POLISH GYNECOLOGY

GINEKOLOGIA POLSKA

Edited since 1922

no 7/vol 91/2020

ORGAN POLSKIEGO TOWARZYSTWA GINEKOLOGÓW I POŁOŻNIKÓW
THE OFFICIAL JOURNAL OF THE POLISH SOCIETY OF GYNECOLOGISTS AND OBSTETRICIANS

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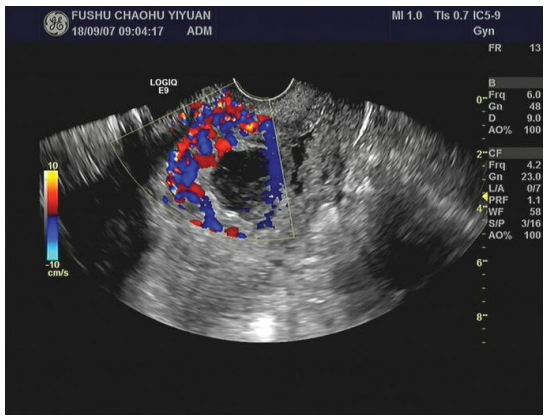

GINEKOLOGIA POLSKA 2020, VOL 91, NO 7, PAGES 373–438

ISSN 0017–0011

VIA MEDICA

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19-0431.001.011

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Ginekologia Polska is published monthly, twelve volumes a year, by VM Media sp. z o.o. VM Group sp.k.,
73 Świętokrzyska St, 80–180 Gdańsk, Poland, phone: (+48 58) 320 94 94, fax: (+48 58) 320 94 60,
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Editorial office address: Woman's Health Institute, School of Health Sciences, Medical University of Silesia in Katowice, 12 Medyków St, 40–752 Katowice, e-mail: ginpol@viamedica.pl

Indexed in: CrossRef, DOAJ, Index Copernicus, Ministry of Science and Higher Education (40), POL-Index, Polish Medical Bibliography, PubMed, Science Citation Index Expanded (0.941), Scimago Journal Rank, Scopus, Ulrich's Periodicals Directory

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19-0202.007.001

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CONTENTS

REVIEW PAPER
OBSTETRICS

RECOMMENDATIONS

VIA MEDICA

ORIGINAL PAPER / GYNECOLOGY

Ginekologia Polska
2020, vol. 91, no. 7, 373–378

ISSN 0017–0011

DOI 10.5603/GP.a2020.0067

Uterine leiomyomas: correlation between histologic composition and stiffness via magnetic resonance elastography — a Pilot Study

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ABSTRACT

Objectives: To evaluate magnetic resonance elastography as a tool for characterizing uterine leimyomas.

Material and methods: At total of 12 women with symptomatic leiomyomas diagnosed in physical and ultrasound examinations were enrolled in this pilot study. Before surgery, all patients underwent magnetic resonance elastography of the uterus using a 1.5 T MR whole-body scanner (Optima, GE Healthcare, Milwaukee, WI, USA). Surgical specimens were forwarded for histological examination. The findings were allocated into 3 categories depending on the percentage content of connective tissue: below 15%, from 15 to 30% and more than 30%. The median stiffness of leiomyomas for each of the group was calculated. The U-Mann Whitney test was used for statistical analysis.

Results: The stiffness of the leiomyomas ranged between 3.7–6.9 kPa (median value 4.9 kPa). The concentration of extracellular components in the leiomyomas did not exceed 40%. An increasing trend of the stiffness with the growing percentage of extracellular component was observed. Stiffness of the leiomyomas obtained by MRE varies depending on microscopic composition.

Conclusions: The value of stiffness shows a trend of increasing with the percentage of extracellular component of the leiomyoma. Further studies are required to assess the usefulness of MRE in diagnostics of uterine leiomyomas.

Key words: leiomyoma; magnetic resonance elastography; histologic composition

Ginekologia Polska 2020; 91, 7: 373–378

INTRODUCTION

Uterine leiomyomas (fibroids) are the most common benign gynaecological tumours, which affect up to 70% of women of a reproductive age [1–3]. They develop as a result of the transformation of myometrial smooth muscle, fibroblasts and the formation of a dysfunctional extracellular matrix [4, 5]. The majority of fibroids remain asymptomatic, 20–40% of women with leiomyomas report significant clinical symptoms (e.g. abnormal uterine bleeding, dysmenorrhea, pelvic pain, infertility, and recurrent pregnancy loss) that require effective gynaecological intervention [2, 6, 7].

The management of uterine fibromas varies significantly depending on the patient's age, symptoms, and reproductive plans. For women who wish to preserve their fertility and avoid surgery, there are numerous medical therapy options available [8]. For symptomatic women after medical treatment failures, surgical procedures are proposed [9]. Strategies for surgical treatment depend on the patient and fibroid characteristics and include myomectomy (in women who want to preserve their uterus or desire future pregnancy) or hysterectomy (for women after a completed childbearing) [9]. Currently, both procedures are mostly performed via laparoscopy with the usage of a power morcellator. Laparoscopic power morcellation is related with a risk of spreading undiagnosed neoplastic tissue within the abdominal cavity, which may significantly worsen the patient's prognosis [10–12]. The true prevalence of uterine sarcomas in presumed fibroids is not exactly known and

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vary from 0.09% to 0,8% depending on the study [13–17]. Also, the medical management of presumed symptomatic leiomyoma, which is found to be sarcoma, may have a negative impact on the outcome due to a delay in appropriate therapy. Despite the fact that some patients' characteristics and abnormal features of uterine tumors on a US or MRI may be suggestive for the presence of leiomyosarcoma, a reliable differential diagnosis is still very difficult [13, 18–20]. Hence, there is an urgent need for finding a new tool that could improve the characterization of uterine masses. In this context, interesting possibilities are offered in recently implemented magnetic resonance elastography (MRE). Malignant transformation often markedly alters the mechanical properties of soft tissue [21, 22], which could be potentially used in the pre-treatment differentiating leiomyosarcoma from the common leiomyoma. On the other hand, elastographic patterns of the leiomyoma, reflecting a relative concentration of cellular and extracellular components, may be helpful in predicting a response to non- excisional therapies such as uterine artery embolization and magnetic resonance–guided focused ultrasound [23]. Both circumstances require knowledge of the typical elastographic features of leiomyomas.

Objectives

Until now, only two studies have been published on the feasibility of MRE for uterine leiomyomas, without regard to their microscopic composition [23, 24]. The aim of this study was to evaluate the correlation between the elasticity of leiomyomas obtained by MRE and their relative concentration of cellular and extracellular components.

MATERIAL AND METHODS

Patient population

This pilot study included 12 patients with symptomatic leiomyomas, who underwent surgical treatment at the Clinical Department of Obstetrics and Gynaecology of Provincial Clinical Hospital No 2, Rzeszow , Poland between September 2016 and February 2017.

Preoperative diagnosis was based on vaginal speculum examination, bimanual examination and the transvaginal ultrasonography of the uterus. Before surgery, all patients underwent laboratory tests, electrocardiography, anesthesiology consultation and magnetic resonance elastography of the uterus. Written consent was obtained from each of the patients before the study commenced. The research protocol was approved by the Bioethics Committee of the University of Rzeszow, Poland (Reg. No. 19/04/2016).

Magnetic Resonance Elastography

A 1.5 T MR whole-body scanner (Optima, GE Healthcare, Milwaukee, WI, USA) was used to perform the MRE scans. The MRE system, includes special acquisition and processing software, as well as hardware consisting of an active and passive driver. The passive driver is a small plastic drum-like device that is placed against the body to transmit mechanical vibrations into tissue. In this study, the passive driver was placed over the uterus in the lower abdomen. The passive driver is connected via flexible tubing to the active driver unit which is located outside the MRI room. The active driver unit generates pressure pulses (at 60 Hz frequency in this study) that are conducted to the passive driver via the flexible tubing.

MRE acquisition was performed using a 16-channel abdominal phase array coil. Shear wave imaging was conducted using a modified 2D gradient–recalled echo-based pulse sequence with the following parameters: matrix size: 256 × 256, slice thickness: 10 mm; TR: 33 ms; TE: 20 ms; flip angle: 30 deg. The resulting wave images were then automatically processed by the scanner using a manufacturer-provided 2D direct inversion algorithm to generate quantitative images depicting tissue stiffness (elastograms) [25–27].

Region of interest (ROI) were drawn manually on the largest leiomyoma, avoiding non-fibroid tissue, using corresponding T2 images as a guide. From the ROI, mean stiffness (kPa) and standard deviation, were reported.

Microscopic evaluation

Surgical specimens were forwarded for histological examination. To visualise the collagenous connective tissue fibers in tissue sections and differentiate them from smooth muscle fibers, Trichrome Stain (Connective Tissue Stain) was applied. In this process staining muscle fibers were dyed red, collagen fibers were stained blue and nuclei stained black/blue (Fig. 1). Due to lack of similar publications and other scientific data, the findings were arbitrarily allocated into 3 categories depending on the percentage content of connective tissue (below 15%, from 15 to 30%, more than 30%).

Statistical analysis

Statistical analysis was performed using Python libraries. The U-Mann Whitney tests were applied. A p value of lower than 0.05 was considered statistically significant.

RESULTS

A greater number of patients were premenopausal than not. Only one patient was postmenopausal. Their age ranged between 26–61 years (median value 40.5 years). The median body mass index (BMI) was 22.45 kg/m^2. The parity status and type of surgery are presented in Table 1.

In all patients, the preoperative diagnosis leiomyoma was confirmed histologically. The diameter of the largest leiomyoma ranged between 40–109 mm (median diameter 68.5 mm). The median value of leiomyoma stiffness obtained

in our series was 4.9 kPa (range, 3.7–6.9) The concentration of extracellular components in the leiomyomas and their stiffness in specific patients are presented in Table 2.

The biggest subgroup was made up of leiomyomas with contents of fibrous tissue up to 15 percent. The median stiffness in this series was 4.46 kPa. Three patients had leiomyomas with a concentration of extracellular components between 15 and 30% and median stiffness of 5.78 kPa, respectively. More than 30% content of fibrous tissue was found in 2 patients. The median stiffness of those leiomyomas was 6.15 kPa. Example ROI's drawn on elastograms for three patients are shown in Figure 2.

Figure 3 depicts a box plot with the mean stiffness measurements among groups with different extracellular component. Despite the low number of samples, the increasing trend of the stiffness with the growing percentage of extracellular component is clearly observable. The p value for the stiffness difference between lesions with extracellular component of < 15% and > 30% was p = 0.05. Other results were not statistically significant.

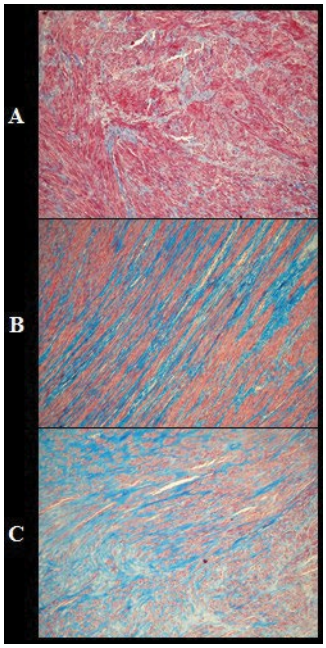

Figure 1. Microscopic pictures of leiomyomas with different histologic composition: fibrous tissue content up to 15% (A), between 15% and 30% (B), and above 30% (C) in trichrome stain

DISCUSSION

Magnetic resonance elastography is a versatile MRI-based technique, using propagating shear waves to

Table 2. Pathology findings and magnetic resonance elastography data of the study group

Patient	Diameter of the leiomyoma [mm]	Extracellular component [%]	Stiffness of the leiomyoma	SD of leiomyomas' stiffness
1	57	< 15	6.18	0.68
2	41	< 15	3.7	1.2
3	109	> 30	6.9	2.8
4	40	< 15	4.5	1.5
5	56	< 15	4.2	1.02
6	62	< 15	4.0	1.2
7	70	< 15	4.9	1.3
8	75	< 15	4.97	1.08
9	67	15–30	4.68	1.06
10	93	> 30	5.39	0.90
11	82	15–30	5.8	2.2
12	80	15–30	5.9	1.6

Table 1. Clinical characteristics of the study group

Patient	Age	Gravidity/Parity	Hormonal status	BMI	Type of surgery
1	49	2/2	premenopausal	20.42	LASH/BS
2	33	0	premenopausal	21.48	laparotomy/myomectomy
3	32	0	premenopausal	24.77	laparotomy/myomectomy
4	28	1/1	premenopausal	19.16	laparoscopy/myomectomy
5	38	3/2	premenopausal	23.42	LASH/BS
6	31	2/2	premenopausal	26.17	LASH/BS
7	43	3/1	premenopausal	20.76	LASH/BS
8	48	2/2	premenopausal	21.09	TLH/BS
9	26	0	premenopausal	27.02	laparotomy/myomectomy
10	46	0	premenopausal	21.05	laparotomy/myomectomy
11	49	2/2	premenopausal	25.10	TLH/BS
12	61	3/1	postmenopausal	27.24	TAH/BSO

LASH — laparoscopic supracervical hysterectomy; TLH — total laparoscopic hysterectomy; TAH — total abdominal hysterectomy; BS — bilateral salpingectomy; BSO — bilateral salpingooophorectom

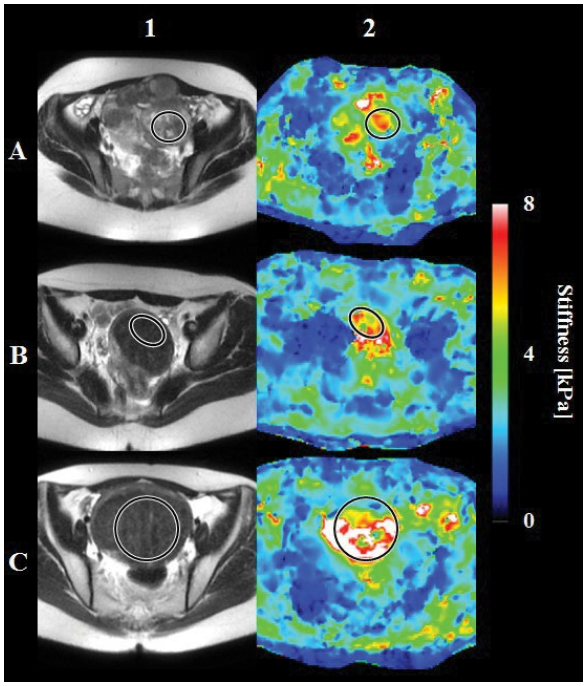

Figure 2. T2w MR images (column 1) and comparison of elastograms (column 2) for patient 6 (row A), 9 (row B) and 3 (row C). The mean stiffness was 3.95 kPa, 4.68 kPa and 6.9 kPa for the above mentioned patients, respectively

assess the mechanical properties of tissue [28]. The most established and documented clinical application of MRE is the evaluation of chronic liver disease [29–33]. In recent years, MRE has also been evaluated in characterization of focal liver lesions [22, 34], and for assessing the spleen, pancreas, kidneys and prostate [35–39]. Experiences with MRE in the field of gynaecology are quite limited. There are only a few publications dealing with the stiffness of a normal uterus [40] and leiomyomas [23, 24]. None of the research groups investigated the stiffness of leiomyomas in correlation with their histologic composition. In this context, our research provides data to fill this gap.

The present study confirms the findings of Stewart et al. [23], that magnetic resonance elastography is a feasible technique for the assessment of mechanical properties of uterine leiomyomas. The median value of leiomyoma stiffness obtained in our series (4.9 kPa) was comparable to that of above cited study.

The stiffness of the leiomyoma is markedly higher than the stiffness of both the normal corpus and cervix uteri, which were evaluated by Jiang et al. using 3D MRE technique [40]. Compared to other pathologic lesions, the elasticity of leiomyomas exceeds those of benign liver tumors (mean 2.7 kPa, range 1.6–3.2 kPa), but it is similar to the elasticity of fibrotic liver disease (mean 5.9 kPa, range 3.1–12.2 kPa) [22].

The content of the extracellular component in leiomyomas from our series did not exceed 40%. The concentration

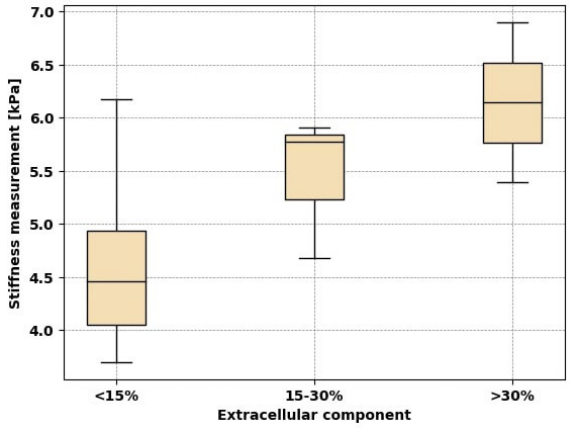

Figure 3. Box plot depicting variance in shear stiffness measurements for all groups of patients

of collagen fibres correlated with the value of stiffness of the leiomyoma (Fig. 3). Leiomyoma stiffness, as an increasing trend, is observable with the increased extracellular component; however, statistical analysis only approached demonstrating a significant difference between the groups with the highest and lowest collagen concentration. The relatively large scatter of stiffness values in the group of lowest extracellular component is probably due to the inhomogeneity of leiomyomas.

To the best of our knowledge, this is the first study investigating the correlation between the elasticity of leiomyomas obtained by MRE and their relative concentration of cellular and extracellular components. The presented observations can be potentially helpful in preoperative differentiating common leiomyomas from their malign counterparts. Because uterine sarcomas tend to be more cellular, they may be able to be distinguished from the leiomyomas based on the altered mechanical properties. This expectation is also related to the need for preoperative distinguishing between common leiomyoma and cellular leiomyoma, as they may have premalignant potential [41, 42]. Our series included neither leiomyosarcomas, nor cellular leiomyoma, so this hypothesis is purely theoretical. However, it seems to be justified based on similar observations regarding breast and liver tumors [21, 22, 34].

The limitation of the presented paper is the small size of the study group, and its one-institutional character. Multi-centre research with a larger patient series will be required to gain appropriate statistical power to objectively assess the usefulness of MRE in evaluating the microscopic composition of leiomyomas. Besides, in our study two-dimensional MRE have been used, which is limited in estimating the true mechanical property of tissue, especially in small lesions. It was the reason for our patient selection and qualifying only those with middle-size and larger leiomyoma. In the follow-

ing investigations a 3D-MRE should be used to overcome this limitation.

CONCLUSIONS

In conclusion, this study demonstrates that stiffness of the leiomyomas obtained by MRE varies depending on their histologic composition. The value of stiffness shows a trend of increasing with growing percentage of extracellular component of the leiomyoma. Further investigations with a larger patient group and 3D-MRE are needed to assess the usefulness of MRE in evaluating leiomyomas and defining its possible clinical application.

Acknowledgments

The study was performed within the project "Centre for Innovative Research in Medical and Natural Sciences" realized by the University of Rzeszów, co- financed within the Regional Operational Program for the Podkarpackie Province for the years 2007–2013 (contract number UDA-RPPK.01.03.00-18-004/12-00).

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VIA MEDICA

ORIGINAL PAPER / GYNECOLOGY

Ginekologia Polska
2020, vol. 91, no. 7, 379–382

ISSN 0017–0011

DOI: 10.5603/GP.2020.0079

Retrospective analysis of the diagnostic effectiveness of the sentinel lymph node biopsy (SLNB) in vulvar cancer

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ABSTRACT

Objectives: Inguinal lymphadenectomy used in the treatment of vulvar cancer often results in complications, such as lymphoedema or abnormal wound healing. Aim of this study was assessment of the diagnostic effectiveness of the sentinel lymph node biopsy (SLNB) procedure in patients treated due to vulvar cancer.

Material and methods: Eighty-four patients diagnosed with squamous cell vulvar carcinoma (FIGO I-IV) underwent preoperative lymphoscintigraphy with technetium 99 to map sentinel lymph node. During surgery sentinel lymph nodes were identified and resected, followed by complete bilateral groin lymphadenectomy.

Results: Sentinel lymph nodes were mapped with lymphoscintigraphy and biopsied in 84.3% and 90.1% of patients, respectively. False negative predictive value (FNPV) was 9.1% and false negative rate (FNR) was recorded in 16.7% of cases. Patients in advanced stages (FIGO III and IV) had significantly lower rate of lymphatic mapping compared to those in stage I and II (OR = 0.148, p = 0.022). Detection of sentinel lymph node in lymphoscintigraphy for tumor grade 2 and 3 was nearly eight times lower than for grade 1 cancers, however without statistical significance (OR = 0.126, p = 0.058).

Conclusions: The use of SLNB should be limited to vulvar cancer patients in early clinical stages.

Key words: sentinel lymph node procedure; vulvar cancer; retrospective analysis

Ginekologia Polska 2020; 91, 7: 379–382

INTRODUCTION

Vulvar cancer accounts for about 5% of all female genital cancers [1]. In 2016, 490 new cases of vulvar cancer were diagnosed in Poland [2]. Lymph nodes involvement is considered as the most important prognostic factor in vulvar cancer [3].

Nowadays, sentinel lymph node biopsy (SLNB) is the standard procedure for surgical assessment of melanoma, breast cancer, penile cancer and female genital cancers, including vulvar cancer. Lymphoscintigraphy requires standardization for appropriate sentinel lymph nodes mapping. Intraoperative identification of sentinel node and histopathological examination are subsequent crucial steps in SLNB.

Implementing sentinel lymph node procedure in clinical practice requires systematic validation. The purpose of this study was a retrospective assessment of the diagnostic effectiveness of the SLNB in the first 7-year period after implementation this method into clinical practice in our department.

MATERIAL AND METHODS

The analysis included patients with vulvar cancer who were treated between 2001 and 2007. Patients were staged according to the FIGO 1994 classification. During this period 115 women were treated at the Department. 17 cases of stage III were treated with radio(chemo) therapy exclusively, 7 patients of stage IV underwent

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chemotherapy based on cisplatin and 5-fluorouracil, 3 patients were disqualified from treatment due to advanced disease and poor general condition. In 4 cases vulvar melanoma was diagnosed — all of these patients were not included in the analysis. Patients with histopathological diagnosis of vulvar squamous cell carcinoma only were eligible for the study. Finally, the analysis included a total of 84 patients.

The sentinel lymph node biopsy procedure was performed in all 84 patients. It consisted of preoperative lymphoscintigraphy, intraoperative detection and biopsy of a radioisotope identified sentinel node, and finally histopathological evaluation.

The SLNB procedure was performed according to the two-day (long) protocol: radioisotope was administered 16–20 hours before surgery. Preoperative lymphoscintigraphy with nano-colloid radiolabelled technetium isotope (^{99m}Tc) was used. The radioactive marker was administered subcutaneously in four injections around the tumor, at a dose of 74 MBq (18.5 MBq × 4). Lymphoscintigraphy imaging was performed with planar technique after 2 hours, using a two-head gamma camera with a low-energy collimator, on the sensor 128 × 128. The energy window was adapted to the energy of the ^{99m}Tc isotope radiation (140 keV) that was used in the procedure. The data obtained was developed using dedicated workstations. The result of the radioisotope examination was transmitted to the operating team. During the surgery, lymph node with the largest isotope uptake in the groins was identified with manual gamma camera. The lymph node was considered as sentinel if isotopic activity in the wound decreased at least three times after its removal. Then a bilateral inguinal lymphadenectomy was performed. In cases with the lack of sentinel node localization, a complete groin lymphadenectomy was performed. Lymph nodes considered as sentinel were sent separately for histopathological examination. This evaluation was carried out with immunohistochemical staining with cytokeratin 7 and 19.

Sentinel lymph node was considered as involved if metastasis was found.

Non-sentinel lymph nodes were considered as to be involved if metastasis was found in at least 1 non-sentinel lymph node.

The medium percentage of lymph nodes detected during the surgery as well as sensitivity, specificity, positive and negative predictive values (PPV, NPV) were estimated. The estimates are given along with 95% confidence intervals. Factors that could possibly affect the detection of sentinel node were also examined. For this purpose, the logistic regression model was used. Grading (G), clinical stage, age, the largest dimension and localization of the tumor were included in this model. To optimize the analysis, continuous variables have been categorized.

Effectiveness of sentinel lymph node identification in lymphoscintigraphy was assessed and potential factors that could affect it were examined. Compatibility of lymphoscintigraphic and surgical sentinel nodes detection was estimated.

All hypotheses were tested at a level of statistical significance of 0.05.

Standard descriptive statistics tools are used to describe the study material. The statistical analysis was carried out with the IBM SPSS Statistics 23 statistical package. Due to the retrospective character of the study, the consent of the bioethics committee was not required.

RESULTS

The study group consisted of 84 women. Mean age was 66 years old (18 to 94, standard deviation: 14). The largest dimension of the tumor ranged from 5 to 90 mm (median: 35 mm), interquartile range (IQR): 22–50. Characteristics of study group was presented in Table 1.

Surgical and pathological evaluation of SLNB

Sentinel lymph node was found in 90.1% of patients. The estimated sensitivity and specificity were 54.5% (25.1––83.9%), and 83.3% (73.9–92.7%), respectively. The positive

Table 1. Clinical characteristics of study group.

		Number of patients	Percentage of patients
FIGO (1994)	IA	1	1.2
	IB	11	13.1
	II	35	41.7
	III	31	36.9
	IV	6	7.1
Grading	1	29	36.7
	2	37	48.1
	3	12	15.2
	missing	6	
Side	right	27	41.8
	left	13	20.9
	midline	44	37.3
Multifocal	no	79	94.1
	yes	5	5.9
Age [years]	< 62	26	31.0
	62–73	30	35.7
	> 73	28	33.3
Maximum tumor size [mm]	≤ 25	31	37.3
	25–45	22	26.5
	≥ 45	30	36.1
	missing	1	

Table 2. The sensitivity[1], specificity[2], PPV[3], NPV[4], FNPV[5], FNR[6] of SLNB in 71 patients. All 84 patients underwent SLNB but in 13 women pathological results were imprecise. Therefore, these patients were not included in the analysis. In these cases, the histopathological report: (1) did not specify which lymph nodes were sentinel; (2) contained the total number of resected and metastatic lymph nodes without taking into consideration site of lymphadenectomy

			Non-sentinel lymph node		Total
			Negative	Positive	
Sentinel lymph nodes	Negative	N	50	5	55
		% within SLN	90.9%[4]	9.1%[5]	100%
		% within non-SLN	83.3%[2]	45.5%	77.5%
	Positive	N	10	6	16
		% within SLN	62.5%	37.5%[3]	100%
		% within non-SLN	16.7%[6]	54.5%[1]	22.5%
	Total	N	60	11	71
		% within SLN	84.5%	15.5%	100%
		% within non-SLN	100%	100%	100%

Table 3. The parameters of the final logistic model for chance of lymph nodes detection in scintigraphy

	Beta coefficient	SE of Beta	p	OR	95%-confidence interval	
Stage G > 1	–2.071	1.093	0.058	0.126	0.015	1.075
Clinical stage (1994) > 2	–1.911	0.832	0.022	0.148	0.029	0.755
Constant	4.527	1.230	< 0.001	92.2		

and negative predictive values (PPV and NPV) were 37.5% (13.8–61.2%) and 90.9% (83.3–98.5%), respectively. False negative predictive value (FNPV) was recorded in 9.1% of patients and false negative rate (FNR) was found in 16.7% of patients. Detailed statistical analysis was presented in Table 2. All analysed factors (*i.e.* age, maximum tumor size, staging, grading) were not significant for intraoperative sentinel lymph node detection ($p > 0.1$).

Lymphoscintigraphy assessment

Lymphoscintigraphy revealed sentinel lymph node in 84.3% (76.5–92.1%) of patients. Patients with FIGO stage I and II were almost 7 times more likely to find sentinel lymph nodes with ^{99m}Tc scintigraphy then those with stage III and IV (OR = 0.148, $p = 0.022$). Correlation between histological grading and lymphoscintigraphy was close to the statistical significance level ($p = 0.058$). Chance for sentinel lymph node detection in tumors G2 and G3 compared to G1 was almost eight times lower (OR = 0.126). Logistic model analysis was presented in Table 3.

Comparison of lymphoscintigraphy and surgery

There was no correlation between lymphoscintigraphy outcome and surgical evaluation of sentinel lymph node site. The estimated values of kappa coefficient for the left and right side were 0.192 ($p = 0.0638$) and 0.048 ($p = 0.628$), respectively.

DISCUSSION

The status of regional lymph nodes is the most essential of all known risk factors for vulvar cancer recurrence [4]. The assessment of lymphatic drainage in vulvar cancer is important, especially in fact that in clinical stage I and II metastases to regional nodes occur at 10.7%, 26.2%, respectively [5]. In the past, surgical treatment of the vulvar cancer relied on en bloc resection of the vulva and inguinal lymph nodes. Postoperative period after such disabling surgeries was complicated by long wound healing, infections and psychological problems. In the 1970s, surgical management of vulvar cancer resection was modified to triple incision technic. It has improved postoperative period significantly, especially wound healing and reducing long hospitalization stay.

In mid 1990s, SLNB was introduced in vulvar cancer [6, 7]. Lymphoscintigraphy with ^{99m}Tc was the most regularly used technique with high accuracy of mapping lymphatic drainage [8–10]. Therefore since 2000, we used this method in our Department to perform SLNB in patients with vulvar cancer.

The study analysed data covering the period between 2001 and 2007; the eligibility criteria for SLNB in vulvar cancer patients were not established. At that time in our department, all patients with malignant vulvar neoplasms were qualified to SLNB, regardless of tumor size (in 32 patients tumor size was > 4 cm, and the largest tumor dimension was 90 mm), abnormal inguinal lymph in physical examination and imaging. 90.1% of patients had at least one sentinel lymph node found

during operation. This result may be disappointing regarding study of Vidal-Sicart et al. [11], who found sentinel lymph nodes in 98% of patients. However, our results are acceptable regarding that SLNB has just been introduced as a new technic in those days and wide eligibility criteria for the procedure. Learning curve in SLNB as well as developing lymphoscintigraphy technique certainly had an impact on such result [12].

None of analysed factors (grading, staging, age, the maximum dimension and localization of the tumor) were relevant in intraoperative sentinel lymph node detection. However, in the meta-analysis, Hassanzade et al. [13] showed that efficacy of sentinel lymph node identification depended on the maximum tumor size and was 7% higher in tumors less than 4 cm. The total efficacy of sentinel lymph node detection was 94.4% (regarding to patient) and 84.6% (regarding to a groin) [13].

Currently, the most regularly used criteria (ESGO and NCCN recommendations) for sentinel lymph nodes detecting include: 1) tumors less than 4 cm, 2) clinically not enlarged groin lymph nodes and 3) lack of abnormal imaging [14, 15]. Nowadays, according to these criteria, only selected patients are qualified to SLNB in our department. The recommendations are the results of the clinical trial — GROINSS V [16]. Patients suffering from squamous vulvar cancer with a maximum tumor diameter < 4 cm were qualified to this study. False negative predictive value was 2.9% in the trial. In our analysis, FNPV was 3 times higher and reached 9.1 %. Probably, this was due to the qualification of patients regardless of tumor size — 36.1% of patients had tumors > 4.5 cm in diameter. It may be caused by complete blockage of lymphatic vessels by cancer cells in large tumors [13]. Results of the GOG 173 study confirmed this thesis — FNPV for tumors 4–6 cm was 7.4%, while in tumors < 4 cm decreased to 2% [17]. In this prospective study FNR was 8.3%, compared to 16.7 % presented in our paper. That is an argument for qualifying patients with tumors up to 4 cm for the procedure of sentinel node detection. According to Levenback et al. [17] FNR can be reduced by using radiocolloid and dye.

We found that staging ($p = 0.022$) and tumor grading ($p = 0.058$) may be related to efficacy of the lymphoscintigraphy. In the literature, no analysis has been found regarding clinicopathological factors and the lymphoscintigraphy results.

The study was a retrospective analysis and had some limitations. Staging of vulvar cancer was conducted according to FIGO classification from 1994. Another problem was related to definition of SLNB. A sentinel lymph node identified by gamma probe have radioactivity at least ten times higher than the background counts. This definition comes from practice guideline in gynecological cancers of The European Association of Nuclear Medicine published in 2014 [18]. In our study, covering the years 2001-2007, radioactivity at least three times the background was adopted to mark the node as SLN. This could affect the results.

CONCLUSIONS

These results became starting point for improving SLNB in clinical practice and conducting further research in this area. In our opinion, SLNB should be limited to patients with vulvar cancer in early clinical stages.

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VIA MEDICA

ORIGINAL PAPER / GYNECOLOGY

Ginekologia Polska
2020, vol. 91, no. 7, 383–388

ISSN 0017–0011

DOI 10.5603/GP.a2020.0084

Should the patients with endometriosis be treated as a risk group of pregnancy complications? Single center experience and literature review

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ABSTRACT

Objectives: Multidirectional influence of endometriosis on fertility impairments is well known. Altered implantation and placentation among affected patients raised concerns regarding possible negative influence on the course of pregnancy. The primary objective of the study was to assess the course of gestation and the incidence of pregnancy complications among women with endometriosis. It also aimed to determine whether the method of conception might impact the primary results.

Material and methods: A single-center cohort study included 64 women with confirmed endometriosis and 296 healthy controls. Data concerning treatment of endometriosis related infertility, course of pregnancy and perinatal outcomes were evaluated.

Results: Patients with endometriosis were older than controls (33.6 +/- 4.2 y vs 31.8 +/- 4.6, p = 0.01) and more often gave birth for the first time (87.5% vs 43.9%, p = 0.001). The age at the time of first delivery was significantly higher within the study group (33.1 y +/- 4.1 vs 29.9 +/- 4.6, p < 0.001). In the study, 81.2% of patients with endometriosis had the diagnosis of infertility. Patients suffering from endometriosis were significantly more prone to spontaneous placental abruption during pregnancy and delivery (4.7 vs 0.3%, odds ratio = 14.5). Several complications occurred more often in endometriotic patients (gestational diabetes mellitus, small-for-gestational-age and anemia); however, without statistical significance. The risk of pregnancy complications was independent from stage of endometriosis and way of conception. The incidences of adverse neonatal outcomes (preterm delivery, low Apgar score, lower birth weight) were similar in both groups.

Conclusions: Endometriosis may adversely affect perinatal outcomes, especially due to increased risk of placenta abruption and operative delivery. Stage of endometriosis and method of conception does not enhance these complications.

Key words: cesarean section; endometriosis; infertility; placenta pathology; pregnancy complications

Ginekologia Polska 2020; 91, 7: 383–388

INTRODUCTION

There are a multitude of possible reasons for decreased fertility among women of reproductive age. Among them is endometriosis, defined as presence of endometrial glands and stroma outside the uterine cavity [1]. Although the pathogenesis of endometriosis is still under debate, it is well known that it affects every part of a woman's reproductive system. The prevalence of endometriosis in the general population is estimated to be 10–15%; however, among infertile females the rate may increase up to 48% [2, 3]. Nevertheless, the symptoms of the disease do not correlate with its' stage, meaning that the real incidence in the general population remains unknown and the prevalence may be underestimated.

Endometriosis can affect the reproductive potential by means of reduced ovarian function, decreased oocyte quality, altered embryo development or implantation failure.

Current literature describes various defects of endometrial functions in patients suffering from endometriosis. Endometrial tissue is characterized by high sensitivity to autocrine and paracrine signaling factors, such as sex hormones or cytokines. Locally unbalanced production of estrogens and cytokines in ectopic endometrium leads to disordered growth and malfunctioning of the tissue [4]. All of the above are involved in altered gene expression in eutopic endometrium and myometrium [5]. Furthermore, inappropriate cytokine secretion causes chronic local and

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systemic inflammatory response and results in the most typical symptoms and signs of endometriosis, such as chronic pelvic pain (especially dysmenorrhea, dyspareunia), pelvic adhesions and distorted pelvic anatomy. Decreased sensitivity to progesterone, due to downregulation of progesterone receptors is the reason why endometriosis is also called *'progesterone-resistant disease'* [6, 7]. The alterations in molecular and cellular profiles of the eutopic endometrium of women with endometriosis were detected. It has been, therefore, hypothesized that endometriosis may influence pregnancy outcomes [8].

There is a strict dependency between proper implantation and placentation. Both are critical for fetal growth and favorable pregnancy outcomes. Nowadays, the correlation between abnormal placentation and several pregnancy complications, such as pregnancy induced hypertension (PIH), preeclampsia, fetal growth restriction, placental abruption (AP) or placenta praevia (PP) is well established. Furthermore, most of them may lead to the iatrogenic preterm birth. All the above may explain why previous investigators raised concerns regarding possible negative influence of endometriosis on the course of pregnancy and possible early pregnancy loss.

Objectives

The primary objective of the presented study was to assess the course of gestation and the incidence of pregnancy complications among women with confirmed endometriosis. It also aimed to determine whether the way of conception might impact the primary results. According to the available literature this issue has not been investigated among the Polish population before.

MATERIAL AND METHODS

A single-center cohort study was carried out at the 1st Department of Obstetrics and Gynecology, Medical University of Warsaw. Multiple gestations and pregnancies miscarried prior to 22 weeks were excluded from the study. The authors identified 64 women with endometriosis, confirmed during previous surgical intervention (laparoscopy or laparotomy), who delivered at the Department between January 2015 and December 2018. Women diagnosed with adenomyosis or other anatomical disorders within genital tract not related to endometriosis (*e.g.* myomas) were excluded from the final analysis due to the suggested additional negative impact on the course of gestation. Data concerning treatment of pre-existing endometriosis, infertility [especially with the usage of assisted reproductive technologies (ART)], course of pregnancy and perinatal outcomes were obtained from medical records. Assessed neonatal outcomes included preterm delivery, Apgar score and birth weight. The stage of endometriosis was conferred according to the revised American Society for Reproductive Medicine classification (rASRM) [9].

The control group (C) consisted of healthy women (without any known chronic diseases before conception; no suspicion of endometriosis, nor the diagnosis of infertility) who delivered at the Department within the same time frame. Finally, the control group consisted of 296 participants.

The baseline and clinical characteristics of both groups were collected from the patients' medical records. Preterm delivery was defined as birth before 37 completed weeks of gestation, while fetal growth restriction (FGR) as estimated fetal weight (EFW) below the tenth percentile in ultrasound examination [10]. PE, PIH and gestational diabetes mellitus were recognized according to guidelines of The Polish Society of Gynecologists and Obstetricians and The Royal College of Obstetricians and Gynaecologists.

The study was conducted in accordance with the Declaration of Helsinki for Medical Research involving human subjects. The ethical approval was obtained from the Ethics Committee of Medical University of Warsaw (AKBE/99/2019).

Statistical analyses

Categorical variables were presented as percentages and continuous ones as means with SD (standard deviation). The baseline and clinical data were compared using parametric (t-Student) and nonparametric (Mann-Whitney U) tests. Univariate odds ratios (ORs) with 95% confidence intervals (95% CI) for the parameters that could affect the course of pregnancy were calculated by Chi-Square test. A multiple logistic regression model was built to estimate which factors influence the risk of pregnancy complications. Statistica 13 software was used for statistical analyses. P-values below the threshold of 0.05 were considered significant. Main calculations were performed for all women with endometriosis. Additional analyses included the adjustment for the stage of endometriosis and the way of conception.

RESULTS

Baseline characteristics of women with or without endometriosis are presented in Table 1. Patients diagnosed with endometriosis were significantly older ($p = 0.01$) than controls and more often gave birth for the first time ($p = 0.001$). Moreover, the age at the time of first delivery was significantly higher in the study group compared to controls (33.1 years, SD = 4.1 vs 29.9, SD = 4.6, $p < 0.01$).

All patients from the study group underwent at least one surgical procedure in the past (62.5% excision of endometrioma, 15.6% diagnostic laparoscopy due to pelvic pain or infertility, 6.3% removal of hydrosalpinx). The mean age at the diagnosis of endometriosis was 29.2 years (SD = 4.5). Most of the women suffered from moderate to severe endo-

Table 1. Baseline characteristics of the groups

	Study group (SD)	Control group (SD)	p value
Sample size	64	296	(–)
Age [years]	33.6 (4.2)	31.8 (4.6)	0.01
BMI before pregnancy [kg/m^2]	22.4 (3.8)	23.4 (4.6)	0.24
Gestational age at delivery [weeks]	38.6 (1.6)	38.7 (2.0)	0.25
Primiparous	87.5%	43.9%	< 0.001
Mean birth weight [g]	3301 (540)	3408 (580)	0.09

BMI — body mass index; SD — standard deviation

Table 2. Pregnancy complications and perinatal outcomes in studied groups

	Study group, n (%)	Control group, n (%)	OR (95% CI)
PIH	5 (7.8)	28 (9.5)	0.8 (0.3–2.2)
Preeclampsia	1 (1.6)	7 (2.4)	0.7 (0.1–5.4)
GDM	11 (17.2)	45 (15.2)	1.2 (0.6–2.4)
FGR	5 (7.8)	12 (4.1)	2.0 (0.7–5.9)
Hypothyroidism	11 (17.2)	69 (23.3)	1.1 (0.1–9.8)
Anemia during pregnancy	9 (14.1)	21 (7.1)	2.1 (0.9–4.9)
Placenta previa	1 (1.6)	0(0)	(–)
Placental abruption	3 (4.7)	1 (0.3)	14.5 (1.5–140)
Imminent fetal asphyxia during labor	6 (9.4)	20 (6.8)	1.4 (0.5–3.7)
Caesarean delivery	43 (67.2)	156 (52.7)	1.8 (1.1–3.2)
Preterm delivery	7 (10.9)	27 (9.1)	1.2 (0.5–2.9)

CI — confidence interval; GDM — gestational diabetes mellitus; OR — odds ratio; PIH — pregnancy induced hypertension; FGR — fetal growth restriction

metriosis (stage 4–15.2%, 3–42.4%, 2–30.3%, 1–12.1%). Patients' BMI significantly differed within subsequent stages of endometriosis [stage 1–22.2 (kg/m^2), (SD = 4.9), 2–23.4 (4.8), 3–20.9 (2.6), 4–24.8 (3.2), p = 0.02]. Moreover, the incidence of overweight and obesity increased with the severity of disease (stage 1–0%, 2–30%, 3–14% and 40% in stage 4), however this factor did not reach statistical significance (p = 0.1). Patients BMI did not impact the severity of endometriosis. Due to comparable prognosis and recommendations concerning the treatment of infertility in patients with stage 1 and 2, as well as stage 3 and 4 of endometriosis, these cases were further evaluated together (called 1 + 2 and 3 + 4 endometriosis).

In the study, 81.2% of patients with endometriosis had the diagnosis of infertility before (65.6% primary and 15.6% secondary). The mean time to conception in the study group equaled 2.6 years (SD = 2.7). Also, 42.9% of women with 1 + 2 endometriosis conceived spontaneously, 21.4% after intrauterine insemination (IUI) and 35.7% after in-vitro fertilization (IVF). Finally, 72% of pregnancies in patients with 3 + 4 endometriosis were a result of IVF, 20% of IUI, while only 8% were conceived naturally. The incidence of spontaneous pregnancies was significantly higher in patients with stage 1 + 2 compared to stage 3 + 4 (p = 0.01).

Table 3. Pregnancy complications and perinatal outcomes adjusted for the stage of endometriosis and the way of conception

	1 + 2 vs 3 + 4 endometriosis OR (95% CI)	Natural conception/IUI vs IVF OR (95% CI)
PIH	0.4 (0.1–2.6)	0.3 (0.1–2.2)
Preeclampsia	(–)	(–)
GDM	0.4 (0.1–1.7)	0.6 (0.2–2.3)
FGR	1.1 (0.1–11.0)	2.4 (0.2–22.6)
Hypothyroidism	0.4 (0.1–1.5)	0.4 (01–1.5)
Anemia during pregnancy	0.4 (0.1–1.8)	0.1 (0.1–0.6)
Placenta previa	(–)	(–)
Placental abruption	(–)	1.1 (0.1–13.2)
Imminent fetal asphyxia during labor	0.5 (0.1–2.9)	1.1 (0.2–6.7)
Caesarean delivery	0.3 (0.1–1.5)	0.8 (0.3–2.5)
Preterm delivery	1.8 (0.2–16.0)	0.7 (0.1–3.5)

CI — confidence interval; GDM — gestational diabetes mellitus; IUI — intrauterine insemination; OR — odds ratio; PIH — pregnancy induced hypertension; FGR —fetal growth restriction

The incidence of pregnancy complications among women from the study and control groups is presented in Table 2. Patients suffering from endometriosis were significantly more prone to spontaneous placental abruption during pregnancy and delivery (OR = 14.5). Several complications related to the course of pregnancy occurred more often in endometriotic patients (gestational diabetes mellitus, FGR or anemia); however, without statistical significance.

Endometriosis increased the risk of operative delivery (OR = 1.8). The most frequent indication for caesarean section (CS) in the study group was the previous history of infertility/ART (elective CS, 27.9%) and excessive bleeding/hemorrhage during labor (emergency CS, 13.9%). Moreover, placental abruption was the most frequent known reason of obstetric hemorrhage. On the contrary, the most frequent reasons to perform CS in the control group included previous caesarean section (18.3%) and labor arrest of (8.1%).

Further sub analysis assessed the risk of pregnancy complications adjusted for the stage of endometriosis and the method of conception (Tab. 3). The risk of the analyzed perinatal complications was not related to any of the above. The only feature that differed in patients with endometriosis was the decreased risk of anemia during IVF pregnancy (4.9% vs 30.4%, p = 0.01).

Most women in both groups delivered full-term newborns. The rate of preterm deliveries among women diagnosed with endometriosis equaled 10.9% compared to 9.1% in healthy controls (p = 0.65). Neonatal outcomes were similar among women with and without endometriosis. There was no significant difference in the mean fetal birth weight (3301 g vs 3408 g in controls, p = 0.09). There were no significant differences in the incidence of low Apgar scores (< 8 points in 1st and 5th minute of life between both studied groups (1.6 vs 3.4%, p = 0.4 and 0 vs 1.7%, p = 0.3 respectively).

DISCUSSION

Pregnancy and delivery related complication are the main reasons of maternal and neonatal morbidity [11]. Identifying and close monitoring of patients with increased risk of adverse perinatal outcomes provide an opportunity to improve the quality of maternity care [12].

According to our findings, endometriosis does not seem to increase the risk of most common pregnancy complications such as PIH, preeclampsia, GDM or FGR. The potential correlation between endometriosis and preeclampsia is still a subject of debate. Previous researchers did not find any association between these conditions either [13]. Hadfield et al. obtained similar results from the longitudinal observation of 3239 Australian women with endometriosis diagnosed prior to pregnancy. In comparison to the healthy controls, neither pregnancy hypertension, nor pre-eclampsia occurred more often in the study group [14]. The rate of complications was also independent from the severity of endometriosis. However, according to Berlac et al., women with endometriosis are more prone to suffer from hypertensive disorders during pregnancy: preeclampsia (OR 1.4), severe preeclampsia, eclampsia or HELLP syndrome (OR 1.7 95%) than healthy controls [15]. Data from Danish reports (82,793 singleton pregnancies) also suggest increased risk of pre-eclampsia in affected females (OR = 1.37, 95% CI 1.06–1.77), regardless of the way of conception (natural vs ART) [16]. The results were again confirmed in a cohort study by Farland et al. [17], where the risk of hypertensive disorders in women with endometriosis was also greater (RR 1.3; 95% CI 1.16–1.45).

Tobias et al. evaluated the risk of GDM among women with a history of infertility – they found no association for endometriosis [18]. Subsequent systematic review published by Perez-Lopez et al. [19] also confirmed no association (OR 1.14, 95% CI 0.86–1.51). However, Farland et al. concluded that endometriosis was associated with a significantly greater risk of GDM (RR 1.35; 95% CI 1.11–1.63). Therefore, even the results from large cohort studies are inconclusive [17].

The incidence of placental abruption differed most between both studied groups in the presented research. Women with endometriosis were at increased, over fourteen-fold, risk of the above complication compared to healthy controls. Moreover, the authors observed higher incidence of placenta previa in the study group (1.6% vs 0%), but the result did not reach significance. These conclusions are concordant with the findings of previous researchers (reported OR 2.0-3.99 for placental abruption and 3.9–15.1 for placenta previa) [13, 15, 20, 21].

According to our results, endometriosis seems to be positively correlated with the incidence of elective caesarean sections (OR = 1.8). This finding is concordant with previous studies (Porpora et al., Horton et al.) [21, 22]. Nevertheless, vaginal labor does not increase the risk of peritoneal injuries among women who underwent surgery for deep infiltrating endometriosis and may reduce the recurrence of endometriosis symptoms after delivery [23, 24].

Further sub-analyses of pregnancy complications regarding the stage of endometriosis and the method of conception did not show any significant differences between groups.

The incidence of most of the adverse perinatal outcomes increases with the age of the woman in general population. Patients with endometriosis were significantly older than controls (33.6 vs 31.8 years); however, this fact did not bias the end results.

The authors of the presented paper did not evaluate the course of early pregnancies (< 22nd week of gestation). Few publications hypothesize that endometriosis may be associated with early pregnancy loses (both spontaneous abortion and ectopic pregnancy), but these findings should be carefully interpreted (Farland et al., Porpora et al.) [21]. Further studies should also focus on these issues.

Neonatal outcomes (rate of preterm deliveries, birth weight and Apgar scores) did not differ between women with or without endometriosis. On the other hand, previous researchers gave evidence of increased risk for preterm delivery and neonatal unit admission following delivery among women diagnosed of endometriosis [22].

The women' age is the strongest indicator of fertility impairments in the future. Of women, 81.2% diagnosed with endometriosis, who delivered at our department, had been diagnosed with infertility before. Furthermore, the average age at the time of the first pregnancy ended with delivery was significantly higher among women with endometriosis compared to healthy controls. The same findings were presented by previous researchers [25]. According to the epidemiological data, endometriosis extends the time to conception (mean time from diagnosis to pregnancy equaled 2 years and 4 months). There is a clear association between endometriosis and infertility due to lower oocyte yield and lower implantation rates. The percentage of known fertility impairments is much higher than the rate observed

in the general population [26]. Previous studies have reported an inverse correlation between advanced stages of endometriosis and the prognosis for fertility treatments [27]. Apart from chronic pelvic pain and dyspareunia, fertility impairments are the most common symptoms among patients suspected of endometriosis [28]. Moreover, literature data proves an increased risk of infertility, over 8-fold, among endometriotic patients [29].

The problem is additionally enhanced by significant diagnostic delay in recognition of endometriosis. The average time from the onset of first symptoms to the final diagnosis of the disease varies greatly among countries (from 4.4 years in USA, up to 10.4 years in Germany and Austria) [30, 31]. The main factors contributing to the above are mainly limited access to gynecological care, time between consultations and high (up to 74%) rates of false diagnoses. The American Society for Reproductive Medicine classification is the most widely used tool for assessing the clinical stage of endometriosis. In the study group, a higher incidence of late forms of endometriosis was observed (stage III and IV). It may be due to the problem of underestimation of the disease prevalence; however, benefits from performing laparoscopy for minimal endometriosis prior to IVF are still under debate [32].

There are some limitations of the above study. It presents only single-center experience and the results regarding adverse perinatal outcome might not reach significance due to small sample size.

CONCLUSIONS

To conclude, the history of endometriosis may adversely affect perinatal outcomes, especially due to impaired placentation and increased risk of operative delivery. However, it does not seem to influence neonatal complications as preterm birth, low Apgar score or low birth weight. Since stage of endometriosis have detrimental effect on female fertility, it seems reasonable to raise awareness of possible fertility impairments especially among women with symptoms typical for endometriosis.

Conflict of interest

The authors declare that there is no conflict of interest.

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VIA MEDICA

ORIGINAL PAPER / GYNECOLOGY

Ginekologia Polska
2020, vol. 91, no. 7, 389–393

ISSN 0017–0011

DOI: 10.5603/GP.2020.0071

The role of day 0 and day 4 β-human chorionic gonadotropin values and initial ultrasound findings in predicting the success of methotrexate treatment in ectopic pregnancy

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ABSTRACT

Objectives: To determine the role of baseline ultrasound findings and the changes between β- human chorionic gonadotropin (hCG) values on day 0 to day 4 in patients receiving single-dose methotrexate (MTX) therapy for tubal ectopic pregnancy.

Material and methods: One hundred fourteen patients who were hospitalized with a diagnosis of ectopic pregnancy and treated with single-dose methotrexate were included in this retrospective study. The successful treatment group (n = 88) comprised patients in whom serum β-hCG levels were resolved with single-dose methotrexate treatment, and the failed treatment group (n = 26) included patients who received second dose methotrexate and/or surgery. Ultrasound findings, laboratory findings, and serum β-hCG values at the time of admission and D4 and D7 β-hCG values were compared.

Results: The success rate of single-dose methotrexate treatment was 77.2%. In the successful treatment group, the initial β-hCG values of the patients were lower than the unsuccessful treatment group (1479.14 ± 1253.49, 4442.88 ± 3392.58, respectively) (p = 0.0001). A decrease of more than 35% between D0-D4 increased the probability of successful treatment (p = 0.017). Although ectopic focus size and abdominal free fluid showed no significant difference between the two groups, endometrial stripe thickness was significantly higher in the unsuccessful treatment group (12.61 ± 5.79, 9.28 ± 3.53) (p = 0.002).

Conclusions: In addition to the basal β-hCG value, endometrial stripe thickness of ultrasound findings should also be considered in determining patients with a high chance of success in single-dose MTX treatment.β-hCG changes between D0-D4 may be advantageous in the clinical management of ectopic pregnancy for earlier evaluation.

Key words: ectopic pregnancy; methotrexate; serum β-hCG; treatment success

Ginekologia Polska 2020; 91, 7: 389–393

INTRODUCTION

Ectopic pregnancy (EP) is a condition in which the developing blastocyst is implanted in a tissue other than the uterine cavity endometrium, most commonly in the fallopian tube (98%) [1]. The incidence of ectopic pregnancy, which can cause severe maternal morbidity and mortality, is around 2% [2]. However, its frequency increases with each passing day due to increasing assisted reproductive technology (ART) applications and increasing pelvic inflammatory disease (PID) [3]. Nowadays, serial β-human chorionic gonadotropin (hCG) measurements and high-resolution ultrasound can be used for early diagnosis. Early diagnosis and treatment reduce maternal mortality, protects from tubal rupture, and allows fertility to be maintained.

Methotrexate (MTX), a folate antagonist, shows anti-mitotic activity in tissues with high proliferative capacity such as chorionic villi [4]. Medical treatment is a good alternative to surgery because it is effective, safe, and economical [5]. It was first reported by Tanaca et al. [6] that MTX was used successfully in the treatment of ectopic pregnancy in 1982. Single-dose, fixed multi-dose, and variable multi-dose regimens have been defined for MTX applications [7]. The most preferred single-dose protocol was developed by Stovall et al. [8] in 1991. Success in the single-dose protocol was defined as a decrease in β-hCG of > 15% between days 4 and 7 of MTX administration. The positive predictive value reaches 93% [9]. However, one-week follow-up increases the length of hospital stay or requires patient compliance

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for β-hCG follow-up. Also, during this time, tubal rupture may occur and emergency surgery may be required. Thus, an earlier predictive value, including baseline ultrasound data, to assess success may allow earlier intervention to those with a potential for treatment failure and make clinical management of ectopic pregnancy more effective.

Objectives

Evaluating the role of baseline ultrasound findings for determining patients with a high chance of success in single-dose MTX treatment. Although the cornerstone of MTX treatment monitoring is the change in β-hCG values between days 7 and 4, we are looking for an answer to the question of whether early prediction of the treatment success by evaluating change in β-hCG values between days 4 and 0 can bring a new perspective to clinical management of ectopic pregnancy.

MATERIAL AND METHODS

The data and patient files of patients who were hospitalized at our Training and Research Hospital with a diagnosis of ectopic pregnancy between May 2016 and December 2018 and treated with methotrexate were retrieved from the hospital's electronic registry system and retrospectively reviewed. Patient age, obstetric history, transvaginal ultrasound findings (ectopic focal size, endometrial stripe thickness, presence and amount of free fluid in the pouch of Douglas), complete blood count parameters, β-hCG values from days 0, 4, and 7 and following weeks, and treatment results were recorded.

The definitive diagnosis of ectopic pregnancy was made if the gestational sac and/or embryo were seen in the adnexal area and trophoblastic tissue was not observed in the uterine cavity on pathologic examination. Possible ectopic pregnancy diagnosis was defined as the presence of suspected adnexal mass or free fluid in the pouch of Douglas in the existence of abnormally increased or plateau β-hCG values or β-hCG values > 1500–2000 IU/L, with no intrauterine pregnancy observed on transvaginal ultrasound (TVUSG). These patients were candidates for methotrexate treatment in the absence of any contraindications to medical treatment; hemodynamic instability, acute abdominal findings, abnormal hematologic, renal, hepatic laboratory values, acute pulmonary disease, active peptic ulcer and breastfeeding mother.

While deciding on medical treatment/surgical treatment in our clinic, the patient's hemodynamic status, desire for fertility, ectopic focus size, serum β-hCG value, fetal heartbeat positivity, and compliance of the patient with the treatment process are considered. A single-dose MTX treatment protocol is applied to patients who are eligible as recommended in the American College of Obstetricians and Gynecologists Application Bulletin [10]. Day 0: β-hCG value, whole blood count, blood group, renal and hepatic function tests and lung radiography are evaluated in patients with a history of lung disease. Day 1: 50 mg/m^2 body surface area, intramuscular MTX is applied. Day 4: β-hCG, and day 7: complete blood count and β-hCG are examined. Successful treatment with single-dose MTX is a > 15% reduction in β-hCG between days 7 and 4, and a decrease in β-hCG of less than < 5 IU/L during weekly β-hCG follow-ups. Failure of single-dose MTX treatment was considered as the requirement for a repeated MTX dose due to a decrease in β-hCG values of days 7 and 4 < 15%, or surgical treatment of tubal rupture due to hemodynamic instability at any stage of treatment.

The study was started after receiving approval from the local ethics committee. The patients were divided into two groups according to the results of single-dose MTX treatment. Age, gravida, parity, laboratory findings, TVUSG findings, and β-hCG values at the start, 4th and 7th days were compared retrospectively between the groups.

Data were analyzed using the IBM SPSS Statistics 18© (SPSS Inc., 1989 2010) software package. The compatibility of continuous variables with normal distribution was examined using the Kolmogorov-Smirnov test. The categorical variables in the study are presented as frequency and percentage, and continuous variables as mean and standard deviation values. Chi-square and Fisher's Chi-square tests were used to analyze categorical variables. Since the independent comparisons of two groups did not meet the parametric test assumptions, the Mann-Whitney U test for independent measures of two group, and dependent groups were analyzed using the Friedman test. Furthermore, the possible factors determined by univariate analyzes were then analyzed by a multiple logistic regression model. The level of statistical significance was accepted as 0.05.

RESULTS

In this retrospective cohort study, the data of 304 patients admitted to our clinic with a diagnosis of ectopic pregnancy between May 2016 and December 2018 were reviewed; 21 patients were excluded from the study due to insufficient data or refusal of treatment. Expectant management was applied to 16 patients, spontaneous resolution was observed, and no additional treatment was required during the follow-up. One hundred fifty-three patients underwent primary surgical treatment.

Single-dose MTX was administered to 114 patients, 88 patients were treated successfully, and the success rate was 77.2%. Of the 26 patients who failed single-dose MTX treatment; 14 patients received a second dose of MTX, 10 patients underwent surgical treatment, and 2 patients had surgical treatment after a second dose of MTX.

The demographic data, and ultrasound and laboratory findings of the groups were divided according to MTX treatment success/failure (Tab. 1). Among the groups, there was no difference in terms of age (31.76 ± 5.77 vs 30.35 ± 5.66 years), gravida (2.84 ± 1.48 vs 2.46 ± 1.30), and parity (1.41 ± 1.09 vs 1.00 ± 0.89). Initial β-hCG values were found as 1479.14 ± 1253.49 in the successful treatment group and 4442.88 ± 3392.58 in the failed treatment group, which was statistically significantly different (p = 0.0001). β-hCG values at day 0, day 4, and day 7 were statistically lower in the successful treatment group than in the unsuccessful treatment group. Ectopic focal size showed no significant difference between the two groups (20.65 ± 10.48, 19.40 ± 5.95, respectively); however, endometrial stripe thickness was significantly higher in the unsuccessful treatment group (12.61 ± 5.79 vs 9.28 ± 3.53) (p = 0.002).

There was no correlation between the presence and amount of free fluid in the abdomen and the success or failure of treatment (Tab. 2).

In a multivariate logistic regression analysis, only two independent determinants; day 4 β-hCG values and day 7 β-hCG values were significantly associated with treatment success (Tab. 3).

The overall success rate of MTX treatment was 77.2%. The success rate was found as 87.5% for those with β-hCG values falling between D0-D4, and 59.5% in those whose values rose in the same period (Tab. 4).

A decrease of more than 35% between D0-D4 increases the probability of successful treatment (p = 0.017). Between D0–D4, 97.1% of those with a reduction of more than 35% had successful treatment (Tab. 5).

Table 1. Demographic data, and laboratory and ultrasonography data

	Successful (n = 88)	Unsuccessful (n = 26)	p value
Age	31.76 ± 5.77	30.35 ± 5.66	0.241
Gravida	2.84 ± 1.48	2.46 ± 1.30	0.288
Parity	1.41 ± 1.09	1.00 ± 0.89	0.131
Endometrial Thickness [mm]	9.28 ± 3.53	12.61 ± 5.79	0.002
Ectopic focus size [mm]	20.65 ± 10.48	19.40 ± 5.95	0.066
Hb	11.75 ± 1.38	11.87 ± 1.08	0.663
Plt	246.35 ± 82.69	253.67 ± 71.71	0.968
WBC	7.99 ± 2.49	8.02 ± 1.74	0.844
Neutrophils	7.94 ± 1.70	4.93 ± 1.54	0.891
Lymphocytes	2.02 ± 0.64	2.19 ± 0.40	0.584
β-hCG Day 0	1479.14 ± 1253.49	4442.88 ± 3392.58	0.0001
β-hCG Day 4	1133.81 ± 1044.38	5315.92 ± 4153.30	0.0001
β-hCG Day 7	609.59 ± 652.20	4779.96 ± 3525.71	0.0001

*Mann-Whitney U Test; Hb — Hemoglobin; Plt — Platelet count; WBC — White Blood Cell

DISCUSSION

Despite the advances in diagnostic and treatment methods, EP, which causes 6–13% of pregnancy-related deaths, is still an important cause of first trimester maternal deaths [1, 11]. Medical treatment with MTX is a good alternative to surgery

Table 2. The relationship between the presence of free fluid in the abdomen and treatment success

	Successful n (%)	Unsuccessful n (%)	Total n (%)	p value
Free liquid in the abdomen				
None	71 (77.2%)	21 (22.8%)	92 (100.0%)	0.149
Minimal	16 (84.2%)	3 (15.8%)	19 (100.0%)	
Plentiful	1 (33.3%)	2 (66.7%)	3 (100.0%)	

Minimal — < 3 cm free fluid; Plentiful — > 3 cm free fluid

Table 3. Multivariate logistic regression analysis of the factors associated with treatment success

Variable	OR	95% CI	p
Endometrial Thickness	1.211	0.942–1.557	0.135
β-hCG Day 0	0.999	0.998–1.000	0.220
β-hCG Day 4	0.996	0.993–1.000	0.027
β-hCG Day 7	1.008	1.003–1.012	0.001

*Nagelkerle R Square: 0.838; OR — Odds Ratio; CI — confidence interval

Table 4. Relationship between β-hCG 0-4 days change values and success rate

	Successful n (%)	Unsuccessful n (%)	Total n (%)	p value
Falling	63 (87.5%)	9 (12.5%)	72 (100.0%)	0.001
Rising	25 (59.5%)	17 (40.5%)	42 (100.0%)	
Total	88 (77.2%)	26 (22.8%)	114 (100.0%)	

*Chi-square test

Table 5. Effect of β-hCG change rates between D0-D4 on treatment success

	Successful n (%)	Unsuccessful n (%)	Total n (%)	p value
Decrease between D0-D4				
≤ 35%	29 (78.4%)	8 (21.6%)	37 (100.0%)	0.017
> 35%	34 (97.1%)	1 (2.9%)	35 (100.0%)	
Total	63 (87.3%)	9 (12.7%)	72 (100.0%)	
Increase between D0–D4				
≤ 18%	14 (66.7%)	7 (33.3%)	21 (100.0%)	0.346
≥ 18%	11 (52.4%)	10 (47.6%)	21 (100.0%)	
Total	25 (59.5%)	17 (40.5%)	42 (100.0%)	

* Chi-square and Fisher Chi-square test

because it is economical, effective, and non-invasive, but may not always be the best treatment option. Hemodynamic stability, the absence of fetal heartbeat, and absence of tubal rupture findings, which are accepted as indication for MTX treatment by most authors, but patient selection remains controversial with regard to the presence of abdominal free fluid and ectopic focus size [7, 10]. Some authors state that the ectopic focal size should be < 3.5 cm [10]. Kimiaei et al. [12] reported that in addition to initial β-hCG, ectopic focus size was also significant in evaluating treatment success. There are also studies reporting that ectopic focal size has no effect on treatment outcome [13, 14].

Gnıscı et al. [15] reported that hemoperitoneum was strongly associated with treatment failure and was more valuable than ectopic focal size and initial β-hCG value in predicting failure, but still found that MTX treatment was successful in more than half of all patients with hemoperitoneum. Lipscomb et al. [16] reported that free peritoneal fluid detection on ultrasound posed no risk for treatment failure in their study of 350 patients treated with MTX. The presence of free fluid in the abdomen may also be physiological [17]. Sargin et al. [18] stated that the first choice in treatment was medical treatment with expectant management or MTX, even if there was free fluid in the abdomen at the initial evaluation in a hemodynamically stable patient.

In our study, neither ectopic focus size nor the presence of free fluid in the abdomen was found to be associated with treatment failure. However, endometrial thickness was found to be significantly higher in the group with unsuccessful treatment (12.61 ± 5.79 mm) than in the successful MTX treatment group (9.28 ± 3.53 mm) (p = 0.002). Similarly, in a study where MTX treatment was successful, the mean endometrial thickness was 6.4 mm and the β-hCG value was 1936.2 mIU/mL, whereas in the group that failed, endometrial thickness was 11.7 mm and the mean β-hCG was found as 6831.3 mIU/mL [19]. In another study, it was reported that the rate of treatment failure with MTX increased if endometrial thickness > 12 mm [20]. Endometrial thickness was said to reflect the serum β-hCG level of the patient.

Soares et al. [21] reported that fast rising β-hCG values before treatment, as another predictive variable in the selection of patients for medical treatment of ectopic pregnancy with MTX, were effective in predicting treatment failure. In previous studies, baseline β-hCG is the most recommended parameter for successful treatment prediction. In the literature, close β-hCG thresholds for MTX treatment success have been reported. Rabischong et al. [22] found this value as 1300 IU/L, Markwitz et al. [23] reported 1790 IU/L, Pulatoglu et al. [24] found 1362 IU/L, and Corsan et al. [25] reported 1500 IU/L. In the current study contrary to expectations initial β-hCG value was not found to be an independent factor for the treatment outcome, similar with Levin at al. [26] Large range (72–12660) of the initial β-hCG values; including patients with a higher β-hCG concentration above the upper concentration limit allowed for single-dose regimen in the American College of Obstetricians and Gynecologists Application Bulletin [10] may have been effective on this finding.

The fact that cytotrophoblasts had a doubling time of 48 hours led investigators to evaluate earlier than 7 days to determine the efficacy of MTX, which inhibits cellular DNA synthesis by inactivating dihydrofolate reductase [27]. In a retrospective study of 30 patients, Nguyen et al. reported treatment success as 100% in patients with a decrease in β-hCG values on day 4, a decrease between D0–D4 was highly predictive, and that these patients might not need to be followed up on day 7, also avoiding an unnecessary second MTX dose [28]. Again, in a retrospective study of 45 patients, the single-dose MTX success rate was 76%, and the treatment success rate was reported as 88% in patients with decreased D0–D4 β-hCG [29]. In a prospective study of 129 patients, Agostini et al. [30] reported that a > 20% reduction in D0-D4 β-hCG values was effective in predicting MTX success with a positive predictive value of 97%. In a case-control study of 140 patients by Mashiach et al. [31], it was reported that an increase of more than 50% of β-hCG between D0–D4 indicated MTX treatment failure; however, it may help clinical management by giving an idea of MTX treatment outcomes in borderline situations rather than making a surgical decision based on this increase. In a recent retrospective study of 121 patients, it was stated that monitoring could be reduced in patients with a > 30% decrease in D0–D4 β-hCG values, and in patients with a > 70% increase, second-dose MTX could be administered [32]. Finally, Levin et al. advocated that β-hCG increment of less than 17% in the 24 hr pretreatment, and a decrease of more than 22% between day1 and day 4 β-hCG concentations might predict the success of single-dose MTX treatment [26]. In our study, the overall success rate was comparable to the literature with 77.2% [13, 24, 28, 29]. The success rate of single-dose MTX treatment for those whose β-hCG values fell between D0–D4 was 87.3%, and 59.5% in those whose levels rose. Single-dose MTX treatment was successful in 97% of patients with D0–D4 β-hCG values with a > 35% decrease. However, an increase rate that predicted success was not determined in patients with increased D0–D4 β-hCG values. A small number of successful patients who had an increase in β-hCG values between D0-D4 might be restrictive.

CONCLUSIONS

Determining the most appropriate patient for MTX treatment and evaluating the early changes in β-hCG values in the medical treatment of EP with MTX will contribute to cost reduction, reduce the patient's anxiety, and provide

further treatment options if needed. Timely surgical intervention will contribute to the preservation of the fertility of the patient. Large-scale prospective studies are needed to determine the direct effect of early changes in β-hCG on clinical outcomes.

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VIA MEDICA

ORIGINAL PAPER / GYNECOLOGY

Ginekologia Polska
2020, vol. 91, no. 7, 394–405

ISSN 0017–0011

DOI 10.5603/GP.2020.0072

Translation, cultural adaptation, and validation and reliability of assessment of pelvic floor disorders and their risk factors during pregnancy and postpartum questionnaire in Turkish population

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ABSTRACT

Objectives: This study was conducted in order to produce translation, cultural adaptation, and validation of Assessment of Pelvic Floor Disorders and Their Risk Factors During Pregnancy and Postpartum Questionnaire (APFDQ) to Turkish in pregnant and postpartum population.

Material and methods: The study included 80 pregnant women. Internal consistency was tested using Cronbach's alpha. Questionnaires were applied three different times in order to assess for sensitivity. Patients were asked to complete the questionnaire first in the third trimester, secondly in postpartum 6th week and finally in postpartum 6th month after birth. For translation process content, face/content validity, reliability, construct validity and reactivity studies were done. All women had undergone pelvic examination and prolapse was assessed by using Pelvic organ Prolapse Quantification System (POP-Q). Urinary symptoms were also evaluated with Urinary Distress Inventory (UDI-6) questionnaire.

Results: The mean age of patients was 27.7 ± 5.5 years. Forty-one (51.25%) of the patients had vaginal delivery and 39 (48.75%) had a cesarean section. Above 96% of the patients had completed the questionnaires. POP-Q assessments and UDI-6 results were used to evaluate construct validity. Cronbach's alpha results were found to be 0.7 for all the subscales of the questionnaire: bladder: 0.702, bowel: 0.744, prolapse: 0.701, sexual function: 0.706 respectively, indicating adequate reliability. The test/retest reliability was studied and Pabak values showed moderate reliability in the bowel, prolapse and sexuality, and good reliability for bladder subscale. The results of the patients were compared between pregnancy and postpartum to assess reactivity and shown to be reactive to changes. Also risk factors of the patients were assessed including, family predisposition, maternal age over 35 years, BMI > 25, nicotine use, subjective inability to contract pelvic floor and sense of postpartum wound pain.

Conclusions: The Turkish version of APFDQ is a reliable and valid tool. It can be used for assessing the risk factors, incidence, assessing degree of PFDs and evaluating the impact on quality of life in pregnant and postpartum women.

Key words: pelvic floor dysfunction; pregnancy; postpartum; validation

Ginekologia Polska 2020; 91, 7: 394–405

INTRODUCTION

Pelvic floor dysfunction (PFDs) is a complex of urinary incontinence (UI), fecal incontinence (FI), pelvic organ prolapse (POP), sexual dysfunction, and other urogenital symptoms [1]. PFDs incidence was shown to be as high 67.5% of the women excluding pregnancy and postpartum period [2]. The prevalence of each pelvic floor was evaluated, and anal incontinence was found 19.8%; urinary incontinence, 50.7%; constipation, 33.2%; and obstructed defecation, 26.8% [3, 4]. Childbirth is shown to be related to PFDs. Parity was

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found to be correlated with urinary incontinence in 50% of the patients and with prolapse in 75% of the cases [5]. Postpartum assessment of pelvic floor in terms of PFDs could lead to early diagnosis and intervention, and we could provide a protective health care [6].

PFDs are linked to physical and emotional stress, causing psychological problems and decreased quality of life [7]. But most of the patients discuss these problems with healthcare providers. Although pregnancy and postpartum periods are accepted as high-risk factors for pelvic floor trauma, it has not been studied thoroughly [8]. Further studies are needed to understand the effect of pregnancy and delivery on the pelvic floor structure.

In our opinion, questionnaires are fundamental for detecting the adverse effect of the disease to quality of life. In Turkey there are no validated questionnaires to address PFDs in pregnant and postpartum women. We aim to translate, validate and culturally adapt a APFDQ which detects PFDs regarding bladder function, bowel function, prolapse and sexual function with risk factors in pregnant and postpartum patients. Postpartum depression is also questioned to clarify the etiology of the decreased quality of life.

This questionnaire was constituted on previously validated German pelvic floor questionnaires in urogynecology patients [9]. New sections were added regarding risk factors, childbirth and impact on quality of life. Some of the questions were removed in order to adapt the questionnaire to younger patients (Annex 1 and 2).

MATERIAL AND METHODS

The original version of APFDQ was adapted to Turkish in the study.

Validation permission for the questionnaire was taken from the developer, Dr. Kaven Baessler for the use. Ethical board approval was taken from Zeynep Kamil Research and Training Hospital (19.12.2018/164).

Translation and cultural adaptation

The following guidelines were followed in order to validate the original version of APFDQ into Turkish [9].

Firstly, forward- backward translations were made for cross-cultural adaptations. The original German version APFDQ was translated to Turkish by a native speaker, then a professional translator performed a backward translation, followed by an expert committee including the researchers evaluated the version of the APFDQ. This version was applied, then volunteers in order to detect if there is any misunderstanding. Finally, the Turkish version of theAPFDQ was edited according to suggestions and used in patients.

Questionnaire

The APFDQ was based on the validated Australian Pelvic Floor Questionnaire which has four domains including bladder, bowel, support and sexual function [10–13]. There are completely newly developed sections in the APFDQ for risk factors and the course of childbirth. Participants fulfilled the childbirth domain at postpartum 6th week, which elucidate the route of delivery, emotional effect of birth and postpartum pain for patient.

Validity

Ten volunteers had completed the questionnaire and were interviewed by the researchers to find out if there were any misinterpretations. The version was also discussed in the study group and counseled to the experts on this topic.

Reliability

Internal consistency and test- retest analysis are used to establish reliability. For an adequate internal consistency, Cronbach's Alpha value should be more 0.7 and more.

The questionnaire was given to patients in weekly intervals during the third trimester, to constitute test- retest reliability. The interval was shorter than the usual period for reliability regarding the concern for maintaining the same conditions in pregnant patients. PABAK value was used to establish the degree of agreement and intraclass correlation coefficient (ICC) to demonstrate the agreement of the test- retest results of the individuals.

Reactivity "sensitivity to change"

The questionnaire was giving weekly two different times first during the third trimester, then again during postpartum at 6th week and 6th month.

Study population and data collection

The questionnaire was giving to 92 women attending routine visits in two tertiary clinics in Istanbul. Inclusion criterias were age between 18–40 years and having uncomplicated pregnancy. Exclusion criterias were inadequate Turkish language knowledge, having chronic diseases, neurological disorders, preeclampsia, gestational diabetes mellitus, or fetal abnormalities.

Sample size was calculated taking into account the previous studies, with a power of 80% and $\alpha = 0.05$ a score change of 1 in a domain (minimal important clinical difference) can be significantly detected from a sample size of $n = 50$ [12].

Analysis of data

The final version was validated according to COSMIN (The Consensus- based Standards for the selection of health Measurement Instruments) International guidelines [13].

Statistical Analysis

Numeric variables were expressed as the mean and standard deviation or as the median (minimum–maximum), depending on the distribution of the data. The normality was determined using the Shapiro-Wilk test. Internal consistency of the scale was assessed with Cronbach's alpha coefficient. Intra class correlation coefficient and Kappa along with PABAK (Prevalence adjusted Bias adjusted Kappa) were used for test-retest reliability. Hence some of the tables included sparse data, *i.e.* concordant cell frequencies were high and discordant frequencies were low, PABAK along with Kappa was reported. Effect sizes of the 6th week to after delivery and the 3rd trimester to after delivery was calculated by dividing the difference between the mean of measurements before and after delivery by the standard deviation of measurement before delivery (Δ/SD) for assessing the responsiveness of the scale. Comparisons of before and after delivery scores were also performed with Wilcoxon signed rank test.

Concurrent and construct validity was assessed with spearman correlation coefficient.

Interpretations of Kappa and PABAK values were performed according to the classification for the strength of agreement, which considers κ values of 1–0.81 to be almost in perfect agreement, 0.80–0.61 to be in substantial agreement, 0.60–0.41 to be in moderate agreement, 0.40–0.21 to be in fair agreement, and < 0.20 to be in slight agreement. $p < 0.05$ was considered statistically significant.

RESULTS

A total of 92 women in the of third trimester pregnancy were included the study. Twelve were excluded due to failure to follow-up. The remaining 80 patients were interviewed during the third trimester, postpartum 6th week and postpartum 6th month. Forty-one (51.25%) patients had vaginal delivery and 39 (48.75%) patients had a cesarean section. Figure 1 shows the study course. Thirty-five (43.75 %) women were primiparous and 56.25% were multiparous. The mean age of the women was 27.7 ± 5.5 years. The mean parity was 1.1 ± 1.1. The mean body mass index was 26.32 ± 3.14 of the patient group. Socio-demographic characteristics of the patients were summarized in Table 1. Mean gravida of the patients was 2.3 ± 1.4. Mean of the maximum weight of the babies delivered was 2332.3 ± 1626.1 grams. None of the patients had operative delivery. Obstetrics characteristics of the patients were summarized in Table 2. Prevalence for PFDs of the study population was shown in Table 3.

Internal consistency reliability

Cronbach's alpha value of domains were calculated and found to be over 0.7 points which is enough to show reliability of the questionnaire.

Test-retest reliability

PABAKvalues and ICC values were used to assess test-retest reliability and shown in Table 4. Therefore, while bladder

Table 1. Sociodemographic characteristics of the population

	Mean ± SD
Age	27.7 ± 5.5
BMI	28.6 ± 4.8
Income status	
Low-income	26 (32.9%)
Middle-income	40 (50.6%)
High-income	13 (16.5%)
Chronic disease	
Yes	69 (87.3%)
No	10 (12.7%)
Previous abdominal surgery	
Yes	55 (69.6%)
No	24 (30.4%)

Mean ± standard deviation was given for quantitative variables, whereas n (%) were given for qualitative ones

Table 2. Obstetric characteristics of the study population

Gravida (mean ± SD)	2.3 ± 1.4
Parity (mean ± SD)	1.1 ± 1.1
Number of vaginal delivery (n, %)	41 (51.25%)
Number of cesarean delivery (n, %)	39 (48.75)
Episiotomy (n,%)	11 (22.91%)
Mean birth wieght (mean ± SD)	2332.3 ± 1626.1

Mean ± standard deviation was given for quantitative variables, whereas n (%) were given for qualitative ones

Table 3. Prevalence of the PFDs in study population

	Third trimester	Postpartum 6th week	Postpartum 6th month
Urinary incontinence n (%)	78 (98.73%)	72 (90%)	64 (80%)
Anal incontinence n (%)	23 (28.75%)	18 (22.5%)	14 (17.5%)
Genital prolapse n (%)	26 (32.5%)	34 (42.5%)	31 (38.75%)
Sexual symptoms n (%)	45 (56.25%)	62 (77.5%)	32 (40%)

Table 4. Test-retest reliability

	Cronbach's alpha	ICC	Pabak
Bladder	0.702	0.863	1.00
Bowel	0.744	0.714	0.90
Prolapse	0.701	0.735	0.54
Sexuality	0.706	0.626	0.67

Table 5. Reactivity

	3rd trimester	6th week	6th month	ES1	p	ES2	p
Bladder	1.88 (0–5)	1.88 (0–4.58)	0.42 (0–3.75)	1.46	< 0.001	1.57	< 0.001
Bowel	1.29 (0–5.16)	0.97 (0–4.52)	0.97 (0–2.26)	0.5	< 0.001	0.41	0.003
Prolapse	0 (0–2.5)	0.6 (0–2.5)	1.25 (0–2.92)	–1.25	< 0.001	–2.03	< 0.001
Sexuality	1.67 (0–4.17)	0.9 (0–3.75)	0.5 (0–2.92)	0.77	0.005	0.4	0.003

Medians (range) were given; ES — Cohen's effect size was calculated by dividing the difference between the mean of measurements before and after delivery by the standard deviation of measurement before delivery (Δ/SD); ES1 — effect size of the third trimester to the 6th week after delivery; ES2 — effect size of after the 6th week to after the 6th month delivery; comparison between the third trimester and postpartum, p values are based on Wilcoxon signed-rank test

and bowel showed acceptable internal consistency along with good test-retest reliability; prolapse and sexuality had acceptable internal consistency along with good and moderate test-retest reliability, respectively.

Content validity

The rate of missing answers did not exceed 4% for any of the questions in the final questionnaire.

Construct validity

Patients' bladder scores of the questionnaire was found to be significantly correlated to UDI-6 (rho: 0.806, p: 0.000), also prolapse scores were correlated to POP-Q scores significantly (rho: 0.574, p: 0.000).

Reactivity and scoring system

Mean scores of the domains were statistically different between pregnant and postpartum patients indicating the questionnaire is reactive to the changes ($p < 0.01$) (Tab. 5).

DISCUSSION

Here in this study we found showing that the Turkish version of the APFDQ is a reliable tool for evaluating pelvic floor disorders in pregnancy and postpartum period. Also it is a reliable questionnaire that we could follow the changes in different situations. The study population had a higher ratio of patients with chronic diseases (87.3%). This might be explained by conducting the study in a tertiary center.

Pelvic floor dysfunction after birth is usually accepted as a "normal" situation that patients do not discuss with their healthcare professionals. So, it is underestimated and not well evaluated unless adressing the symptoms [14]. Questionnaires are accepted as a part of standard evaluation methods for pelvic floor disorders [15]. Pregnancy and delivery are well known factors for PFDs [16]. Yet there are not comprehensive questionnaires in the literature for pregnant and postpartum patients.

In the literature there are questionnaires which evaluates PFDs such as Pelvic Floor Disorders Inventory-20 (PFDI-20), Pelvic Floor Distress Inventory (PFIQ-7), Pelvic Floor Disorders Inventory-46 (PFDI-46), Pelvic Floor Distress Inventory (PFIQ-31), International Consultation on Incontinence- Vaginal Symptoms (ICIQ-VS), Australian Pelvic Floor Questionnaire (or Australian PFQ), Pelvic Floor Bother Questionnaire (PFBQ), electronic Personal Assessment Questionnaire ePAQ-PF, and Pelvic Floor Dysfunction (PFD) [17–19].

PFDI-46 and PFIQ-31 are very time consuming, so new shorter versions were established as PFDI-20 and PFIQ-7. However, the new versions do not cover all the aspects of the PFDs and quality of life [20–21]. ICIQ-VS does not contain bladder and bowel functions [22]. From the above mentioned questionnaires, ePAQ, FPFQ and PFBQ are the only ones that evaluate all these areas but there are not widely used in the literature [23, 24]. ePAQ is not commonly used because of a license obligation. PFBQ is only translated to four languages so far and questions were not well distributed. FPFQ seems to address all the areas as it is newly developed, and it has not been widely translated to other languages [25–26].

None of the questionnaires above except APFDQ were originally developed to postpartum patients. APFDQ is also designed to evaluate specific risk factors for PFDs in postpartum period.

It is important to detect these symptoms in the early period to prevent future advanced PFDs, and make an appropriate intervention. In this study we aimed to translate this questionnaire in order to detect PFDs in our population and reduce the adverse effect of PFDs to quality of life. Administering pelvic muscle training in the postpartum period (PFMT) is proven to improve pelvic floor function and quality of life (QOL) of the patients [27]. Although there are conflicting data in the literature, a recent randomised study showed that a two-tiered, self-selection approach had increased the pelvic floor function and QOL in women with or without incontinence. The two- tiered approach consists of an informative session about anatomy and physiology and then practical data about exercise was taught and a PFMT was constituted for home [27]. Cochrane review published in 2014 also suggests that PFMT could prevent incontinence for 6 months in continent women during pregnancy [28]. Also, women with urinary incontinence were found to benefit from PFMT up to 1 year after delivery [28]. Cochrane review published in 2017 suggested that if offered to continent women in early pregnancy, PFMT programme could reduce urinary incontinence in late pregnancy and postpartum period [29].

CONSLUSIONS

Linguistic validation is an important step in the validation process. In order to have a better understanding, translations were done by native speakers then it was controlled by the expert committee. At first, 10 volunteers were involved to the study and interviewed face to face in order to modify misunderstandings.

According to the results of this study, the Turkish version of APFDQ was a valid and reliable tool to assess pelvic floor disorders in the period of pregnancy and postpartum. The Turkish version of APFDQ could be used to evaluate the immediate status of the patients during pregnancy and postpartum or could be used to follow the changes according to the score changes. Discriminant validity showed a significant difference between the pregnancy and postpartum periods in all the subscales of the questionnaire. The Turkish version of APFDQ has high internal consistency, is reproducible and high construct validity, and can detect the degree of pelvic floor dysfunction. It has a high correlation with UDI 6 and moderate correlation with POP-Q.

The Turkish version of the self-administered APFDQ seems to be a reliable and valid instrument for evaluating PFDs symptoms severity and quality of life in Turkish speaking women.

Disclosure

All the authors state no financial disclosures or conflict of interest related to the content of this work.

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MODULE RISK FACTORS				RISK
Height ☐☐☐ cm	Weight ☐☐☐ kg	Weight before pregnancy For BMI ☐☐☐ kg	BMI ☐☐.☐	☐ > 25
Age			☐☐ years	☐ > 35
Are there any women in your family to whom you are related by blood who have urinary incontinence, fecal incontinence, or prolapse of the pelvic organs?		☐ no	☐ don't know	☐ yes
Do you smoke?		☐ no	☐ stopped	☐ yes
Can you voluntarily contract your pelvic floor?		☐ yes	☐ don't know	☐ no

Bladder function	0	1	2	3
1. How often do you urinate during the day? Pollakiuria	Every 3 hours	Every 2 hours	Once every hour	More often
2. How often do you wake up at night because you need to urinate? Nocturia		2×	3×	More than 3×
3. Do you lose urine in your sleep? Nocturnal enuresis	Never	Sometimes — less than once a week	Often — once a week or more	Usually — every day
4. Is the urge to urinate so strong that you must immediately rush to the toilet? Strong urge to urinate	Never	Sometimes — less than once a week	Often — once a week or more	Usually — every day
5. When you have a sudden strong urge to urinate, do you leak urine before you reach the toilet? Urge incontinence	Never	Sometimes — less than once a week	Often — once a week or more	Usually — every day
6. Do you leak urine when coughing, sneezing, laughing, lifting or during sports? Stress incontinence	Never	Sometimes — less than once a week	Often — once a week or more	Usually — every day
7. Is your urinary stream weak, slow or prolonged? Urinary stream	Never	Sometimes — less than once a week	Often — once a week or more	Usually — every day
8. Do you feel that you can accurately assess how full your bladder is? Bladder estimate	Yes — always	Usually	Sometimes	No — never
9. Do you feel that you cannot completely empty your bladder? Residual urine	Never	Sometimes — less than once a week	Often — once a week or more	Usually — every day
10. Do you need to squeeze to urinate? Squeeze	Never	Sometimes — less than once a week	Often — once a week or more	Usually — every day
11. Do you wear panty liners or sanitary pads because of urine leakage? Pads	Never	Sometimes — only as prophylaxis	Often — during sports/during colds	Usually — every day
12. Do you limit the amount you drink to avoid leaking urine? Drinking patterns	Never	Sometimes — less than once a week	Often — once a week or more	Usually — every day
13. Do you experience a burning or dragging sensation or pain when you urinate? Dysuria	Never	Sometimes — less than once a week	Often — once a week or more	Usually — every day
14. How often do you have urinary tract infections? UTI	Rarely or never	1–3x per year	4–12× per year	1× or more/month

→

Annex 1. The new version of the questionnaire*; Pelvic Floor Questionnaire for pregnant and post partum women
*This is a simple translation of the questionnaire. This version has not been validated in English

15. Does the involuntary loss of urine adversely affect your daily life? (e.g. sports activities, job, shopping, going out) QoL	☐ Not applicable, I do not have symptoms	Not at all	A little	Quite a lot	Very much
16. How much do your bladder symptoms bother you? Psychological stress from bladder symptoms	☐ Not applicable, I do not have symptoms	Not at all	A little	Quite a lot	Very much

Bowel function	**0**	**1**	**1**	**2**
1. How often do you have a bowel movement? Frequency	Every 3 days to once a day	More than 1x per day	Every 3 days or less often	less than once a week
2. What is the normal consistency of your stools? Consistency	soft or shaped	varying consistency	very hard	thin/mushy
Bowel function	**0**	**1**	**2**	**3**
3. Do you need to strain to have a bowel movement? Straining	Never	Sometimes — less than once a week	Often — once a week or more	Usually — every day
4. Do you suffer from constipation? Constipation	Never	Sometimes — less than once a week	Often — once a week or more	Usually — every day
5. Do you experience involuntary flatulence which you cannot suppress? Flatus incontinence	Never	Sometimes — less than once a week	Often — once a week or more	Usually — every day
6. Do you experience an urge to defecate which you cannot suppress? Urge bowel incontinence	Never	Sometimes — less than once a week	Often — once a week or more	Usually — every day
7. Do you find traces of fecal soiling on your underwear or pads? Stool smears	Never	Sometimes — less than once a week	Often — once a week or more	Usually — every day
8. Do you experience accidental bowel leakage with loss of feces? Fecal incontinence	Never	Sometimes — less than once a week	Often — once a week or more	Usually — every day
9. Do you have the feeling that you cannot completely empty your bowels? Bowel dysfunction	Never	Sometimes — less than once a week	Often — once a week or more	Usually — every day
10. Do the symptoms adversely affect your daily life? (planning your day, sports activities, job, shopping, going out) QoL	☐ Not applicable, I do not have symptoms	Not at all	A little	Quite a lot	Very much
11. How much do your bowel symptoms bother you? Psychological stress from bowel symptoms	☐ Not applicable, I do not have symptoms	Not at all	A little	Quite a lot	Very much

→

Prolapse		**0**	**1**	**2**	**3**
1. Do you feel as though there is a foreign body in your vagina? Foreign body		Never	Sometimes — less than once a week	Often — once a week or more	Usually — every day
2. Do you feel that your vagina or uterus may have dropped? Prolapse feeling		Never	Sometimes — less than once a week	Often — once a week or more	Usually — every day
3. Do you have the feeling that your vagina or uterus drops when you lift something, walk or run? Prolapse under stress		Not at all	A little	Quite a lot	Very much
4. Do these symptoms adversely affect your daily life? (e.g. sports activities, job, shopping, going out) QoL	☐ Not applicable, I do not have symptoms	Not at all	A little	Quite a lot	Very much
5. How much does prolapse bother you? Psychological stress from prolapse	☐ Not applicable, I do not have symptoms	Not at all	A little	Quite a lot	Very much

Sexuality				
Are you sexually active? Sexually active	☐ Not at all	☐ Rarely	☐ Regularly	
If you do not have sexual intercourse, why not? Abstinent because	☐ no partner	☐ partner has problems/ /is impotent	☐ don't get aroused/ /not interested	☐ Sex is unpleasant for me because .....
Have you had sexual experiences which distress you very much? Sexual trauma	☐ No		☐ Yes	
	0		**1**	
1. Does your vagina sufficiently self-lubricate during intercourse? Lubrication	Yes		No	
	0	**1**	**2**	**3**
2. How does your vagina feel during intercourse? Vaginal sensation	feel a lot	don't feel much	don't feel anything	painful
3. Do you think that your vagina is too slack or too wide? Vaginal width	No — never	Sometimes	Often	Always
4. Do you think that your vagina is too tight or too firm? Vaginismus	No — never	Sometimes	Often	Always
5. Do you experience pain during intercourse? Dyspareunia	No — never	Sometimes	Often	Always
	1	**1**		**2**
6. If you experience pain during intercourse, where is the pain sited?	at the beginning of the vagina	deep inside/in the pelvis		Both

→

		0	1	2	3
7. Do you have involuntary loss of urine or feces during sex? Coital incontinence		No — never	Sometimes	Often	Always
8. Do these symptoms adversely affect your sexuality? QoL	☐ Not applicable, I do not have symptoms	Not at all	A little	Quite a lot	Very much
9. How much do these symptoms bother you? Psychological stress because of sex	☐ Not applicable, I do not have symptoms	Not at all	A little	Quite a lot	Very much

Score (please leave these fields empty)			
Bladder function	Questions 1–16	Score ☐☐ / 48 = ☐.☐☐	× 10 = ☐☐☐
Bowel function	Questions 1–11	Score ☐☐ / 31 = ☐.☐☐	× 10 = ☐☐☐
Prolapse	Questions 1–5	Score ☐☐ / 15 = ☐.☐☐	× 10 = ☐☐☐
Sexuality	Questions 1–9	Score ☐☐ / 24 = ☐.☐☐	× 10 = ☐☐☐
Bladder score + bowel score + prolapse score + sex score =		☐☐.☐☐	☐☐☐☐

Postpartum module					**Risk**
How many children have you born?	☐☐	How many births were ventouse (vacuum, suction cup)-assisted births?			☐
How many were born by cesarean section?	☐	How many births were forceps-assisted births?			☐
How heavy was your heaviest child at birth?		☐☐☐☐ g			☐ > 4000g
Was the sphincter muscle, bowel or perineum injured during any of your births (3rd or 4th degree perineal tear)?		☐ No			☐ Yes
Did you have pain postpartum in the area of the vagina, perineum or bowel/anus/rectum?		☐ No			☐ Yes
Do you feel that you have since been able to process the birth pains or the pain experienced after the birth?		☐ Yes	☐ Largely	☐ A little	☐ No
Do you feel that you have since been able to process the fears you had during the birth?		☐ Yes	☐ Largely	☐ A little	☐ No

AUSTRALIAN PELVIC FLOOR QUESTIONNAIRE	**Patient's Name:** ..... **Date of Birth:** ..... **Date completed:**	
Please circle your most applicable answer. Consider your experience during the last month.		
BLADDER FUNCTION (..... / 45)		
Q1. How many times do you pass urine in a day? 0 Up to 7 1 Between 8–10 2 Between 11–15 3 More than 15	**Q2. How many times do you get up at night to pass urine?** 0 0–1 1 2 2 3 3 More than 3 times	**Q3. Do you wet the bed before you wake up at night?** 0 Never 1 Occasionally — less than once per week 2 Frequently — once or more per week 3 Always — every night
Q4. Do you need to rush/hurry to pass urine when you get the urge? 0 Can hold on 1 Occasionally must rush — less than once/week 2 Frequently must rush — once or more/week 3 Daily	**Q5. Does urine leak when you rush or hurry to the toilet or can't you make it in time?** 0 Not at all 1 Occasionally — less than once per week 2 Frequently — once or more per week 3 Daily	**Q6. Do you leak with coughing, sneezing, laughing or exercising?** 0 Not at all 1 Occasionally — less than once per week 2 Frequently — once or more per week 3 Daily
Q7. Is your urinary stream (urine flow) weak, prolonged or slow? 0 Never 1 Occasionally — less than once per week 2 Frequently — once or more per week 3 Daily	**Q8. Do you have a feeling of incomplete bladder emptying?** 0 Never 1 Occasionally — less than once per week 2 Frequently — once or more per week 3 Daily	**Q9. Do you need to strain to empty your bladder?** 0 Never 1 Occasionally — less than once per week 2 Frequently — once or more per week 3 Daily
Q10. Do you have to wear pads because of urinary leakage? 0 None — Never 1 As a precaution 2 When exercising/during a cold 3 Daily	**Q11. Do you limit your fluid intake to decrease urinary leakage?** 0 Never 1 Before going out 2 Moderately 3 Always	**Q12. Do you have frequent bladder infections?** 0 No 1 1–3 per year 2 4–12 per year 3 More than one per month
Q13. Do you have pain in your bladder or urethra when you empty your bladder? 0 Never 1 Occasionally — less than once per week 2 Frequently — once or more per week 3 Daily	**Q14. Does urine leakage affect your routine activities like recreation, socializing, sleeping, shopping etc?** 0 Not at all 1 Slightly 2 Moderately 3 Greatly	**Q15. How much does your bladder problem bother you?** 0 Not at all 1 Slightly 2 Moderately 3 Greatly
Other symptoms (haematuria, pain etc.)		
BOWEL FUNCTION (..... / 34)		
Q16. How often do you usually open your bowels? 0 Every other day or daily 1 Less than every 3 days 2 Less than once a week 0 More than once per day	**Q17. How is the consistency of your usual stool?** 0 Soft 0 Firm 0 Hard (pebbles) 1 Variable 2 Watery	**Q18. Do you have to strain to empty your bowels?** 0 Never 1 Occasionally — less than once per week 2 Frequently — once or more per week 3 Daily
Q19. Do you use laxatives to empty your bowels? 0 Never 1 Occasionally — less than once per week 2 Frequently — once or more per week 3 Daily	**Q20. Do you feel constipated?** 0 Never 1 Occasionally — less than once per week 2 Frequently — once or more per week 3 Daily	**Q21. When you get wind or flatus, can you control it, or does wind leak?** 0 Never 1 Occasionally — less than once per week 2 Frequently — once or more per week 3 Daily

→

Annex 2. The old version of the questionnaire

AUSTRALIAN PELVIC FLOOR QUESTIONNAIRE	**Patient's Name:** ..... **Date of Birth:** ..... **Date completed:**	
Q22. Do you get an overwhelming sense of urgency to empty bowels? 0 Never 1 Occasionally — less than once per week 2 Frequently — once or more per week 3 Daily	**Q23. Do you leak watery stool when you do not mean to?** 0 Never 1 Occasionally — less than once per week 2 Frequently — once or more per week 3 Daily	**Q24. Do you leak normal stool when you do not mean to?** 0 Never 1 Occasionally — less than once per week 2 Frequently — once or more per week 3 Daily
Q25. Do you have a feeling of incomplete bowel emptying? 0 Never 1 Occasionally — less than once per week 2 Frequently — once or more per week 3 Daily	**Q26. Do you use finger pressure to help empty your bowel?** 0 Never 1 Occasionally — less than once per week 2 Frequently — once or more per week 3 Daily	**Q27. How much does your bowel problem bother you?** 0 Not at all 1 Slightly 2 Moderately 3 Greatly
PROLAPSE SYMPTOMS (..... / 15)		
Q28. Do you have a sensation of tissue protrusion/lump/bulging in your vagina? 0 Never 1 Occasionally — less than once per week 2 Frequently — once or more per week 3 Daily	**Q29. Do you experience vaginal pressure or heaviness or a dragging sensation?** 0 Never 1 Occasionally — less than once per week 2 Frequently — once or more per week 3 Daily	**Q30. Do you have to push back prolapse in order to void?** 0 Never 1 Occasionally — less than once per week 2 Frequently — once or more per week 3 Daily
Q31. Do you have to push back your prolapse to empty your bowels? 0 Never 1 Occasionally — less than once per week 2 Frequently — once or more per week 3 Daily	**Q32. How much does your prolapse bother you?** 0 Not at all 1 Slightly 2 Moderately 3 Greatly	**Other Symptoms:** (problems: walking/sitting, pain, vaginal bleeding) ....
SEXUAL FUNCTION (..... / 21)		
Q33. Are you sexually active? ☐ No ☐ Less than once per week ☐ Once or more per week ☐ Daily or most days ***If you are not sexually active, please continue to answer questions 34 & 42.***	**Q34. If you are not sexually active, please tell us why?** ☐ Do not have a partner ☐ I am not interested ☐ My partner is unable ☐ Vaginal dryness ☐ Too painful ☐ Embarrassment due to the prolapse/ /incontinence ☐ Other reasons:	**Q35. Do you have sufficient vaginal lubrication during intercourse?** ☐ Yes ☐ No
Q36. During intercourse vaginal sensation is: 0 Normal/pleasant 1 Minimal 2 Painful 3 None	**Q37. Do you feel that your vagina is too loose or lax?** 0 Never 1 Occasionally 2 Frequently 3 Always	**Q38. Do you feel that your vagina is too tight?** 0 Never 1 Occasionally 2 Frequently 3 Always
Q39. Do you experience pain with sexual intercourse? 0 Never 1 Occasionally 2 Frequently 3 Always	**Q40. Where does the pain during intercourse occur?** 0 Not applicable, I do not have pain 1 At the entrance to the vagina 2 Deep inside, in the pelvis 3 Both at the entrance & in the pelvis	**Q41. Do you leak urine during sexual intercourse?** 0 Never 1 Occasionally 2 Frequently 3 Always
Q42. How much do these sexual issues bother you? ☐ Not applicable 0 Not at all 1 Slightly 2 Moderately 3 Greatly	**Q43. Other symptoms?** (faecal incontinence, vaginismus etc)	

VIA MEDICA

ORIGINAL PAPER / OBSTETRICS

Ginekologia Polska
2020, vol. 91, no. 7, 406–411

ISSN 0017–0011

DOI: 10.5603/GP.2020.0065

Clinical characteristics and treatment of different types of cesarean scar pregnancy

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ABSTRACT

Objectives: The purpose of this study was to evaluate the clinical characteristics and compare the treatment efficacy of different types of cesarean scar pregnancy (CSP).

Material and methods: We performed a retrospective chart review of 66 women (69 cases) with CSP who received treatment with mifepristone/methotrexate (MTX) plus curettage, uterine artery embolization (UAE) plus curettage, additional MTX, or laparotomy, and compared the clinical characteristics, treatment efficacy, and occurrence of complications among 3 types of CSP (partial, complete, and mass type).

Results: Review of the 69 cases revealed a considerable increase of gestational duration($p < 0.001$), sac/lesion size($p < 0.001$) and vaginal bleeding ($p < 0.05$) in patients with mass-type CSP compared to that of other types. All CSP cases were successfully treated, 4 cases of mass-type received laparotomy and none of the cases required a hysterectomy. Severe bleeding was observed in 2 cases of partial-type and complete-type, respectively, and 3 cases for mass-type. Moreover, bleeding occurred during initial treatment with mifepristone plus curettage in partial-type cases, but not with UAE plus curettage.

Conclusions: UAE plus curettage is a more effective treatment option for partial- and complete-type of CSP than mifepristone plus curettage. The cases of mass-type often need surgery and are prone to have longer gestational duration, larger lesions, and more vaginal bleeding.

Key words: cesarean scar pregnancy; clinical characteristics; treatment efficacy; complication

Ginekologia Polska 2020; 91, 7: 406–411

INTRODUCTION

The increasing rate of cesarean section has attracted worldwide concerns in recent decades [1]. The post-cesarean era and requirement of two-child policy in China has made the situation worse, although the occurrence of cesarean section without medical indication was controlled. Long-term complications of a cesarean section, such as diverticulum which induced prolonged menstruation and irregular vaginal bleeding, the complications and treatment used in partial, complete, and mass-type CSP cases were shown in Table 1. The most severe complication, cesarean scar ectopic pregnancy (CSP) which was defined as an ectopic pregnancy in which the fertilized egg is implanted in the previous cesarean section scar, may cause uncontrollable bleeding, uterine rupture, hysterectomy, placenta previa, and can be life-threatening [2]. CSP was reported to be sporadic in case reports decades ago [3, 4]; however, in recent years there have been increased reports of CSP emerged, including randomized control trials (RCTs) [5–10], cohort studies [11–13], and comparative case studies [14]. Thus, CSP is no longer a rare form of ectopic pregnancy.

Table 1. Clinical features of the 69 CSP cases (n = 66)

Characteristic	Mean ± SD (%)
Age [y]	32.39 ± 4.25
No. of curettage [n]	1.75 ± 1.75
No. of prior cesarean delivery [n]	1.41 ± 0.52
Time since previous cesarean delivery, y [%]	1 (10.14%) ≥ 2 (89.86 %)
Gestational weeks at time of diagnosis [weeks]	7.75 ± 2.14 (5–16)
Presence of fetal heartbeat [n]	29.16 ± 17.43 (5–74)
Abdominal pain [n]	7 (10.14%)
Vaginal bleeding	39 (56.5%)

Data are presented as n, mean ± SD, median (range), or n (%)

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Table 2. Clinical features of CSP in partial-type, complete-type, and mass-type cases

Characteristic	Partial	Complete	Mass	p-value
Case number [n]	33	28	8	
Age [y] (mean ± SD)*	32.1 ± 4.4	33.2 ± 4.2	30.9 ± 3.6	0.326
No. of curettage (mean ± SD)*	1.30 ± 1.29	1.25 ± 1.17	1.50 ± 1.41	0.884
No. of prior cesarean delivery (mean ± SD)*	1.36 ± 0.55	1.50 ± 0.51	1.25 ± 0.46	0.407
Time since previous cesarean delivery [y]#				
1	4	3	0	0.867
≥ 2	29	25	8	
Gestational weeks (mean ± SD)*	7.24 ± 1.58	7.43 ± 1.75	11.0 ± 2.78	< 0.001*
Presence of fetal heartbeat#	13	7	0	0.273
Abdominal pain#	2	4	1	0.442
Vaginal bleeding#	18	13	8	0.019*

*ANOVA test; #Chi-squared test

Currently, to the best of our knowledge, the consensus or guidelines on the diagnosis and treatment of CSP is unclear. Hence, a retrospectively study involving 69 cases of CSP (partial-, complete-, and mass-type CSP) was conducted to compare the clinical characteristics, treatment efficacy, and occurrence of complications among the different types.

MATERIAL AND METHODS

This is a retrospective case series of patients with diagnosis of CSP who treated at Chaohu Hospital (the Affiliated Chaohu Hospital of Anhui Medical University, Hefei, Anhui, PR China) from January 2016 to January 2019. Thirteen women were excluded because the absence of related clinical characteristics, lost for follow-up or unclear ultrasound images, and 79 women diagnosed with CSP were selected based on the following criteria: clear ultrasound images, no absence of data or follow-up. Sixty-six women with CSP (69 cases) met the criteria were enrolled in the study. This study was approved by the Ethics Committee of the hospital (approval no. 201901-kyxm-02).

Clinical characteristics of the patients are summarized in Table 2 which include age, gestational weeks, pregnancy duration, abortion and curettage time, cesarean section time, interval since previous cesarean section, gestational sac/lesion size, fetal heartbeat, initial serum β-human chorionic gonadotropin β-(hCG) level, vaginal bleeding, and abdominal pain. The ultrasonographic images were evaluated based on the criteria [15], the abdominal and vaginal ultrasonographic instruments used were Mylab 90 of Baisheng (made in China) and GE-LOGIQ E9(made in America). According to the classification rules [16], diagnosis and treatment consensus [17] and mass type of CSP commonly observed in clinic [18], the 69 cases were divided into 3 types: partial-, complete-, and mass-type. The partial-type is defined when the gestational sac is partially embedded in the myometrium of the scar, and a part or most of the gestational sac has grown toward the endometrial cavity, with the gestational sac deformed, elongated, with a sharp angle at the lower end, and surrounded by vasculature. In complete-type CSP, the gestational sac is totally embedded in the myometrium of the scar, with an empty endometrial cavity and cervical canal surrounded by vasculature. Mass-type CSP is defined when there are mixed echoes located in the scar of the lower uterine segment, protruding toward the bladder, with the local muscular layer thinned, and abundant blood flow surrounding it.

The clinical characteristics, treatment efficacy, and occurrence of complications were compared in all cases. Successful treatment was considered as a reduction or disappearance of the mass and/or significant normalization of the serum β-hCG level.

Several therapeutic approaches used for these cases involving mifepristone or methotrexate (MTX) plus curettage; uterine artery embolization (UAE) plus curettage; additional MTX; and laparotomy treatment. Curettage was performed via the method of dilatation and suction with the guidance of ultrasound. The embolic agents used in UAE were gelatin sponge granules and sponge strips

Statistical analysis was performed using SPSS version 19.0. Continuous variables were expressed as means standard deviations for normal distribution and median for non-normal distribution, statistical significance was tested using Student's t-test and Mann–Whitney U-test, respectively. One-way ANOVA followed by Bonferonni's test was used to compare the difference among groups. Categorical data were presented as frequencies or percentages and compared by Chi-square test or Fisher's exact test. A two-sided p-value of 0.05 was considered statistical significance.

RESULTS

From January 2016 to January 2019, 69 cases of CSP(66 patients) were managed in our unit (1 case of partial-type and 2 cases of complete-type turned into mass-type CSP after treatment, the initial and subsequent treatment of these 3 cases were conducted in Chaohu Hospital). The clinical characteristics of 69 cases are shown in Table 2. Of the 69 cases, 1 of them with partial-type CSP became pregnant 11 months after treatment with mifepristone-progesterone and curettage, additional methotrexate (MTX) with second curettage; she delivered a healthy female infant weighing 3675 g with an Ap-

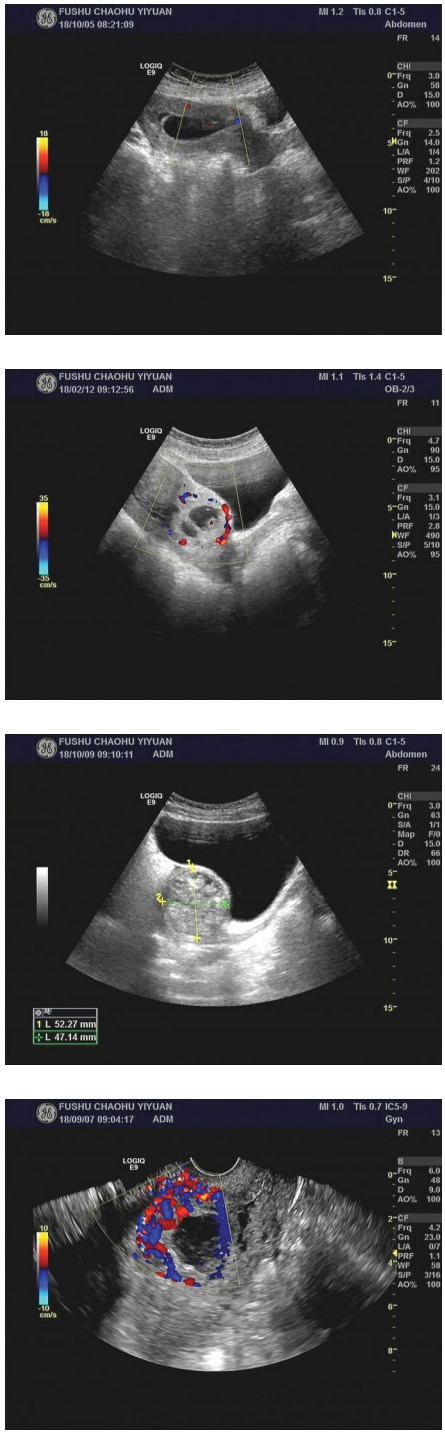

Figure 1. Ultrasound images of the 3 types of CSP. A, partial type. B, complete type. C and D, mass type

gar score of 9 at 1 min and 10 at 5 min via cesarean section at term. Placenta previa and partial adhesion were observed during the operation, and the estimation of blood loss was 400 mL. Another case was a recurrent scar pregnancy diagnosed in 15 months ago, where she underwent treatment with mifepristone combined with uterine curettage.

Sixty-nine cases of CSP, including 33 partial-type cases, 28 complete-type cases, and 8 mass-type. Among the 8 mass-type cases, 1 case was diagnosed by transvaginal ultrasound, presenting menopause of 50 days with vaginal bleeding. The other 7 cases were diagnosed after medical intervention such as suction curettage or drug-induced abortion, and the time of diagnosis varies from hours to 2 months. Out of 7 cases 3 received initial and subsequent treatment at the same hospital, whereas the other 4 cases received initial treatment at other hospitals. The ultrasonographic images of the 3 types of CSP were shown in Figure 1.

The clinical characteristics of patients among the 3 CSP subgroups were shown in Table 2. We found there were no significant differences in age, curettage times, cesarean section times and intervals, gestational weeks, cardiac activities, gestational sac/lesion size, vaginal bleeding, and abdominal pain between partial- and complete-type CSPs. Compare to the partial- and complete-type of CSP, the gestational duration was significantly increased ($p < 0.001$), so was the sac/lesion size ($p < 0.001$) and vaginal bleeding ($p < 0.01$) in mass-type patients, but there was no significant difference in age, curettage times, cesarean section times and intervals, as well as abdominal pain.

All of 69 CSP cases were successfully treated with one or more combined treatments. There were 12 of 33 cases with partial-type CSP initially treated with mifepristone plus curettage, and 10 cases were successful treated in which 2 cases received additional MTX, moreover, 2 cases received UAE due to bleeding during the treatment. The success rate of treatment with mifepristone plus uterine curettage ± MTX in partial-type CSP was 83.3% (10/12). The initial treatment with UAE plus curettage of twenty cases were successful which presented no excessive bleeding. Therefore, the success rate of UAE plus curettage in partial-type CSP was 100.0% (20/20). One case referred from other institutions had been previously misdiagnosed as intrauterine pregnancy and artificial abortion was performed directly. After that, the repeated vaginal bleeding occurred for 2 months until the second time to hospital and was misdiagnosed with trophoblastic neoplasm before the surgical treatment was performed, it has been confirmed as CSP by the intraoperative findings and postoperative pathology.

In the group with complete-type of CSP, 6 of 28 first-consulted patients were successfully treated with drug plus curettage (4 with mifepristone, and 2 with MTX). The other 22 were treated with UAE and curettage initially in which 20 cases (including 1 case that accepted additional MTX) underwent successful treatment, whereas 2 had a stable pregnancy (mass-type) later. As a result, the success rate of UAE plus curettage with or without MTX in complete-type CSP was 90.9% (20/22).

In the group with mass-type of CSP, 4 of 8 were treated with UAE plus curettage and 1 with additional MTX. The laparotomy was performed in other 4 cases; 1 case was the preceding partial-type CSP which was misdiagnosed initially, and turned into a mass-type after a medical abortion, and the other 3 cases treated with MTX, of which 2 were preceding complete-type CSP which underwent treatment of UAE plus uterine curettage. All 4 surgeries were performed by laparotomy and scar repair, and no severe bleeding was observed during operation.

As one of the major complications, hysterectomy had not been observed in any cases of our series, the complications and treatment used in partial, complete, and mass-type CSP cases were shown in Table3. As showed in our data, moderate bleeding (> 200 mL) occurred in 4 partial-type, 3 complete-type, and 1 mass-type case, while severe bleeding (> 500 mL) occurred in 2 partial-type, 2 complete-type, and 3 mass-type cases. However, patients of partial-type experienced bleeding during the initial treatment of mifepristone combined with curettage, but not for the treatment regimen of UAE plus curettage which showed no severe bleeding. In 2 complete-type and 3 mass-type of patients developed bleeding during the UAE plus curettage ± MTX.

DISCUSSION

In our study, we found that vaginal bleeding is the most common symptom among patients in CSP. Mass-type CSP cases are prone to have longer gestational duration, larger lesions, and more vaginal bleeding than partial- and complete-type. In addition, we noted that UAE plus curettage is a more effective therapeutic approach than mifepristone plus curettage which is the basic treatment for CSP. Moreover, most of the mass-type CSPs were developed from complete- and partial-type CSP after medical treatment and surgery is unavoidable to remove lesions.

A retrospective case-control study by Luo et al. [19] has shown that 58.7% of CSP cases experience vaginal bleeding and 15% experience abdominal pain as early symptoms. Kim et al. [20] reported that 53.4% of CSP cases had no symptoms around gestational weeks 6.5 ± 1.1. In our study, 39 (56.5%) cases experienced vaginal bleeding and 7 cases (10.14%) experienced abdominal pain, which were consistent with the previous reports. Approximately half of the CSP patients had no obvious early symptoms, based on these reports and our results we strongly recommended to pay more attention to patients after cesarean section, especially when they experience vaginal bleeding. Timor-Tritsch et al. [21] have suggested that routine ultrasound screening for CSP should be performed in pregnant women with a history of cesarean section at gestational weeks 5–7 like screening for aneuploidy and preeclampsia. Early detection of CSP is critical to prevent its progression and improve the long-term prognoses.

The clinical features of CSP differ among different types. Our study showed that there were no significant differences in age, curettage times, cesarean section times and intervals, gestational weeks, cardiac activities, gestational sac/lesion size, vaginal bleeding, and abdominal pain between partial- and complete-type CSP. However, the results indicated that the characteristics of mass-type CSP involving the occurrence in later gestational week, a larger lesion, vaginal bleeding tendency, and it often develops from partial- and complete-type CSP after medical treatment, which is consistent with the previous report of Ying et al. [22].

To the best of our knowledge, CSP represents a diagnostic and therapeutic challenge for the unclear guidelines of the classification and treatment till date. Our study showed that in partial-type CSP, the success rate of treatment with mifepristone plus curettage ± MTX was 83.3% (10/12), and 17 cases were successfully treated with UAE plus curettage. The success rate of treatment with UAE plus curettage ± MTX in complete-type CSP was 90.9% (20/22). This result was

Table 3. Treatment modalities and complications in partial, complete, and mass-type CSP cases

Type	Initial treatment (n)	Successful with no intervention	Successful with additional MTX	Success rate (initial treatment + additional MTX)	Eventual success with UAE or laparotomy, or became mass type	Bleeding (mL)	
						>200	>500
Partial	Mifepristone plus curettage (12)	7	3	83.3% (10/12)	UAE (2)	4	2
	UAE plus curettage (0)	20	0	100% (20/20)	0	0	0
	Direct induced abortion (1)	0			Turned into mass (1)		
Complete	Mifepristone plus curettage (4)	4			0	2	0
	Additional MTX plus curettage (2)	2			0	1	0
	UAE plus curettage (22)	19	1	90.9% (20/22)	Turned into mass (2)	0	2
Mass	UAE plus curettage (4)	3	1	1		1	1
	MTX (3)	0			laparotomy (3)	0	2
	Laparotomy(1)	1				0	0

consistent with that of previous reports [7, 23]. However, the safety of the patients, who underwent UAE treatment, to become pregnant again is under controversial. The risks include ovarian failure, infertility, abortion, premature delivery, and postpartum hemorrhage [24, 25]. However, in other cases, such as partial-type CSP with a thicker musculature, UAE should be used when emergency massive hemorrhage occurs or as a second-line treatment instead of routine treatment.

The curative effect didn't show an increase with the treatment of uterine curettage followed by MTX, in addition, it showed the ability to prolong the length of hospitalization [26]. MTX should not be used as an initial treatment because the fibrous tissue surrounding the gestational sac reduces the absorption and effectiveness of MTX [27]. However, as a remedy, MTX has a certain success rate due to the viability of trophoblasts. In our study, 4 of 6 cases of partial- and complete-type CSP received additional MTX which had been successfully treated.

A previous report [12] has shown that the thinner the uterine myometrium between the gestational sac and the bladder, the treatment would be more difficult, and the more likely to have a surgery with more complications. Because there was no description of muscle thickness in some images in our retrospective study, it was not possible to further classify complete-type CSP. The mass-type in our study appeared to be a large lesion, protruding toward the bladder, with a thin muscular wall and abundant blood flow. In our study, 4 of 8 cases with mass-type CSP underwent UAE; 3 were successfully treated and 1 required additional MTX with success. The remaining 4 were eventually treated surgically. In our series, three cases of mass-type CSP developed severe bleeding during treatment with UAE plus curettage and MTX, but not with an operation. Therefore, for the treatment of mass-type CSP, surgery was the most recommended option to remove the lesions because it would increase the possibility to bleeding and prolong the recovery time.

The mean gestational duration in our study was 7.75 ± 2.14 weeks, and an early diagnosis contributed to the early treatment. None of the 69 cases underwent hysterectomy, and seven of 8 cases of mass-type CSP developed after abortion or drug interference. Therefore, β-hCG levels and ultrasound should be monitored regularly after abortion of scar pregnancy in case the occurrence of pregnancy. Surgery is unavoidable once mass-type CSP develops. Although surgical treatment is considered the optimal treatment choice, medical drug plus curettage can achieve similar results for patients who have non-mass-type CSP with a thicker scar and with low economic status to undergo surgery. Thus, how to remove the pregnancy safety and effectively, and to reduce the bleeding and injury to prevent hysterectomy in CSP cases are need for further study.

There are some limitations in our study. There is no description of muscle thickness and blood flow in some images in our retrospective study, it is not possible to further typing complete CSP. We did not make comparisons of β-hCG for the levels of β-hCG (*e.g.* > 10,000 IU/L, other than a defined figure such as 12,000 mIU/mL) were not given for some CSP patients. In addition, the therapeutic approaches of UAE in partial-type CSP were slightly more, and which may affect credibility to some extent.

In conclusion, UAE combined with curettage is a more effective treatment instead of mifepristone plus curettage, which is the basic treatment for partial- and complete-type CSP. Mass-type CSP has features such as occurrence at late gestational duration, larger lesion size, and more vaginal bleeding tendency. Most mass-type CSPs develop from partial- and complete-type CSPs after medical treatment, and many cases require surgery to remove the lesions. Improper treatment may induce the increase of bleeding and impede the patients' recovery.

Author contributions

Design, planning, methodology, conduct, validation, data analysis and manuscript writing: Xuai Yin; Validation: Shihai Huang.

Acknowledgments

We thank all the staff of Department of Obstetrics and Gynecology and archives at the Affiliated Chaohu Hospital of Anhui Medical University, Hefei, Anhui, PR China.

Conflicts of interest

The authors have no conflicts of interest.

Ethical Statement

This manuscript has not been published or presented elsewhere in part or in entirety and is not under consideration by another journal. All study participants provided informed consent, and the study design was approved by the appropriate ethics review board. We have read and understood your journal's policies, and we believe that neither the manuscript nor the study violates any of these.

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VIA MEDICA

REVIEW PAPER / GYNECOLOGY

Ginekologia Polska
2020, vol. 91, no. 7, 412–416

ISSN 0017–0011

DOI: 10.5603/GP.2020.0070

The role of diet and probiotics in prevention and treatment of bacterial vaginosis and vulvovaginal candidiasis in adolescent girls and non-pregnant women

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ABSTRACT

The article raises important issues regarding the use of diet and probiotics in prevention and treatment of vaginitis.

Vaginitis is defined as any condition with symptoms of abnormal vaginal discharge. The most common causes of vaginitis are vulvovaginal candidiasis (VVC), trichomoniasis and bacterial vaginosis (BV). Vaginitis has been linked to itching, burning, pain, discharge, irritation and also adverse reproductive and obstetric health outcomes. Moreover, microorganisms that build vaginal flora in the state of bacterial vaginosis are a source of cervicitis and endometritis (often in subclinical forms) and pelvic inflammatory disease (PID)

The proper diet and probiotics consumption may influence the composition of the gut microbiota, improve gut integrity, and have an impact on maintaining and recovering the normal vaginal microbiota.

Future studies and reviews investigating the role of diet and probiotics in changes to gut and vaginal microbiome need to focus on deciphering the mechanismus of host bacteria interaction in vulvovaginal health.

Key words: vaginal infections; vaginitis; bacterial vaginosis; vulvovaginal candidiasis; diet; probiotics; prebiotics

Ginekologia Polska 2020; 91, 7: 412–416

INTRODUCTION

In adolescent girls and non-pregnant women, especially with a decrease in immunity, vaginitis, including fungal infections, can occur, which clinically manifests as abnormal vaginal discharge, irritation, itching, burning, discomfort. Sexually transmitted diseases are a particularly problematic in women [1–9].

Vaginitis is a general term that refers to inflammation of the vaginal wall, generally caused by one of three disorders: yeast infections, bacterial vaginosis or trichomoniasis. The normal bacterial flora of the vagina and cervix protect against the development of pathogenic strains, while abnormal flora tend to be the most common starting point for the development of infections.

During adolescence, bacterial vaginosis episodes affect 3–7% of non-sexually related and 4–15% of sexually active girls 13–18 years of age. This is a significant problem, because the microorganisms that build vaginal flora in the state of bacterial vaginosis are a source of cervicitis and endometritis (often in subclinical forms) and pelvic inflammatory disease (PID) [1–8].

ETIOLOGY

Female genitalia are a natural biotope for commensal flora. Proper biocenosis of the genital environment determines protection against the development of inflammatory processes. Anatomical and physiological conditions of the genital organs — moisturizing and the proximity of the urethra and anal opening - favor the development of infection. Genital inflammation is most often caused by neglecting hygiene, mechanical injury or infection (viruses, chlamydia, fungi, protozoa). A certain group of these inflammations also

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occurs on an allergic basis (*e.g.* allergy to cleaning products). The most common causes of vaginitis are bacterial vaginosis (Bacterial vaginosis, BV), vulvar and vaginal candidiasis (Vulvovaginal candidiasis, VVC) and trichomoniasis. BV is involved in 40% to 50% of cases when the cause is identified, VVC accounts for 20% to 25%, and trichomoniasis accounts for 15% to 20% of vaginitis. Non-infectious causes, including atrophic, irritating, inflammatory and allergic vaginosis occur less frequently and account for 5% to 10% of cases of vaginitis [2]. The effectiveness of defense mechanisms and their mutual compensation is different in different periods of a woman's life, which is hormonally determined [1–8, 10]. The vaginal microflora also changes during menstrual bleeding [11].

In the female newborn, who is still under the influence of estrogens from the period of intrauterine life, the pH of the vagina after colonization with acid-forming rods (*Lactobacillus acidophilus*) is acidic. In the subsequent months of the girl's life, the level of estrogen gradually decreases. The vaginal epithelium consists only of the basal and basal layers, without glycogen grains in the cells, which determines the development of acid-forming bacilli — the pH changes. During the so-called estrogenic silence, which lasts until the onset of puberty, the pH changes to neutral, at which time, the mixed bacterial flora of grains and sticks settles. A narrow vagina, adhesion of its walls, the presence of the hymen and the vaginal folds (*plicae palmatae*) constitute a mechanical compensation for the described lack of biochemical defenses during this period of life. During puberty, the concentration of estrogens increase and the vaginal epithelium becomes multilayered. The intermediate layer cells contain glycogen, which allows the development of acid-forming bacilli and prevents the settlement of pathogenic microorganisms. A mature woman develops further defenses. These include the intensification of the process of exfoliation of genital epithelial cells, the formation of secretion, which is removed actively (*e.g.*, epithelial shutter epithelium) or passively along with microorganisms and cell debris, as well as a specific pH value on individual genital floors. In girls who have not had sexual intercourse, inflammation of the internal genital organs occurs relatively rarely, although descending (purulent tonsils, teeth) or through continuity (appendicitis) is also possible. Regardless of the age group analyzed, inflammatory problems in the genitals most often relate to vulvovaginitis [1–8]

This inflammation can be caused by viruses, chlamydia, bacteria, fungi (most often Candida Albicans), and vaginal trichomes (*Trichomonas Vaginalis*). Some authors also recognise non-specific vulvovaginitis. Genital infections can be caused by endogenous vaginal bacterial flora or by exogenous bacterial flora (sexually transmitted and extrinsic) [1, 5, 7, 12].

In girls and women who have started sexual intercourse, an increase in vulvovaginitis and, as a result, an increase in internal genital inflammation due to the ascending route is observed [1, 5, 7, 12].

This review aimed to determine the role of proper diet and probiotics and prebiotics use in relation to therapy and profilaxis of vulvovaginal candidiasis (VVC) and bacterial vaginosis (BV) in non-pregnant women and girls.

THE ROLE OF DIET IN PREVENTION OF BV AND VVC

Numerous studies have proven that diet is a key modifiable factor affecting the composition of the intestinal microflora [12–21].

It is also known that educating patients in the field of balancing the diet (reducing the consumption of sweets, increasing the consumption of vegetables, fruits and dairy products) has a significant role in the treatment of vaginitis [14].

The use of functional foods and supplements containing probiotics and prebiotics has a beneficial effect on genital inflammation [3, 9].

From the point of view of the proper function and prevention of inflammation, it is important that the genital organs receive metabolism products from the blood: fats, proteins and carbohydrates. From metabolic products obtained through blood vessels, mucus is produced, which is necessary for proper vaginal hydration. Unfortunately, the predominance of carbohydrates, especially simple sugars, promotes the development of abnormal vaginal flora and conditions become favorable for the development of yeast-like fungi [14–16].

To prevent inflammation, it is important to create an appropriate intestinal barrier. For protect the vaginal environment properly against excessive multiplication of pathogenic microorganisms, including yeast-like fungi, it is therefore important to have a properly balanced diet, low glycemic load, low fat, containing folic acid, vitamins D, E, C, A and beta carotene, as well as products rich in calcium and betaine [14–16].

An unbalanced diet can be a risk factor for BV. Women tend to be more exposed to BV if they have poor micronutrient status, including vitamins A, E, D, C and beta carotene — indicating a lower fruit and vegetable intake. In recent years, scientists have found that the richer the diet is in nutrients, the lower the risk of apparent bacterial infection. Routine consumption of dairy products and fresh fruit and vegetables reduces the likelihood of vaginitis, while eating sweets increases the likelihood [14–16].

Sweets and other carbohydrate sources can affect the human glycemic response. Chronic and continuous exposure to hyperglycemia after a meal can have an adverse effect on health and has been linked to oxidative damage by its reducing plasma antioxidant defense and increasing inflammation due to free radical production. It is possible that chronic exposure to diets with high energy value and

high energy density can affect host responses to bacterial colonization, particularly BV pathogenesis, through oxidative stress and impaired immune function [16].

Yasmin et al. proved that increased dietary fat intake (39% of energy from fat), especially total fat, saturated fat and monounsaturated fat, can increase vaginal pH, thus increasing the risk of bacterial vaginosis. In addition, dietary fat may be a factor that inhibits the immune functions of the intestinal mucosa. It is likely that a high dietary fat intake may affect the mucosal immune system and thus increase the risk of bacterial infections associated with BV. The studies cited did not show a relationship between BV and carbohydrate or protein intake, and this means that high fat intake is a predictor of BV independent of energy intake [16–18].

A proper calcium supply is also important in preventing inflammation in women and girls. Genital infections are more common in cases where there are low levels of calcium in the body. The sources of calcium are milk and dairy products such as cheese or yogurt, but also legumes (*e.g.* white beans), seeds (*e.g.* sesame) and dark green vegetables (such as broccoli or spinach). Yasmin et al. proved significant inverse relationships between severe BV and calcium intake, as well as with folic acid, and vitamin E [18].

With the weakening of the immune system in women and girls, the likelihood of infection increases, and vitamin E (a powerful antioxidant) and folic acid can improve the immune response, thereby reducing the risk of BV [18, 19].

But since there is a relationship between taking ascorbic acid and boosting the immune system, the diet must be rich in products containing vitamin C. In addition, it has been shown that subclinical iron deficiency (measured based on soluble transferrin receptor) can be a significant predictor of BV [19].

An unbalanced diet can be a risk factor for BV, because it affects the microbial population of the mucosal surface in the digestive and reproductive tracts. In turn, bacterial colonization of the intestine can act as a reservoir for the vaginal microflora. Antonio et al. found agreement between Lactobacillus species in the rectum and vagina, suggesting that the rectum may serve as a potential source of vaginal colonization. The authors suggest that the adhesion properties of specific bacteria in the rectum may determine which species adhere to the vaginal epithelium [20].

In a recently published study, Tuddenham et al. proved that lower energy-adjusted intake of betaine was associated with an increased risk of molecular-BV. Betaine might have direct effects on the vaginal microenvironment or may be mediated through the gut microbiota. Betaine can be found in the diet in such products as bran and wheatgerm, goji berries, spinach or beets [21].

Additional studies are needed to confirm that higher intake of selected dietary ingredients, such as betaine, reduces the risk of BV and BV-related symptoms [21].

THE ROLE OF PROBIOTICS IN THE PREVENTION AND TREATMENT OF BV AND VVC

Probiotics are live microorganisms that, when administered in adequate amounts, confer a health benefit to the host [20]. Probiotics can be ingested as part of the diet or in supplement form [23, 24].

Probiotics have been reported to be useful when used either vaginally or orally [25].

The biochemical activity of probiotics (as a natural food ingredient or added as starter cultures) affects not only the nutritional, dietary and organoleptic characteristics of the product, but also has preventive and therapeutic effects. Probiotics are microorganisms, mainly lactic acid bacteria, that can colonize the human digestive tract. They may contain individual strains of lactic acid bacteria (*Lactobacillus spp.*, *Streptococcus spp.*), strains of yeast (*Saccharomyces spp.*), mold cultures (*Aspergillus spp.*), or also lactic acid bacteria, together with selected yeast strains. Probiotics have a positive effect on gastrointestinal transit time and ensure the proper development of the microflora inhabiting the body. The word‚probiotic' comes from Greek and means„fit for life". This term was first used in 1965 by Lilly and Stillwell, who described probiotics as substances produced by microorganisms that stimulate human and animal growth. Fuller added to the name in 1989 by defining that:„probiotics are live, bacterial food additives that improve the functioning of the host's digestive tract" [5].

In order to call a given bacterial strain a probiotic strain, it must come from the natural healthy microflora of the large intestine, be an absolute or relative anaerobic, and belong to a specific genus and species that has been assigned to it by molecular methods. It is advisable for it to be resistant to the acidic pH of gastric juice, bile salts and digestive enzymes. It should not exhibit pathogenic or toxic properties, and it is also recommended that it exhibits antagonistic activity against harmful gastrointestinal bacteria, have the ability to attach to the surface and colonize the colon, produces antibacterial substances, and have genetic stability. Active growth and division, as well as high lactic acid yield during fermentation of monosaccharides, disaccharides and complex sugars, is also important. Its positive effects should be scientifically confirmed and must retain all their properties in processing and storage. Most of these features allow probiotic bacteria to survive in the digestive tract and enter the large intestine, where they perform their functions. It has been proved that consuming probiotics has positive effects on the management of some gastrointestinal conditions (Irritable Bowel Syndrome, diarrhea). Probiotics can also counteract the pathogenic activity of microflora in the intestines, which penetrate as a result of non-compliance with food hygiene [9].

Probiotics are used after antibiotic therapy, and to produce functional food (especially milk products) and supplements [25–27].

The positive effects of probiotics on the immune system can be used to treat intestinal infections caused by HIV that penetrate the lining of the large intestine. The protective function is fulfilled by the previously mentioned biofilm constituting a natural immune barrier, and also by antibiotics produced by the intestinal microflora and the free radical lactactoxidase system. Probiotics can stimulate cellular and humoral immune responses. Many studies proved that regulated use of probiotics, administered both orally and vaginally, are effective in the prevention and treatment of vaginal infections such as BV and VVC [23, 24, 28].

Bacterial vaginosis is characterized by a reduction or depletion of lactobacilli and overgrowth of Gardnerella vaginalis, Mycoplasma hominis, Prevotella species, and other pathogenic anaerobic bacteria [9].

The Lactobacillus species produces lactic and acetic acid and hydrogen peroxide (H_2O_2), maintains the vaginal pH around 4.5 or less, hampers the growth of pathogenic bacteria and Candida albicans, and is thus considered protective against VVC and BV [28, 29].

Due to the production of lactic acid by probiotics, the electro-chemical potential of cell membranes and intracellular protein denaturation of harmful microflora are neutralized. Hydrogen peroxide is toxic to pathogens. Probiotics destroy pathogens as a result of their competing for nutrients and for receptors in the mucosa and epithelium. They also produce bacteriocins that remove pathogens from the digestive tract. They are heterogeneous chemicals that inhibit the activity of pathogenic bacteria — *Staphylococcus aureus*, *Salmonella enteritidis*, *Bacillus cereus*, or *Pseudomonas aeruginosa*, are mainly produced by *Lactobacillus acidophilus*. Bastani confirmed the potential efficacy of lactobacilli as a non-chemotherapeutic means to restore and maintain normal urogenital flora, and showed that probiotic bacteria especially *L. acidophilus*, *L. rhamnosus GR-1* and *L. fermentum RC-14* when administered over 10^8 CFU for 2 months can most appropriately normalize vaginal flora, help cure the existing infection and prevent recurrence of BV. Longer periods of probiotic administration may be useful for long-term control of BV relapses after conventional therapy with metronidazole [25].

According to Xie HY et al., probiotics used as adjuvant therapy may increase the incidence of short-term clinical and mycological cure and reduce the relapse rate within one month, but not act as a long-term cure. The benefits and drawbacks of probiotics in vulvar and vaginal candidiasis in non-pregnant women should be considered carefully.

There is a need to conduct large-scale, long-term, randomized control tests with adequate blindness of participants and staff, and to do so in different age groups. Where probiotics are intended to be used as adjunct agents to conventional drugs, a placebo should be used in the control group. The effect of different strains should also be checked, and possible effects from different routes of administration observed [30].

THE IMPORTANCE OF PREBIOTICS AND SYNBIOTICS IN THE DIET

To create a positive environment for probiotics, it is important to provide prebiotics that support the development of probiotic strains. Prebiotics are defined as non-digestible food ingredients that selectively stimulate the growth or activity of one or a specified number of types of bacteria in the colon that favorably affect the health of the host. Prebiotics can be introduced artificially into foods to improve the nutritional and health value, *e.g.* inulin, fructooligosaccharides, lactulose, or galactose and β-glucan derivatives. They are a breeding ground for probiotics, stimulate their growth and, unlike them, do not contain microorganisms. Prebiotics are not digested by endogenous enzymes in the human body, remain practically undigested as they reach the colon, where they are completely fermented and broken down by saccharolytic bacteria (*e.g. Bifidobacterium*) [13].

The basic criteria that prebiotics should meet are that they should lower the pH of the digestive tract and should not undergo hydrolysis or absorption through the gastrointestinal tract. Their task is also to stimulate the growth of lactic acid bacteria and inhibit the activity of harmful intestinal microflora. It has been proved that prebiotic consumption is associated with growth of *Bifidobacterium*, *Lactobacillus* and lactic acid bacteria [31]. Researchers suggest that consumption of prebiotics has a positive impact not only on gut microbial composition, but also on health outcomes, because probiotics produce beneficial metabolites [13].

Studies have shown that ingestion of prebiotics significantly affects the composition of the intestinal microflora and its metabolic activity. This is due to the modulation of lipid metabolism, increased calcium absorption, their impact on the immune system and modification of intestinal function. Prebiotics occur naturally in over 36,000 plant-derived products, including garlic (9–16%), chicory (13–20%), artichokes (15–20%), asparagus (10–15%), onions (2–6%), wheat (1–4%) and bananas (0.3–0.7%) [9]. Artificially produced prebiotics include lactulose, galactooligosaccharides, fructooligosaccharides, malotoligosaccharides, cyclodextrins and lactosaccharose. Synbiotics are a combination of pre- and probiotic and these have a synergistic effect. They affect the development of beneficial intestinal microflora due to stimulation of probiotics with prebiotics. They also inhibit the development of pathogenic bacterial flora in the intestines. Synbiotics contribute to reducing the concentration of unwanted metabolites in the body, inactivat-

ing nitrosamines and carcinogens, as well as preventing putrefaction in the intestines and preventing constipation and diarrhea of various etiologies. Synbiotics also reduce harmful microflora (Clostridium perfringensi of other endopathogens) while multiplying beneficial bacteria. They lower cholesterol and blood pressure and are used to treat patients with liver disease [9]. They improve the absorption of magnesium and phosphorus and calcium, which, as mentioned, has a beneficial effect on the prevention of inflammation in gynecology [1, 4, 5, 7–9].

SUMMARY

Gynecologists, obstetricians, general practitioners and dieticians should share their findings, and also raise awareness among the general population as to the importance of optimal nutrition, probiotics and prebiotic use to prevent infections of the genital tract, reduce associated disease, and maintain reproductive health.

Future reviews investigating dietary and biochemical indicators of nutritional status, and the role of diet in changes to gut and vaginal microbiome need to focus on further elucidating the biological mechanisms for these findings.

Further research is needed on the long-term influence of diets and probiotics use on vulva and vagina health before clinical recommendations can be made.

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VIA MEDICA

REVIEW PAPER / OBSTETRICS

Ginekologia Polska
2020, vol. 91, no. 7, 417–423

ISSN 0017–0011

DOI: 10.5603/GP.2020.0106

COVID-19 during pregnancy, delivery and postpartum period based on EBM

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ABSTRACT

The pandemic caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has become the reason of the global health crisis. Since the first case of diagnosed COVID-19 pneumonia was reported in Wuhan, Hubei Province, China, in December 2019, the infection has spread rapidly to all over the world.

The knowledge gained from previous human coronavirus infection outbreaks suggests that pregnant women and their foetuses represent a high-risk population during infectious disease epidemics.

Moreover, a pregnancy, due to the physiological changes involving immune and cardiopulmonary systems, is a state predisposing women to respiratory complications of viral infection.

The constantly increasing number of publications regarding the course of COVID-19 infection in pregnant women has been published, however, the available data remains limited and many questions remain unanswered. The aim of this review was to summarize the literature data and adjusted to current recommendations regarding pregnancy care, delivery and postpartum period.

An extremely important issue is the need to register all the cases of COVID-19 affected women and the course of these pregnancies to local, regional, or international registries, which will be helpful to answer many clinical and scientific questions and to create guidelines ensuring an adequate level of care for women affected by COVID-19 infection during pregnancy, delivery and during postpartum period, as well as their newborns.

Key words: COVID-19; SARS-CoV-2; coronavirus; pandemic; pregnancy; respiratory distress syndrome

Ginekologia Polska 2020; 91, 7: 417–423

INTRODUCTION

Coronaviruses are a group of RNA viruses which are one of the largest RNA viruses in terms of the genome (~ 30,000 nucleotides) and virus size (spherical, 80–180 nm in diameter). Their name derived from the glycoprotein spikes of the coronavirus double-layer nucleocapsid, which creates an image of the corona in the electron microscope [1, 2].

Until the end of the 20th century, known coronaviruses infected people much less frequently, causing infections mainly in animals, being an etiological factor in the incidence of birds, cats, dogs, pigs, mice, horses, whales, camels and bats [3].

Human Coronavirus (HCoV), known as aetiological factors of about 15–30% of mild, seasonal infections of the lower and upper respiratory tract, can also cause gastrointestinal and rarely found nervous system infections. Thus far, eight human-infecting coronaviruses are known: HCoV-229E, HCoV-OC43, HCoV-NL63, HCoV-HKU1, HCoV-SARS, HCoV-MERS and SARS-CoV-2, the last five of which were described in the 21st century [4, 5]. Coronaviruses have one of the largest genomes among RNA viruses, which, combined with the high variability characteristic of RNA viruses, leads to the accumulation of genome sequence changes, which can result in the formation of different virus variants and a change in cellular tropism [6].

The first reports of human coronaviruses originated during the 1960s when two pathogens - HCoV-229E and HCoV-OC43 — were isolated and described — causing respiratory diseases in humans [7]. For over 40 years they were the only representatives of the Coronaviruses with the capability of causing infections in humans. The image of human coronaviruses as relatively harmless pathogens changed with the emergence of the new highly infectious human coronavirus species in the Chinese province of Guangdong in November 2002 — the SARS-CoV virus, which causes severe acute respiratory syndrome (SARS) [8, 9].

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During one season, the virus spread to 37 countries, 8273 cases of infection were found, of which 775 were fatal [10]. The MERS-CoV virus (Middle East Respiratory Syndrome Coronavirus) was first isolated in a patient from Saudi Arabia in 2012 [3]. By July 2017, 2040 infections were recorded, of which 712 were fatal [11].

The first cases of COVID-19 were recorded in the city of Wuhan with a population of over 11 million, the capital of the Hubei Province (60 million inhabitants) in Central China, at the beginning of December 2019. The location, transport and logistics, conducive to migration of infected people, have enabled the extremely rapid spread of the virus across all continents [12].

According to ECDC (European Center for Disease Prevention and Control) data, between December 31, 2019, and July 9, 2020, there were 12 017 118 cases of infection found, of which 549 6276 were fatal [13].

Comparison of genetic materials of coronavirus known to date indicates that SARS-CoV-2 is most likely a mutated bat-borne coronavirus that is often the asymptomatic carrier of many coronavirus species [14]. SARS-CoV-2 coronavirus has obtained human-to-human transmission ability through mutations. Its genome is 80% identical to the genome of the SARS-CoV-1 virus and 50% identical to the MERS-CoV [15].

Particular coronaviruses use different cell receptors, which was used to divide them into three groups — depending on which receptor they recognize. The viruses belonging to group 2, which includes the SARS CoV virus, use human angiotensin 2 convertase [4]. HACE2 receptors are found on cells of many human tissues, but the strongest expression of these receptors occurs in the lungs and kidneys [16]. Protein molecules are located in the outer shell of the SARS-CoV-2 virus, which specifically binds to angiotensin 2 converting enzyme present on the surface of the airway epithelial cells and alveoli. The number of ACE2 receptors is characterized by individual variability — there are 3.5 times fewer receptors in alveoli in women than in men, which may explain the differences in COVID-19 in both sexes [17, 18].

Transmission of SARS-CoV-2 virus between people is mainly via a droplet route through a carrier, which is an aerosol and microdroplets emitted from the respiratory tract of an infected person containing replicated viruses. Infection can also occur through contact with the patient's secretions, the virus is not absorbed through the skin, but it can be involuntarily transmitted to the mucosa or conjunctiva. The presence of SARS-CoV-2 RNA in feces, urine and — in the case of severe infections — the blood of patients [19]. Although isolation of live virus is possible from faeces in some patients, according to a joint WHO-China report, the transmission of faecal-oral infection does not appear to be particularly important in the spread of infection [20]. Unlike other droplet-transmitted RNA viruses, such as Zika virus (ZIKV) [21] or Ebola virus (EBOV) [22], SARS CoV 2 virus has not been found in vaginal secretions in women [23, 24].

The current, constantly deteriorating epidemiological situation worldwide, forces ongoing review of existing recommendations regarding pregnancy care, delivery and after postpartum period, considering obstetric knowledge and experience as well as an individual approach to the patient.

Some physiological changes occurring during pregnancy may increase the susceptibility of the pregnant woman to infections. Anatomical changes, such as an increase in the transverse dimension of the chest and an increase in the height at which the diaphragm is located, are factors reducing the tolerance of a pregnant woman to hypoxia [25]. Dyspnoea is a symptom affecting approximately 18% of patients with confirmed COVID-19. However, it should be remembered, that during pregnancy physiological shortness of breath is caused by increased maternal oxygen demand due to increased metabolism and oxygen consumption by the fetus, which requires differentiation from pathological dyspnoea as a manifestation of the disease [26]. Changes in lung volume and vasodilatation can lead to swelling of the mucosa and increased secretion in the upper respiratory tract. Also, changes in the immune system in relation to cellular immunity contribute to an increased susceptibility of pregnant women to infections caused by viruses [27]. Concerning the fetus and newborn, the immaturity of the immune system makes it highly prone to infections. It is particularly important to determine whether a given infectious agent can infect the fetus or newborn through vertical transmission.

Therefore, pregnant women and newborns should be assessed as potential risk groups in the current COVID-19 pandemic.

MATERIAL

The knowledge about coronavirus infection during pregnancy is limited. It is partly based on the experience of the SARS and MERS epidemics, which indicate that infection with these viruses may result in adverse clinical outcomes, including life-threatening maternal disease, which in some cases requires hospitalization, intensive care, and ventilation support. SARS and MERS infections can lead to death of pregnant women, but no specific risk factors for death during pregnancy have been identified [28].

The current review of data obtained from all published reports on pregnancy and neonatal results in women with confirmed COVID-19 is available in the Cochrane Gynecology and Fertility Group [29].

In general, although the data on pregnancy outcomes are reassuring, they should be interpreted with caution. Besides, due to the duration of the pandemic, these reports mainly relate to infections in the third trimester of preg-

nancy. So far, no information is available on the possible impact of COVID-19 infection on the development of the first trimester of pregnancy, as well as no studies on the potential teratogenic effect on embryo-fetal development.

The collection of this information is carried out on an ongoing basis, taking the form of a wide-ranging study, *e.g.* the prospective ASPIRE (Assessing the Safety of Pregnancy In the Coronavirus Pandemic) cohort study is conducted in the United States, covering women who have become pregnant naturally or through assisted reproduction methods in the period from December 31, 2019, to March 1, 2020, or global reports on individual cases of pregnancies obtained as a result of assisted reproduction methods in women with confirmed infection collected by the European Society of Reproduction and Embryology [30].

In the initial period of the pandemic, the American Society for Reproductive Medicine (ASRM) and the European Society for Reproduction and Embryology (ESHRE) independently presented their opinion in which it was recommended to stop reproductive care, except in the most urgent cases [31, 32]. Recently, thanks to effective strategies to limit the spread of COVID-19 infections in some areas, gradual resumption of full reproductive care has begun. In a document of May 29, 2020, ASRM, ESHRE and the International Federation of Fertility Societies (IFFS) jointly confirmed the opinion emphasizing the importance of continuing reproductive care during the COVID-19 pandemic. Besides, ASRM, ESHRE and IFFS work together to support patients and collect data and resources to better understand COVID-19 regarding reproduction, pregnancy, and fetal and neonatal effects [33].

The basis for current guidelines in force in Poland are the joint recommendations published on March 16, 2020, regarding the treatment of infertility of the Polish Society of Reproductive Medicine and Embryology (PTMRiE), the Fertility and Infertility Section of the Polish Society of Gynecologists and Obstetricians (PTGiP) and the National Consultant in the field of Gynecological Endocrinology and reproduction.

According to these recommendations, in the case of patients undergoing medically assisted procreation (ART) treatment, if they are at risk (*i.e.* who have been in places with a high incidence rate, were in contact with an infected person, are suspected of being infected COVID-19 or exhibit symptoms of inflammation of the upper respiratory tract), depending on the stage of therapy, it is recommended to stop or postpone the treatment and use the procedure of freezing oocytes or freezing embryos. If patients undergoing therapy are not at risk and are healthy, it is recommended to complete initiated infertility treatment procedures with possible consideration of deferment of the transfer. When using immunomodulatory therapies, if for any reason they are used in addition to infertility treatment, it is recommended to stop them, because in the period of the epidemic threat it can be a serious threat to health and life. Pregnant women and patients undergoing treatment or planning treatment should strictly avoid contact with infected people, those who are undergoing quarantine and avoid places where the risk of infection is increased.

All patients trying to conceive, those who are planning infertility treatment and those who are undergoing treatment, even if they do not meet the diagnostic criteria for COVID-19 infection, are advised to take precautions during therapy or postpone the treatment (limited to freezing of oocytes or embryos) [34].

There are currently no data that would indicate an increased risk of miscarriage in patients infected with SARS CoV-2. Studies in early pregnancy in women infected with SARS-CoV and MERS-CoV also showed no significant association between infection and an increased risk of miscarriage [35].

There have been several systematic reviews in recent weeks regarding the course of COVID-19 infection in pregnant women. Zaigham et al. in a systematic review of 18 papers refer to 108 pregnant women hospitalized mainly in China, as well as from the USA, Sweden, Korea and Honduras, in whom COVID-19 infection was confirmed by PCR between December 2019 and April 2020. The average age of infected pregnant women was 29–32 years, most of the infections occurred in the third trimester. Only 22 women were in early pregnancy and were discharged without significant complications, with preserved pregnancy. Additional risk factors were found in pregnant women like chronic diseases or pregnancy complications, such as gestational diabetes, hypertension, preeclampsia and hypothyroidism [36]. Regarding the clinical course of COVID-19 infection, in most cases, the disease usually begins with fever, fatigue and dry cough. The less common symptoms include shortness of breath and tachypnoea, rhinitis, sore throat, hemoptysis, shortness of breath, headaches, and more rarely diarrhoea. According to the literature data, about 20% of patients have symptoms of interstitial pneumonia causing respiratory failure of varying severity, which requires mechanical ventilation in 3% of cases [15].

Symptoms in pregnant women may be nonspecific, besides, the asymptomatic course is often observed. Zaigham et al. report that fever (68%) and dry cough (34%) dominated among the clinical symptoms presented by pregnant women at the time of admission to the hospital. Fatigue (13%), shortness of breath (12%) and diarrhoea (6%) were less frequently observed symptoms. Additional laboratory tests showed lymphocytopenia (59%) and increased levels of C-reactive protein (70%). As far as the pregnancy outcome is concerned 92% of women gave birth by caesarean section, 7 out of 85 women had a vaginal birth. There were no deaths among women in this group [36].

In the group of 43 pregnant women described by Breslin et al. with confirmed infection, 29 (67.4%) manifested symptoms of infection while admitted to the hospital. Dry cough (65%), fever (48%) and myalgia (38%) were the most common among the reported symptoms. Less common symptoms included: headache (27%), shortness of breath (24%), and chest pain (17%). Twenty-five women in this group (86.2%) did not require oxygen therapy or additional treatment and were discharged home in a stable condition. In the remaining four patients, the condition deteriorated, which was manifested by fever and increased respiratory effort, and the need for respiratory support and additional treatment. In one pregnant woman, an X-ray examination confirmed severe interstitial pneumonia and required admission to the ICU. The remaining 14 women did not present signs of infection at admission, 12 of them remained asymptomatic throughout the infection [37]. Breslin et al. noted in this group 2 cases of patients requiring hospitalization in ICU conditions. These women were found to have comorbidities and/or pregnancy complications such as pre-existing type 2 diabetes, poorly controlled gestational diabetes, gestational hypertension, gestational cholestasis, asthma, and BMI above 35 kg/m^2. Both patients delivered by caesarean section due to failure of progress or failed induction of delivery. In one patient, the surgery was complicated by uterine atony and perinatal haemorrhage. A second patient experienced respiratory failure 25 hours after cesarean section. On the fifth day after surgery, she still required oxygen therapy, and she developed acute obstetric kidney injury [38].

The effect of COVID-19 infection did not demonstrate as a cause of foetal growth restriction [39]. The presence of placental pathologies found after delivery of women infected with SARS [40] has not been confirmed.

Regarding infant mortality, Zhu et al. reported one case of neonatal death and six cases of neonates requiring admission to the Neonatal Intensive Care Unit. A symptom that occurred in all the described newborns was shortness of breath. Also, some of them had a fever, thrombocytopenia, liver dysfunction, tachycardia and vomiting. The neonatal death case concerned a premature newborn born at the 34th week of pregnancy, the result of a throat swab for SARS-CoV 2 performed on the ninth day of life was negative. As factors that contributed to the death of a newborn, Zhu et al. recognize the immaturity of the neonate's immune system with accompanying high viremia in the mother [41]. 1 case of intrauterine fetal death has been reported.

Currently, there is no literature data available confirming the possibility of intrauterine vertical transmission. The most reliable evidence for intrauterine vertical transmission would be confirmation of SARS-CoV-2 replication in fetal lungs, which is technically not possible. Intrauterine viral infection is determined based on confirmation of the presence of the virus in samples of the placenta, amniotic fluid, umbilical cord blood and newborn throat swab. To avoid contamination of samples, they should be taken immediately after delivery using aseptic technique. The first study, which examined the possibility of intrauterine transmission of COVID-19 infection, was conducted by identification of SARS-CoV-2 in samples of amniotic fluid, umbilical cord blood and neonatal throat swabs using quantitative reverse transcriptase-polymerase (qRT-PCR) chain reaction in six pregnant women with confirmed COVID-19 infection and mild to moderate symptoms. Negative qRT-PCR results for SARS-CoV 2 RNA were recorded in all samples of the placenta, amniotic fluid, umbilical cord blood and nasopharyngeal swabs, indicating that there was no intrauterine fetal infection in the third trimester of pregnancy [42].

Lei et al. [43] in a study of four pregnancies in which maternal COVID-19 infection was confirmed, also showed no evidence of the intrauterine vertical transmission in the third trimester.

In March this year, two reports were published describing three cases of newborns with elevated IgM anti-SARS-CoV-2 titers in serological tests, even though the results of repeated nasopharynx swabs in qRT-PCR were negative [44, 45]. The reason for this could be, however, the susceptibility of IgM tests to false positive and false negative results, as well as the possible cross-reactions [46].

So far, only one case of positive qRT-PCR has been described in both mother and newborn [47]. The pregnant woman was admitted to the hospital with a fever at 40 weeks of pregnancy, the nasopharyngeal swab for SARS-CoV-2 qRT-PCR test was positive, thoracic computerized tomography scan showed ground-glass opacities indicating bilateral interstitial pneumonia. A newborn was born by caesarean section in good condition. During the operation, the woman wore an N95 mask, the newborn had no contact with her after birth and was admitted to the Neonatology Department for observation. Despite the stable clinical status, the newborn had lymphocytopenia, liver dysfunction and elevated creatine kinase. A nasopharyngeal swab was taken from the newborn 36 hours after birth and came back positive. QRT-PCR results of umbilical cord blood and placenta samples were negative, but the possible transmission of SARS-CoV-2 from mother to child cannot be excluded. Both mother and child recovered and were discharged without any complications in good general condition [36].

Concerning ultrasound diagnostics during pregnancy, the Ultrasound Section of the Polish Society of Gynecologists and Obstetricians issued recommendations to minimize the risk of SARS-CoV-2 transmission. These recommendations include pre-selection of patients allowing

ultrasound examinations only for asymptomatic patients with a negative history.

In the case of patients with a negative epidemiological history, no fever, but with cold symptoms, it is advisable to postpone the examination until the symptoms resolve. Pregnant women with a positive interview should be quarantined for 14 days and postpone the ultrasound screening examinations. In case of emergency, hospital care in a dedicated hospital is recommended. Pregnant women with diagnosed COVID-19 or with a positive SARS-CoV-2 test should have ultrasound examinations performed only in case of justified medical indications in COVID-19 dedicated hospitals. In suspected or confirmed cases of COVID-19 infection, ultrasound examination of fetal growth, amniotic fluid and umbilical artery blood flow should be performed when clinically necessary. Depending on the situation, these parameters should be monitored every 2–4 weeks. If COVID-19 infection is confirmed during the first or early second trimester of pregnancy, an ultrasound examination should be performed between 18 and 24 weeks of pregnancy. In the case of outpatients, the first, second and third trimester scans should be performed, the remaining examinations should be postponed. Although the presence of virus RNA in the vaginal secretion has not been confirmed, due to the increased risk of virus transmission during a vaginal examination, the number of procedures performed with the vaginal transducer should be reduced, it is recommended to perform cervical length measurement by transabdominal examination [48].

According to the RCOG (Royal College of Obstetricians and Gynaecologists) recommendations from 19 June 2020 regarding the method of delivery in women with confirmed COVID-19 infection, there is no evidence indicating a specific way of delivery and it should be determined based on the obstetric situation and fetal well-being [49].

According to current recommendations of the National Consultant of Obstetrics and Gynecology, National Consultant of Neonatology, National Consultant of Perinatology, Polish Society of Gynecologists and Obstetricians, Polish Society of Neonatology and the Polish Society of Perinatal Medicine, in the case of confirmed COVID-19 infection, caesarean section for epidemiological indications should be considered, except in situations where labor is advanced when neonate will be delivered within a short time. This recommendation aims to minimize the likelihood of infection of the newborn with a virus that may be found in the birth canal. The potential exposure to maternal excretions during caesarean section is incomparably lower compared to the vaginal delivery. Also, due to the potentially shorter duration of caesarean section compared to vaginal birth, the risk of intrauterine infection, especially after rupture of amniotic membranes and perinatal infection, is significantly reduced. The above recommendations also consider the risk of transmission to the medical personnel and aim to reduce the exposure time [50].

In case of pregnant women who underwent COVID-19 without requiring admission to hospital, ended their isolation and are considered convalescents, there is no indication to modify the prior plans for the delivery [49].

In the case of anesthesia, there are no contraindications for the use of epidural or spinal anesthesia in the case of COVID-19 infection. If general anesthesia is required during cesarean section, intubation is an infectious respiratory aerosol-generating procedure, which significantly increases the risk of medical personnel infection during surgery. However, there is no evidence indicating that aerosol particles would be generated by the inhalation of a mixture of nitrous oxide and oxygen (Entonox) [51].

There are discrepancies between the recommendations for umbilical cord clamping. Chinese guidelines, to reduce the risk of vertical transmission and to isolate the newborn from the infected mother as soon as possible, do not recommend delayed umbilical cord clamping [52]. The ISUOG (International Society of Ultrasound in Obstetrics and Gynecology) guidelines do not recommend umbilical cord clamping delay [53]. The RCOG guidelines take a different opinion, indicating that delayed umbilical cord clamping should be practiced, arguing that there is no significant increase in the risk of the infection transmission in the event of an additional minute of placental transfusion [49].

Regarding breastfeeding, Martins-Filho et al. reviewed the eight available publications regarding breastfeeding of 24 symptomatic women infected with COVID-19. Biological samples were taken immediately after delivery. Nasopharyngeal swabs in newborns and placental tissue samples showed negative results for the presence of SARS-CoV-2 in qRT-PCR. Also, all breastmilk samples of infected mothers were negative. However, given the small number of cases, these reports should be treated with extreme caution, because an additional significant risk factor for the infection of the newborn during breast-feeding is close contact between the woman and the child [54].

Due to the limited data, assessment of the risk of the transmission during lactation and determination whether standard pasteurization effectively eliminates the virus is not possible. In the cases of women suspected of infection, breastmilk should be drawn, pasteurized and, while following aseptic principles, can then be given to the newborn. Breastmilk of women with confirmed infection should be utilized. However, lactation should not be suppressed in infected women if there is no medical indication so that when there is no risk of infection, they can feed naturally.

As far as the latest guidelines and the experts' statement on COVID-19 infection is concerned, newborns should be

isolated from their mothers who have been infected until the risk of the infection stops [50]. There is no data available to determine the specific length of isolation and decisions about its end should be made individually as a result of discussions between the team of obstetricians and neonatologists [55].

RCOG in consultation with RCPCH (Royal College of Pediatrics and Child Health) advises against the routine separation of newborns from mothers with COVID-19 infection [49].

According to the Centers for Disease Control and Prevention (CDC), temporary separation of the newborn from the mother with suspected or confirmed COVID-19 should be considered to reduce the risk of transmission. The risks and benefits of temporary separation of mother and newborn should be discussed with the patient. Decisions regarding temporary separation should be made according to the wishes of the mother. If the mother decides to temporarily separate, to reduce the risk of spreading the virus and would like to breast-feed, she should obtain the breast milk with a breast pump. The obtained breast milk can be given to a newborn baby by a healthy caregiver.

If a mother with suspected or confirmed COVID-19 does not decide to be temporarily separated from the neonate in hospital, she should take precautions to avoid spreading the virus to the newborn, including proper hygiene and disinfection, keeping the right distance, using barrier protection equipment, using physical barriers, *e.g.* an incubator [56].

DISCUSSION

Pregnant women should use standard precautions, with emphasis on personal hygiene, frequent hand sanitizing, wearing face masks, and respect social distancing and isolation.

Emphasis should be placed on routine screening for COVID-19 infection in pregnant women. Studies carried out so far show that infection in this group is usually asymptomatic or mildly symptomatic and the screening strategy allows detection of infection cases in pregnant women. Although some of the asymptomatic pregnant women developed symptoms, the severity of the disease in pregnant women appears to be similar to the general population (mild — 86%; severe — 9.3%, critical — 4.7%).

Thanks to the strategy of universal screening of pregnant women, it is possible to identify a subgroup of asymptomatic women at the beginning or throughout the infection period, who have limited access to the tests. These women are currently an under-represented group in population studies [57].

Despite the constantly increasing number of publications on COVID-19 infection in pregnancy, we still do not have sufficient data to be able to draw unequivocal conclusions about the course of infection in pregnant women, effects on foetal development, maternal and neonatal outcomes, as well as vertical transmission.

Therefore, an immensely important issue is the need for systematic reporting of data on women affected by COVID-19 and the course of these pregnancies, considering the maternal and neonatal outcomes [26]. Over time, this will help to create the recommendations and guidelines that will ensure an adequate level of care for a patient affected by COVID-19 infection during pregnancy, delivery and postpartum period as well as improvement of the medical personnel protection.

Conflict of interest

None of the authors have direct or indirect conflict interest associated with publishing the article.

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VIA MEDICA

RECOMMENDATIONS

Ginekologia Polska
2020, vol. 91, no. 7, 424–427

ISSN 0017–0011

DOI: 10.5603/GP.a2020.0101

The Polish Society of Gynecologists and Obstetricians statement on surgery in gynecology during the COVID-19 pandemic

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ABSTRACT

The publication presents recommendations on the performance of surgical procedures in gynecology during the COVID-19 pandemic. The recommendations were prepared by the Polish Society of Gynecologists and Obstetricians, based on current knowledge of SARS CoV-2. These recommendations contain the latest guidelines of scientific societies related to the subject of operational procedures.

Key words: gynecology, surgery; SARS-CoV-2; COVID-19

Ginekologia Polska 2020; 91, 7: 424–427

OBJECTIVES

The purpose of these recommendations is to develop management in gynecological surgery during the Coronavirus disease 2019 (COVID-19) pandemic. The guidelines are based on the latest literature reports and the authors' experience.

INTRODUCTION

We have been witnessing the COVID-19 pandemic for several weeks. Considering the growing problem related to the preparation and surgical procedure in gynecology, the Polish Society of Gynecologists and Obstetricians has developed recommendations in the field of dealing with patients requiring emergency, urgent and elective surgery. The purpose of the publication is to collect and present the most current information on surgical procedures during the Severe acute respiratory syndrome coronavirus 2 (SARS CoV-2) pandemic. The recommendations are based on the authors' experience and contain the latest guidelines of scientific societies related to the subject of operational procedures like The American Association of Gynecologic Laparoscopists, The American College of Surgeons, The Society of American Gastrointestinal and Endoscopic Surgeons, The Society of American Gastrointestinal and Endoscopic Surgeons, The European Association for Endoscopic Surgeons, The Royal College of Surgeons of England, The Royal College of Surgeons of Edinburgh and The Royal College of Surgeons of Ireland, and The Spanish Association of Surgeon and The Society of Polish Surgeons. The authors reserve the right to update recommendations, according to the latest scientific reports and the development of a pandemic.

RECOMMENDATIONS

The Polish Society of Gynecologists and Obstetricians recommends the following:

1. A multi-specialist team should be responsible for making decisions and prioritizing patients' surgical treatment.
2. If a patient is qualified for surgery during the COVID-19 pandemic, the urgency of the surgical procedure should be determined. We recommend the modified

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Table 1. Suggestions for handling the scheduling of gynecological surgical cases during COVID19 pandemic [1]

Emergency surgeries — no delay
Ectopic pregnancy Spontaneous abortion Adnexal torsion Rupture of tubal-ovarian abscess Tubal-ovarian abscess not responding to conservative therapy Rupture of ovarian cysts not responding to conservative therapy Acute and severe vaginal bleeding Cesarean section Emergency cerclage of the cervix based on pelvic exam/USG findings
Surgeries that if significantly delayed could cause significant harm — urgent surgery
Cancer or Suspected cancer Cerclage of the cervix to prevent premature delivery based on history Legal pregnancy termination
Surgeries that could be delayed for a few weeks — elective surgery
Chorionic villus sampling/amniocentesis D&C with or without hysteroscopy for abnormal uterine bleeding when cancer is suspected Cervix and cervical canal biopsy if cytology suspected Cervical conization or LEEP to exclude cancer if p16/Ki-67 test positive Excision of precancerous or possible cancerous lesions of the vulva
Surgeries that can be delayed several months — elective surgery
Surgery for fibroids (when sarcoma is not suspected) Surgery for endometriosis, pelvic pain Surgery for adnexal masses (when are most likely benign) Surgery for pelvic floor prolapse Surgery for urinary and/or fecal incontinence Therapeutic D&C for abnormal uterine bleeding when cancer is not suspected Cervical conization or LEEP for high grade squamous intraepithelial lesions Infertility procedures Genital plastic surgery

D&C — dilation and curettage; LEEP — loop electrosurgical excision procedure; p16 — protein encoded by the cyclin-dependent kinase inhibitor 2A; Ki-67 — protein encoded by the *MKI67* gene

triage proposed by the American College of Surgeons "COVID 19: Elective Case Triage Guidelines for Surgical Care" — Table 1 [1].

3. We recommend dividing surgical procedures into three categories: emergency, urgent and elective. Below we present an algorithm for emergency, urgent (Fig. 1) and elective procedures (Fig. 2) [2–4].

Emergency procedure

Each patient should be considered potentially infected with SARS-CoV-2. We recommend conducting an epidemiological questionnaire with risk assessment, measuring body temperature, assessing typical symptoms of SARS-CoV-2 infection and performing a SARS-CoV-2 test. Reverse-transcriptase polymerase chain reaction (RT-PCR) is the gold standard. Before surgery, it is recommended to perform a SARS-CoV-2 test if the patient's condition allows waiting for the test result. Chest computer tomography (CT)/ /radiograph (X-Ray) and 3 quadrant lung ultrasonography (USG) may also be helpful to assess the risk of pneumonia. If it is necessary to perform a CT scan of the abdominal cavity, it is recommended to extend the test by a CT scan of the chest. In situations where conservative therapy is possible, it should be performed. The typical laboratory findings of COVID-19 patients should also be considered, such as normal leukocytes or mild leukopenia, decreased platelets and lymphocytes, elevated CRP, D-dimer, lactate dehydrogenase (LDH), serum ferritin and Interleukine 6 (IL-6) [5]. In all cases where epidemiological assessment is not possible, we recommend treating the patient as a positive SARS-CoV-2 result.

Urgent procedures

Each patient admitted to the ward must undergo a thorough epidemiological questionnaire with risk assessment, measuring body temperature and assessment of the most common symptoms of SARS-CoV-2 infection. Each patient requiring urgent surgery reports a CoV-2 test result or has a swab taken in the clinic no earlier than 2 days before admission. RT-PCR is the gold standard. Suspected or positive patients should be referred to hospitals dedicated to patients with SARS-CoV-2 (dedicated hospitals). Initial diagnostics should include a CT or X-Ray of the chest or alternatively 3 quadrant lung USG if CT scan not available. Procedures for oncological indications should be approved by multidisciplinary oncological consultations. In the absence of the possibility of using alternative treatment and threatening the progression of cancer, the patient should be qualified for surgical treatment.

Elective procedures

Each patient admitted to the ward must undergo a thorough epidemiological questionnaire with risk assessment, measuring body temperature and assessment of the most common symptoms of SARS-CoV-2 infection. Each patient requiring elective surgery reports a CoV-2 test result or has a swab taken at the outpatient clinic no earlier than 2 days before admission. RT-PCR is the gold standard. Keep in mind that RT-PCR may remain positive for as long as 6 weeks with SARS-CoV-2 infection. Pharyngeal virus shedding is highest during the first week of symptoms. Negative RT-PCR tests may result from improper sampling techniques, low viral load in area sampled and mutations in viral genome. However, due to the limited possibilities of performing RT-PCR testing, we allow the possibility of testing for antibodies if RT-PCR is not available. Antibody testing confirms

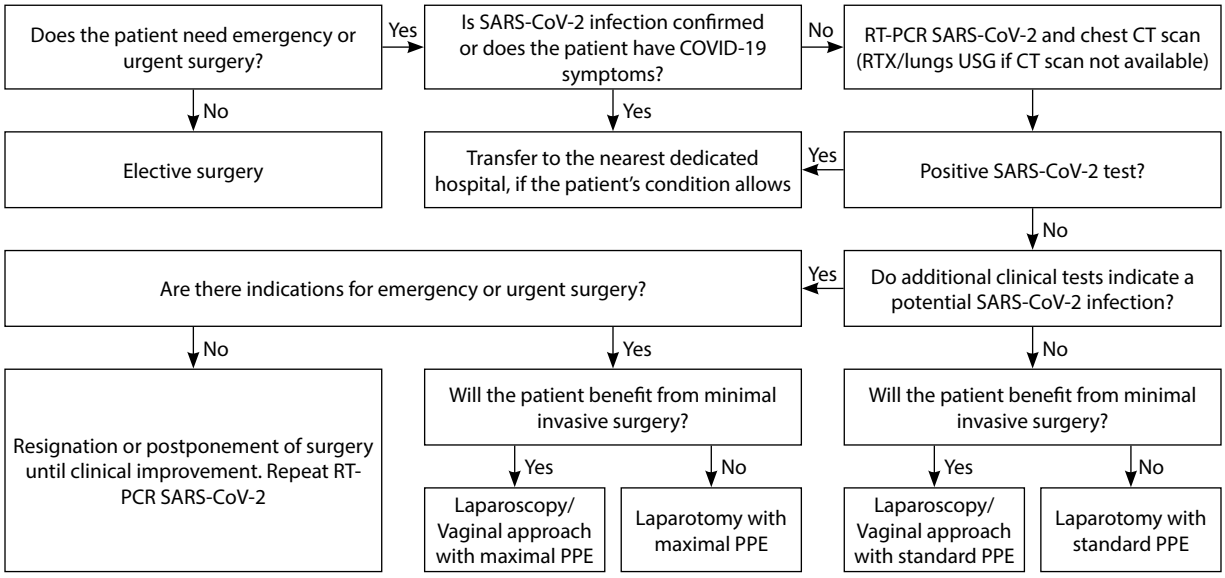

Figure 1. Algorithm for emergency and urgent gynecological procedures; PPE — Personal protective equipment; RT-PCR — reverse-transcriptase polymerase chain reaction; CT — computer tomography; USG — ultrasonography

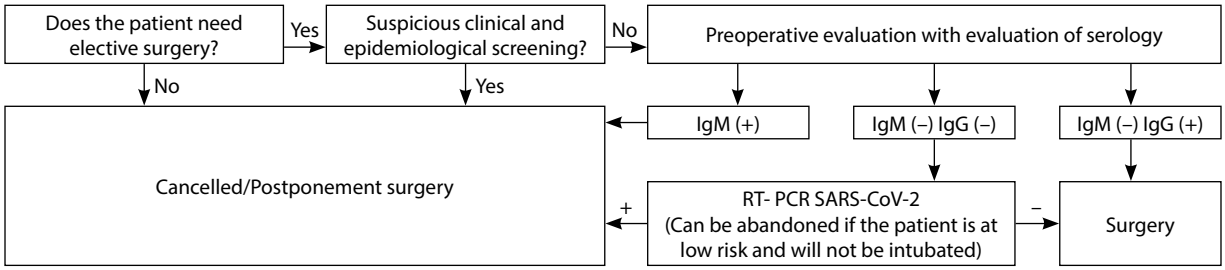

Figure 2. Algorithm for elective gynecological procedures; RT-PCR — reverse-transcriptase polymerase chain reaction; IgM — Immunoglobulin M; IgG — Immunoglobulin G

previous exposure and immunity to SARS-CoV-2 but may not be specific. Because of this, surgery should be delayed at least 14 days from positive antibody test or RT-PCR SARS-CoV-2 should be performed to validate no active infection [4, 6, 7].

Recommended personal protective equipment

In the current pandemic situation, there are three types of patients requiring surgical interventions:

1. Patient with confirmed SARS-CoV-2 infection or high suspected infection, referred and operated in dedicated hospitals.
2. Patients with suspected SARS-CoV-2 infection or with equivocal coronavirus testing.
3. Patients who are not suspected of having an infection or have a negative RT-PCR SARS-CoV-2 test or with positive IgG antibodies indicating a disease history.

In the first and second case, we recommend maximal personal protective equipment, which should include:

1. Surgical disposable mask and disposable head cap for patient
2. Filtering facepiece certified by the U.S. National Institute for Occupational Safety and Health (N95)/ Filtering facepiece certified by European Union — EN 149 standard (FFP3) mask (FFP2 if there is no FFP3 mask)
3. Surgical mask
4. Protective goggles and visors
5. Disposable head caps
6. Waterproof disposable overall
7. Waterproof barrier coat
8. Disposable three pairs of nitrile gloves
9. Disposable long shoe covers

For patients with low risk or with negative RT-PCR SARS-CoV-2 swab or with immunologically confirmed recovery from COVID-19, we recommend standard personal protective equipment, which should include:

1. Surgical disposable mask and disposable head cap for patient

2. Surgical mask
3. Protective goggles or visors
4. Disposable head caps
5. Waterproof barrier coat
6. Disposable pair of nitrile gloves
7. Disposable shoe covers

In addition, participation in surgeries should be limited only to personnel essential to the safe performance of the surgery in order to avoid exposure and preserve PPE resources [8, 9].

Surgical approach

The available literature lacks conclusive evidence for SARS-CoV-2 transmission through an abdominal route from patients to the operating theatre. The main problem is the aerosolization of particles during electrosurgery and the use of ultrasound devices during laparotomy and transvaginal surgery. It is important to be aware of the risks and be able to deal with them. It should be emphasized that the decision on the use of a particular technique should be made individually in relation to the patient, the disease and the gynecologist's experience. However, according to publications, minimally invasive surgery (vaginal and laparoscopic access) is associated with lower mortality, shorter hospitalization and lower hospital costs. Laparoscopy allows for faster discharge from hospitals and less dealing with surgical wounds and surgical site infections and can reduce the aerosol spread in relation to open surgery. [2, 8–10]. It should also be emphasized that transvaginal surgery under regional anesthesia is appropriate to avoid aerosol-generating intubation and extubation. [11, 12].

Laparoscopy/robot-assisted approach

The following procedures should be followed during laparoscopic and robot-assisted surgeries:

1. Pre-operative examination of laparoscopic equipment
2. Set up electrosurgical and ultrasonic devices to minimize production of plume
3. If available, use closed smoke evacuation/filtration system with ultra low particulate air filtration (ULPA) capability
4. Use laparoscopic suction to remove surgical plume and desufflate the abdominal cavity
5. Pneumoperitoneum loss into the theatre is prohibited
6. Use low intra-abdominal pressure 8–11 mmHg
7. Avoid rapid desufflation or loss of pneumoperitoneum
8. Tissue extraction should be performed with minimal CO2 loss
9. Minimize blood/fluid droplet spray or spread
10. Minimize leakage of CO2 from trocars [11–13]

Vaginal/laparotomic approach

The following procedures should be followed during vaginal surgeries:

1. Dissection and vascular control using non-electrosurgical techniques where possible
2. Set up electrosurgical and ultrasonic devices to minimize production of plume
3. Monopolar devices are preferred
4. If available, use smoke evacuation/filtration system with ULPA capability
5. Use a suction device to remove any surgical plume as it is produced
6. Minimize blood/fluid droplet spray or spread
7. Stoma formation rather than anastomosis to reduce post-operative critical care for complications [11–13]

SUMMARY

These recommendations standardize and summarize publications on women's surgery during the SARS-CoV-2 pandemic. The authors are aware that coronavirus situation is very dynamic and unpredictable, which is why we plan to update our remarks in the near future, along with the latest scientific data on pandemic.

Conflict of interest

The authors declare that there is no conflict of interest in the presented recommendations.

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VIA MEDICA

RECOMMENDATIONS

Ginekologia Polska
2020, vol. 91, no. 7, 428–431

ISSN 0017–0011

DOI: 10.5603/GP.2020.0103

Possible deferral of diagnostic and therapeutic procedures for patients with abnormal screening tests results in cervical cancer secondary prevention in current SARS-CoV-2 pandemic Interim guidelines of the Polish Society of Gynecologists and Obstetricians and the Polish Society of Colposcopy and Cervical Pathophysiology

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ABSTRACT

The Polish Society of Gynecologists and Obstetricians and Polish Society of Colposcopy and Cervical Pathophysiology Interim Guidelines goal at aiding gynecologists in providing a cervical cancer prevention care during the evolving SARS-CoV-2 pandemic. Presented guidelines were developed on a review of limited data and updated when new relevant publications were revealed. Timing for deferrals of diagnostic-therapeutic procedures were mostly covered in the guidelines. Also, a support for the existing Polish recommendations on abnormal screening results in a subject of minor and major screening abnormalities terminology were given. The guidelines are obligatory for the specified COVID-19 pandemic period only and they might be changed depending on the new available evidence.

Key words: cervical cancer prevention; abnormal screening results; HPV testing; cervical cytology; selfsampling; SARS-CoV-2 pandemic; guidelines

Ginekologia Polska 2020; 91, 7: 428–431

Update: 2. May 2020

The recommendations present current management that can be modified and changed in justified cases, after careful analysis of a given clinical situation, which in the future may constitute grounds for their modification and updating. Interim guidelines are obligatory for specified period only.

INTRODUCTION

The current national epidemiological situation rapidly changed due to the SARS-CoV-2 pandemic and a public health threat has arisen [1, 2]. The clinical management and diagnostic-therapeutic procedures performed so far in the secondary cervical cancer prevention in Poland need to be revisited to avoid the unnecessary virus spreading. The temporary guidelines for the pandemics time have been already introduced by some countries [3] for the patients' management with abnormal screening tests results. Understanding the pandemic period restrictions, Polish interim guidelines for deferral of all non-essential medical office

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Table. 1. Recommended management during the SARS-CoV-2 pandemic in women with the minor cervical cancer screening abnormalities. The different screening models were given

Model of screening and detected minor screening abnormalities	Recommended management*
Primary cytology	1. Deferral of diagnostic tests up to 6-12 months or 2. Continuation of screening that do not require leaving the place of residence with the use of previously sampled liquid-based cytologic material (if applicable)
ASC-US or LSIL	
ASC-US or LSIL followed by negative HRHPV testing	
ASC-US or LSIL followed by negative p16/Ki67 test	
ASC-US or LSIL followed by positive HRHPV N16/N18 and negative p16/Ki67 testing	
Primary co-testing	
ASC-US or LSIL HRHPV-negative	
ASC-US or LSIL HRHPV N16/N18-positive	

ASC-US — atypical squamous cells of undetermined significance; LSIL — low-grade squamous intraepithelial lesion; HRHPV — high-risk human papillomavirus type
*In individual cases the management might be modified depending on a clinical- and a patient-related status and/or depending on changes in a present healthcare environment

appointments and elective procedures in the secondary cervical cancer screening have been developed, pursuant to the President of the Polish Society of Gynecologists and Obstetricians (PTGiP) statement of the 20th of March 2020, and the joint recommendations of the Polish national consultants in obstetrics and gynecology together with the national consultants in perinatology of the 19th of March 2020 [4, 5]. Guidelines for possible deferral of diagnostic and therapeutic procedures in cervical cancer prophylaxis are obligatory for the specified COVID-19 pandemic period only.

RECOMMENDATIONS

The Interim guidelines are supplementary to the existing Polish recommendations [6–8] for the secondary cervical cancer prevention in the subject of a terminology for minor and major screening abnormalities.

Minor screening abnormalities — a definition and the recommended management

Minor screening abnormalities in the pre-colposcopic stage encompass the following screening test results:

- in the primary cytology-based model the following results:
  - ASC-US,
  - LSIL,
  - ASC-US or LSIL followed by negative HRHPV test,
  - ASC-US or LSIL followed by negative p16/Ki67 test,
  - ASC-US or LSIL followed by positive HRHPV type non-16/non-18 and negative p16/Ki67 test;
- in the primary cotesting-based model the following results:
  - ASC-US or LSIL HRHPV-negative,
  - ASC-US or LSIL HRHPV types non-16/non-18-positive.

Patients with minor cervical cancer screening abnormalities may have deferred of diagnostic tests up to 6–12 months [3].

The following management in the secondary cervical cancer prevention in women with abnormal minor screening tests results during the SARS-CoV-2 pandemic period is recommended (Tab. 1).

Continuation of previously started screening that do not require leaving the place of residence is recommended, especially with the use of the liquid-based preparation systems. This concerns molecular testing for the high-risk HPV (HRHPV) and immunocytochemical p16/Ki67 testing in a case of ASC-US or LSIL cytology result [6–8].

HRHPV selfsampling at home is recommended if a primary molecular testing is required, or if a reflex testing is required in case of an ASC-US or LSIL abnormal cytology result [9].

Major Screening Abnormalities – a definition and the recommended management

Major screening abnormalities in the pre-colposcopic stage encompass the following screening test results:

- in the primary cytology-based model the following results:
  - ASC-H,
  - HSIL,
  - ASC-US or LSIL followed by positive HRHPV type 16 and/or 18,
  - ASC-US or LSIL followed by positive p16/Ki67 test;
- in the primary cotesting-based model the following results:
  - HRHPV type 16 and/or 18 positive,
  - ASC-H, HSIL and AGC cytology results, regardless the HPV status;
- in the primary HRHPV-based selfsampling model - HRHPV type 16 and/or 18 positive. For HRHPV types non-16/non-18 positive results obtained in selfsampling a management algorithm depends on clinical situation and screening history.

Patients with major cervical cancer screening abnormalities may have deferred of diagnostic tests and treatment maximum up to 3 months [3].

Table. 2. Recommended management during the SARS-CoV-2 pandemic in women with the major cervical cancer screening abnormalities. The different screening models were given

Model of screening and detected major screening abnormalities	Recommended management*
Primary cytology	Deferral of diagnostic tests or treatment maximum up to 3 months
ASC-H or HSIL	
ASC-US or LSIL followed by positive HRHPV 16 and/or 18	
ASC-US or LSIL followed by positive p16/Ki67	
Primary co-testing	
Positive HRHPV 16 and/or 18	
ASC-H, HSIL, AGC regardless HRHPV status	

ASC-US — atypical squamous cells of undetermined significance; LSIL — low-grade squamous intraepithelial lesion; ASC-H — atypical squamous cells cannot exclude HSIL; HSIL — high-grade squamous intraepithelial lesion; AGC — atypical glandular cells; HRHPV — high-risk human papillomavirus type
*In individual cases the management might be modified depending on a clinical- and a patient-related status and/or depending on changes in a present healthcare environment

The following management in the secondary cervical cancer prevention in women with abnormal major screening tests results during the SARS-CoV-2 pandemic period is recommended (Tab. 2).

Histologic HSIL treatment

Specific guidelines of the gynecological societies adapted for the COVID-19 pandemic vary worldwide in the framework of histologic HSIL priority treatment [10, 11] and available data and evidence are limited. The conization due to histologic HSIL is considered by the European Society of Medical Oncology as a low-priority medical procedure while including an oncologic cervical cancer treatment of all clinical stages [10]. At the end of April, the joint American statement (of the eight gynecological and non-gynecological societies) was revealed in which authors took into account an epidemiological situation in a post-peak infectious curve when the risk of SARS-CoV-2 infection will be diminished and 'a normal new' will appear. In that document for benign gynecological indications on re-introduction of hospital and office-based procedures for the practicing gynecologists the CIN2 or CIN3 (HSIL) treatment was incorporated as an elective surgery of high acuity [12, 13]. Therefore, Polish interim guidelines suggest in the decision-making that a prioritization of patients should be established after a careful analysis of a clinical status and a patient-related situation, and also should be modified according with the dynamically changing national healthcare environment related to COVID-19.

Invasive cervical disease

In patients with suspected invasive cervical disease the recommendations for a clinical management remain unchanged.

SUMMARY

The above Polish interim guidelines for a possible deferral of diagnostic and therapeutic procedures for patients with abnormal screening tests results in cervical cancer secondary prevention in current SARS-CoV-2 pandemic present not the final management to proceed the patients with abnormal screening test results in the secondary cervical cancer prevention. They do not replace a full clinical assessment of each individual case. The guidelines should always be considered in the context of the patient's health interest. They may change depending on new available data.

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VIA MEDICA

RECOMMENDATIONS

Ginekologia Polska
2020, vol. 91, no. 7, 432–437

ISSN 0017–0011

DOI: 10.5603/GP.2020.0104

Polish Society of Gynecologists and Obstetricians recommendation on the use of antiseptics for treatment of inflammatory vaginitis

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Undertook the analysis of literature, specialist knowledge and clinical experience on treatment options for non-specific vaginal inflammations of bacterial, fungal, mixed and unknown aetiology.

The recommendation presents the current state of knowledge on this subject on the day of the published analysis. However, the expert group reserves the right to update this position in the event of new and significant scientific reports.

INTRODUCTION

Research on the vaginal ecosystem dates back to the nineteenth century and is associated with Döderlein's description of the role and significance of lactobacilli. These gram-positive bacteria were then assigned the role of maintaining normal vaginal secretions. Further studies have shown that other aerobic and anaerobic bacteria are also present in the vagina and form the vaginal ecosystem. This physiological bacterial flora of the vagina creates a sophisticated and closed ecosystem. It can change depending on woman's age, her hormonal status, especially estrogen, sexual activity, performed vaginal procedures, drugs and exposure of vaginal mucosa to external substances [1].

Changes in the quantitative and qualitative ratio of the vaginal bacterial flora, in the absence of an infective factor, were previously called Non-specific Vaginitis (NSV) and are now referred to as Bacterial Vaginosis (BV).

Bacterial vaginosis (BV) means changes in vaginal bacterial flora. It consists of the reduction of lactobacillus producing hydrogen peroxide and an increase of other microorganisms. These include Gram-negative bacteria *(Gardnerella Vulgaris, Prevotella sp., Atopobium vaginae, Porphiromonas spp., Mobiluncus spp., Bacteroides spp.* and many other) that thrive in the anaerobic environment.

Expansion of Gardnerella colonies leads to the formation of a biofilm rich in proteolytic enzymes on the surface of epithelial cells, which causes exfoliation of the epithelium creating colonisation sites for other anaerobes [1, 2].

Vaginal ecosystem changes observed in BV also predispose to HSV-2, Trichomonas vaginalis, Neisseria gonorrhoeae and Chlamydia trachomatis superinfections. The risk of HIV infection and transmission increases. Also, chronic BV is conducive to the survival of HPV infection, and patients have a higher risk of being diagnosed with abnormal cells in a cytological examination, and thus, under certain favourable conditions, a higher risk of developing CIN. Untreated BV predisposes to more frequent infections of the upper floors of the genital organ like the endometrium and appendages, including fallopian tubes. In pregnant women, BV is a risk factor for spontaneous miscarriage or premature delivery [2].

Imbalance in the composition of the vaginal bacterial flora, decreased number of *Lactobacillus species (Lactobacillus acidophilus L. jensenii, L. brevies, L. Plantarum L. crispatus, L. casei, L. fermentum, L. Gasperi*) leads to a change in the vaginal pH and the possibility of various type of ailment, including pathological and symptomatic excessive vaginal discharge.

The dominant symptoms of BV are discharge, often with a different colour and smell, discomfort, burning, itching, mucosal oedema, and dyspareunia. The clinical picture of vaginal infections and biochemical changes depends on whether the infection results from aerobic, anaerobic bacteria or fungal origin. Vaginal flora abundant for *Lactobcilus*

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bacteria results in vaginal pH increase above 6 and an increase of pro-inflammatory cytokines.

Differences in the composition of various elements of the human microbiome can lead to functional disorders, which may include the genital organs. The microbiome has a protective function by competing for nutrients and points of adhesion. It can also change with age. The bacterial flora composition can vary depending on the stage of life and hormonal status. Vaginal microbiome disorders may occur under the influence of antibiotic therapy, during menopause, during pregnancy, due to increased exposure to microorganisms, the use of hormonal drugs, and immunosuppression.

Disorders of the vaginal bacterial flora that change the pH of secretions can present with little or no symptoms. In these situations, the measurement of vaginal pH is of diagnostic importance for early asymptomatic, non-specific vaginal inflammation. Abnormal pH should prompt the clinician to implement optimal early therapeutic management.

Based on the aetiology, non-specific vaginal infections can be bacterial and non-bacterial.

The most commonly diagnosed bacterial infections are BV — (20% to more than 60%, depending on the source), followed by Candida-type infections (17%–39%) and infections caused by Trichomonas (4%–30%). Approximately every woman, at least once in her life, has a bacterial or fungal infection of the vagina [1, 2].

The second group of infections is fungal inflammation, with the most common form being candidiasis. Infections with other types of fungi occur less often. Candida infections are diagnosed based on the symptoms of vaginitis and vulva in the presence of the microorganisms mentioned above. In the case of fungal infections, Candida albicans accounts for 80% to 92% of vaginal and vulvar mycoses.

Diabetes, antibiotic therapy and immunosuppression are predisposing factors for the rapid growth of yeast colonies [1].

Factors that cause vaginal infection and subsequent symptomatic inflammation may also have a mixed aetiology: bacterial-fungal.

Bacteriological smears or cultures are not always available for diagnosis or require time to obtain a result. **Therefore, the introduction of treatment before obtaining culture results is justified for antiseptic drugs. Effectiveness of these drugs is described in numerous reports [3, 4].**

In postmenopausal women, due to a decrease in estrogen levels, atrophic genital lesions are common, which are the primary cause of developing non-specific vaginal inflammation.

Menopausal sex hormone deficiency causes an increase in vaginal pH and disappearance of physiological bacterial flora, which consequently increases the susceptibility to infections, mainly caused by bacteria migrating from the vulva and anal area (*Streptococcus sp., Enterococcus sp., E. coli*). Vaginal swabs have a higher incidence of severe leukocytic reactions and poor exfoliation of epithelial cells. The decrease in the physiological vaginal flora coexists with the appearance of numerous pathogens.

In postmenopausal women, Gram-positive cocci are 2.5 times more common than before menopause. *Staphylococcus aureus* strains are isolated in bacterial cultures (5 times more often than before menopause), *Corynebacterium sp.,* (3 times more often), *Streptococcus agalactiae* and *Enterococcus faecalis* (2 times more often), *E. coli* (2 times more often), and also *K. pneumoniae, P. mirabilis, C. freundii,* not seen before menopause. Due to lack of glycogen and increased pH in the genital tract, strains of Candida albicans occur less frequently than in the group of premenopausal women [5].

Among the etiological factors of inflammatory vaginosis in women of childbearing age, bacterial aetiology remains the first, although a significant increase in the percentage of fungal infections has been observed in recent years. In turn, 1/3 of vaginitis in postmenopausal women has a bacterial, fungal or trichomoniasis aetiology. The remaining 2/3 consist of vaginal atrophy, allergic factors, dermatological causes, and general diseases [5].

The standard of management in women with decreased estrogen levels is the elimination of inflammation. In the second stage by local estrogenization, the vaginal epithelium is restored. A similar effect is obtained by using laser vaginal revitalisation. This method seems to have particular application in women with contraindications for estrogen use [6, 7].

The current recommendations of the Center for Disease Control and Prevention (CDC) on the treatment of BV include treatment with antibiotics and chemotherapeutic agents (clindamycin, metronidazole, tinidazole) used orally or vaginally. These methods of treatment are associated with a reasonably good prognosis in terms of short-term treatment rates, and unfortunately, in the long run, they do not prevent recurrence of BV in half of the cases.

The increasing resistance to antibiotics often used excessively in various forms of vaginitis, increasingly hinders the effectiveness of this therapy. Low efficacy of antibiotics has lead to limiting their use and replacing with antiseptics as the first-line treatment

It has been proven that the use of typical BV treatment with antibiotics and chemotherapeutic agents such as clindamycin and metronidazole, due to the increasingly occurring drug resistance, can be ineffective. In one study evaluating the effect of the above treatment on 30 bacterial strains grown in BV, it was shown that all strains tested were resistant to metronidazole and tinidazole, and 67% were also resistant to clindamycin [8].

The same is true for fungal infections. Due to the development of resistance to fluconazole by Candida, new therapeutic options are becoming necessary [9]. Also, new information on the structure and function of vaginal colonisation helps explain why antibiotic treatment has only limited use in infections involving microbial biofilms. The low effectiveness of antibiotics in preventing relapses is caused by the inability to eliminate bacteria associated with the vaginal biofilm, which is only temporarily suppressed, and quickly recovers its activity after stopping treatment. Besides, in the case of bacterial inflammatory vaginosis (BV), antibiotic treatment is often limited by the patient's general condition, and side effects associated with systemic administration may occur.

Therefore, in BV cases it is necessary to consider the forms of treatment known before the antibiotic era, but in a new technological edition using the achievements of modern pharmaceutical technologies, i.e. the use of vaginal antiseptics [2, 10].

Modern antiseptics are an alternative to antibiotic treatment, provided they combine a broad antimicrobial spectrum with low toxicity and high tissue biocompatibility. Topical antiseptics should now be the first choice in the treatment of local microbial vaginal infections.

Therefore, new antimicrobial agents that will act in a targeted manner without drug resistance and elimination of biofilm should dominate BV treatment as a first-line approach.

A full arsenal of vaginal products is available. They are tested for efficacy and safety in the treatment of non-specific inflammation of the vagina: BV, candidiasis or viral infections.

They include:

— Polyhexamethylene biguanide (poliheksanid, PHMB) [2, 11–28],
— Dequaline chloride [2, 5, 19, 20, 25, 29, 31, 32],
— Povidone iodine [33, 34],
— Sliver ions [26, 30, 35–40],
— Boric acid [41–45],
— Chlorhexidine [46–48],
— Lactic acid bacteria with or without estriol [49, 50].

BRIEF DESCRIPTION OF AVAILABLE ANTISEPTIC COMPOUNDS USED IN THE TREATMENT OF INFLAMMATORY VAGINOSIS OF VARIOUS ETIOLOGIES

Polyhexamethylene biguanide (poliheksanid, PHMB)

Polyhexanide is an antiseptic with a broad spectrum of antimicrobial activity, including Gram-positive and Gram-negative bacteria, including MRSA, VRE, *Escherichia coli, Pseudomonas aeruginosa*, HPV, HSV-1, HIV viruses fungi (Candida albicans and others), protozoa causing keratitis (Acanthamoeba) [2, 11–13].

PHMB has three mechanisms of action:

— blocks adhesion of microorganisms to surfaces [11, 14, 15],
— increases the liquidity and permeability of the bacterial cell membrane, which leads to a loss of its integrity and ultimately to cell death [11, 16–19],
— inhibits the metabolism of bacterial cells, has a higher efficiency in an environment with pathologically elevated pH, and effectively prevents the re-emergence of biofilm [11, 19-22].

PHMB does not generate bacterial resistance and reduces the number of bacteria.

PHMB has Lactobacillus spp. sparring effects due to differences in cell- wall binding [23].

Polyhexanide (PHMB) has good efficacy and safety in the topical application in the treatment of non-specific vaginal infections of bacterial, fungal, viral and mixed aetiology as well as perioperative prophylaxis before vaginal procedures [24]. No adverse effects were found even with prolonged use, and the frequency of allergies is low [25, 26].

There are preliminary reports of the effectiveness of the treatment in doubtful cases and a small degree of cytological abnormalities in combination with an existing HPV infection. The above statements are very promising and may form the basis for further research in this direction [27].

PHMB summary

1. When used vaginally, PHMB has no inhibitory effects on Lactobacillus spp. growth [23].
2. The effectiveness of treatment without bacterial resistance and the elimination of biofilm [2, 20].
3. Good tolerability with a small number of side effects even with prolonged use, low rate of allergic reactions [25, 26].
4. There is no convincing evidence of safety in pregnancy [28].

Dequalinium chloride

Dequalinium chloride as a quinoline derivative with a broad spectrum of biological activity, including antibacterial activity. It is used to treat vaginitis of bacterial, fungal, mixed and unknown aetiology [5].

It shows a broad spectrum of antibacterial activity against aerobic Gram-positive bacteria (*Enterococcus faecalis Lactobacillus spp., Staphylococcus aureus, Streptococcus agalactiae, Streptococcus pyogenes*), Gram-negative (*Enterobacter spp., Escherichia coli, Klebsiella spp. Spp.)*, anaerobic bacteria (*Bacteroides spp., Fusobacteria, Gardnerella vaginalis, Prevotella spp., Peptostreptococci, Poryphyromonas spp.*) [19, 20, 29].

Clinical studies report its use in the treatment of vaginal inflammation in pregnant women (in all trimesters) and during lactation [2, 25].

This compound shows activity between 24 and 72 hours after the first dose.

Treatment usually lasts about six days.

Summary — dequaline chloride

1. Efficacy in the treatment of BV.
2. Good tolerance - side effects occur at a frequency of 7.8% and may include mainly vaginal candidiasis, vaginal discharge, vulva and vaginal itching, and burning sensation within the vulva and vagina [29, 31, 32].
3. Due to the chemical nature of the substance - a quaternary ammonium compound, anionic substances such as soaps, detergents and surfactants, may additionally weaken the antibacterial effect of dequalinium chloride. Therefore, concomitant use of soaps, spermicides or irrigation is not recommended [29, 31, 32].
4. The manufacturer declares the possibility of use in pregnant women (in all trimesters) and during lactation [29].
5. It is contraindicated in cases of ulceration of the vaginal epithelium and vaginal part of the cervix, and in girls who have not yet started menstruation, i.e. have not reached [29, 31].

Povidone-iodine

Iodopovidone (povidone-iodine) is characterised by a broad spectrum of action against Gram-positive bacteria, including strains of *Lactobacillus spp.*, and Gram-negative bacteria, bacterial spores, viruses, protozoa, as well as fungi and yeast [33].

The main application according to Kramer's study is the use in disinfection of the surgical field, puncture sites, puncture, catheterisation, blood collection and as an active agent for short-term disinfectant use [34].

In the form of vaginal globules, it can be used in various types of vaginal inflammation, especially in bacterial vaginitis caused by Gardnerella vaginalis or infections by vaginal trichomes (*Trichomonas vaginalis*) [33]. It is used in the prevention of infections before surgical and diagnostic procedures within the vagina.

Due to the risk of thyroid dysfunction, povidone-iodine, in all forms of use, has additional restrictions, i.e.

— it should not be used for more than seven days,
— use before and after radioiodine treatment is contraindicated,
— combined use with octenidine and/or silver in the form of vaginal globules is contraindicated.

Summary — povidone-iodine

1. One-time preparation of the operating field — rinsing the vagina before the vaginal procedure.
2. Preparation of the vagina before vaginal surgery in the form of vaginal globules.

Silver ions

The antiseptic mechanism of silver ions is to inhibit cell division, damage the bacterial cell membrane, disruption transport in the cell, which leads to its death. Silver, as a local antiseptic, has a different mechanism of action from antibiotics and multidirectional effect on a bacterial cell, which means that the likelihood of developing resistance to silver is very low [35, 36].

The creation of TIAB silver, i.e. titanium dioxide particles on which active nanoparticles of Ag + silver ions have been deposited, in combination with benzalkonium chloride, has allowed an increase in antimicrobial and antiviral activity. The TIAB molecule is characterised by increased stability compared to other antiseptics based on silver compounds [30, 37].

Silver in the TIAB molecule is effective against such microorganisms as: *Staphylococcus aureus, Escherichia coli, Pseudomonas aeruginosa, Acinetobacter baumannii, Klebsiella pneumoniae, Neisseria gonorrhoeae, Enterococcus faecalis, Listeria monocytosis, Streptomidisis, Gardneidcus) Chlamydia trachomatis.* Besides, the spectrum of this form of silver also includes pathogens characterised by high antibiotic resistance, including staphylococci (MRSA) and vancomycin-resistant enterococci (VRE) and **prevents the formation of bacterial biofilm.**

Compounds containing the TIAB silver complex may also be recommended for patients with an abnormal low-grade cytological test or a low-grade ASC-US and L-SIL lesion. The mixture is useful in the treatment of inflammation and abnormal cytological smears [26, 38].

This compound is also characterised by high activity against yeast-like fungi: *Candida albicans, Candida glabrata* and mould — *Aspergillus niger*.

It has also been shown that it helps combat viral infection by showing antiviral activity, among others influenza (A / H1N1), polio, cytomegalovirus, smallpox, herpes zoster, HIV, HSV-1, HSV-2, hepatitis A, B, E, rubella, adenoviruses, herpes, mumps, enteroviruses, rhinoviruses, astroviruses or coronaviruses [37, 39, 40].

There are preliminary reports on the beneficial effects of silver compounds in the treatment of HPV infection. This requires further evaluation and validation of prospective studies involving a more significant number of people [26].

Summary — silver ions

1. Effectiveness in the treatment of bacterial infections, including those characterised by antibiotic resistance, including Staphylococcus (MRSA) and vancomycin-resistant enterococci (VRE).
2. A broad spectrum of anti-inflammatory properties including antifungal activity.
3. Possibility of use in II/III trimester of pregnancy.
4. Good tolerance and safety when applied locally.

Boric acid

Boric acid (Boric acid borax, orthoboric acid) - an inorganic chemical compound in the form of a weak acid

(Acidum boricum). In nature, it can be found in some plants, in sea salts and minerals (e.g. in sassoline) [41].

The mechanism of bactericidal and fungistatic activity of boric acid is not fully understood. The bactericidal and fungistatic effect of boric acid is believed to be through penetration through the cell wall, and damage to the cell membrane of fungi [42].

The effectiveness of boric acid in the treatment of vaginal infections caused by Candida albicans has been proven [43] Boric acid products are also drugs of choice in the treatment of acute and recurrent fungal vaginitis and vulva caused by fungal species other than Candida albicans [44, 45].

Due to its unique drying, astringent and antiseptic properties, and low per cent solution, it is used as a disinfectant and to promote granulation in wound healing.

Boric acid in the form of vaginal globules is useful especially in the treatment of vaginitis caused by infection with *C.glabrata and C.krusei.*

Summary — boric acid

1. Maintenance therapy of especially fungal vaginosis and recurrent infections
2. Prophylaxis of BV in patients with risk factors, especially during antibiotic therapy and hypoestrogenism.

Chlorhexidine

Chlorhexidine is a substance that has antibacterial activity. It damages the cell membrane of bacteria, which in turn leads to an increase in its permeability and cell breakdown.

Chlorhexidine has a strong bactericidal effect on Gram-positive bacteria, and less strongly on Gram-negative bacteria [46, 47].

Chlorhexidine resistance is observed for some pathogens such as methicillin-resistant *S. aureus,* as well as *P. aeruginosa* and *A. Baumannie*. In the treatment of bacterial vaginosis, chlorhexidine can be used vaginally.

Compared to standard therapies, topical treatment of bacterial vaginosis with chlorhexidine is characterszed by a low frequency of side effects [48].

Summary — chlorhexadin

1. Efficacy in the treatment of BV.
2. Element of prevention and supportive therapy before and after gyanecological surgical procedures.

Lactic acid bacteria with or without estriol

The administration of lactobacilli is intended to restore the physiological bacterial flora after topical or systemic treatment with anti-infectious agents or chemotherapeutic agents.

The combination of administration of the above lactobacilli with estriol increases the regenerative effect on the vagina, especially on its atrophic inflammation in the period of menopause and supportive therapy in menopausal hormone therapy (HTM).

The mechanism of action is based on strengthening the vaginal ecosystem after anti-infectious treatment by exogenous use of live lactic acid bacteria. There is no evidence of an adverse effect on the pregnancy or the condition of the fetus/newborn. Lactobacilli can be used in pregnancy, while a compound containing a combination of Lactobacillus acidophilus and estriol can be used during pregnancy with more significant benefit for the patient than the risk related to estrogen activity [49].

Summary — lactic acid bacteria with or without estriol

1. Used in the second stage of anti-inflammatory treatment as maintenance therapy.
2. To support that development of physiological vaginal flora in recurrent inflammation after treatment with other compounds, especially in the presence of vaginal atrophy [50].
3. Good tolerance.

FINAL CONCLUSION

The treatment of vaginal infections with non-antibiotic compounds is an effective method, especially in the case of BV, and can be successfully used as a first-line treatment instead of antibiotic therapy carrying possible complications and the risk of antibiotic resistance.

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