów modulacji układu odpornościowego ciężarnej, znaczenia mikrobioty, profilaktyki antybiotykowej, odporności matki i noworodka, ale nadal temat ten pozostaje polem do dyskusji naukowej.

Konferencja powstała pod auspicjami **Polskiego Towarzystwa Ginekologów i Położników** oraz **Polskiego Towarzystwa Medycyny Perinatalnej** i jest adresowana do **ginekologów i położników, neonatologów, położnych, farmaceutów i diagnostów laboratoryjnych.** Chcemy, aby efektem spotkania była wspólna dyskusja dotycząca najnowszych standardów postępowania w zakresie zakażeń oraz, aby przedstawione informacje okazały się pomocne w naszej codziennej praktyce zarówno w oddziałach szpitalnych, jak i w gabinetach lekarskich.

Wierzymy, że dobór zagadnień i doświadczonych wykładowców, w tym gości zagranicznych, będzie przekładał się na poziom naukowy i edukacyjny konferencji a przekazana wiedza przyczyni się do poprawy opieki medycznej nad kobietami i ich dziećmi w naszym kraju.

Zapraszamy do Poznania!

Prof. Krzysztof Drews
Honorowy Przewodniczący Komitetu Organizacyjnego

Prof. Agnieszka Seremak-Mrozikiewicz
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Dr hab. Hubert Wolski
Instytut Medyczny, Akademia Nauk Stosowanych w Nowym Targu

PROGRAM

- **PPROM:** PPROM poniżej 23 t.c. (M. Wielgoś); PPROM 24-37 t.c. (H. Huras); zakażenia a poronienia (P. Sieroszewski); kolonizacja i zakażenia dróg rodnych u ciężarnych (K. Czajkowski)
- **Chorioamnionitis:** chorioamnionitis – the diagnostic and therapeutic challenge – obstetrician (M. Muller); the presence of chorioamnionitis changes risks for adverse outcomes and responses to medication – the therapeutic dilemma (B. Kramer); AI w zakażeniach okołoporodowych – teraźniejszość czy przyszłość (G. Brębborowicz); laktoferyna (J. Kalinka)
- **TORCH – zakażenia w okresie perinatalnym:** toksoplazmoza (M. Grzesiak); cytomegalia (M. Freud-Świątkowska); medycyna podróży a ciąża (D. Bomba-Opoń)
- **Metody diagnostyczne:** CRP, PCT, IL-6 w zakażeniach w ginekologii i położnictwie (K. Drews); metody diagnostyczne w PPROM (S. Kwiatkowski); nowe metody diagnostyczne zakażeń w ciąży (K. Ziółkowska)
- **Kontrowersje w perinatologii:** antybiotykoterapia w ciąży i podczas karmienia (M. Krekora); diagnostyka obrazowa w zakażeniach (P. Kaczmarek, P. Kruczek); diagnostyka zaburzeń częstości pracy serca płodu i noworodka w zakażeniach okołoporodowych (W. Markwitz, D. Madajczak)
- **Szczepienia i profilaktyka okresie okołoporodowym:** RSV (J. Mazela); krztusiec (I. Małecka); grypa (J. Wysocki); COVID (P. Grzesiowski)
- **Zakażenia okołoporodowe – epidemiologia:** zakażenia szpitalne w okresie okołoporodowym (P. Grzesiowski); następstwa zakażeń wewnątrzmacicznych (E. Helwich); zakażenia szpitalne w okresie noworodkowym (I. Maruniak-Chudek); antybiotykoterapia u ciężarnych a drobnoustroje alarmowe (J. Woroń); działania organizacyjne w profilaktyce zakażeń szpitalnych (M. Ziarnik)
- **VARIA:** HPV; nowy algorytm wykrywania śródnabłonkowej neoplazji szyjki macicy (W. Kędzia); zakażenia grzybicze (A. Markowska); stany zapalne a płodność (M. Brązert)
- **Probiotyki – wiele hałasu o nic?:** probiotyki a zakażenia wewnątrzmaciczne (A. Seremak-Mrozikiewicz); probiotyki a NEC (B. Królak-Olejnik); probiotyki w eradykacji Streptococcus agalactiae (GBS) (A. Bartnicka); probiotyki w ciąży a zdrowie dziecka (M. Socha)
- **SESJA SATELITARNA:** leczenie ran w ginekologii i położnictwie (T. Paszkowski, H. Wolski, P. Hudemowicz)
- **WARSZTATY PRAKTYCZNE:** praktyczne wyzwania dla położnych za sali porodowej, diagnostyka USG w zakażeniach noworodkowych (P. Kruczek)

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