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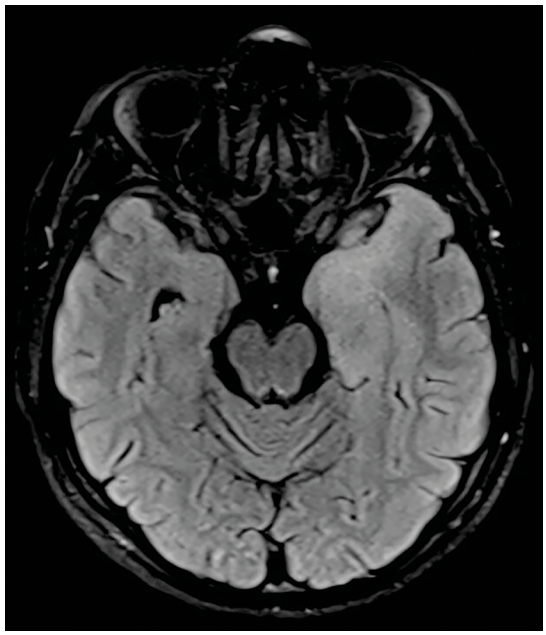

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CONTENTS

VIA MEDICA

RECOMMENDATIONS

CLINICAL VIGNETTES

VIA MEDICA

ORIGINAL PAPER / GYNECOLOGY

Ginekologia Polska
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Collagen and elastin differences in vulvar tissue of women with lichen planus, lichen sclerosus and healthy women

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ABSTRACT

Objectives: Lichen sclerosus and lichen planus are two debilitating dermatoses. Their etiology remains unknown. Skin changes resulting from these disorders are important to understand, so we can provide targeted treatment to patients.

We examined the differences in collagen (*COL1A1, COL1A2, COL3A1, COL5A1, COL5A2, COL5A3*) and elastin (*ELN*) expression between vulvar tissue of women with lichen planus, lichen sclerosus and healthy women.

Material and methods: Vulvar tissue was taken from areas affected by lichen planus or lichen sclerosus. In healthy controls, we biopsied vulva at five and eight o'clock in a standardized manner. The tissue was simultaneously sent for pathological and genetic analysis. When either lichen planus or sclerosus or healthy tissue was confirmed by pathologist, we processed the genetic sample. RNA was isolated, transcribed and gene expression was analyzed using Real Time Custom Panel 96-16 and LightCycler 480 Probe Master. Kolmogorov-Smirnov test was employed to determine if the data on the population show normal distribution. For genes with normal distribution, t-Test was employed and for those lacking normality, we used Mann-Whitney 1-tail test. The threshold for p value was set less than 0.05.

Results: Thirty-nine vulvar samples were examined. The mean expression of *COL1A1* was 11.13, *COL1A2* was 6.72, *COL3A1* was 8.43, *COL5A1* was 11.91, *COL5A2* was 10.62 and *COL5A3* was 12.79. The mean expression of elastin (*ELN*) was 13,13. We found statistically significant difference in expression of collagen (*COL1A2)* and elastin (*ELN)* between healthy controls and patients with lichen planus ($p = 0.4$). We did not find differences for other genes ($p < 0.05$).

Conclusions: Collagen and elastin are differentially expressed between patients with lichen planus and healthy controls.

Keywords: collagen; elastin; lichen sclerosus; lichen planus; vulva

Ginekologia Polska 2024; 95, 3: 171–174

INTRODUCTION

Collagen, as a main component of the extracellular matrix, remains the most widespread protein in the human body. Its distinguishing feature is the presence of a long triple-helical domain. Twenty-eight types of collagens have been identified. The amount of triple helical component may vary from as little as under 10% of the whole collagen structure in collagen type XII to as much as 96% in collagen type I. Apart from forming supramolecular assemblies in the extracellular matrix, some collagens exist in a soluble form [1].

Elastin is another major element of the extracellular matrix. Contrary to collagen, elastin provides tissues with elasticity. Elastin is produced mainly by fibroblasts in the form of its precursor called tropoelastin. To create a complete elastin molecule, tropoelastin molecules must undergo aggregation and crosslinking processes. Elastin is a crucial protein in ligaments, tendons, blood vessels and lung tissue. Similarly, to collagen, elastin mutations lead to a variety of disorders affecting different parts of the body [2].

Lichen planus (LP) is a T-cell mediated inflammatory dermatosis that affects both keratinized and nonkeratinized

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squamous epithelium. Three types are described on the vulva: erosive, classic, and hypertrophic [3]. Lichen sclerosus (LS), similarly to LP is a T-cell–mediated inflammatory dermatosis, however it is directed against unknown epitopes on basal cells of squamous epithelium. Typically, LS affects anogenital skin of women and girls but may also occur on extragenital sites and in males [4].

Previously, damage of collagen IV has been described in oral lichen planus due to an inflammatory response [5]. This leads to destruction of the epithelial-connective tissue interface in oral LP. Furthermore, antibodies against collagen XVII are present in lichen planus [6].

Autoantibodies against the extracellular matrix protein 1 (ECM 1) and basement membrane antigens BP180 and BP230 have been shown to play a role in pathophysiology of lichen sclerosus. ECM1 autoantibodies lead to disruption of the basement membrane by affecting the binding of ECM1 to proteins (*i.e.*, collagen IV) at the dermoepidermal junction (DEJ). Another pathogenetic mechanism in LS is stimulation of fibroblasts resulting in abnormal collagen synthesis and increased hyalinization and sclerosis in the skin [7].

In lichen planus, the characteristic feature is a scarcity of elastin fibers, varying from a partial reduction to complete destruction in the papillary dermis [8]. Vulvar tissue affected by lichen sclerosus showed reduced numbers of elastin fibres [9].

Collagens and elastins in the skin are probably heavily affected by vulvar LS yet is less investigated in LP. It seems important to investigate the gene expression of collagens and elastin in women with LP and LS to compare if they are differently expressed. Thus, our aim was to compare the expression of the following genes: collagen 1A1 (*COL1A1*), collagen 1A2 (*COL1A2*), collagen 3A1 (*COL3A1*), collagen 5A1 (*COL5A1*), collagen 5A2 (*COL5A2*), collagen 5A3 (*COL5A3*), elastin (*ELN*) and *ECM1* in vulvar tissue of women with lichen planus, lichen sclerosus and in healthy vulvar tissue.

MATERIAL AND METHODS

The study was conducted between 2018 and 2021 among women who were admitted to the Department of Gynecology, Obstetrics and Oncological Gynecology, Medical University of Silesia, Bytom, Poland for invasive diagnostic procedures related to their complaint of vulvar pruritus or irritation. After pathologic confirmation of lichen planus or lichen sclerosus, vulvar tissue was further processed as described below. The control group consisted of women who had gynecological procedures performed due to other indications and agreed to provide vulvar biopsy for the purpose of this study. After the pathologic confirmation that the vulvar tissue was normal, it was processed as described below. Exclusion criteria included: lack of consent, pathologic report indicating disorders other than lichen sclerosus or lichen planus or defining any type of pathologic abnormality in case of controls.

The vulvar biopsies were taken from areas suspected of disease or in case of controls from macroscopically healthy vulva at five and eight o'clock by an experienced gynecologist under local anesthesia with one percent lidocaine. Vulvar biopsies were immediately divided into two probes for standard pathological analysis to confirm the diagnosis and for genetical analysis.

The study was approved by Ethical Committee of Medical University of Silesia, Katowice, Poland.

Genetic analysis

The genetic assessment procedure was described previously by our group with details [10].

The following genes were examined: *COL1A1*, *COL1A2*, *COL3A1*, *COL5A1*, *COL5A2*, *COL5A3*, *ELN* and *ECM1*.

Statistical analyses

To confirm the normal distribution within the examined genes we applied Kolmogorov-Smirnov test. In genes with normal distribution, we t-Test was employed. For the data not normally distributed the non-parametric test: Mann-Whitney 1-tail test was engaged. The threshold for p value was set less than 0.05.

RESULTS

Total of 39 vulvar samples were assessed. Table 1 presents collagen gene expression.

The mean level of *ELN* was 13.13 (SD $\pm$ 2.16) and *ECM1* was 10.24 (SD $\pm$ 1.73).

In genes with normal distribution, we used t-Test and found no statistical difference for comparison between control and lichen planus samples, control and lichen sclerosus samples and between LP and LS samples for *COL1A1*, *COL5A1*, *ECM1* ($p > 0.05$). Data shown in Table 2.

In genes without normal distribution, we used Mann Whitney test and found statistically significant difference for *COL1A2* and *ELN* in controls vs LP ($p = 0.4$). Other genes (*COL3A1*, *COL5A2*, *COL5A3*) did not show statistical difference between the groups. Data presented in Table 3.

Fold change was negative for *COL1A2* and *ELN* in comparison between controls and LP (respectively, –3.566, –2.336). The mean expression of *COL1A2* in controls was 5.91 and 7.74 in LP patients. The mean expression of *ELN* in controls was 12.60 and *ELN* 13.83 in LP patients.

DISCUSSION

Both vulvar lichen planus and lichen sclerosus are debilitating diseases with still unknown pathophysiology. Our study adds new information to unveiling skin changes that appear in these disorders. We showed increased expression

Table 1. Analysis of collagen genes normalized to two reference genes: *GAPDH* and *RN18S1*

	COL1A1	*COL1A2*	*COL3A1*	*COL5A1*	*COL5A2*	*COL5A3*
Average	11.13	6.72	8.43	11.91	10.62	12.79
SD	3.08	2.66	2.7	1.96	2.25	1.58
Normality test	Yes	No	No	Yes	No	No

SD — standard deviation

Table 2. Gene expression comparison between lichen planus (LP), lichen sclerosus (LS) and controls in genes with normality distribution

	Controls vs LP	Controls vs LS	LP vs LS
	p value	p value	p value
COL1A1	0.186848788	0.126708	0.442694
COL5A1	0.124498298	0.434763	0.177186
ECM1	0.474049492	0.161499	0.214463

Table 3. Gene expression comparison between lichen planus (LP), lichen sclerosus (LS) and controls in genes without normality distribution

	Controls vs LP	Controls vs LS	LP vs LS
	p value	p value	p value
COL1A2	0.044748	0.277867	0.180029
COL3A1	0.115	0.249369	0.252821
COL5A2	0.075704	0.263422	0.194954
COL5A3	0.441809	0.473902	0.380151
ELN	0.037058	0.388327	0.106002

of *COL1A2* and *ELN* in vulvar lichen planus in compare with healthy vulvar tissue. It is important to focus on the role of *COL1A2* and *ELN*. COL1A2-derived protein promotes fibroblast cell proliferation and collagen type I synthesis [11]. It also enhances wound healing and elastin production. However, it should be noted that *COL1A2* is highly expressed in cancer cells [12] and COL1A2 antibodies is highly present in serum of patients with glioblastoma [13]. Thus, our finding of increased expression of *COL1A2* in patients with LP comparing to healthy tissue may indicate the possible precancerous changes in LP cells. However, this requires further, targeted both *in vitro* and *in vivo* studies. The prevalence of simultaneous LP and vulvar squamous cell cancer ranges from 1 to 33% [14], therefore expanding knowledge about this disease related to its underlying mechanism may be important.

On the other hand, COL1A2 has an important role in fibroblast stimulation and activation. It was proven that lncRNA COL1A2-AS1, also known as lncRNA8975-1, inhibits hypertrophic scar fibroblast proliferation [15]. So, when the expression is downregulated, it may lead to improper healing mechanism, through disruption of fibroblast apoptosis [15]. The role of upregulated *COL1A2* expression in patients with LP remains unknown for fibroblast proliferation and should be further investigated. Our findings should be accounted in assessing the role of COL1A2, aside of TGF-β and other markers on skin fibroblasts [16].

Another finding was that elastin gene expression (*ELN*) is elevated in LP comparing to healthy vulvar tissue. It is interesting as loss of dermal elastin fibers was described both in vulvar LS and LP [17]. Furthermore, elastin is decreased in patients with oral LP comparing to buccal normal mucosa, with increased levels of neutrophil elastase in patients with LP [18]. Thus, we hypothesize that the elevation of elastin gene expression in vulvar tissue of patients with LP may also evoke from increased elastin degradation and secondary rebound.

CONCLUSIONS

Finally, our research adds new information about skin changes in vulvar lichen planus and lichen sclerosus which may prompt further studies to better understand cell changes in these diseases. It may help guide targeted therapies for women suffering from these disorders.

Article information and declarations

Data availability statement

Data available within the article.

Ethics statement

The study was approved by the Ethics Committee at Medical University of Silesia

Author contributions

Marzec Adrianna: data analysis, manuscript writing.
Augusciak-Duma Aleksandra: project development, samples processing, data analysis, manuscript writing.
Lubik Dominika: data collection.
Olejek Anita: project development.
Gabriel Iwona: project development, data analysis, manuscript writing.

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None.

Conflict of interest

Authors report no conflict of interest.

Supplementary material

None.

REFERENCES

1. Ricard-Blum S. The collagen family. Cold Spring Harb Perspect Biol. 2011; 3(1): a004978, doi: 10.1101/cshperspect.a004978, indexed in Pubmed: 21421911.
2. Kristensen JH, Karsdal MA. Elastin. Biochemistry of Collagens, Laminins and Elastin. 2016: 197–201, doi: 10.1016/b978-0-12-809847-9.00030-1.
3. Day T, Weigner J, Scurry J. Classic and Hypertrophic Vulvar Lichen Planus. J Low Genit Tract Dis. 2018; 22(4): 387–395, doi: 10.1097/LGT.0000000000000419, indexed in Pubmed: 29994816.
4. Day T, Moore S, Bohl TG, et al. Comorbid Vulvar Lichen Planus and Lichen Sclerosus. J Low Genit Tract Dis. 2017; 21(3): 204–208, doi: 10.1097/LGT.0000000000000307, indexed in Pubmed: 28369011.
5. Shimada K, Ochiai T, Shen FC, et al. Phenotypic alteration of basal cells in oral lichen planus; switching keratin 19 and desmoglein 1 expression. J Oral Sci. 2018; 60(4): 507–513, doi: 10.2334/josnusd.17-0396, indexed in Pubmed: 30146538.
6. Powell AM, Sakuma-Oyama Y, Oyama N, et al. Collagen XVII/BP180: a collagenous transmembrane protein and component of the dermoepidermal anchoring complex. Clin Exp Dermatol. 2005; 30(6): 682–687, doi: 10.1111/j.1365-2230.2005.01937.x, indexed in Pubmed: 16197389.
7. Corazza M, Schettini N, Zedde P, et al. Vulvar Lichen Sclerosus from Pathophysiology to Therapeutic Approaches: Evidence and Prospects. Biomedicines. 2021; 9(8), doi: 10.3390/biomedicines9080950, indexed in Pubmed: 34440154.
8. Santhosh P, George M. Annular atrophic lichen planus: a review of the literature. Int J Dermatol. 2022; 61(10): 1213–1217, doi: 10.1111/ijd.16038, indexed in Pubmed: 35064678.
9. Farrell AM, Dean D, Millard PR, et al. Alterations in fibrillin as well as collagens I and III and elastin occur in vulval lichen sclerosus. J Eur Acad Dermatol Venereol. 2001; 15(3): 212–217, doi: 10.1046/j.1468-3083.2001.00250.x, indexed in Pubmed: 11683283.
10. Marzec A, Augusciak-Duma A, Kupny-Bujoczek D, et al. Expression of heat shock proteins HSPA1A, HSPA1B and TP53 in vulval lichen planus and vulval lichen sclerosus. Ginekol Pol. 2023 [Epub ahead of print], doi: 10.5603/GP.a2023.0011, indexed in Pubmed: 36929788.
11. Hwang SuJ, Ha GH, Seo WY, et al. Human collagen alpha-2 type I stimulates collagen synthesis, wound healing, and elastin production in normal human dermal fibroblasts (HDFs). BMB Rep. 2020; 53(10): 539–544, doi: 10.5483/BMBRep.2020.53.10.120, indexed in Pubmed: 32843132.
12. Li G, Jiang W, Kang Y, et al. High expression of collagen 1A2 promotes the proliferation and metastasis of esophageal cancer cells. Ann Transl Med. 2020; 8(24): 1672, doi: 10.21037/atm-20-7867, indexed in Pubmed: 33490184.
13. Wang Yi, Sakaguchi M, Sabit H, et al. COL1A2 inhibition suppresses glioblastoma cell proliferation and invasion. J Neurosurg. 2023; 138(3): 639–648, doi: 10.3171/2022.6.JNS22319, indexed in Pubmed: 35932265.
14. Leis M, Singh A, Li C, et al. Risk of Vulvar Squamous Cell Carcinoma in Lichen Sclerosus and Lichen Planus: A Systematic Review. J Obstet Gynaecol Can. 2022; 44(2): 182–192, doi: 10.1016/j.jogc.2021.09.023, indexed in Pubmed: 34678521.
15. Li J, Gao Y, Li Q, et al. LncRNA COL1A2-AS1 promotes skin fibroblast apoptosis by repressing p-Smad3 and promoting β-catenin expression. Experimental Dermatology. 2021; 30(8): 1090–1098, doi: 10.1111/exd.14269.
16. Ramirez F, Tanaka S, Bou-Gharios G. Transcriptional regulation of the human alpha2 (I) collagen gene (COL1A2), an informative model system to study fibrotic disease. Matrix Biol. 2006; 25: 365–72.
17. Niamh L, Naveen S, Hazel B. Diagnosis of vulval inflammatory dermatoses: a pathological study with clinical correlation. Int J Gynecol Pathol. 2009; 28(6): 554–558, doi: 10.1097/PGP.0b013e3181a9fb0d, indexed in Pubmed: 19851203.
18. Liao SC, Hsieh PC, Huang JS, et al. Aberrant keratinization of reticular oral lichen planus is related to elastolysis. Oral Surgery, Oral Medicine, Oral Pathology and Oral Radiology. 2012; 113(6): 808–816, doi: 10.1016/j.oooo.2012.02.007.

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Transvaginal natural orifice endoscopic surgery (vNOTES) for elderly patients

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ABSTRACT

Objectives: To evaluate the feasibility and safety of transvaginal natural orifice transluminal endoscopic surgery (vNOTES) in patients 70 years and over.

Material and methods: The study consisted of eleven patients aged 70 and over who underwent vNOTES for a variety of gynaecological indications at a tertiary referral hospital. The medical and surgical data were noted: age, parity, history of comorbidity, number and type of previous surgeries, body mass index (BMI), operating time, the requirement of intraoperative conversion, the presence of intra- or postoperative complication, estimated blood loss, pre-and postoperative hemoglobin levels, visual analog scale (VAS) pain scores at 6th, 12th and 24th hours, length of hospital stay, and the final pathology results.

Results: vNOTES surgery was performed safely and successfully in eleven patients. There were no intra- and postoperative complications or instances of conversions to conventional laparoscopy or laparotomy. The mean age of patients was 75.91 ± 6.47 (range 70–93), and the mean BMI was 42.49 ± 8.77 kg/m^2 (range 30.2–56). Seven cases of endometrioid adenocarcinoma, two cases of uterine leiomyoma, one case of complex atypical hyperplasia, and one case of postmenopausal uterine bleeding due to atrophic endometrium were diagnosed. All endometrial carcinomas were early stage; no adjuvant therapy was needed.

Conclusions: vNOTES seems to be a safe and feasible approach for the treatment of gynecologic pathologies in elderly patients. This study suggests that vNOTES become a viable treatment option for existing minimally invasive procedures since it offers better surgical outcomes in various gynecologic surgeries.

Keywords: elderly; hysterectomy; natural orifice surgery; transvaginal NOTES

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INTRODUCTION

Improvements in social, economic, public health, and medicine have reduced premature deaths and remarkably increased average life expectancy and the ageing of the population over the past century. According to the United Nations (UN), the elderly population is defined as people aged 65 and over. In 2020, there were 727 million people aged 65 and over worldwide, and women constitute the majority of the population, especially at advanced ages [1].

Advanced age is one of the most important risk factors for postoperative morbidity and mortality [2, 3]. For this reason, it is important to evaluate the elderly in terms of cognitive function, nutritional status, cardiac and pulmonary condition, endocrinological diseases, musculoskeletal problems, mobility status, pain, and analgesia before and after surgery [4]. Minimally invasive methods seem to be a promising surgical option for elderly patients that offers shorter operation time, less postoperative pain, earlier

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ambulation, shorter hospital stay, and faster return to routine activities in this age group [5–7]. Natural orifice transluminal endoscopic surgery (NOTES) is a novel technique in the field of minimally invasive surgery [8]. Transvaginal natural orifice transluminal endoscopic surgery (vNOTES) is a combination of endoscopic and vaginal surgery and has gained popularity in gynecology practice over the last ten years [9, 10]. vNOTES can be performed safely and feasibly in malign and benign gynecologic procedures. However, there is still a lack of cumulative data regarding the feasibility of vNOTES procedures in patients over 70 years and over.

Therefore, in this study, we aimed to assess the feasibility and efficacy of the vNOTES technique for elderly patients who underwent vNOTES for benign and malignant gynecological diseases.

MATERIAL AND METHODS

The study comprised 11 patients over 70 years old who underwent vNOTES at the Kartal Dr.Lütfi Kırdar City Hospital, between June 2021 and December 2021 for a variety of gynecological indications, such as uterine leiomyoma, endometrioid cancer, complex atypical endometrial hyperplasia, and postmenopausal uterine bleeding.

The study protocol was in line with the tenets of the Declaration of 1964 Helsinki and approved by the ethics committee of Kartal Dr.Lütfi Kırdar City Hospital (Approval number: 2021/514/202/19). Verbal and written informed consent forms were obtained from all study participants prior to the study.

The following data were retrieved from the hospital's electronic medical records system: age, parity, history of comorbidity, number and type of previous surgeries, body mass index (BMI), operating time, the requirement of intraoperative conversion, the presence of intra- or postoperative complication, estimated blood loss, pre-and postoperative hemoglobin levels, visual analog scale (VAS) pain scores at 6^{th}, 12^{th} and 24^{th} hours, length of hospital stay, and the final pathology results. All patients were preoperatively staged according to the International Federation of Gynecology and Obstetrics (FIGO) system. Pain scores were evaluated using a Likert-type VAS (0 = no pain, 10 = worst pain imaginable) during the postoperative periods. The operation time was calculated from the first incision of the posterior vaginal wall to the end of vaginal closure. Intra-and postoperative complications were defined as intraoperative blood loss exceeding 300 mL, excessive postoperative bleeding requiring transfusion or reoperation, vaginal vault hematoma or abscess, conversion to another technique, and injuries to the bladder, ureter, bowel, and/or major vessels. Hemoglobin change was defined as the difference between the hemoglobin level recorded one day before surgery and the first postoperative day.

Patients

All patients were evaluated preoperatively by past medical and surgical histories, gynecologic examination, blood tests (complete blood count, tumor markers, and inflammatory markers), cervicovaginal smear, radiologic imaging (transvaginal ultrasonography and magnetic resonance imaging), endocervical curettage, and endometrial biopsy.

Exclusion criteria were as follows; any contraindication for pneumoperitoneum, the dorsal lithotomy position, general anesthesia, sepsis, severe renal failure, severe cardiopulmonary disease, history of colorectal surgery, suspicion of uterine sarcoma, blood coagulation disorders, history of pelvic radiotherapy, tubo-ovarian abscesses, and an obliteration of the pouch of Douglas (uterine immobility in pelvic examination, endometriosis, and pelvic inflammatory disease).

All surgeries were performed by a single surgeon with extensive experience in minimally invasive surgery.

Surgical technique

Patients were positioned in the 15° Trendelenburg position under general anesthesia. The anterior lip of the cervix was grasped with a tenaculum. A circumferential cervical incision was made via an 11-mm scalpel and/or cautery. Then, the cervical fascia was dissected by blunt and sharp dissections, and anterior and posterior colpotomy was performed. A GelPoint vPath (Applied Medical Resources Corp., Rancho Santa Margarita, CA, USA) was inserted into the vaginal opening.

After pneumoperitoneum with 12–15 mm Hg CO_2 insufflation, a 10-mm 30° telescope (Karl Storz, Tuttlingen, Germany) was introduced for optimal imaging. Conventional laparoscopic devices such as graspers, a suction-irrigation device, scissors, bipolar forceps, and tissue sealing devices (LigaSure, 5-mm diameter, blunt tip; Covidien) were used where needed. Sacro-uterine ligaments, uterine arteries, and adnexal roots were sealed and cut caudally to cranially. The uterus and adnexa were extracted through the vaginal opening. The vaginal opening was closed with a Vicryl 1–0 suture (Ethicon, Piscataway, NJ, USA).

RESULTS

We reviewed 11 elderly patients who underwent hysterectomy and bilateral salpingo-oophorectomy via the vNOTES approach for benign or malign indications between June 2021 and December 2021. There were no intra- and postoperative complications or instances of conversions to conventional laparoscopy or laparotomy. The mean age of patients was 75.91 ± 6.47 (range 70–93), and the mean BMI was 42.49 ± 8.77 kg/m^2 (range 30.2–56). All patients were multiparous (mean = 3.91; range, 2–8) and no one had delivered by cesarean sections. Only two patients had no

Table 1. Baseline characteristics of patients

Patient no	Age [years]	BMI [kg/m^2]	Parity	History of C/S	Previous surgeries	Systemic Diseases	Indication for surgery
1	75	51.1	3	0	Nephrectomy	DM, HT and Chronic renal failure	Endometrioid adenocarcinoma Grade 1
2	73	46.7	4	0	Cholecystectomy	DM and HT	Leiomyoma uteri + dysfunctional uterine bleeding
3	76	45	5	0	Nill	HT and Thrombocytosis	Endometrioid adenocarcinoma Grade 1
4	72	40	5	0	Heart surgery	HT, chronic heart failure and atrial fibrillation	Endometrioid adenocarcinoma. Grade 1
5	81	30.2	3	0	Cholecystectomy	HT	Endometrioid adenocarcinoma Grade 1
6	71	38	4	0	Appendectomy	DM and HT	Leiomyoma uteri + dysfunctional uterine bleeding
7	72	46	5	0	Thyroidectomy	Hypothyroidism	Endometrioid adenocarcinoma Grade 1
8	75	50.7	4	0	Nil	DM and HT	Complex atypical hyperplasia
9	77	56	5	0	Heart surgery	DM, chronic heart failure and atrial fibrillation	Endometrioid adenocarcinoma Grade 1
10	70	33.3	2	0	Nil	HT	Endometrioid adenocarcinoma Grade 1
11	93	30.4	3	0	Bilateral hip replacement	Chronic heart failure	Postmenopausal uterine bleeding — atrophic endometrium

C/S — cesarean section; BMI — body mass index; DM — diabetes mellitus; HT — hypertensive disorder; BMI is calculated by the formula of kg/m^2 where kg is a person's weight in kilograms and m^2 is their height in metres squared

systemic disease, while nine patients had one or more systemic diseases such as diabetes mellitus, hypertension, chronic renal failure, thrombocytosis, hypothyroidism, chronic heart failure or atrial fibrillation. Of patients, two had a history of prior heart surgery, one had nephrectomy, two patients had cholecystectomy, one patient had appendectomy, one patient had thyroidectomy, one patient had bilateral hip replacement. Seven cases of endometrioid adenocarcinoma, two cases of uterine leiomyoma, one case of complex atypical hyperplasia, and one case of postmenopausal uterine bleeding due to atrophic endometrium were diagnosed. All endometrial carcinomas were early stage; no adjuvant therapy was required. The TNM stage was T1aN0M0, and the histological type endometrioid carcinoma (type 1) for these patients. The demographics and clinical data are presented in Table 1.

The mean operation time was 66.18 ± 25.69 min (range, 40–136). The mean estimated blood loss was 43.64 ± 14.50 mL (range, 30–80). Mean hemoglobin change was 1.463 g/dL. The mean duration of postoperative hospital stay was 2.55 ± 1.21 days (range, 2–6). The mean postoperative VAS pain scores at 6, 12 and 24 h were 2.9, 2.0, and 0.8 respectively (Tab. 2). The surgical outcomes are shown in Table 3.

Table 2. Main outcomes of the study

Variables	Mean ± SD	Median (Min.–Max.)
Age [y]	75.91 ± 6.47	75 (70–93)
BMI [kg/m^2]	42.49 ± 8.77	45 (30.2–56)
Parity	3.91 ± 1.04	4 (2–5)
Operation time [min]	66.18 ± 25.69	60 (40–136)
Estimated blood loss [mL]	43.64 ± 14.50	40 (30–80)
Hb change [g/dL]	1.463 ± 0.23	1.4 (1.2–2)
Postoperative hospital stay [d]	2.55 ± 1.21	2 (2–6)
Postoperative pain score (VAS)		
6 h	2.91 ± 0.70	3 (2–4)
12 h	2.00 ± 0.63	2 (1–3)
24 h	0.82 ± 0.75	1 (0–2)

y — year; BMI — body mass index; min — minute; d — day; h — hour; VAS — visual analog scale; SD — standard deviation; Hb — hemoglobin levels; BMI is calculated by the formula of kg/m^2 where kg is a person's weight in kilograms and m^2 is their height in metres squared

DISCUSSION

To the best of our knowledge, this is the first report of vNOTES to treat elderly patients with benign or malign gynecologic diseases. To date, data on the feasibility of vNOTES for gynecologic surgeries in the elderly group remain scarce. This could be attributed to the lack of visualization and surgeons experience with vaginal surgeries in the era of minimally invasive surgery.

With the improvement of the treatment of acute or chronic diseases, perioperative care, the development of advanced surgical techniques and equipment, and the

Table 3. The surgical characteristics and postoperative treatment

Patient	Operation	Operation time [minute]	Estimated blood lose [mL]	Hb change [g/dL]	Postoperative hospital stay [day]	Postoperative pain score VAS VAS VAS (6h) (12h) (24h)
1	vNOTES hysterectomy + BSO	40	30	–1.4	2	3 2 0
2	vNOTES hysterectomy + BSO	55	40	–1.3	2	3 1 0
3	vNOTES hysterectomy + BSO	50	40	–1.5	2	3 2 0
4	vNOTES hysterectomy + BSO	60	60	–1.6	3	4 2 1
5	vNOTES hysterectomy + BSO	70	40	–1.5	2	3 2 1
6	vNOTES hysterectomy + BSO	60	40	–1.2	2	3 2 1
7	vNOTES hysterectomy + BSO	65	30	–1.4	2	2 1 0
8	vNOTES hysterectomy + BSO	65	35	–1.2	2	2 2 1
9	vNOTES hysterectomy + BSO	80	45	–1.7	3	3 3 2
10	vNOTES hysterectomy + BSO	47	40	–1.3	2	2 2 1
11	vNOTES hysterectomy + BSO	136	80	–2	6	4 3 2

BSO — bilateral salpingo-oophorectomy; Hb — hemoglobin levels; VAS — visual analog scale

increment in the longevity of the population, the elderly has become an increasing proportion of the world's population. It can be concluded that more surgical procedures will then be necessary as the elderly population increases. It is now well established from a variety of studies that traditional laparoscopic surgery (LS) and Robotic surgery (RS) are safe, feasible treatment options for the elderly population [11, 12]. In a comprehensive study that compares the elderly with younger patients undergoing robotic-assisted gynecologic surgery, it was concluded that RS is safe in the elderly population. Similarly, several studies have reported that LS had some advantages, such as less postoperative pain, quicker recovery, and less blood loss, and reported that LS is a feasible, safe, and efficient surgical choice in the elderly group for benign gynecological disease [11, 13, 14].

Recently, researchers have shown an increased interest in vNOTES, a combination of laparoscopic techniques and vaginal surgery. It has been proposed as a promising approach over both LS and RS in the gynecology practice due to its advantages such as shorter operating time, less postoperative pain, less estimated blood loss, early hospital discharge, improved intraoperative visualization of the surgical field, lower rate of wound site infection, and better cosmetic outcomes [15–20]. In addition, vNOTES has been shown to be a feasible technique for gynecological emergencies, obese, benign gynecological surgeries and apical pelvic organ prolapse [21–24]. The RS has some disadvantages compared with vNOTES. That is, high operational cost, the absence of haptic tactile feedback, restricted positioning the operating table after docking the robot, limited patient access, and an interprofessional team is required in terms of emergency undocking [25–27].

Our technique has some innovative features over our previously described technique [13]. A colpotomy was performed via an 11-mm scalpel and/or cautery instead of ultrasonic scalpel. This allowed us to reduce operating time. In the 15° Trendelenburg position, we placed GelPoint vPath (Applied Medical, Rancho Santo Margarita, CA) instead of a self-construct glove port, which helped us to reduce the operative time. Subsequently, we performed a total hysterectomy and salpingo-oophorectomy without first detaching the uterus. These steps facilitated adequate exposure to the surgical field, shortened operative time, as well as maintained adequate pneumoperitoneum.

Controversies still exist regarding the appropriate Trendelenburg angle. Although previous research has established that at least a 30–35° Trendelenburg angle is required in the minimally invasive gynecological robotic and laparoscopic procedures, we used a 15° Trendelenburg positioning to avoid hemodynamic and cardiac consequences for the elderly [11, 28]. A recent systematic literature review concluded that vNOTES had significantly lower values for the duration of surgery and length of hospital stay compared to laparoscopy, whereas no difference was found in the VAS scores and hemoglobin change between pre-and postoperative 24 h [20]. In the present study, the VAS pain scores were consistently decreased at the postoperative 6th, 12th, and 24th hours. We believe this to be attributed to the technique of removing the uterus with both ovaries and fallopian tubes without pulling the uterine ligaments and the lack of an abdominal wall incision [8]. This combination of findings provides some support for the conceptual premise that the vNOTES procedure is feasible and safe in the elderly groups.

The strength of our work lies in providing the first comprehensive assessment of vNOTES in elderly patients who

underwent gynecologic surgeries. The fact that all the surgeries were performed by an experienced gynecologic surgeon may be interpreted as both a strength and a limitation, as it may contribute to the production of more consistent data, but it may not be representative of all physicians who perform minimally invasive surgery. Another point worth mentioning is that the present study focused on elderly patients, as these patients are vulnerable to postoperative morbidities and complications. This is due to their prolonged steep Trendelenburg positioning during surgeries and reduced function of several organs. In our study, we have described the application of vNOTES techniques, such as the utilization of a commercial vNOTES glove port system, the insufflation pressure, the degree of tilt, and removing ovaries with the uterus, which all were effective and provides significant advantages to the elderly group.

We are aware that the present study has several limitations to be acknowledged. One limitation was its small sample size and a single-center experience, as our data came from eleven patients. Notwithstanding the relatively limited sample, this work has gone some way towards enhancing our understanding of vNOTES techniques in the elderly group. Further large prospective multi-center randomized trials need to be carried out in order to determine the efficacy, safety, and feasibility of vNOTES for gynecologic surgeries in elderly patients. Research questions that could be asked include women's health and comparative financial cost.

CONCLUSIONS

The present study has demonstrated, for the first time, that vNOTES could be a safe and feasible approach for the treatment of gynecologic pathologies in elderly patients. By advancing both surgeons' expertise and instruments, vNOTES seem to be the next frontier in the gynecology practice. We might speculate that vNOTES become a viable treatment option for existing minimally invasive procedures since it offers favorable surgical outcomes in various gynecologic surgeries.

Article information and declarations

Data availability statement

The data that support the findings of this study are available on request from the corresponding author.

Ethics statement

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The study was approved by the Research Ethics Committee of the Kartal Dr. Lütfi Kırdar City Hospital (Date: 26.05.2021, No: 2022/514/222/7). Informed consent was obtained from all individual participants included in the study.

Author contributions

All authors attest they meet the International Committee for Medical Journal Editors (ICMJE) criteria for authorship. Emre Mat: conceptualization, study design and organization, supervision, investigation and writing-original draft. Pınar Yıldız: investigation and writing-reviewing and editing Rezzan Berna Temoçin: investigation, data acquisition and manuscript writing-reviewing, editing and revisions. Özgür Kartal: conceptualization, methodology, investigation and writing-reviewing and editing. Esra Keles: manuscript writing-reviewing, editing, critically revised the work for important intellectual content. All authors approved the final submitted version. and agree to be accountable for all aspects of the work.

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None.

Conflict of interest

The authors declare no competing interests.

Supplementary material

None.

REFERENCES

1. United Nations Department of Economic and Social Affairs, Population Division (2020) World Population Ageing 2020 Highlights: Living arrangements of older persons (ST/ESA/SER.A/451). https://www.un.org/development/desa/pd/sites/www.un.org.development.desa.pd/files/undesa_pd-2020_world_population_ageing_highlights.pdf.
2. Turrentine FE, Wang H, Simpson VB, et al. Surgical risk factors, morbidity, and mortality in elderly patients. J Am Coll Surg. 2006; 203(6): 865–877, doi: 10.1016/j.jamcollsurg.2006.08.026, indexed in Pubmed: 17116555.
3. Raats JW, van Eijsden WA, Crolla RM, et al. Risk Factors and Outcomes for Postoperative Delirium after Major Surgery in Elderly Patients. PLoS One. 2015; 10(8): e0136071, doi: 10.1371/journal.pone.0136071, indexed in Pubmed: 26291459.
4. Hughes S, Leary A, Zweizig S, et al. Surgery in elderly people: preoperative, operative and postoperative care to assist healing. Best Pract Res Clin Obstet Gynaecol. 2013; 27(5): 753–765, doi: 10.1016/j.bpobgyn.2013.02.006, indexed in Pubmed: 23507431.
5. Weber DM. Laparoscopic surgery: an excellent approach in elderly patients. Arch Surg. 2003; 138(10): 1083–1088, doi: 10.1001/archsurg.138.10.1083, indexed in Pubmed: 14557124.
6. Scarpa M, Di Cristofaro L, Cortinovis M, et al. Minimally invasive surgery for colorectal cancer: quality of life and satisfaction with care in elderly patients. Surg Endosc. 2013; 27(8): 2911–2920, doi: 10.1007/s00464-013-2854-2, indexed in Pubmed: 23468328.
7. Robinson CN, Balentine CJ, Marshall CL, et al. Minimally invasive surgery improves short-term outcomes in elderly colorectal cancer patients. J Surg Res. 2011; 166(2): 182–188, doi: 10.1016/j.jss.2010.05.053, indexed in Pubmed: 21276980.

8. Kale A, Sarıibrahim B, Başol G. Hysterectomy and salphingoopherectomy by Transvaginal Natural Orifice Transluminal Endoscopic Surgery(NOTES): Turkish surgeons' initial experience. Int J Surg. 2017; 47: 62–68, doi: 10.1016/j.ijsu.2017.09.062, indexed in Pubmed: 28951308.
9. Li CB, Hua KQ. Transvaginal natural orifice transluminal endoscopic surgery (vNOTES) in gynecologic surgeries: A systematic review. Asian J Surg. 2020; 43(1): 44–51, doi: 10.1016/j.asjsur.2019.07.014, indexed in Pubmed: 31444108.
10. Baekelandt J, Kapurubandara S. Benign Gynaecological procedures by vaginal Natural Orifice Transluminal Endoscopic Surgery (vNOTES): Complication data from a series of 1000 patients. Eur J Obstet Gynecol Reprod Biol. 2021; 256: 221–224, doi: 10.1016/j.ejogrb.2020.10.059, indexed in Pubmed: 33248377.
11. Jeon SW, Choi JS, Lee JH, et al. Is laparoscopic surgery safe in women over 70 years old with benign gynecological disease? J Obstet Gynaecol Res. 2011; 37(6): 601–605, doi: 10.1111/j.1447-0756.2010.01465.x, indexed in Pubmed: 21349134.
12. Madden N, Frey MK, Joo L, et al. Safety of robotic-assisted gynecologic surgery and early hospital discharge in elderly patients. Am J Obstet Gynecol. 2019; 220(3): 253.e1–253.e7, doi: 10.1016/j.ajog.2018.12.014, indexed in Pubmed: 30557552.
13. Mat E, Kale A, Gundogdu EC, et al. Transvaginal natural orifice endoscopic surgery for extremely obese patients with early-stage endometrial cancer. J Obstet Gynaecol Res. 2021; 47(1): 262–269, doi: 10.1111/jog.14509, indexed in Pubmed: 33059387.
14. Cengiz H, Dagdeviren H, Kanawati A, et al. Is gynaecological laparoscopic surgery safe for elderly women? A comparison study. J Obstet Gynaecol. 2014; 34(7): 616–619, doi: 10.3109/01443615.2014.919575, indexed in Pubmed: 24911111.
15. Kaya C, Alay İ, Ekin M, et al. Hysterectomy by vaginal-assisted natural orifice transluminal endoscopic surgery: Initial experience with twelve cases. J Turk Ger Gynecol Assoc. 2018; 19(1): 34–38, doi: 10.4274/jtgga.2017.0075, indexed in Pubmed: 29503260.
16. Mat e, Yıldız G, Basol G, et al. Laparoscopic management of bladder injury during total laparoscopic hysterectomy. Southern Clinics of Istanbul Eurasia. 2021;32(2):176-180, doi: 10.14744/scie.2021.86094.
17. Yang E, Nie D, Li Z. Comparison of Major Clinical Outcomes Between Transvaginal NOTES and Traditional Laparoscopic Surgery: A Systematic Review and Meta-analysis. J Surg Res. 2019; 244: 278–290, doi: 10.1016/j.jss.2019.06.012, indexed in Pubmed: 31302326.
18. Kaya C, Alay I, Cengiz H, et al. Conventional Laparoscopy or Vaginally Assisted Natural Orifice Transluminal Endoscopic Surgery for Adnexal Pathologies: A Paired Sample Cross-Sectional Study. Journal of Investigative Surgery. 2020; 34(11): 1185–1190, doi: 10.1080/08941939.2020.1789246.
19. Mat E, Yıldız P, Yılmaz TG, et al. Total laparoscopic hysterectomy experience: retrospective results of a tertiary center. Southern Clinics of Istanbul Eurasia. 2021;32(3): 315-315, doi: 10.14744/scie.2021.16023.
20. Housmans S, Noori N, Kapurubandara S, et al. Systematic Review and Meta-Analysis on Hysterectomy by Vaginal Natural Orifice Transluminal Endoscopic Surgery (vNOTES) Compared to Laparoscopic Hysterectomy for Benign Indications. J Clin Med. 2020; 9(12), doi: 10.3390/jcm9123959, indexed in Pubmed: 33297354.
21. Karakaş S, Kaya C, Yildiz Ş, et al. Comparison of vNOTES technique with conventional laparoscopy in gynecological emergency cases. Minim Invasive Ther Allied Technol. 2022; 31(5): 803–809, doi: 10.1080/13645706.2021.2025111, indexed in Pubmed: 35073493.
22. Kaya C, Yıldız Ş, Alay İ, et al. The Comparison of Surgical Outcomes following Laparoscopic Hysterectomy and vNOTES Hysterectomy in Obese Patients. J Invest Surg. 2022; 35(4): 862–867, doi: 10.1080/08941939.2021.1927262, indexed in Pubmed: 34036898.
23. Tekin AB, Yassa M, Kaya C, et al. Implementing the transvaginal natural orifice transluminal endoscopic surgery (vNOTES) "first" strategy in benign gynecological surgeries. Arch Gynecol Obstet. 2023; 307(4): 1007–1013, doi: 10.1007/s00404-022-06859-9, indexed in Pubmed: 36445449.
24. Alay I, Kaya C, Cengiz H, et al. Apical pelvic organ prolapse repair via vaginal-assisted natural orifice transluminal endoscopic surgery: Initial experience from a tertiary care hospital. Asian J Endosc Surg. 2021; 14(3): 346–352, doi: 10.1111/ases.12863, indexed in Pubmed: 32967055.
25. Gupta K, Mehta Y, Sarin Jolly A, et al. Anaesthesia for robotic gynaecological surgery. Anaesth Intensive Care. 2012; 40(4): 614–621, doi: 10.1177/0310057X1204000406, indexed in Pubmed: 22813488.
26. Marengo F, Larraín D, Babilonti L, et al. Learning experience using the double-console da Vinci surgical system in gynecology: a prospective cohort study in a University hospital. Arch Gynecol Obstet. 2012; 285(2): 441–445, doi: 10.1007/s00404-011-2005-8, indexed in Pubmed: 21779771.
27. Judd JP, Siddiqui NY, Barnett JC, et al. Cost-minimization analysis of robotic-assisted, laparoscopic, and abdominal sacrocolpopexy. J Minim Invasive Gynecol. 2010; 17(4): 493–499, doi: 10.1016/j.jmig.2010.03.011, indexed in Pubmed: 20621010.
28. Takmaz O, Asoglu MR, Gungor M. Patient positioning for robot-assisted laparoscopic benign gynecologic surgery: A review. Eur J Obstet Gynecol Reprod Biol. 2018; 223: 8–13, doi: 10.1016/j.ejogrb.2018.02.002, indexed in Pubmed: 29428480.

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Ultrasonographic diagnosis of ovarian tumors through the deep convolutional neural network

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ABSTRACT

Objectives: The objective of this study was to develop and validate an ovarian tumor ultrasonographic diagnostic model based on deep convolutional neural networks (DCNN) and compare its diagnostic performance with that of human experts.

Material and methods: We collected 486 ultrasound images of 192 women with malignant ovarian tumors and 617 ultrasound images of 213 women with benign ovarian tumors, all confirmed by pathological examination. The image dataset was split into a training set and a validation set according to a 7:3 ratio. We selected 5 DCNNs to develop our model: MobileNet, Xception, Inception, ResNet and DenseNet. We compared the performance of the five models through the area under the curve (AUC), sensitivity, specificity, and accuracy. We then randomly selected 200 images from the validation set as the test set. We asked three expert radiologists to diagnose the images to compare the performance of radiologists and the DCNN model.

Results: In the validation set, AUC of DenseNet was 0.997 while AUC was 0.988 of ResNet, 0.987 of Inception, 0.968 of Xception and 0.836 of MobileNet. In the test set, the accuracy was 0.975 with the DenseNet model vs 0.825 ($p < 0.0001$) with the radiologists, and sensitivity was 0.975 vs 0.700 ($p < 0.0001$), and specificity was 0.975 vs 0.908 ($p < 0.001$).

Conclusions: DensNet performed better than other DCNNs and expert radiologists in identifying malignant ovarian tumors from benign ovarian tumors based on ultrasound images, a finding that needs to be further explored in clinical trials.

Keywords: ultrasound; diagnosis; ovarian tumor; deep learning; radiologist

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INTRODUCTION

Ovarian cancer is one of the deadliest gynecological malignancies. According to the Global Cancer Statistics 2020 [1], it is estimated to be 313 959 new cases and 207 252 deaths of ovarian cancer in 2020 in the world. The global 5-year survival is below 45% [2]. Ovarian cancer generally affects women over 50. The treatment is based on surgery and chemotherapy.

Ultrasound examination is the most appropriate first-line diagnostic technique for the preoperative evaluation of women with adnexal lesions. Ovarian cancer is usually diagnosed through ultrasound features such as the shape of the pelvic mass, the proportion of solid tissue, the presence of ascites, the number of papillary projections, and blood flow signals [3]. Whether a pelvic mass is benign or malignant, an expert radiologist discriminates through these features. Radiologists are limited in their abilities, and their judgment is subject to the influence of their working experience [4]. The accuracy of discriminating a pelvic mass through ultrasound by radiologists is approximately 82–92% [5]. Therefore, it is necessary to improve the precision of ultrasonographic diagnosis of ovarian tumors.

With the rapid development of artificial intelligence, the technique of computer-assisted image diagnosis in medicine has made substantial strides in the area of image--recognition [6, 7]. Recent advances in deep convolutional

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neural networks (DCNN) have shown great promise for ultrasound diagnosis of diseases such as thyroid nodules and breast nodules [8, 9]. However, studies on ultrasonographic diagnosis of ovarian tumors through DCNN are few so far [10]. In contrast to typical machine learning algorithms, DCNN does not employ features that human experts identified as input. By taking raw image pixels and the corresponding class labels as inputs, DCNN automatically learns feature representations in a generalized manner [11].

One of the main challenges of DCNN models is vanishing gradients. A practical solution is to increase the connection between layers. This problem was overcome in some DCNN models such as ResNet [12], Highway Networks [13], and Stochastic depth [14]. Although these algorithms have different network structures, they all take advantage of short paths to link early and later layers. Therefore, we used the concept of DenseNet [15] to design our model architecture. A DenseNet network is an improved DCNN model that continues the idea mentioned above by directly connecting all layers to ensure maximum information flow between layers, using a shortcut connection to pass input from one block to another. Thus, DenseNet may offer great help for diagnosis of image-based examinations in clinical work.

Objectives

In this study, we aim to develop a DCNN-based ultrasound image analysis model and evaluate its performance for the automated diagnosis of ovarian tumors using real-world ultrasound images compared with human radiologists.

MATERIAL AND METHODS

Dataset

We retrospectively collected ultrasound images of ovarian tumors from the First Affiliated Hospital of Soochow University between May 1st, 2017, to June 30th, 2020. Patients were included based on the following two eligibility criteria. The first requirement was that they were at least 18 years old. Secondly, all patients with benign or malignant ovarian tumors underwent a pathological examination. The pathological examination reports were provided by the pathological department of the First Affiliated Hospital of Soochow University.

If the patients fulfilled the inclusion criteria, ultrasound images within 120 days before the surgery were collected. The ultrasound imaging was manufactured by GE Healthcare system. Image quality control was performed by excluding images not containing tumor nidus based on the pathological review report, such as the uterus and opposite normal ovaries. The images were all in jpg format. As a final step, we established our image dataset of 1103 ultrasound images, including 486 images of malignant ovarian tumors from 192 patients and 617 images of benign ovarian tumors from 213 patients.

The construction of the DCNN models

The dataset was split into a training set and a validation set at random in a 7:3 ratio. The training set was utilized to learn the parameters of the ultrasound images, and the validation set was used to estimate the prediction error for hyperparameter tuning and model selection. The training set consisted of 340 images of malignant ovarian tumors and 432 images of benign ovarian tumors. The validation set consisted of 146 images of malignant ovarian tumors and 185 of benign ovarian tumors. Our training dataset was augmented with image data to increase training data and avoid overfitting artificially [16]. Image augmentation was not applied to the validation set. It is reported that after adopting the data enhancement method, the accuracy of the final recognition results can be improved by 3–4% [17]. We used the following methods to effectively enhance the ultrasound image data, including rotation ± 20°, horizontal translation 20°, vertical translation 20°, zoom 20%, and horizontal flip. The effect of augmentation of specific data is shown in Figure S1.

Afterwards, we selected five different DCNNs to develop our diagnostic models, including Inception [18], Mobilenet [19], Resnet, Xception [20], and DenseNet. We trained 50 rounds on the training set and evaluated the DCNN models using the training set. The output of the last layer was shown as the predicted probability of malignancy.

All experiments were conducted on a device with a Windows 10 system. The hardware capabilities included NVIDIA RTX 3080 GPU (10 GB memory), CPU AMD 5600X, and 32 GB RAM. In the experiment process, the size of all the images was set at 299 × 299 mm. We set the batch size to 16 due to GPU memory limitations. All programs were implemented by TensorFlow and Keras. The optimizer was Stochastic Gradient Descent, and the initial learning rate was 0.001. The momentum was 0.9, and the weight decay was 0.0001. We set the epoch at 50. Moreover, the warm-up was employed during the training process. A stable distribution could aid in maintaining the deep stability of the model, which could help to slow down the early overfitting of the mini-batch at the start of the model.

Comparison with radiologists

Futhermore, DenseNet showed the best performance among the five DCNN models and was used to compare whether the DCNN model has advantages over human radiologists in recognizing malignant ovarian tumors. Then, we randomly selected 200 images from the validation set as the test set. Three expert radiologists were invited to analyze the 200 images and determine whether they were malignant. The performance of human radiologists was

then compared with the DenseNet model on the test set. All radiologists had working experience more than six years and were required to complete the task within two hours independently.

Statistical analysis

The predictions of DCNN models and radiologists were compared with the pathological reports, considered the diagnostic gold standard. We applied the receiver operating characteristic (ROC) curve to compare the diagnostic abilities of different DCNN models in discriminating malignant ovarian tumors from benign ones. The ROC curve was drawn by plotting the true positive rate (sensitivity) against the false positive rate (1-specificity) by varying the predicted probability threshold, and the area under the curve (AUC) was calculated. We also calculated the accuracy, sensitivity, specificity, positive predicted values (PPV) and negative predictive values (NPV) to assess the diagnostic abilities of different DCNN models and radiologists. Sensitivity is the fraction of recognizing malignancies in the malignant data verified by pathological examination. Specificity is the fraction of recognizing benignities in benign data verified by pathological examination. Accuracy is the fraction of recognizing malignant/benign data in malignant/benign data verified by pathological examination. PPV is the fraction of malignancies verified by pathological examination in malignancies diagnosed by DCNN models or radiologists. NPV is the fraction of benignities verified by pathological examination in benignities diagnosed by DCNN models or radiologists. We calculated 95% confidence intervals (CIs) for sensitivity, specificity, accuracy, PPV, and NPV with the Clopper–Pearson method [21]. We also calculated kappa values and F1 scores. Kappa value measures the agreement between the prediction of one diagnostic method and the pathological reports. F1 score was calculated as the harmonic mean of sensitivity and PPV, which measures the accuracy of one diagnostic method against the pathological report.

We used the radiologists' average sensitivity, specificity, and accuracy when comparing the performance with the DenseNet model. A binomial test was applied to evaluate the difference in sensitivity, specificity, and accuracy between the DenseNet model and the radiologists. A p value less than 0.05 was considered statistically significant. The inter-radiologist agreement rate and Fleiss' kappa value [22] were also calculated. The figure plotting and statistical analyses were done with GraphPad Prism (version 8.0) and R software (version 4.0.3).

The flowchart depicting the process of our study is shown in Figure 1.

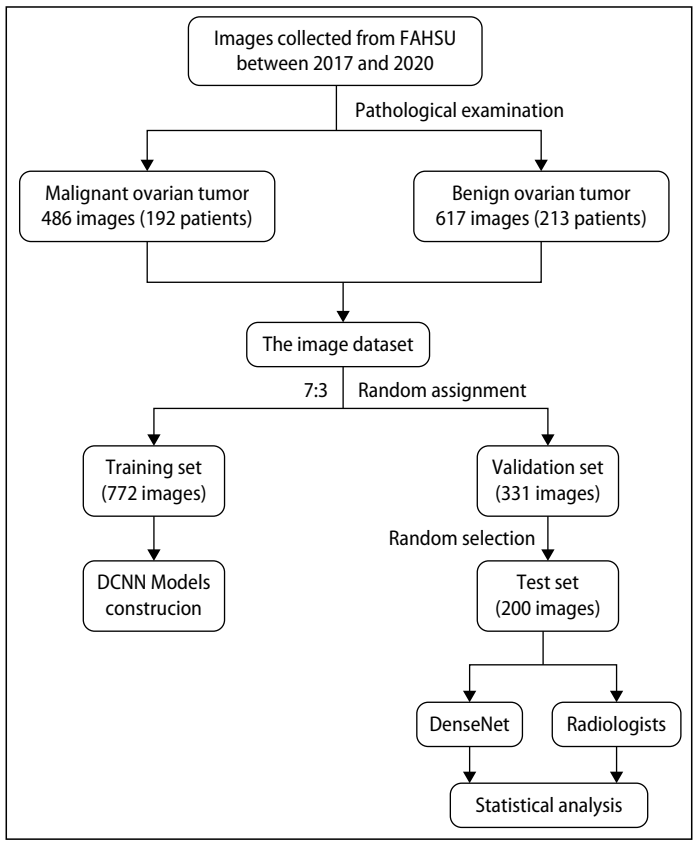

Figure 1. The flowchart of the study; FAHSU — the First Affiliated Hospital of Soochow University

Table 1. Baseline characteristics of the study. Data are n [%] or median (IQR)

	Training set (n = 282)		Validation set (n = 123)	
	Malignant group	Benign group	Malignant group	Benign group
Patients	137	145	55	68
Images	340	432	146	185
Age [years]	55 (49–64)	35 (30–45)	56 (49–66)	33 (28–44)
≤ 45 years	18 (13.1%)	109 (75.2%)	10 (18.2%)	52 (76.5%)
> 45 years	119 (86.9%)	36 (24.8%)	45 (81.8%)	16 (23.5%)
Histology				
Serous	95 (69.3%)	NA	46 (83.6%)	NA
Mucinous	9 (6.6%)	NA	3 (5.5%)	NA
Endometrioid	13 (9.5%)	NA	1 (1.8%)	NA
Clear cell	13 (9.5%)	NA	2 (3.6%)	NA
Others	7 (5.1%)	NA	3 (5.5%)	NA
FIGO				
Stage I	32 (23.4%)	NA	8 (14.5%)	NA
Stage II	16 (11.7%)	NA	9 (16.4%)	NA
Stage III	66 (48.2%)	NA	23 (41.8%)	NA
Stage IV	23 (16.8%)	NA	15 (27.3%)	NA

FIGO — International Federation of Gynecology and Obstetrics; NA — not applicable

Table 2. Performance of different different deep convolutional neural network (DCNN) models, assessed on the validation set. Data are n (95% CI)

	MobileNet	Xception	Inception	ResNet	DenseNet
Sensitivity	0.747 (0.668–0.815)	0.863 (0.796–0.914)	0.973 (0.931–0.991)	0.945 (0.895–0.976)	0.952 (0.904–0.981)
Specificity	0.795 (0.729–0.850)	0.941 (0.896–0.970)	0.849 (0.789–0.897)	0.957 (0.917–0.981)	0.973 (0.938–0.991)
Accuracy	0.773 (0.724–0.817)	0.906 (0.870–0.935)	0.903 (0.866–0.933)	0.952 (0.923–0.972)	0.964 (0.938–0.981)
Positive predictive value	0.741 (0.663–0.810)	0.920 (0.861–0.959)	0.835 (0.771–0.888)	0.945 (0.895–0.976)	0.965 (0.921–0.989)
Negative predictive value	0.799 (0.734–0.854)	0.897 (0.845–0.936)	0.975 (0.938–0.993)	0.957 (0.917–0.981)	0.963 (0.924–0.985)
Kappa	0.541	0.809	0.807	0.902	0.926
F1	0.744	0.890	0.899	0.945	0.959

CI — confidence interval; DCNN — deep convolutional neural networks

RESULTS

The baseline characteristics of the training set and the validation set are shown in Table 1. The median age of participants showed no apparent differences between the training set and the validation set, while the median age was higher in the malignant group than in the benign group [55 years (IQR 49–64) vs 35 years (30–45) in training set; 56 years (IQR 49–66) vs 33 years (28–44) in the validation set]. Since malignant ovarian tumors usually occur in older women, the proportion of participants over 45 was 86.9% in the malignant group, while the proportion was only 24.8% in the benign group in the training set. The age of onset was similar in the validation set. There were no significant differences between the training and validation sets regarding the histology of malignant ovarian tumors. Most of the participants were at stage III or IV, according to the International Federation of Gynecology and Obstetrics (FIGO).

The performance of different DCNN models on the validation set after 50 rounds of training is shown in Table 2, and the corresponding ROC curves are shown in Figure 2A. As the ROC curves show, the DenseNet model achieved the best performance in identifying benign malignant ovarian tumors in the validation set, with AUC of 0.997 (95% CI 0.995–1.000). AUC were 0.988 (0.980–0.997) of ResNet, 0,987 (0.978–0.996) of Inception, 0.968 (0.952–0.984) of Xception and 0.836 (0.792–0.880) of MobileNet. Moreover, the DenseNet model achieved the highest accuracy, sensitivity, specificity, PPV, and NPV on the validation

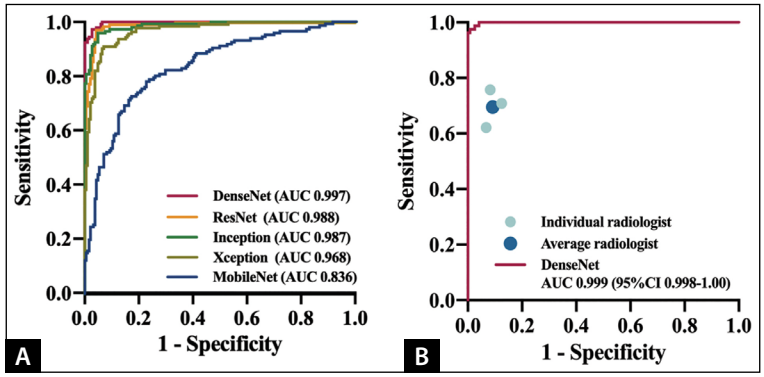

Figure 2. Performance of different deep convolutional neural network (DCNN) models and the radiologists in discriminating malignant ovarian tumors from benign ones; **A.** The receiver operating characteristic (ROC) curves for the performance of different DCNN models in the validation set; **B.** ROC for the performance of the DenseNet model versus 3 radiologists in the test set; AUC — area under the curve

Table 3. Performance of the DenseNet model versus radiologists, assessed on the test set

	Radiologist 1	Radiologist 2	Radiologist 3	Radiologist' mean	DenseNet	p value
Sensitivity	0.625 (0.510–0.731)	0.763 (0.654–0.851)	0.713 (0.600-0.808)	0.700 (0.587–0.797)	0.975 (0.913–0.997)	< 0.0001
Specificity	0.933 (0.873–0.971)	0.917 (0.852–0.959)	0.875 (0.802-0.928)	0.908 (0.842–0.953)	0.975 (0.929–0.995)	< 0.001
Accuracy	0.810 (0.749–0.862)	0.855 (0.798–0.901)	0.810 (0.749-0.862)	0.825 (0.765–0.875)	0.975 (0.943–0.992)	< 0.0001
Positive predictive value	0.862 (0.746–0.939)	0.859 (0.756–0.930)	0.792 (0.680-0.878)	0.836 (0.725–0.915)	0.963 (0.896–0.992)	
Negative predictive value	0.789 (0.712–0.853)	0.853 (0.780–0.909)	0.820 (0.743-0.883)	0.820 (0.744–0.881)	0.983 (0.941–0.998)	
Kappa	0.585	0.692	0.597	0.625	0.948	
F1	0.725	0.808	0.750	0.762	0.969	

set. For the DenseNet model, accuracy was 0.964 (0.938–0.981), sensitivity was 0.952 (0.904–0.981), specificity was 0.973 (0.938–0.991), PPV was 0.965 (0.921–0.989), and NPV was 0.963 (0.924–0.985). For the ResNet model, accuracy was 0.952 (0.923–0.972), sensitivity was 0.945 (0.895–0.976), specificity was 0.957 (0.917–0.981), PPV was 0.945 (0.895–0.976), and NPV was 0.957 (0.917–0.981). For the Inception model, accuracy was 0.903 (0.866–0.933), sensitivity was 0.973 (0.931–0.991), specificity was 0.849 (0.789-0.897), PPV was 0.835 (0.771–0.888), and NPV was 0.975 (0.938–0.993). For the Xception model, accuracy was 0.906 (0.870–0.935), sensitivity was 0.863 (0.796–0.914), specificity was 0.941 (0.896–0.970), PPV was 0.920 (0.861–0.959), and NPV was 0.897 (0.845–0.936). For the MobileNet model, accuracy was 0.773 (0.724–0.817), sensitivity was 0.747 (0.668–0.815), specificity was 0.795 (0.729–0.850), PPV was 0.741 (0.663–0.810), and NPV was 0.799 (0.734–0.854). Furthermore, the DenseNet model also had a higher kappa coefficient and F1 score than other DCNN models. From the above results, the DenseNet model has the best diagnostic capability compared to other DCNN models.

The performance of DenseNet versus the expert radiologists in the test set is shown in Figure 2B and Table 3. In the test set, the AUC value of the DenseNet model was 0.999 (95% CI 0.998–1.000). Among the radiologists, accuracy ranged from 0.810 (0.749–0.862) to 0.855 (0.798–0.901), sensitivity ranged from 0.625 (0.510–0.731) to 0.763 (0.654–0.851), specificity ranged from 0.875 (0.802–0.928) to 0.933 (0.873–0.971), PPV ranged from 0.792 (0.680–0.878) to 0.862 (0.746–0.939), and NPV ranged from 0.789 (0.712–0.853) to 0.853 (0.780–0.909). The interradiologist agreement rate was 0.735 (95% CI 0.668–0.795; Fleiss' kappa 0.667). Compared with the expert radiologists, the DenseNet model achieved higher performance in discriminating malignant ovarian tumors from benign ones. The accuracy was 0.975 (0.943–0.992) with the DenseNet model vs 0.825 (0.765–0.875; $p < 0.0001$) with the radiologists, and sensitivity was 0.975 (0.913–0.997) vs 0.700 (0.587–0.797; $p < 0.0001$), and specificity was 0.975 (0.929–0.995) vs 0.908 (0.842–0.953; $p < 0.001$). Furthermore, the DenseNet model also had higher PPV, NPV, kappa coefficient, and F1 score compared with the performance of the radiologists.

The ultrasound images misdiagnosed by DenseNet are shown in Figure S2. The confusion matrices reporting the number of true positive, false positive, false negative and true negative results achieved by Inception, MobileNet,

ResNet, Xception, DenseNet, and the radiologists are shown in Table S1 and Table S2.

DISCUSSION

In this study, an automatic DCNN model was developed and validated to discriminate malignant from benign tumors of the ovary on ultrasound images. According to the above results, DenseNet performed better than other DCNN models in the validation set with respect to AUC, accuracy, sensitivity, and specificity. Consequently, DenseNet was selected for the comparison with expert radiologists. The diagnostic capability of the DenseNet model significantly exceeded the average level of radiologists.

At present, studies on the application of deep learning in ovarian cancer are limited. The application fields include diagnosis, pathological classification and prognostic prediction. Meanwhile, magnetic resonance imaging and ultrasonography essentially take equal share of studies focusing on image recognition of ovarian tumor through deep learning. By February 2023, only 6 articles [23–28] on ultrasonographic diagnosis of ovarian tumor through deep learning were retrieved. A retrospective single-center study in South Korea [23] constructed a CNN-CAE model to make diagnoses through ultrasound images of ovarian tumors. The model consisted of two parts. The first part could automatically remove interfering information such as characters and rulers on ultrasound images through the CAE program, and the second part was the DenseNet model, which was used for image diagnosis. The accuracy of CNN-CAE model was 0.972 in distinguishing ovarian tumors from normal ovarian tissues, and the accuracy was 0.901 in recognizing malignant ovarian tumors. Another study from Taiwan, China [24] tested the performances of ten common DCNN models, and three of them with the highest accuracy (ResNet-18, ResNet-50 and Xception) were selected to construct an assembled diagnostic model. The average accuracy of the assembled model reached 0.922. However, none of the above deep learning models have been compared with the diagnostic performance of expert radiologists. Chen et al. [25] included a number of ultrasound images from 422 patients with ovarian tumors and trained two deep learning models based on ResNet, $DL_{decidion}$ and $DL_{feature}$. Then, the two models were compared with radiologists and the Ovarian-Adnexal Reporting and Data System (O-RADS). However, $DL_{decidion}$ and $DL_{feature}$ did not show superior diagnostic performances than radiologists and O-RADS. Radiologists from Shanghai represents the highest diagnostic level in China to a certain extent.

Another multicenter retrospective study [26] involving 106,400 patients showed that the AUC of the DenseNet-121 model reached 0.911 in the internal validation set, as well as 0.870 and 0.831 in the two external validation sets. With the assistance of the DCNN model, the average diagnostic accuracy of radiologists was improved from 0.783 to 0.876, revealing the great potential of DCNN model in the assistance of image diagnosis.

Since ultrasound examination is the most crucial assistant examination in the diagnosis of ovarian lesions, the accurate recognition of ovarian malignant tumors is dispensable. However, the discrimination of ovarian tumors is entirely up to radiologists, leading to subjective mistakes in accurate recognition and consistent interpretation of ovarian tumors by radiologists, as shown by the inter-radiologist agreement rate in the test set. Nevertheless, DenseNet is highly robust and can significantly avoid this defect since it learns the feature representations without subjectivity [29]. Thus, diagnostic consistency and reproducibility could be maintained by the DenseNet model effectively. On the one hand, fresh radiologists, without much experience, may be able to improve the accuracy of their diagnoses using the DenseNet model [27]. On the other hand, two radiologists are required to perform the ultrasonographic diagnosis during clinical work, one with less experience assessing the images to reach a primary diagnosis, and the other with more experience responsible for checking the primary diagnosis and offering the conclusion. The DenseNet model may relieve labor requirement, which may offer great help to remote areas in the lack of medical resources.

Furthermore, the DenseNet model has great application potential. Firstly, the DenseNet model works well for other diseases in addition to ovarian tumors, as mentioned above. Moreover, it could be applied not only in ultrasound examination but also in computerized tomography (CT), magnetic resonance imaging, retinal fundus photographs and other examinations requiring image generation [30, 31]. Finally, because the DenseNet model report is instantaneous, the diagnosis model may be integrated into the ultrasound workstations, creating a real-time diagnosis of dynamic images.

However, our study has some limitations. Firstly, we did not set up external validation sets. Secondly, we excluded patients with borderline ovarian tumors because it may lead to confusion of features between samples. And the sample size of patients with borderline ovarian tumors is too small for DCNN to obtain enough effective features to ensure the accuracy of the DenseNet model. Lastly, the three radiologists were asked to make their judgments through only one single ultrasound image in our study. However, in the real world, radiologists usually make a comprehensive judgment by referring to more than one image. Not only that, but the blood flow signals also help them make diagnoses. Therefore, the diagnostic accuracy of human radiologists based on multi-modality data would likely be higher than the performance of DCNN.

CONCLUSIONS

To conclude, the Densnet model is valuable despite its limitations. In future, we plan to include more ultrasound images from external medical centers. We will also make efforts to refine our diagnostic model of ovarian tumors. And we hope our study will make a step to improve the accuracy of the diagnoses of ovarian tumors and to help the realization of AI-assisted ultrasonographic diagnoses in clinical work, which could bring benefit to both the patients and the radiologists.

Article information and declarations

Informed consent statement

Informed consent from patients with ovarian tumors was waived as the study design was based on a retrospective review of medical records and ultrasound images.

Ethics statement

This study was approved by the ethical committee of the First Affiliated Hospital of Soochow University in accordance with the principles of the Declaration of Helsinki [No:(2023)033, 2023/01/31].

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Acknowledgements

All listed authors have made essential contributions to the work. Min Xi collected the data, performed the data analysis and drafted the original manuscript. Jun Qian and Chaomei Chen helped collect the data. Runan Zheng wrote DCNN program. Xinxian Gu and Mingyue Wang helped filtrate the ultrasound images and judge on the test set. Jinhua Zhou and Xiu Shi supervised the project design and reviewed the manuscript. All authors have read and approved the final manuscript for publication.

Conflict of interest

The authors declare no conflict of interest.

Supplementary material

Figure S1, S2, Table S1, S2.

REFERENCES

1. Sung H, Ferlay J, Siegel RL, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin. 2021; 71(3): 209–249, doi: 10.3322/caac.21660, indexed in Pubmed: 33538338.
2. Webb PM, Jordan SJ. Epidemiology of epithelial ovarian cancer. Best Pract Res Clin Obstet Gynaecol. 2017; 41: 3–14, doi: 10.1016/j.bpobgyn.2016.08.006, indexed in Pubmed: 27743768.
3. Froyman W, Timmerman D. Methods of assessing ovarian masses: international ovarian tumor analysis approach. Obstet Gynecol Clin North Am. 2019; 46(4): 625–641, doi: 10.1016/j.ogc.2019.07.003, indexed in Pubmed: 31677746.
4. Van Holsbeke C, Daemen A, Yazbek J, et al. Ultrasound experience substantially impacts on diagnostic performance and confidence when adnexal masses are classified using pattern recognition. Gynecol Obstet Invest. 2010; 69(3): 160–168, doi: 10.1159/000265012, indexed in Pubmed: 20016188.
5. Timmerman D, Schwärzler P, Collins WP, et al. Subjective assessment of adnexal masses with the use of ultrasonography: an analysis of interobserver variability and experience. Ultrasound Obstet Gynecol. 1999; 13(1): 11–16, doi: 10.1046/j.1469-0705.1999.13010011.x, indexed in Pubmed: 10201081.
6. Bi WL, Hosny A, Schabath MB, et al. Artificial intelligence in cancer imaging: Clinical challenges and applications. CA Cancer J Clin. 2019; 69(2): 127–157, doi: 10.3322/caac.21552, indexed in Pubmed: 30720861.
7. Hosny A, Parmar C, Quackenbush J, et al. Artificial intelligence in radiology. Nat Rev Cancer. 2018; 18(8): 500–510, doi: 10.1038/s41568-018-0016-5, indexed in Pubmed: 29777175.
8. Li X, Zhang S, Zhang Q, et al. Diagnosis of thyroid cancer using deep convolutional neural network models applied to sonographic images: a retrospective, multicohort, diagnostic study. Lancet Oncol. 2019; 20(2): 193–201, doi: 10.1016/S1470-2045(18)30762-9, indexed in Pubmed: 30583848.
9. Li J, Bu Y, Lu S, et al. Development of a deep learning-based model for diagnosing breast nodules with ultrasound. J Ultrasound Med. 2021; 40(3): 513–520, doi: 10.1002/jum.15427, indexed in Pubmed: 32770574.
10. Xu HL, Gong TT, Liu FH, et al. Artificial intelligence performance in image-based ovarian cancer identification: A systematic review and meta-analysis. EClinicalMedicine. 2022; 53: 101662, doi: 10.1016/j.eclinm.2022.101662, indexed in Pubmed: 36147628.
11. LeCun Y, Bengio Y, Hinton G. Deep learning. Nature. 2015; 521(7553): 436–444, doi: 10.1038/nature14539, indexed in Pubmed: 26017442.
12. He K, Zhang X, Ren S, et al. Deep Residual Learning for Image Recognition. In Proceedings of the Proceedings of the IEEE Conference on Computer Vision and Pattern Recognition. Las Vegas, NV, USA, 2016.
13. Rupesh KS, Klaus G,Jürgen S. Highway Networks. In Proceedings of the International Conference on Machine Learning. Lille, France, 2015.
14. Huang G, Sun Yu, Liu Z, et al. Deep networks with stochastic depth. Computer Vision – ECCV 2016. 2016: 646–661, doi: 10.1007/978-3-319-46493-0_39.
15. Huang G, Liu Z, Van ML, et al. Densely Connected Convolutional Networks. In Proceedings of the Proceedings of the IEEE Conference on Computer Vision and Pattern Recognition. Honolulu, HI, USA, 2017.
16. Esteva A, Kuprel B, Novoa RA, et al. Dermatologist-level classification of skin cancer with deep neural networks. Nature. 2017; 542(7639): 115–118, doi: 10.1038/nature21056, indexed in Pubmed: 28117445.
17. Forrest I, Matt M, Sergey K, et al. DenseNet: implementing efficient ConvNet descriptor pyramids. Computer Science. 2014.
18. Szegedy C, Vanhoucke V, Iofe S, et al. Rethinking the inception architecture for computer vision. In Proceedings of the Proceedings of the IEEE Conference on Computer Vision and Pattern Recognition. Las Vegas, NV, USA, 2016.
19. Howard AG, Zhu M, Chen B, et al. MobileNets: Efficient Convolutional Neural Networks for Mobile Vision Applications. arXiv 2017.
20. Chollet F. Xception: Deep learning with depthwise separa-ble convolutions. In Proceedings of the Proceedings of the IEEE Conference on Computer Vision and Pattern Recognition. Seattle, WA, USA, 2017.
21. CLOPPER CJ, PEARSON ES. The use of confidence or fiducial limits illustrated in the case of the binomial. Biometrika. 1934; 26(4): 404–413, doi: 10.1093/biomet/26.4.404.
22. Fleiss JL. Measuring nominal scale agreement among many raters. Psychological Bulletin. 1971; 76(5): 378–382, doi: 10.1037/h0031619.
23. Jung Y, Kim T, Han MR, et al. Ovarian tumor diagnosis using deep convolutional neural networks and a denoising convolutional autoencoder. Sci Rep. 2022; 12(1): 17024, doi: 10.1038/s41598-022-20653-2, indexed in Pubmed: 36220853.
24. Hsu ST, Su YJ, Hung CH, et al. Automatic ovarian tumors recognition system based on ensemble convolutional neural network with ultrasound imaging. BMC Med Inform Decis Mak. 2022; 22(1): 298, doi: 10.1186/s12911-022-02047-6, indexed in Pubmed: 36397100.

25. Chen H, Yang BW, Qian Le, et al. Deep learning prediction of ovarian malignancy at US compared with O-RADS and expert assessment. Radiology. 2022; 304(1): 106–113, doi: 10.1148/radiol.211367, indexed in Pubmed: 35412367.
26. Gao Y, Zeng S, Xu X, et al. Deep learning-enabled pelvic ultrasound images for accurate diagnosis of ovarian cancer in China: a retrospective, multicentre, diagnostic study. Lancet Digit Health. 2022; 4(3): e179–e187, doi: 10.1016/S2589-7500(21)00278-8, indexed in Pubmed: 35216752.
27. Christiansen F, Epstein EL, Smedberg E, et al. Ultrasound image analysis using deep neural networks for discriminating between benign and malignant ovarian tumors: comparison with expert subjective assessment. Ultrasound Obstet Gynecol. 2021; 57(1): 155–163, doi: 10.1002/uog.23530, indexed in Pubmed: 33142359.
28. Wang H, Liu C, Zhao Z, et al. Application of deep convolutional neural networks for discriminating benign, borderline, and malignant serous ovarian tumors from ultrasound images. Front Oncol. 2021; 11: 770683, doi: 10.3389/fonc.2021.770683, indexed in Pubmed: 34988015.
29. Gu J, Wang Z, Kuen J, et al. Recent advances in convolutional neural networks. Pattern Recognition. 2018; 77: 354–377, doi: 10.1016/j.patcog.2017.10.013.
30. Akazawa M, Hashimoto K. Artificial intelligence in gynecologic cancers: Current status and future challenges — A systematic review. Artif Intell Med. 2021; 120: 102164, doi: 10.1016/j.artmed.2021.102164, indexed in Pubmed: 34629152.
31. Guo C, Yu M, Li J. Prediction of different eye diseases based on fundus photography via deep transfer learning. J Clin Med. 2021; 10(23), doi: 10.3390/jcm10235481, indexed in Pubmed: 34884192.

SUPPLEMENTARY MATERIALS

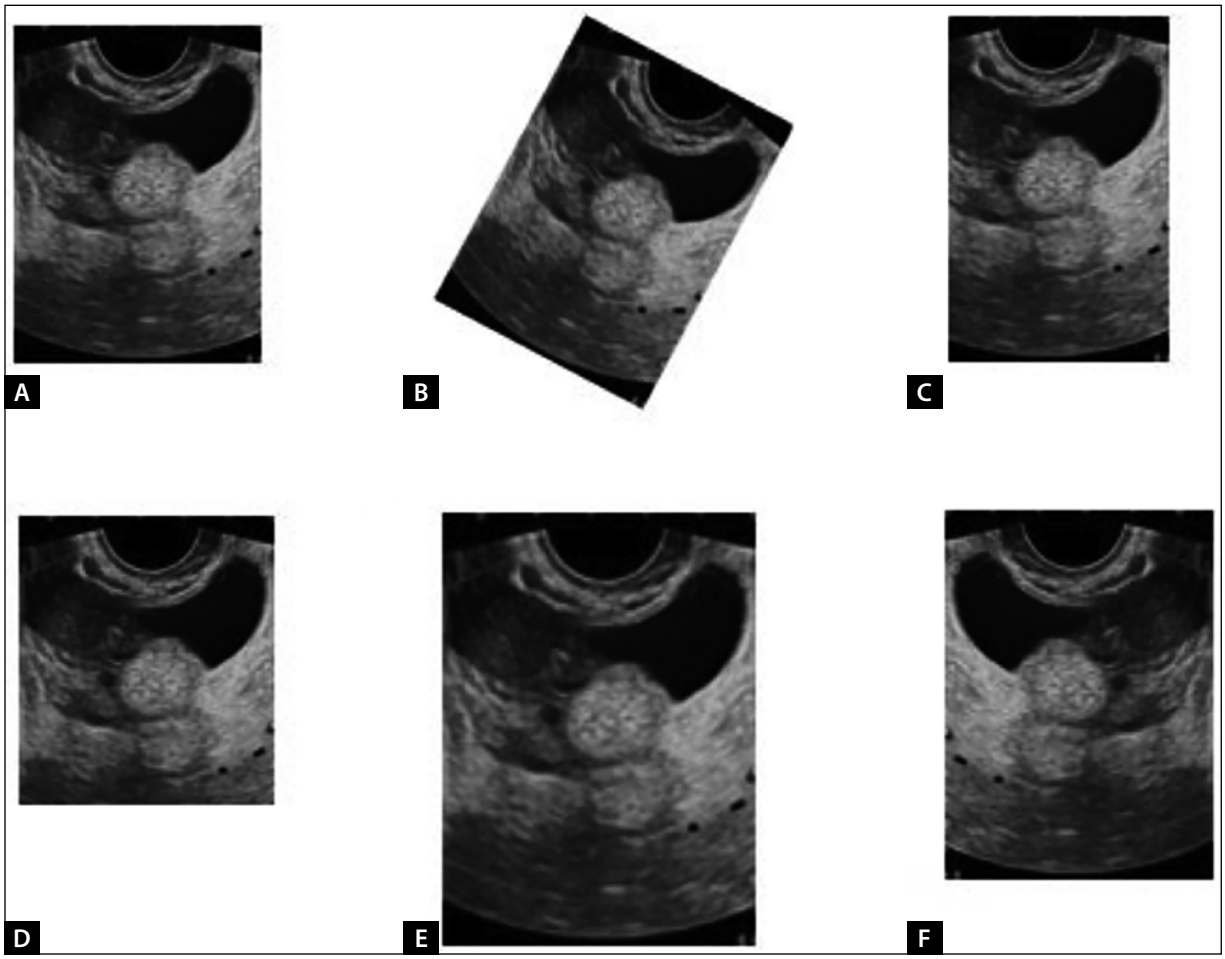

Figure S1. Data augmentation effect; **A.** Original image; **B.** Rotate; **C.** Horizontal translation; **D.** Vertical translation; **E.** Zoom; **F.** Horizontal flip

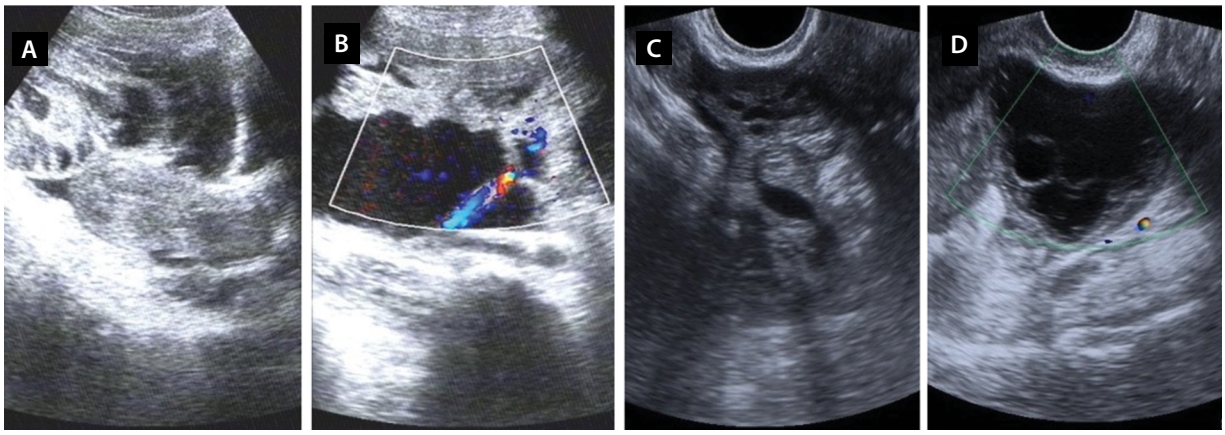

Figure S2. Images misdiagnosed by the DenseNet Model; **A, B.** Malignant images classified as be-nign; **C, D.** Benign images classified as malignant

Table S1. Confusion matrices of different different deep convolutional neural network (DCNN) models on the validation set

	MobileNet		Xception		Inception	
	Truth		Truth		Truth	
Prediction	Malignancy	Benign	Malignancy	Benign	Malignancy	Benign
Malignancy	109	38	126	11	142	28
Benign	37	147	20	174	4	157
	ResNet		DenseNet			
	Truth		Truth			
Prediction	Malignancy	Benign	Malignancy	Benign		
Malignancy	138	8	139	5		
Benign	8	177	7	180		

Table S2. Confusion matrices of radiologists and DenseNet on the test set

	Radiologist 1		Radiologist 2		Radiologist 3	
	Truth		Truth		Truth	
Prediction	Malignancy	Benign	Malignancy	Benign	Malignancy	Benign
Malignancy	50	8	61	10	57	15
Benign	30	112	19	110	23	105
	DenseNet					
	Truth					
Prediction	Malignancy	Benign				
Malignancy	78	3				
Benign	2	117				

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Incisional hernia after ovarian debulking surgery

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ABSTRACT

Objectives: The purpose of our study was to explore the incidence and contributing variables of an incisional hernia after debulking surgery for advanced ovarian cancer.

Material and methods: The imaging of patients who underwent debulking surgery with an extended vertical incision was re-evaluated for incisional hernias at one-year follow-up, and their medical records were reviewed. We performed univariate and multivariate analysis to find out the risk factors for an incisional hernia.

Results: The overall annual incidence of incisional hernia was 26.7 percent (46 of 172). Univariate analysis revealed a statistically significant relationship between age, body mass index (BMI), and the length of the incision and the incidence of an incisional hernia. The only factor identified by multivariate analysis as being independently related with the development of an incisional hernia within a year of the operation was BMI (OR 1.12, 95% CI 1.01–1.25, p = 0.04).

Conclusions: Incisional hernia rates were high after ovarian cancer surgeries, and BMI was the independent factor significantly linked to hernia formation. To reduce the high ratio of incisional hernia among these group of patients, preventative strategies should be researched and applied.

Keywords: incisional hernia; ventral hernia; ovarian cancer; cytoreductive surgery

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INTRODUCTION

Incisional hernia occurs after laparotomy at a rate of 5–20%, and up to 43% in high-risk individuals [1]. The risk of an incisional hernia is influenced by some variables of surgical technique and patient characteristics such as age, chronic pulmonary disease, anemia, the type of surgery, postoperative coughing, wound infection, obesity, hypoalbuminemia & poor nutrition, sepsis, chronic glucocorticoid therapy, ascites, chemotherapy and malignancy [2]. To know these factors are important for counselling both before and after surgery.

In recent years, maximal cytoreductive surgery has become cornerstone treatment of ovarian cancer, and to accomplish it, generally an extended midline incision is required [3]. Patients with cancer appear to have a larger baseline risk of developing a hernia after surgery than patients having surgery for benign conditions. However, there are few studies examining incisional hernia in patients underwent surgery for ovarian cancer [4–6].

Our study's goal was to investigate the incidence and factors connected to the development of an incisional hernia after debulking surgery for ovarian cancer.

MATERIAL AND METHODS

After the ethics committee approved the study (institution review board number: E-29624016-050.99-907831), retrospective data was collected from single centre's medical records of the patients underwent cytoreductive surgery for advanced disease of ovarian cancer (also peritoneal and tubal cancers were included and accepted as ovarian cancer), at Gynaecological Oncology Department, between January 2017 and December 2021.

Participants aged over 18 years were included. Patients who had a history of incisional or umbilical hernia before

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the surgery and patients who were lost during the follow-up within 12 months of the operation, were excluded. Patients who had a relaparotomy due to complications such as anastomotic leak and whose fascia was not closed, were also excluded.

Preoperative mechanical bowel preparation was used in all patients. Antibiotic prophylaxis was given, and we used povidone-iodine for antisepsis of the skin. The team of gynaecological oncologic surgeons (gyn-oncology team consisted of 8 surgeons, two surgeons performed each surgery: one was a senior/consultant and the other was a fellow) performed all the operations through a midline laparotomy. Laparotomy was performed with a scalpel for skin incision, extending from the pubic symphysis to the xiphoid process; followed by diathermy in cut mode for the subcutaneous tissue. A little section of fascia was opened with a scalpel and then cut with scissors. The preperitoneal fat was bluntly dissected from the peritoneum by sweeping the index finger. Once it was marked, the peritoneum was raised with forceps and opened longitudinally with scissors. For exploration, a Thompson retractor was used. At the end of the surgery, we used a continuous-suture technique with tissue bites of approximately 8 mm every 8 mm for closing the fascia with slowly absorbable monofilament loop suture, polydioxanone (PDS) no 1. Subcutaneous tissue was closed with absorbable multifilament polyglactin no 2–0 and skin was closed with metal staples. A drain was put in a Douglas pouch. Subcutaneous drains were not used.

Until the patients were discharged, all wounds were examined daily. Patients were asked to use an abdominal corset for six weeks postoperatively. The metal staples were removed between the 14th and 21st postoperative day. Patients were followed up every 3 months according to our ovarian cancer follow-up protocol, and magnetic resonance imaging (MRI)/computed tomography (CT) scan was performed in the first year after the surgery. We reviewed their reports that had been evaluated by radiologists. And the imagings were double-checked by a gyn-oncologist. Demographic characteristics, preoperative serum albumin levels, the American Society of Anaesthesiology (ASA) score of patients, type of surgery, intraoperative details, the duration of hospital stay and early (within 30 days) postoperative complications including infection, evisceration were noted. Those who received preoperative chemotherapy regardless of primary or recurrent surgery were considered neoadjuvant chemotherapy. A wound infection was described as pus discharge. The presence of wound dehiscence without evisceration was also considered a sign of wound infection. All imaging (CT or MRI) performed within the first year of follow up, were reviewed and if a fascial defect along the incision (larger than 1 cm) was detected, it was noted as an incisional hernia.

Patients still alive were called for the purpose of measuring the incision length and informed consent was obtained.

The Statistical Package for the Social Sciences (SPSS) 21.0 version was used for all statistical analyses. Comparison of categorical variables were performed using exact Fisher's test and Yates continuity correction. After the normality of variables were examined by Shapiro–Wilk test, comparisons of continuous variables were compared using an independent-samples T-test or Mann–Whitney U test. P values < 0.05 were considered statistically significant. Data were expressed as mean ± standard deviation (SD) or median and interquartile range (IQR) for continuous variables, and absolute numbers and percentages for categorical values. Multivariate logistic regression was performed for the variables that were significant in the univariate analysis.

RESULTS

One hundred seventy-two patients were included for analysis. Thirty-seven of the patients (21.5%) were operated for recurrence, the rest were operated for primary ovarian cancer at advanced stage. Forty-one of the 122 patients (23.8%) received neoadjuvant chemotherapy. All patients received chemotherapy (platinum-based regimen) postoperatively, three refused to complete treatment and four interrupted due to toxicity. Hyperthermic intraperitoneal chemotherapy (HIPEC) was administered to a total of eleven patients. Sixteen patients (9.3%) had remaining implants that were greater than 1 cm.

The total incidence of incisional hernia during a year time was 26.7% (46 of 172). Table 1 and 2 display the characteristics and operative details of the patients according to whether an incisional hernia is present (or not).

Of all patients, mean age was 53.1 ± 12.1 years and median body mass index (BMI) was 28 kg/m^2 (IQR 24–33). Of the 69 patients we could measure, median incision length was 30 cm (IQR 27–32). According to a univariate analysis, an association between age, BMI, the length of the incision and the development of an incisional hernia was found statistically significant. After include age, BMI, the length of the incision into a multivariate logistic regression model, BMI was the only factor that was independently linked to the development of an incisional hernia within a year of surgery [odds ratio (OR) 1.12; 95% confidence interval (CI) 1.01–1.25, p = 0.04]. The outcomes of the multivariate analysis are listed in Table 3.

DISCUSSION

Incisional hernia rate in our series were slightly higher than those reported in the literature. The high-risk group (*e.g.*, perioperative chemoradiation and malnutrition) and surgical characteristics (major surgical procedures and extensive incision length; xiphoid-pubic distance with

Table 1. Characteristics of patients

	Patients with incisional hernia (n = 46)	Patients without incisional hernia (n = 126)	p value*
Age [y]	55.9 ± 10.5	51.7 ± 13.2	0.04
Parity	2 (1–8)	2 (1–6)	0.18
BMI [kg/m^2]	30.8 (25–33)	26.5 (23.5–32)	< 0.001
Smoking, n [%]	3 (6.5)	17 (13.5)	0.12
Neoadjuvant chemotherapy, n [%]	15 (32.6)	26 (20.6)	0.22
Postmenopausal, n [%]	30 (65.2)	79 (62.7)	0.91
Preoperative serum albumin level [mg/dL]	3.86 ± 0.61	3.85 ± 0.67	0.47
ASA score (3–4), n [%]	13 (28.3)	18 (14.3)	0.1
Diabetes mellitus, n [%]	9 (19.6)	11 (8.7)	0.15
Hypertension, n [%]	12 (26.1)	33 (26.1)	0.99
Ascites, n [%]	44 (95.7)	121 (96)	0.99
History of midline incision, n [%]	17 (36.9)	32 (25.4)	0.31

*p ≤ 0.05 is regarded as statistically significant. Statistical significance was calculated using exact Fisher's test (smoking, ascites) and Yates continuity correction [menopausal status, neoadjuvant chemotherapy, American Society of Anaesthesiology (ASA) score, diabetes, hypertension, history of midline incision] for categorical variables. P values for continuous variables were calculated using Mann–Whitney test [parity, body mass index (BMI)] and independent-samples t test (age and serum albumin level)

Table 2. Operative data of patients

	Patients with incisional hernia (n = 46)	Patients without incisional hernia (n = 126)	p value*
Type of incision, n [%] Transumbilical Periumbilical	 20 (43.4) 26 (56.6)	 56 (44.4) 70 (55.6)	0.99
Incision length [cm]	30 (27–32) n = 21	28.5 (26–30.8) n = 48	0.03
Suboptimal cytoreduction, n [%]	3 (6.5)	13 (10.3)	0.16
HIPEC, n [%]	4 (8.7)	7 (5.5)	0.26
Duration of surgery [min]	225 (165–290)	270 (190–330)	0.08
Bowel resection, n [%]	10 (21.7)	38 (30.2)	0.50
Stoma, n [%]	5 (10.9)	19 (15.1)	0.35
Hospitalization period [day]	7 (5–9)	6 (4–8)	0.94
Wound infection, n [%]	6 (13)	9 (7.1)	0.59
Surgical site infection (except the wound), n [%]	5 (10.9)	7 (5.5)	0.29

*p ≤ 0.05 is regarded as statistically significant. Statistical significance was calculated using exact Fisher's test [cytoreduction, hyperthermic intraperitoneal chemotherapy (HIPEC), surgical site infection] and Yates continuity correction (type of incision, bowel resection, stoma, wound infection) for categorical variables. P values for continuous variables were calculated using Mann–Whitney test (incision length, duration of surgery, hospitalization period)

Table 3. Multivariate logistic regression

	OR	95% CI	p value
Age	1.00	0.947–1.06	0.89
BMI	1.12	1.01–1.25	0.04
Incision length	1.11	0.90–1.37	0.32

OR — odds ratio; CI — confidence interval; BMI — body mass index

a median of 30 cm) could be an explanation of the overall incisional hernia rate. Moreover, since we considered any gap in the fascia as a hernia in CT scan/MRI images, there is no situation that could underestimate hernia rates with physical examination as in other studies. In 2016, Guitarte et al. [4] reported 16 (6.3%) incisional hernias among the 252 patients, 28% of whom had ovarian cancer. In that

retrospective study, incisional hernias were only discovered through physical examination, and the mean BMI of the patients was 35.9 kg/m^2, which might have impeded examination-based detection. According to Long et al. [5], after primary laparotomy for ovarian cancer, the first-year hernia rate was 8.8% (21/239) and the second-year hernia rate was 23.4% (39/167). One of the main limitations of that study was the fact that not all included patients underwent radiological examination and that the authors do not specify, the number of hernias diagnosed by CT scan or physical examination. They found a significant relationship between BMI and the development of incisional hernias in both the first and second years, which was compatible with our findings. They also discovered intraperitoneal chemotherapy to be significant for the first-year hernias and advanced stage for the second-year hernias. All the patients in our series had advanced disease, and eleven of them received HIPEC treatment; the results were not significantly different. HIPEC was discovered to be an independent factor linked to the development of an incisional hernia in patients with peritoneal surface cancers treated by cytoreduction and HIPEC, according to a retrospective analysis [7]. Spencer et al. [6] found 9.8% of patients (n = 265) and an additional 7.9% of patients (n = 189) developed hernias in the first and second years, respectively. Poor nutritional status and suboptimal cytoreduction were independent predictors for the creation of first-year hernias, while age was the sole factor linked to the development of incisional hernias for the second year. In our research, age was identified as a risk factor by a univariate test, however multivariate modelling invalidated this finding. Poor nutritional status and suboptimal cytoreduction were not associated with the occurrence of an incisional hernia.

The typical risk variables for incisional hernia reported by general surgeons [2], apart from BMI, were not found to be relevant in our series. The physical and nutritional health of cancer patients is worse. Malignancy and chemotherapy can deteriorate the process of tissue repair [7]. Even though preoperative ASA score and the albumin serum levels of our patients were not statistically different, it would be incorrect to assess their condition solely based on these. Additionally, because of major surgery, prolonged operation time may impair the surgeon's performance, which could result in a less-than-ideal abdominal closure.

It is known that suture: wound length ratio and closure technique (*e.g.*, size of the bite) are crucial for hernia development [8, 9], which were not well documented in our medical records. The STITCH trial [9] demonstrated that in comparison to suturing with the traditional large bites (10 mm) approach, continuous small bites (5 mm) suturing of the fascia after abdominal midline incision lowers the incidence of incisional hernia. They used PDS 2-0 with a 31 mm needle for small bites and double loop PDS 1 with a 48 mm needle for large bites. Five hundred sixty patients at surgical and gynaecological departments were randomized and at one year follow-up, 57 (21%) of 277 patients in the large bites group and 35 (13%) of 268 patients in the small bites group had incisional hernia (p = 0.0220, covariate adjusted odds ratio 0.52, 95% CI 0.31–0.87; p = 0.0131). They stated that three-quarters of patients received radiological imaging during follow-up. We used loop sutures (PDS 1) to close each laparotomy. Guitarte et al. [4] reported that incisions closed with loop suture had a hernia risk that was more than five times higher than those closed without loop suture.

The prevention of incisional hernias by prophylactic mesh augmentation may have a significant impact for high-risk patients. Due to concerns over mesh infection and consequences, surgeons are hesitant to use prophylactic mesh, but studies did not show an increased risk of surgical-site infection [10, 11]. The European and American Hernia Societies stated in their guidelines: Prophylactic mesh augmentation after elective midline laparotomy can be considered to reduce the risk of incisional hernia [12]. On the other hand, studies on the use of mesh after cytoreductive surgeries are insufficient. It is controversial whether it is rational to use it in cases as ovarian cancer which has a high recurrence rate and necessitates repeated surgeries.

The strengths and limitations

Our study's disadvantages were its retrospective design and, accordingly, the lack of data about detailed closure technique and ratio of suture length to wound length. To minimize the bias brought forth by various surgical closure methods performed by different surgeons and avoid the heterogeneity of closure techniques, we restricted our search to the years 2017–2021 to ensure that all surgeries were performed by the same team. The absence of identification of the chemotherapeutic drugs, particularly bevacizumab, which was found to deteriorate wound healing and expedite the development of incisional hernias [5], was another weakness of our investigation. To our knowledge, this is the study with the highest number of patients among the studies in which ovarian cancer surgery was performed with a midline incision between the xiphoid-pubis. The main strength of our study was that all individuals who completed follow-up underwent imaging. This procedure prevented underestimation of the number of patients with incisional hernia, because radiological examination is more sensitive than physical examination alone.

CONCLUSIONS

Women who had ovarian cancer surgery were found to be at a high risk of developing incisional hernias. The sole variable that was significantly associated to the development of hernias was BMI. Incision should be closed

by a skilled surgeon and should be treated with the same seriousness as all other surgical procedures. Focus should be placed on risk-reducing strategies as continuous small bite technique and prophylactic mesh augmentation.

Article information and declarations

Ethics statement

The study was approved by University School of Medicine Ethics Committee (institution review board number: E-29624016-050.99-907831).

Author contributions

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by HYC, MMC and HMB. The first draft of the manuscript was written by HYC and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

HYC: Conception of the work, manuscript writing, analysis and interpretation of data.

MMC: Acquisition of data and literature research.

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Conflict of interest

The authors declare that they have no conflict of interest.

Supplementary material

None.

REFERENCES

1. Baucom RB, Ousley J, Beveridge GB, et al. Cancer Survivorship: Defining the Incidence of Incisional Hernia After Resection for Intra-Abdominal Malignancy. Ann Surg Oncol. 2016; 23(Suppl 5): 764–771, doi: 10.1245/s10434-016-5546-z, indexed in Pubmed: 27743227.
2. van Ramshorst GH, Nieuwenhuizen J, Hop WCJ, et al. Abdominal wound dehiscence in adults: development and validation of a risk model. World J Surg. 2010; 34(1): 20–27, doi: 10.1007/s00268-009-0277-y, indexed in Pubmed: 19898894.
3. Colombo N, Sessa C, du Bois A, et al. ESMO-ESGO Ovarian Cancer Consensus Conference Working Group. ESMO-ESGO consensus conference recommendations on ovarian cancer: pathology and molecular biology, early and advanced stages, borderline tumours and recurrent disease†. Ann Oncol. 2019; 30(5): 672–705, doi: 10.1093/annonc/mdz062, indexed in Pubmed: 31046081.
4. Guitarte C, Grant J, Zhao H, et al. Incisional hernia formation and associated risk factors on a gynecologic oncology service: an exploratory analysis. Arch Gynecol Obstet. 2016; 294(4): 805–811, doi: 10.1007/s00404-016-4100-3, indexed in Pubmed: 27101367.
5. Long KC, Levinson KL, Diaz JP, et al. Ventral hernia following primary laparotomy for ovarian, fallopian tube, and primary peritoneal cancers. Gynecol Oncol. 2011; 120(1): 33–37, doi: 10.1016/j.ygyno.2010.09.015, indexed in Pubmed: 20947151.
6. Spencer RJ, Hayes KD, Rose S, et al. Risk factors for early-occurring and late-occurring incisional hernias after primary laparotomy for ovarian cancer. Obstet Gynecol. 2015; 125(2): 407–413, doi: 10.1097/AOG.0000000000000610, indexed in Pubmed: 25568995.
7. Cascales Campos PA, González-Gil A, Gómez-Ruiz AJ, et al. Risk factors and management of incisional hernia after cytoreduction and hyperthermic intraperitoneal chemotherapy (HIPEC) in patients with peritoneal surface malignancies. Hernia. 2020; 24(2): 257–263, doi: 10.1007/s10029-019-01962-4, indexed in Pubmed: 31069579.
8. van Rooijen MMJ, Lange JF. Preventing incisional hernia: closing the midline laparotomy. Tech Coloproctol. 2018; 22(8): 623–625, doi: 10.1007/s10151-018-1833-y, indexed in Pubmed: 30094713.
9. Deerenberg EB, Harlaar JJ, Steyerberg EW, et al. Small bites versus large bites for closure of abdominal midline incisions (STITCH): a double-blind, multicentre, randomised controlled trial. Lancet. 2015; 386(10000): 1254–1260, doi: 10.1016/S0140-6736(15)60459-7, indexed in Pubmed: 26188742.
10. Jairam AnP, Timmermans L, Eker HH, et al. PRIMA Trialist Group. Prevention of incisional hernia with prophylactic onlay and sublay mesh reinforcement versus primary suture only in midline laparotomies (PRIMA): 2-year follow-up of a multicentre, double-blind, randomised controlled trial. Lancet. 2017; 390(10094): 567–576, doi: 10.1016/S0140-6736(17)31332-6, indexed in Pubmed: 28641875.
11. Depuydt M, Allaeys M, de Carvalho LA, et al. Prophylactic Mesh After Midline Laparotomy: Evidence is out There, but why do Surgeons Hesitate? World J Surg. 2021; 45(5): 1349–1361, doi: 10.1007/s00268-020-05898-0, indexed in Pubmed: 33558998.
12. Deerenberg EB, Henriksen NA, Antoniou GA, et al. Updated guideline for closure of abdominal wall incisions from the European and American Hernia Societies. Br J Surg. 2022; 109(12): 1239–1250, doi: 10.1093/bjs/znac302, indexed in Pubmed: 36026550.

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Can an apparent diffusion coefficient of uterine fibroid before uterine artery embolization predict potential fibroid response?

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ABSTRACT

Objectives: ACOG guidance confirms the use of uterine artery embolisation (UAE) as an alternative to hysterectomy or myomectomy.

The main objective of this article is to evaluate the ability of preoperative magnetic resonance ımaging (MRI) to study the relationship between uterine fibroid reduction and diffusion coefficient (ADC) value after UAE. This is a relevant topic with the growing interest in using ADC as a noninvasive imaging biomarker for monitoring tissue changes and predicting uterine fibroid response to UAE over the past years.

Material and methods: In this prospective controlled non-randomized trial; uterine fibroid volume, fibroid diameter, uterine volume, fibroid ADC and normal myometrium ADC were recorded before and after UAE. Wilcoxon test was used in the analysis of the dependent quantitative data. Pearson correlation coefficients were calculated between post-UAE uterine volume, fibroid volume, and average fibroid diameter reduction and the patient's age, parity, gravidity, fibroid ADC and myometrial ADC before UAE.

Results: The mean fibroid volume reduction was 36.0% (range between 17.3–77.7%). Mean fibroid diameter, fibroid volume, uterine volume, and myometrium ADC values after UAE were significantly lower than before the procedure ($p = 0.002$, < 0.001, 0.001, 0.006 respectively), but the decrease in fibroid ADC is not significant. As a result decrease in fibroid volume was greater as pre-UAE fibroid ADC values increased, and that finding may contribute to the selection of the patients for the procedure.

Conclusions: The ADC value before UAE was positively correlated with fibroid volume reduction.

Keywords: embolization; gynecology; myoma; uterine artery

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INTRODUCTION

Uterine artery embolization (UAE) has been used as a non-surgical treatment option for symptomatic fibroids [1]. Atlantic Canada Oncology Group (ACOG) guidance confirms the use of UAE as an alternative to hysterectomy or myomectomy [2]. The goal of UAE is to permanently occlude the uterine arterial branches that supply leiomyomas and eventually lead to the myomas' devascularization and infarction [3]. Magnetic resonance imaging (MRI) is the choice of radiological technique for determining patient eligibility and for assessing the possible procedural risk. It is a useful tool for evaluating potential treatment outcomes and for diagnosing complications after UAE [4, 5].

The efficacy of UAE is determined by symptom relief of the patient and the symptom is heavy menstrual bleeding or dysmenorrhea caused by intramural fibroids. Most patients (73 to 90 percent) report improvement or disappearance of heavy menstrual bleeding symptoms up to 10 years after the treatment [6, 7]. In the embolization versus hysterectomy randomized trial 62% of patients in the UAE group reported that menorrhagia had completely resolved at two years. At five years 83% of the patients reported no menorrhagia. The cumulative secondary hysterectomy rate after the UAE procedure was 24% at two years, 28% at five years, and 35% at 10 years respectively [6, 8, 9]. Uterine artery embolization also affects lower abdominal pain and dysmenorrhea symptoms

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of uterine fibroids in up to 80% of patients. In the EMMY study, UAE compared with the hysterectomy group; 85 and 78% at least moderate improvement in terms of dysmenorrhea at two years were found respectively [8]. Another study, the Ontario Uterine Fibroid Embolization Trial was a multicenter prospective study that reported after bilateral UAE there is an improvement of dysmenorrhea in 77% of 538 patients [10]. When we look at the pelvic pressure and bulk-related symptoms in large cohort studies it is found that up to 90% of patients reported improvement in bulk-related complaints and in the EMMY trial compared with hysterectomy the improvements found as 66 vs 69% respectively [8, 11, 12].

In meta-analyses of randomized trials comparing UAE with surgeries such as myomectomy, hysterectomy, and laparoscopic uterine artery occlusion; UAE resulted in the faster resumption of daily activities, lower rates of blood transfusions odds ratio (OR) 0.07, 95% CI 0.01–0.52], lower risks of major complications [risk ratio (RR) 0.45, 95% CI 0.22–0.95] and higher risks of minor complications (RR 1.65, 95% CI 1.32–2.06) [13, 14].

Some of the existing literature emphasizes the utility of diffusion-weighted imaging (DWI) sequences in MRI [15]. DWI is a functional imaging technique that could reflect the varying tissue cellularity and it is a noninvasive imaging modality that does not require the administration of contrast agents [16]. The apparent diffusion coefficient (ADC) which was calculated from DWI, can characterize tumor architecture like cellularity, cell membrane integrity, and vascularity [17]. Fibroids that show high signals on T1W images and low vasculature before embolization are likely to respond poorly to UAE [4, 18].

Ideal candidates for UAE include premenopausal patients that have heavy menstrual bleeding or dysmenorrhea due to uterine fibroid and who have no desire for future pregnancy. It is important to identify patients who will benefit from this procedure before the UAE. This benefit may be objectively assessed by a reduction in uterine and fibroids volume/size or clinical improvement. In this study, we investigated whether myometrial ADC and fibroid ADC examined by MRI before UAE were associated with fibroid shrinkage potential.

MATERIAL AND METHODS

This prospective self-controlled nonrandomized trial was approved by the institutional review board and a waiver of consent was granted. All procedures were carried out by the ethical rules and the principles of the Declaration of Helsinki. Eighteen patients diagnosed with uterine fibroids were included in the study for two years. Fifteen of them refused surgery, and three could not be operated on because the operation was risky due to cardiac causes. All the patients who want UAE and refuse/could not have an operation are accepted to the study, which is why there is not any bias in choosing the cases. All UAE patients are included to the study during those two years in our clinic.

Lower abdominal conventional MRI and DWI examinations were performed using an 8-channel body coil with a 1.5 Tesla superconducting MRI device (Signa HDxt, GE Medical Systems, Milwaukee, Wisconsin, USA). In all investigations, sagittal T2A, axial T1A FSE, fat-printed axial T2A FRFSE, coronal STIR, axial and sagittal contrast images, and DAG images are obtained. Diffusion-weighted imagings are obtained by using b = 0 and b = 800 values. Apparent diffusion coefficient maps are created on a separate workstation (Advantage Workstation 4.4-GE Medical Systems) using the software program (Functool). Measurements were performed using the ROI to include 80% of the fibroids on the ADC map. In addition, ADC values were measured from normal myometrium without fibroids.

During ADC calculations, all fibroids greater than 4.7 cm were included and largest fibroid was chosen for the calculations. Before and after UAE, fibroid and uterus volumes, using an ellipsoid formula [$4/3*pi(\pi)*r^1*r^2*r^3$ (r = radius)], were measured on axial and sagittal T2 weighted images. Before and after the UAE, fibroids volume, mean fibroids diameter, uterine volume, fibroids ADC and normal myometrium ADC were recorded.

Embolization technique

Under fluoroscopy, first the internal iliac and then the uterine artery is catheterized with a microcatheter through a macrocatheter. After uterine arteriography, embolic material was injected into the uterine artery till the occlusion of all vessels of the fibroid has achieved. According to the size of the uterine artery, bead block microspheres were injected in the form of 100–300 or 300–500 particles. All patients experienced mild-to-severe ischemic pain requiring parenteral analgesia but pain severity gradually decreased after the first 24 hours. Tramadol 50 mg IV infusion was given for the first 24 hours, and oral non-steroid anti-inflammatory analgesic (NSAID) was given for 72 hours after discharge. No complications were observed during or after the procedure.

Statistical analysis

All statistical analyzes were calculated SPSS version 16 for Windows. Descriptive statistics were used to describe the content and frequencies. Wilcoxon test was used in the analysis of the dependent quantitative data. Pearson correlation coefficients were calculated between post-UAE uterine volume, fibroid volume, and average fibroid diameter reduction and the patient's age, parity, gravidity, fibroid ADC and myometrial ADC before UAE.

Table 1. The demographical features of the patient

Characteristics	Value
Age [years] mean ± SD	41.1 ± 8.8
Gravida, median (min–max)	1.5 (0–6)
Parity, median (min–max)	1.5 (0–4)
Multipl myom, n	2
Single myom, n	16
Fibroid volume [cc^3] mean ± SD (min–max)	272.7 ± 240.1 (29–730)
Fibroid volume reduction, mean (min–max)	36.0% (17.3–77.7%)

SD — standard deviation

Table 2. Uterus volume, fibroid volume, fibroid apparent diffusion coefficient (ADC) and myometrium ADC; mean standard deviation (SD) and p values

		Mean ± SD	p value
Average myom diamater			
	Before UAE	74.5 ± 22.7	
	After UAE	64.8 ± 24.1	0.002[w]
Uterine volume			
	Before UAE	655.0 ± 410.2	
	After UAE	473.1 ± 289.2	0.000[w]
Fibroid volume			
	Before UAE	272.7 ± 240.1	
	After UAE	197.3 ± 212.4	0.001[w]
Fibroid ADC [× 103]			
	Before UAE	0.82 ± 0.39	
	After UAE	0.57 ± 0.52	0.352[w]
Myometrium ADC [× 103]			
	Before UAE	1.00 ± 0.42	
	After UAE	0.42 ± 0.52	0.006[w]

[w]Wilcoxon test; UAE — uterine artery embolisation

RESULTS

The mean age of the patients included in the study was 41.1 ± 8.8, and the median gravidity and parity were 1.5 (0–6) and 1.5 (0–4), respectively (Tab. 1). Multiple myomas in two patients and single myomas in other patients were present. Fibroid volumes ranged from 29 to 710 cc^3. Uterine volume was over 1000 cm3 in four patients. Duration between UAE and follow-up MRI was 90 days.

Mean myoma diameter, uterine volume, fibroid volume, and myometrium ADC values after UAE were significantly lower than before the procedure ($p = 0.002$, $p < 0.001$, $p = 0.001$, $p = 0.006$ respectively), but the decrease in fibroid ADC was not significant. The mean fibroid volume reduction (VR) was 36.0% (range 17.3–77.7%) in the follow-up MRI. Table 2 shows the average myoma diameter, uterine volume, fibroid volume, fibroid ADC and myometrium ADC which were calculated by the Wilcoxon test before and after the UAE procedure.

Table 3. Pearson correlation analysis results

		UVR	FVR	AFDR
Age	r	0.07	–0.46	–0.62
	p	0.77	0.86	0.82
Gravity	r	0.06	–0.32	–0.21
	p	0.83	0.22	0.44
Parity	r	0.06	–0.24	–1.18
	p	0.83	0.36	0.50
Pre-UAE fibroid ADC	r	0.11	0.61	0.06
	p	0.65	0.01	0.98
Pre-UAE myometrial ADC	r	0.15	0.41	0.13
	p	0.56	0.11	0.63

UVR — uterine volume reduction, FVR — fibroid volüme reduction; AFDR — average fibroid diameter reduction; ADC — apparent diffusion coefficient

According to Pearson's correlation analysis, there was a significant positive correlation between pre-UAE fibroid ADC and fibroid volume reduction but not with myometrium ADC. Age, gravidity, parity, uterine volume before UAE, and fibroid volume were not correlated with volume reduction.

Table 3 shows the correlation of age, gravidity, parity, pre-UAE fibroid ADC and pre-UAE myometrial ADC with uterine volume reduction, fibroid volume reduction, and average fibroid diameter reduction calculated by Pearson analysis.

DISCUSSION

Uterine artery embolization treatment of fibroids has been performed worldwide since it was introduced for the treatment of symptomatic fibroids in 1995 [19, 20]. There are many options for treatment, including hormonal therapy, myomectomy, and hysterectomy. Uterine artery embolization provides a minimally invasive and uterine-sparing treatment option. Ideal candidates for UAE include premenopausal women who had no desire for future pregnancy and who have heavy menstrual bleeding or pelvic pain caused by intramural fibroids. Good prognostic factors that have been described are heavy menstrual bleeding (rather than other symptoms), smaller leiomyoma size, and submucosal location [21]. Larger fibroids and more numerous fibroids predict symptom recurrence [22]. Hypervascular fibroids before UAE predict a high regrowth-free interval [23].

In this study, significant reductions in uterine and fibroid volume and fibroid size were detected after the UAE procedure. The primary aim of our study was to investigate the

factors that may be associated with the reduction of myoma size. We found that diameters and volumetric shrinkages were not significantly correlated with age, gravidity, or parity. Only fibroid ADC values before UAE were significantly correlated with the reduction in myoma diameter and volume. ADC provides functional information about the cellular microscopic water molecule motions associated with cellularity, water content, and microvascular perfusion [8–10].

There is some research related to ADC of uterine fibroid as a predictor of the potential response to UAE and ADC value is significantly related to volume reduction [24–26]. In a study by Hecht et al, researchers found a positive correlation between pre-UAE ADC and fibroid volume reduction after UAE [24]. They found that using a threshold of 0.875×10^{-3} mm^2/s, ADC could predict > 50% VR with sensitivity and specificity of 70% and 83%, respectively at 207 days follow-up MRI. Indeed in our study, we found that the mean fibroid VR was 36.0%.

Cao et al. [27] reported that VR was 58.9% at the end of 6 months, and fibroid ADC was positively correlated with VR after UAE. The total number of fibroids was 16. The mean ADC of fibroids was 1.37×10^{-3} mm^2/s (range 1.05×10^{-3}–2.32×10^{-3} mm^2/s) before UAE [27]. Similarly, Lee et al. [9] found that the rate of fibroid VR was 44.1% and that ADC and fibroid VR were significantly associated.

In our study, although the uterine fibroid volume was above 1000 cm^3 in four patients, there were not any complications. Smeets et al. in their studies on the relationship between fibroid volume and complications reported that in women with a dominant fibroid of >10 cm and/or a uterine volume of > 700 cm^3 before UAE, they found no increase in the risk of serious complications [28]. However, Hysterectomy or Percutaneous Embolisation for Uterine Leiomyomata (HOPEFUL) study showed a 2.6% incidence of septicemia after uterine fibroid embolization, with 1.1% of the women requiring emergency hysterectomy [29].

A systemic review and meta-analysis which included 11 studies showed that there is no correlation between baseline ADC values and leiomyoma VR at approximately six months ($r = 0.40$; 95% CI from –0.07 to 0.72; $I^2 = 69.7\%$) [30]. Heterogenicity in this topic may be due to variations in technical factors, DWI assessment and sequencing methods used, biological characteristics of uterine leiomyomas, and embolization techniques.

There were some limitations of our study. First, the small sample size is a major limitation of this study but in the literature, there are two prospective studies with 11 samples and 49 samples so this study is also important in terms of contribution to literature; the main reason for less sample size is the techniques itself is not so commonly chosen by the patients. More accurate results will be achieved by increasing the number of fibroids. We also follow the patients after UAE for three months (in the literature there are some six months followed up studies but generally they are retrospective studies; on the other hand prospective studies have the follow-up period in the literature is similar to our study and is limited to three months as well) but the decrease in size may continue up to 12 months. Evaluating during a longer follow-up period might be more useful in determining VR. Thirdly, we did not consider the localization of the myoma; but categorization of myoma localization and calculation through those categories would be more accurate.

CONCLUSIONS

In conclusion, ADC derived from DWI, a functional imaging technique on MRI, reflects hypervascularity and cellularity [9]. The decrease in fibroid volume was greater as the pre-UAE fibroid ADC value increased. This finding may be useful in determining which patients will benefit more from this procedure. Eventually, with the help of more studies in this field, it would be easier to choose the right patient for the UAE procedure. Heterogeneity in the literature about this topic may be overcome by the standardization of ADC calculation and interpretation approaches.

Article information and declarations

Data availability statement

All the data are available and can be achieved by authors via email.

Ethics statement

All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. Local ethical committee approval has been taken and written informed consent forms from the patients were collected.

Author contributions

All authors work for data collection. Ceren Turan Bektaş: do the embolization; Özgür Uzun: do the statistics; Ahmet Birtan Boran: supervisor, article writting; Sezgi Güllü Erciyestepe: article writting, interpretation, literature search.

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Conflict of interest

The authors declare no conflicts of interest.

Supplementary material

None.

REFERENCES

1. Bulman JC, Ascher SM, Spies JB. Current concepts in uterine fibroid embolization. Radiographics. 2012; 32(6): 1735–1750, doi: 10.1148/rg.326125514, indexed in Pubmed: 23065167.
2. American College of Obstetricians and Gynecologists. ACOG practice bulletin. Alternatives to hysterectomy in the management of leiomyomas. Obstet Gynecol. 2008; 112(2 Pt 1): 387–400, doi: 10.1097/AOG.0b013e318183fbab, indexed in Pubmed: 18669742.
3. Tomislav S, Josip M, Liana CS, et al. Uterine artery embolization as non-surgical treatment of uterine myomas. ISRN Obstet Gynecol. 2011; 2011: 489281, doi: 10.5402/2011/489281, indexed in Pubmed: 22191046.
4. Deshmukh SP, Gonsalves CF, Guglielmo FF, et al. Role of MR imaging of uterine leiomyomas before and after embolization. Radiographics. 2012; 32(6): E251–E281, doi: 10.1148/rg.326125517, indexed in Pubmed: 23065174.
5. Jha RC, Ascher SM, Imaoka I, et al. Symptomatic fibroleiomyomata: MR imaging of the uterus before and after uterine arterial embolization. Radiology. 2000; 217(1): 228–235, doi: 10.1148/radiology.217.1.r00se49228, indexed in Pubmed: 11012449.
6. de Bruijn AM, Ankum WM, Reekers JA, et al. Uterine artery embolization vs hysterectomy in the treatment of symptomatic uterine fibroids: 10-year outcomes from the randomized EMMY trial. Am J Obstet Gynecol. 2016; 215(6): 745.e1–745.e12, doi: 10.1016/j.ajog.2016.06.051, indexed in Pubmed: 27393268.
7. Spies JB. Current evidence on uterine embolization for fibroids. Semin Intervent Radiol. 2013; 30(4): 340–346, doi: 10.1055/s-0033-1359727, indexed in Pubmed: 24436560.
8. Volkers NA, Hehenkamp WJK, Birnie E, et al. Uterine artery embolization versus hysterectomy in the treatment of symptomatic uterine fibroids: 2 years' outcome from the randomized EMMY trial. Am J Obstet Gynecol. 2007; 196(6): 519.e1–519.11, doi: 10.1016/j.ajog.2007.02.029, indexed in Pubmed: 17547877.
9. van der Kooij SM, Hehenkamp WJK, Volkers NA, et al. Uterine artery embolization vs hysterectomy in the treatment of symptomatic uterine fibroids: 5-year outcome from the randomized EMMY trial. Am J Obstet Gynecol. 2010; 203(2): 105.e1–105.13, doi: 10.1016/j.ajog.2010.01.049, indexed in Pubmed: 20579960.
10. Pron G, Bennett J, Common A, et al. Ontario Uterine Fibroid Embolization Collaboration Group. The Ontario Uterine Fibroid Embolization Trial. Part 2. Uterine fibroid reduction and symptom relief after uterine artery embolization for fibroids. Fertil Steril. 2003; 79(1): 120–127, doi: 10.1016/s0015-0282(02)04538-7, indexed in Pubmed: 12524074.
11. Spies JB, Bruno J, Czeyda-Pommersheim F, et al. Uterine artery embolization for leiomyomata. Obstet Gynecol. 2001; 98(1): 29–34, doi: 10.1016/s0029-7844(01)01382-5, indexed in Pubmed: 11430952.
12. Walker WJ, Pelage JP. Uterine artery embolisation for symptomatic fibroids: clinical results in 400 women with imaging follow up. BJOG. 2002; 109(11): 1262–1272, doi: 10.1046/j.1471-0528.2002.01449.x, indexed in Pubmed: 12452465.
13. Gupta JK, Sinha A, Lumsden MA, et al. Uterine artery embolization for symptomatic uterine fibroids. Cochrane Database Syst Rev. 2014.
14. Fonseca MCM, Castro R, Machado M, et al. Uterine Artery Embolization and Surgical Methods for the Treatment of Symptomatic Uterine Leiomyomas: A Systemic Review and Meta-analysis Followed by Indirect Treatment Comparison. Clin Ther. 2017; 39(7): 1438–1455.e2, doi: 10.1016/j.clinthera.2017.05.346, indexed in Pubmed: 28641997.
15. Liapi E, Kamel IR, Bluemke DA, et al. Assessment of response of uterine fibroids and myometrium to embolization using diffusion-weighted echoplanar MR imaging. J Comput Assist Tomogr. 2005; 29(1): 83–86, doi: 10.1097/01.rct.0000146111.48570.64, indexed in Pubmed: 15665689.
16. Koh DM, Collins DJ. Diffusion-weighted MRI in the body: applications and challenges in oncology. AJR Am J Roentgenol. 2007; 188(6): 1622–1635, doi: 10.2214/AJR.06.1403, indexed in Pubmed: 17515386.
17. Meyer HJ, Garnov N, Surov A. Comparison of Two Mathematical Models of Cellularity Calculation. Transl Oncol. 2018; 11(2): 307–310, doi: 10.1016/j.tranon.2018.01.020, indexed in Pubmed: 29413764.
18. Williams PL, Coote JM, Watkinson AF. Pre-uterine artery embolization MRI: beyond fibroids. Cardiovasc Intervent Radiol. 2011; 34(6): 1143–1150, doi: 10.1007/s00270-011-0124-z, indexed in Pubmed: 21331454.
19. Silberzweig JE, Powell DK, Matsumoto AH, et al. Management of Uterine Fibroids: A Focus on Uterine-sparing Interventional Techniques. Radiology. 2016; 280(3): 675–692, doi: 10.1148/radiol.2016141693, indexed in Pubmed: 27533290.
20. Ravina JH, Herbreteau D, Ciraru-Vigneron N, et al. Arterial embolisation to treat uterine myomata. Lancet. 1995; 346(8976): 671–672, doi: 10.1016/s0140-6736(95)92282-2, indexed in Pubmed: 7544859.
21. Spies JB, Myers ER, Worthington-Kirsch R, et al. FIBROID Registry Investigators. The FIBROID Registry: symptom and quality-of-life status 1 year after therapy. Obstet Gynecol. 2005; 106(6): 1309–1318, doi: 10.1097/01.AOG.0000188386.53878.49, indexed in Pubmed: 16319257.
22. Marret H, Cottier JP, Alonso AM, et al. Predictive factors for fibroids recurrence after uterine artery embolisation. BJOG. 2005; 112(4): 461–465, doi: 10.1111/j.1471-0528.2004.00487.x, indexed in Pubmed: 15777445.
23. Isonishi S, Coleman RL, Hirama M, et al. Analysis of prognostic factors for patients with leiomyoma treated with uterine arterial embolization. Am J Obstet Gynecol. 2008; 198(3): 270.e1–270.e6, doi: 10.1016/j.ajog.2007.09.026, indexed in Pubmed: 17997392.
24. Lee MS, Kim MD, Jung DC, et al. Apparent Diffusion Coefficient of Uterine Leiomyoma as a Predictor of the Potential Response to Uterine Artery Embolization. J Vasc Interv Radiol. 2013; 24(9): 1361–1365, doi: 10.1016/j.jvir.2013.05.054.
25. Hecht EM, Do RKG, Kang SK, et al. Diffusion-weighted imaging for prediction of volumetric response of leiomyomas following uterine artery embolization: a preliminary study. J Magn Reson Imaging. 2011; 33(3): 641–646, doi: 10.1002/jmri.22459, indexed in Pubmed: 21563247.
26. Sutter O, Soyer P, Shotar E, et al. Diffusion-weighted MR imaging of uterine leiomyomas following uterine artery embolization. Eur Radiol. 2016; 26(10): 3558–3570, doi: 10.1007/s00330-016-4210-0, indexed in Pubmed: 26801165.
27. Cao MQ, Suo ST, Zhang XB, et al. Entropy of T2-weighted imaging combined with apparent diffusion coefficient in prediction of uterine leiomyoma volume response after uterine artery embolization. Acad Radiol. 2014; 21(4): 437–444, doi: 10.1016/j.acra.2013.12.007, indexed in Pubmed: 24594413.
28. Smeets AJ, Nijenhuis RJ, van Rooij WJ, et al. Uterine artery embolization in patients with a large fibroid burden: long-term clinical and MR follow-up. Cardiovasc Intervent Radiol. 2010; 33(5): 943–948, doi: 10.1007/s00270-009-9793-2, indexed in Pubmed: 20066419.
29. Dutton S, Hirst A, McPherson K, et al. A UK multicentre retrospective cohort study comparing hysterectomy and uterine artery embolisation for the treatment of symptomatic uterine fibroids (HOPEFUL study): main results on medium-term safety and efficacy. BJOG. 2007; 114(11): 1340–1351, doi: 10.1111/j.1471-0528.2007.01526.x, indexed in Pubmed: 17949376.
30. Dao D, Kang SJ, Midia M. The utility of apparent diffusion coefficients for predicting treatment response to uterine arterial embolization for uterine leiomyomas: a systematic review and meta-analysis. Diagn Interv Radiol. 2019; 25(2): 157–165, doi: 10.5152/dir.2019.18294, indexed in Pubmed: 30774092.

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Effect of mRNA COVID-19 vaccine on ovarian reserve of women of reproductive age

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ABSTRACT

Objectives: To evaluate the effect of messenger ribonucleic acid (mRNA) vaccines developed for severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2) on the ovarian reserve of women of reproductive age.

Material and methods: This prospective study was conducted between July and December 2022 in a tertiary care hospital affiliated with a university. A total of 117 patients were included in the study. The patients were divided into two groups. The first group (n = 62) consisted of women of reproductive age who received two doses of Pfizer-BioNTech COVID-19 vaccine administered 21 days apart. The control group (n = 55) included women with the same demographic characteristics who did not plan to be vaccinated. Hormonal values and basal antral follicle count were compared between two groups.

Results: The mean age of the study group was 26.3 ± 3.6 years, and the mean age of the control group was 25.4 ± 6.2 years (p = 0.332). In the vaccinated group, mean follicular stimulating hormone (FSH) on day 2 was 5.29 ± 2.28; luteinizing hormone (LH): 5.18 ± 1.3; E2: 46.43 ± 24.51; anti-Mullerian hormone (AMH): 4.17 ± 2.1; antral follicle count: 16.23 ± ± 8.04; right ovarian volume: 6.4 ± 1.7; left ovarian volume: 6.2 ± 2.1. FSH measured at D2 in the control group was 5.68 ± ± 1.89; LH: 5.22 ± 2.2; E2: 48.41 ± 27.12; AMH: 4.30 ± 1.74; number of antral follicles: 15.64 ± 9.04; right ovarian volume: 6.1 ± 1.8; left ovarian volume: 6.3 ± 1.4. There were no statistically significant differences for FSH, LH, E2, AMH, ovarian volume, and number of antral follicles on the second day of menstruation between the groups.

Conclusions: According to the results of the present study, the mRNA SARS-CoV-2 vaccine does not affect the ovarian reserve of patients.

Keywords: SARS-CoV-2 mRNA vaccine; AMH; ovarian reserve; COVID-19; fertility

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INTRODUCTION

Upon the increase in the number of pneumonia cases in Wuhan, Hubei province of China in December 2019, it was determined that the causative agent of the outbreak was a type of RNA virus from the beta coronavirus group of coronaviruses. This virus spread rapidly, causing an outbreak across China, and then spreading to all continents of the world except Antarctica, causing a pandemic [1].

The severity of coronavirus disease 2019 (COVID-19) ranges from mild symptoms to severe illness requiring long-term respiratory support in intensive care, depending on the immune system's response to the disease. Therefore, the COVID-19 pandemic put enormous pressure on scientists to develop a safe and effective vaccine. The genetic sequence of the virus was determined at the beginning of the pandemic, and vaccine studies against the virus were started by many countries [2].

Cell entry by severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2) is similar to that of SARS-CoV-1; the viral spike protein is first cut and shaped by a cell protease (TMPRSS2) on the host cell surface, and afterwards the shaped spike protein is recognized by the ACE-2 receptor and can enter the cell [3]. Angiotensin converting enzyme 2 (ACE-2) has been determined in many different organs,

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including the respiratory tract, heart, kidney, ovaries, uterus, vagina, placenta, testis, and gastrointestinal tract [4]. Since ACE-2 is known to be expressed in the ovarian tissues of women of reproductive age, it is thought that SARS-CoV-2 infection may cause ovarian damage and impairment of ovarian function, leading to decreased oocyte quality, which may result in infertility or miscarriage [5].

The spike protein of the virus has been considered to be suitable for use as a presenting antigen in mRNA vaccines because the spike protein on the virus surface binds strongly to the ACE-2 receptor in the host cell and can enter the host cell [6]. The basic working principle of mRNA vaccines is based on the delivery of mRNA artificially synthesized to encode antigenic immunogens to the cytoplasm of the host cell within lipid nanoparticles [7]. Afterwards, the translation of the ribosome of the host cell with the transcript entering the cell takes place. Finally, the immunogenic proteins formed are expressed and presented at the cell membrane or released. It drives the production of viral S-protein in the host cells [8]. It has been investigated whether such a mechanism could negatively affect the integrity of the ovary [9, 10]

Although there have been studies on the effect of COVID-19 infection on ovarian reserve, the effect of mRNA vaccines developed for the COVID-19 pandemic on ovarian reserve is still unknown. Misinterpretation of the vaccine's biodistribution data has led to claims that the lipid nanoparticles contained in the mRNA vaccine are concentrated in the ovary and that the spike protein produced there will cause infertility. This type of misinformation about the COVID vaccine has contributed to vaccine hesitancy and strengthened the hand of anti-vaccination groups [11]. The safety of the vaccine was publicly questioned by various anti-vaccine groups [12]. Concerns that mRNA vaccines would negatively affect fertility in the future spread rapidly through social media, influencing individuals' decision-making and vaccination rates [13]. Women of reproductive age and their parents have been reluctant to get vaccinated because of concerns about reduced fertility in the future due to this non-evidence-based information. It is important to reduce concerns about vaccination and increase vaccination rates, especially in the young age group, which is a leading population in the spread of the disease in developing countries.

The aim of this study is to determine the effect of mRNA vaccines that were developed for the COVID-19 pandemic on ovarian reserve and thus to help inform the reproductive age group experiencing this common concern. For this purpose, we investigated the effects of the mRNA vaccine on ovarian reserve by looking at values such as antral follicle count, basal follicular stimulating hormone (FSH), E2, luteinizing hormone (LH) level, anti-Mullerian hormone (AMH), and ovarian volume in the vaccinated and non-vaccinated groups.

MATERIAL AND METHODS

This prospective cross-sectional study was initiated with ethical approval from the Ethics Committee of Gaziosmanpaşa Training and Research Hospital (date: 27/07/2022, NO: 100). All procedures done in the study complied with the ethical standards of the 1964 Declaration of Helsinki. Informed consent was obtained from the patients.

Including the 62 vaccinated and the 55 non-vaccinated groups, a total of 117 patients were included in the study. The study group included patients between the ages of 18 and 35 who were admitted to the gynecology outpatient clinic, who did not have COVID-19, had regular menstruation, had no current pregnancy, and had received the mRNA vaccine for SARS-CoV-2 in two doses (BioNTech) 21 days apart. The control group consisted of individuals who were not vaccinated, who did not have COVID-19, and who did not plan to be vaccinated.

Patients who were pregnant at the time of the study, had a history of infertility, comorbidities (hypo/hyperthyroidism, PCOS), genetic disorders (Turner syndrome, *etc.*), systemic chronic diseases (diabetes, kidney, heart, GIS, *etc.*), previous ovarian surgery, the presence of an ovarian mass (endometrioma), or use of any medication that could affect ovarian reserve were all excluded.

In the study group, blood was collected from the antecubital vein for the measurement of FSH, LH, estradiol and AMH in serum on the 3rd day of the menstrual cycle and at least three months after mRNA vaccination. Blood samples for FSH, LH, and estradiol measurements were analyzed by chemiluminescence (Advia Centaur XP, Siemens AG, Munich, Germany) without delay. Blood samples for AMH measurement were centrifuged within 30 minutes (10 minutes at 3000 rpm) and stored at –20°C. AMH was measured by the enzyme immunoassay method [Elabscience, USA, detection limit: 0.09 ng/mL; coefficient of variation (CV): < 10%]. On the same day, the number of antral follicles (2–10 mm) and ovarian volume were determined by transvaginal ultrasonographic evaluation. In the control group, FSH, LH, E2, and AMH levels were measured on the 3rd day of the menstrual cycle; ovarian size and number of antral follicles were evaluated by TVUSG. Ultrasonography was performed by a single operator. The total number of antral follicles measuring 2–10 mm in both ovaries was recorded. Ovarian volume was calculated automatically (length*width*depth*0.52 = = volume) by USG by accepting the two widest diameters of the ovary (length and width) and the diameter (depth) obtained by turning the probe 90 degrees in two dimensions. A basal serum E2 value of < 80 pg/mL and an FSH value of 5–10 mIU/mL on the 2nd–3rd day of menstruation indicate adequate ovarian reserve. FSH values between 10–15 mIU/mL indicate limited reserve, while FSH levels above this level and

Table 1. Comparison of socio-demographic characteristics of the cases

	Group 1 (the vaccinated group) n = 62	Group 2 (unvaccinated group) n = 55	p^a value
Age	26.3 ± 3.6	25.4 ± 6.2	0.3325
Gravidity	2.2 ± 1	2.4 ± 1	0.2825
Parity	1.4 ±1	1.3±1	0.5903
Body mass index (BMI)	23.4 ± 3.1	22.8 ± 2.2	0.2353
Smoking	15 (24.1%)	11 (20%)	0.5957
Menstruation frequency [days]	27.4 ± 4.6	26.2 ± 3.8	0.1296
Menstruation length [days]	4.9 ± 2.1	4.3 ± 2.3	0.1430
Educational status			
Primary school	24 (38.7)	25 (45.4)	
High school	27 (43.5)	26 (47.2)	p^b: 0.234862.
University	11 (17.7)	4 (7.2)	X^2: 2.8975.
Employment			
Not working (housewife)	50 (80.6%)	48 (87.2%)	p^b: 0.4721
Working	12 (19.3%)	7 (12.7)	X^2: 0.517
Marital status			
Married	47 (75.8%)	49 (89%)	p^b: 0.103
Single	15 (24.1%)	6 (10.9%)	X^2: 2.649

P^a a independent samples t-test; Continuous variables are expressed as mean ± standard deviation; P^b Yates corrected chi-square test or Pearson chi-square test were used

E2 values > 80 pg/mL are associated with poor reproductive outcomes [14].

The total number of antral follicles in bilateral ovaries is a useful measurement as an indicator of ovarian reserve and also AMH is considered the best biochemical marker of ovarian function in many clinical situations [15, 16]. We aimed to recruit women of reproductive age with and without vaccination to investigate the effects of vaccination on ovarian reserve by comparing ovarian reserve markers between the two groups.

Statistical analysis

The statistical evaluation of the data in this study was performed using the Statistical Package for the Social Sciences, version 15.0 (SPSS Inc., Chicago, IL, USA). The results were given as a mean standard deviation or as a number (percentage). Normally distributed variables between the groups were analyzed using the independent samples t-test, and non-normally distributed variables were analyzed using the Mann–Whitney U test. Nominal and categorical variables were evaluated with appropriate chi-square tests depending on the expected values. A value of $p < 0.05$ was considered statistically significant.

RESULTS

The study consisted of a total of 117 women. Group-1 included 62 people who received two doses of the mRNA (BioNTech) vaccine 21 days apart. Group-2 included 55 unvaccinated individuals. The demographic characteristics of the cases are shown in Table 1. No significant differences were found between the groups in terms of age, gravidity, parity, body mass index, smoking, educational status, marital status, employment status, or length and frequency of menstrual periods (Tab. 1). The groups were homogeneous in terms of specified characteristics.

The mean FSH value was 5.29 ± 2.28 mIU/mL, the mean E2 value was 46.43 ± 24.51 pg/mL, the mean LH value was 5.18 ± 1.3 mIU/ML, the mean basal antral follicle number was 16.23 ± 8.04, mean right ovarian volume 6.4 ± 1.7 cm, mean left ovarian volume 6.2 ± 2.1 cm, and AMH value was 4.17 ± 2.1 ng/mL in the vaccinated group. In Group-2 who were unvaccinated, the mean FSH value was 5.68 ± 1.89 mIU/mL, mean LH value was 5.22 ± 2.2 mIU/mL, mean E2 value was 48.41 ± 27.12.pg/mL, mean basal antral follicle count was 15.64 ± 9.04, mean right ovarian volume was 6.1 ± 1.8 cm, mean left ovarian volume was 6.3 ± 1.4 cm, and mean AMH value was 4.30 ± 1.74.ng/mL. There were no statistically significant differences between the groups in terms of ovarian reserve parameters ($p > 0.005$) (Tab. 2).

DISCUSSION

The pandemic caused by SARS-CoV-2, a novel coronavirus, is the most important health challenge of the 21st century. The humanitarian and economic impact of the COVID-19 pandemic has made it mandatory to develop next-generation vaccine technology platforms [17]. Before

Table 2. Comparison of ovarian reserve markers between the two groups

	Group 1 (the vaccinated group) n = 62	Group 2 (unvaccinated group) n = 55	p[a] value
Day 3 FSH levels (mIU/mL)[a]	5.29 ± 2.28	5.68 ± 1.89	0.3195
Day 3 LH levels (mIU/mL)[a]	5.18 ± 1.3	5.22 ± 2.2	0.9037
Day 3 estradiol levels (pg/mL)[a]	46.43 ± 24.51	48.41 ± 27.12	0.6790
AMH levels (ng/mL)	4.17 ± 2.1	4.30 ± 1.74	0.7181
Basal antral follicle count	16.23 ± 8.04	15.64 ± 9.04	0.7093
Ovarian volume			
Right ovarian volume	6.4 ± 1.7	6.1 ± 1.8	0.3560
Left ovarian volume	6.2 ± 2.1	6.3 ± 1.4	0.7655

[a]Baseline FSH and LH estradiol levels measured in hormone panel test at day three of menstrual period; AMH — anti-Mullerian hormone; FSH — follicular stimulating hormone; LH — luteinizing hormone; p[a] — Independent samples t-test; Continuous variables are expressed as mean ± standard deviation

the COVID-19 pandemic, it took an average of 10 to 15 years to develop a vaccine [18]. This period was shortened after the COVID-19 virus was isolated and the entire genome of the virus was made available to researchers. Next-generation mRNA vaccines which have been intensively researched based on genetic bases over the last two decades, could be produced cheaply in a short time for SARS-CoV-2 [19].

False and misleading claims, such as that these lipid particles containing mRNA spread throughout the body and accumulate particularly in the ovaries, have been advanced and discussed publicly by opponents of vaccination. Such unsubstantiated claims have caused a certain amount of fertility-related concern among the public. The biodistribution and persistence of LNP-mRNA vaccine formulations for COVID-19 and other diseases have been studied in rodents and primates. Animal studies have shown that the highest concentration of lipid nanoparticle mRNA remains at the injection site. This was followed by the liver (up to 21.5%) and much less in the spleen (≤ 1.1%), adrenal glands (≤ 0.1%), and ovaries (≤ 0.1%). Mean concentrations and tissue distribution patterns did not differ between genders [20, 21].

Bowman et al. [22] published in May 2021 the results of their study on the effects of mRNA vaccines on the reproductive function of female mice. They found no changes in mating, fertility, or the size and volume of the uterus and ovary in female mice after vaccination.

Jing et al. [4] reported in a review that COVID-19 does not only infect the female reproductive organs but can also infect the placenta via the ACE receptor. They suggested that COVID-19 can cause infertility and menstrual irregularities, as well as fetal distress in pregnant women. They therefore recommended that women with COVID-19 delay their pregnancies. The data on the impact of SARS-CoV-2 infection and SARS-CoV-2 mRNA vaccines on fertility and ovarian function in humans are limited. In a retrospective study published in 2021, no difference was found in the comparison of serum FSH and AMH levels in the follicular phase between 237 women after recovery of COVID-19 infection and the uninfected population [23] .

Mohr-Sasson et al. [24] investigated the effect of the mRNA COVID-19 vaccine on AMH, which is a marker of ovarian reserve in women of reproductive age. Their study group consisted of 129 women of reproductive age who received two mRNA vaccines 21 days apart. Subjects with ovarian failure, infertility treatment, pregnancy, previous mRNA vaccination, or COVID-19 infection were excluded from the study. Plasma AMH levels before vaccination and three months after the first vaccination were analyzed in different age groups. There was no significant difference in AMH levels before and after vaccination in all age groups. Also, Sason examined COVID-19 antibody levels in all vaccinated women at the end of three months and found no association between COVID-19 antibody levels and AMH levels. Therefore, Sason et al. stated in their study that SARS--CoV-2 mRNA vaccines were not associated with a decrease in ovarian reserve [24]. Similarly, Soysal et al. [25] studied the effect of mRNA vaccination on ovarian reserve. They compared AMH levels between the groups vaccinated with the mRNA vaccine and the unvaccinated group in their study. However, no significant difference was found between the AMH values of the vaccinated group and the control group after three months of vaccination in the study group. In our study, in addition to the ovarian reserve marker AMH, other ovarian reserve markers such as AFC (antral follicle count), basal FSH, basal LH, E2, and ovarian volume were compared between the mRNA vaccine group and the control group. A total of 117 cases were included in the study. The cases were selected from women of reproductive age without fertility problems. It was determined that there was no significant difference between the vaccinated and non-vaccinated groups according to parameters such as AFC, basal FSH, basal LH, E2, AMH, and ovarian volume.

There are also studies in the literature investigating the effect of the SARS-CoV-2 mRNA vaccine on IVF frequencies.

Bentov et al. [26] published in July 2021 the first study investigating the effects of mRNA vaccine in a cohort study of 32 patients with infertility and planned IVF. Group-1 (n = 9) included people who had received mRNA vaccine, group-2 (n = 9) included people who had COVID-19 infection, and group-3 (n = 14) included people who did not receive mRNA vaccine and did not have infection. As a conclusion of this study, it was observed that there was no deterioration in ovarian follicle quality and function in individuals with SARS--CoV-2 infection and mRNA vaccination [26]. Horowitz et al. compared AMH concentrations before and after vaccination in a group of 31 infertile patients undergoing IVF and found no significant difference. Ortrento et al. [27] compared oocyte stimulation and embryologic characteristics before and after mRNA COVID-19 vaccination in an IVF patient group of 36 couples. In their study, they found no difference in the dose of gonadotropin used, peak estrogen and progesterone levels, number and quality of aspirated oocytes, fertilization rates, and embryo quality between IVF cycles in the same patient group before and after vaccination. In another study, they examined IVF treatment parameters and outcomes in 32 vaccinated and 22 non-vaccinated patients. Similar to the above results, no difference was found between the number of follicles formed, number of oocytes collected, oocyte quality, fertilization rates, and pregnancy rates in the vaccinated and non-vaccinated patient groups [28].

CONCLUSIONS

In this study, we aimed to estimate the effects of mRNA vaccines developed for COVID-19 on ovarian reserve and found that there was no significant difference between the vaccinated and unvaccinated groups in terms of ovarian reserve markers. The most important limitation of this study is the small number of cases, as in other published studies [24–27]. The second limitation of our study is the lack of long-term results of the mRNA vaccine on ovarian reserve functions. Additional studies with a larger number of cases and longer follow-up are required to determine the effect of the mRNA vaccine on ovarian reserve.

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Data availability statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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REFERENCES

1. Wang C, Horby PW, Hayden FG, et al. A novel coronavirus outbreak of global health concern. Lancet. 2020; 395(10223): 470–473, doi: 10.1016/S0140-6736(20)30185-9, indexed in Pubmed: 31986257.
2. Polack FP, Thomas SJ, Kitchin N, et al. C4591001 Clinical Trial Group. Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine. N Engl J Med. 2020; 383(27): 2603–2615, doi: 10.1056/NEJMoa2034577, indexed in Pubmed: 33301246.
3. Tu YF, Chien CS, Yarmishyn AA, et al. A review of SARS-CoV-2 and the ongoing clinical trials. Int J Mol Sci. 2020; 21(7): 2657, doi: 10.3390/ijms21072657, indexed in Pubmed: 32290293.
4. Jing Y, Run-Qian Li, Hao-Ran W, et al. Potential influence of COVID-19/ACE2 on the female reproductive system. Mol Hum Reprod. 2020; 26(6): 367–373, doi: 10.1093/molehr/gaaa030, indexed in Pubmed: 32365180.
5. Sun J. The hypothesis that SARS-CoV-2 affects male reproductive ability by regulating autophagy. Med Hypotheses. 2020; 143: 110083, doi: 10.1016/j.mehy.2020.110083, indexed in Pubmed: 32679425.
6. Hamming I, Cooper ME, Haagmans BL, et al. The emerging role of ACE2 in physiology and disease. J Pathol. 2007; 212(1): 1–11, doi: 10.1002/path.2162, indexed in Pubmed: 17464936.
7. Kowalzik F, Schreiner D, Jensen C, et al. mRNA-based vaccines. Vaccines (Basel). 2021; 9(4): 390, doi: 10.3390/vaccines9040390, indexed in Pubmed: 33921028.
8. Schoenmaker L, Witzigmann D, Kulkarni JA, et al. mRNA-lipid nanoparticle COVID-19 vaccines: Structure and stability. Int J Pharm. 2021; 601: 120586, doi: 10.1016/j.ijpharm.2021.120586, indexed in Pubmed: 33839230.
9. Reis FM, Bouissou DR, Pereira VM, et al. Angiotensin-(1-7), its receptor Mas, and the angiotensin-converting enzyme type 2 are expressed in the human ovary. Fertil Steril. 2011; 95(1): 176–181, doi: 10.1016/j.fertnstert.2010.06.060, indexed in Pubmed: 20674894.
10. Hamming I, Cooper ME, Haagmans BL, et al. The emerging role of ACE2 in physiology and disease. J Pathol. 2007; 212(1): 1–11, doi: 10.1002/path.2162, indexed in Pubmed: 17464936.
11. Morris R, Morris A, IL N. Exposure of ovaries to COVID-19 vaccination does not impair fertility. Fertility and Sterility. 2021; 116(3): e473, doi: 10.1016/j.fertnstert.2021.08.027.
12. Rameneni T, Sayeed T, Kumar S. A perspective on COVID-19 vaccine hesitancy in India. National Journal of Community Medicine. 2022; 13(07): 491–493, doi: 10.55489/njcm.130720221612.
13. Lamptey E. Overcoming barriers to COVID-19 vaccination of pregnant women. Gynecology and Obstetrics Clinical Medicine. 2022; 2(1): 29–33, doi: 10.1016/j.gocm.2022.01.007.
14. Buyalos RP, Daneshmand S, Brzechffa PR. Basal estradiol and follicle-stimulating hormone predict fecundity in women of advanced reproductive age undergoing ovulation induction therapy. Fertil Steril. 1997; 68(2): 272–277, doi: 10.1016/s0015-0282(97)81514-2, indexed in Pubmed: 9240255.
15. Hsu A, Arny M, Knee AB, et al. Antral follicle count in clinical practice: analyzing clinical relevance. Fertil Steril. 2011; 95(2): 474–479, doi: 10.1016/j.fertnstert.2010.03.023, indexed in Pubmed: 20434151.
16. Moolhuijsen LME, Visser JA. Anti-Müllerian hormone and ovarian reserve: update on assessing ovarian function. J Clin Endocrinol Metab. 2020; 105(11): 3361–3373, doi: 10.1210/clinem/dgaa513, indexed in Pubmed: 32770239.
17. Thanh Le T, Andreadakis Z, Kumar A, et al. The COVID-19 vaccine development landscape. Nat Rev Drug Discov. 2020; 19(5): 305–306, doi: 10.1038/d41573-020-00073-5, indexed in Pubmed: 32273591.
18. Kis Z, Shattock R, Shah N, et al. Emerging technologies for low-cost, rapid vaccine manufacture. Biotechnol J. 2019; 14(1): e1800376, doi: 10.1002/biot.201800376, indexed in Pubmed: 30537361.
19. Anderson EJ, Rouphael NG, Widge AT, et al. mRNA-1273 Study Group. Safety and immunogenicity of SARS-CoV-2 mRNA-1273 vaccine in older adults. N Engl J Med. 2020; 383(25): 2427–2438, doi: 10.1056/NEJMoa2028436, indexed in Pubmed: 32991794.
20. European Medicines Agency. Assessment Report EMA/707383/2020 Corr.1*: Comirnaty COVID-19 MRNA Vaccine (NucleosideModified); Assessment Report; European Medicines Agency: Volume 31, pp. 1–140 Amsterdam, The Netherlands, 2021.

21. 'European Medicines Agency. Assessment Report EMA/15689/2021 Corr.1*: Covid-19 Vaccine Moderna; European Medicines Agency: Volume 11, p. 169'. Amsterdam, The Netherlands, 2021.
22. Bowman CJ, Bouressam M, Campion SN, et al. Lack of effects on female fertility and prenatal and postnatal offspring development in rats with BNT162b2, a mRNA-based COVID-19 vaccine. Reprod Toxicol. 2021; 103: 28–35, doi: 10.1016/j.reprotox.2021.05.007, indexed in Pubmed: 34058573.
23. Li K, Chen Ge, Hou H, et al. Analysis of sex hormones and menstruation in COVID-19 women of child-bearing age. Reprod Biomed Online. 2021; 42(1): 260–267, doi: 10.1016/j.rbmo.2020.09.020, indexed in Pubmed: 33288478.
24. Mohr-Sasson A, Haas J, Abuhasira S, et al. The effect of Covid-19 mRNA vaccine on serum anti-Müllerian hormone levels. Hum Reprod. 2022; 37(3): 534–541, doi: 10.1093/humrep/deab282, indexed in Pubmed: 34935913.
25. Soysal Ç, Yılmaz E. The effect of COVID-19 vaccine on ovarian reserve. Saudi Med J. 2022; 43(5): 486–490, doi: 10.15537/smj.2022.43.5.20220007, indexed in Pubmed: 35537728.
26. Bentov Y, Beharier O, Moav-Zafrir A, et al. Ovarian follicular function is not altered by SARS-CoV-2 infection or BNT162b2 mRNA COVID-19 vaccination. Hum Reprod. 2021; 36(9): 2506–2513, doi: 10.1093/humrep/deab182, indexed in Pubmed: 34364311.
27. Orvieto R, Noach-Hirsh M, Segev-Zahav A, et al. Does mRNA SARS-CoV-2 vaccine influence patients' performance during IVF-ET cycle? Reprod Biol Endocrinol. 2021; 19(1): 69, doi: 10.1186/s12958-021-00757-6, indexed in Pubmed: 33985514.
28. Odeh-Natour R, Shapira M, Estrada D, et al. Does mRNA SARS-CoV-2 vaccine in the follicular fluid impact follicle and oocyte performance in IVF treatments? Am J Reprod Immunol. 2022; 87(5): e13530, doi: 10.1111/aji.13530, indexed in Pubmed: 35220640.

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Social marketing in gynecological cancer prevention after the COVID-19 pandemic

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ABSTRACT

Objectives: Assessment of the development and description of social marketing features in Poland and the United States regarding the prevention of gynecological cancer and attainments of these countries.

Material and methods: The description research based on the comparative analysis of five social campaigns in Poland and five social campaigns in the United States that were focused on the gynecological cancer prevention.

Results: In the United States, there are more materials available on social campaigns dedicated to the prevention of gynecological cancer, and there are more public organizations that are involved in health promotion activities than in Poland. As opposed to American campaigns, Polish social campaigns did not cover all types of gynecological cancer. The study revealed that Facebook is the most used social media platform by the social campaign organizers.

Conclusions: Social marketing tools are underutilized in gynecologic cancer prevention in both Poland and the United States, leaving ample room for future improvement in its use.

Keywords: social marketing; prevention; gynecological cancer(s); cervical cancer

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INTRODUCTION

Social marketing seems to be a relatively new area of marketing that uses the methods and techniques of commercial marketing but differs from it in terms of the subject of interest, which is creating social behavior rather than selling a particular product. However, the oldest and most frequently used term of social marketing is the definition by Kotler and Zaltman [1], according to whom social marketing means design, implementation and monitoring of programs that are designed to influence the admissibility of social ideas and involve the issues of product planning, pricing, communication, distribution and marketing research. Over the years, many new or modified definitions of social marketing have emerged, but the essence of these definitions has remained constant: changing negative behaviors in society. A basic element of social marketing is the social campaign. It represents a primary approach to health issues, because its design makes the target group think and change behavior, and it encourages them to explore the subject of a given campaign.

Social marketing used in health care aims to improve society's health and habits. The problems of modern society, including health, social and economic problems, have contributed to a new approach to marketing. Traditional marketing focuses on particular products, while social marketing sells ideas.

Gynecological cancer refers to diseases, such as vulvar cancer, vaginal cancer, cervical, endometrial cancer, and ovarian cancer. The best way (both in terms of population health and economy) to combat these diseases is prevention and early diagnosis. Although mortality from gynecological cancers worldwide is relatively moderate and constant, they are still a major epidemiological problem. A strong downward trend can only be observed in ovarian cancers (from 9.5 in 1992 to 6.0 in 2019) [2]. Mortality from cervical cancers has increased in recent years, even though there is certain

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improvement in Poland, since approximately 30–40% of the sub-population are covered by preventive programs. Oncological morbidity and mortality are affected by many different socio-economic, behavioral, and other environmental factors, including poverty, race, access to health care, health care quality, education, obesity, nutrition and stimulants [3]. Prevention, which is aimed at counteracting deviations from health, requires considerable effort and commitment in creating and implementing health programs. Marketing, public relations, and social advertising are only some of the tools that are used to minimize the effort put into disease prevention [4]. Prevention in Poland is comparatively limited and requires constant improvement. This can be illustrated by the fact that only 2.3% of the expenditures on health care in 2018 were spent on prevention and public health, whereas as much as 62.5% were spent on treatment and rehabilitation services [5]. Increasing funding for prevention could result in a reduction in expenditure on the treatment and medicinal products. A disease itself is economically less viable, both for the state and society, than the disease prevention. Therefore, it is important to constantly implement and improve health promotion, an important element of which is marketing and social campaigns. This topic seems to be of key importance particularly nowadays when the COVID-19 pandemic is indicated by a reduced epidemiological threat and society is exposed to its severe long-term effects.

Objectives

The aim of the study was to analyze the use of social marketing in gynecological cancers prevention in Poland and the United States, and to compare the achievements of these countries in this respect. The perspective after COVID-19 pandemic was presented.

MATERIAL AND METHODS

The research methodology was based on a review of the literature on PubMed, ScienceDirect, Google databases and the reference list of key papers were searched to retrieve research literature. We used terms: 'social marketing', 'gynecological cancers', 'Poland, USA', 'prevention'. Searches were limited to the period 2016–2021 and English language. We included full-text articles of any study design. We excluded articles when the full text was not available.

The case study was conducted based on an analysis of five social campaigns in Poland and five social campaigns in the United States, which were dedicated to the gynecological cancer prevention. The analysis included the following criteria:

- basic goals;
- slogans used in the campaign;
- messages for the society;
- use of statistical data or medical facts;
- faces of the campaigns;
- creative methods;
- means of communication;
- use of social media.

All the elements presented above made it possible to perform an effective analysis, as a result of which certain aspects of the campaign were distinguished that could impact the effectiveness of the enforcement of a campaign, and which allowed for a comparison between Poland and the United States regarding the use of social marketing in the prevention of gynecological cancers.

RESULTS

The analysis of the Polish and American campaigns aimed at showing the social marketing features in the prevention of gynecological cancers, including the main goals of the campaigns, the nature of transmitted messages and the means of communication. The summary of the results is presented in Table 1 and descripted below.

As part of the study, Polish and American social marketing campaigns mentioned below were analyzed. The first Polish campaign subject to analysis was a campaign focusing on cervical cancer that was carried out by the Kwiat Kobiecości Foundation in 2019 in the framework of the 10th edition of the nationwide social campaign "She's beautiful because she's healthy" [6]. Due to the difficulties in finding social campaigns matching the subject of the analysis, two campaigns of the Kwiat Kobiecości Foundation were included in the study. The other one focused on ovarian cancer, "Diagnostics of the ovary". Another campaign was the "Coalition for Life" carried out by the Polish Amazons Social Movement in 2020, and the first edition of this campaign focused on ovarian cancer [7]. In January 2022, the Medistica medical group launched a campaign "Do a checkup and live!" as part of the project co-financed by the European Union from the Regional Program of the Lesser Poland Voivodeship [8]. The last Polish campaign subject to analysis was the 2013 campaign carried out by a coalition of several organizations "For Her. We can do more", which focused on ovarian cancer [9]. Regarding the American resources, the first campaign was the 2021 campaign "Our Way Forward" created by one of the biggest pharmaceutical companies GlaxoSmithKline (GSK) in cooperation with the National Ovarian Cancer Coalition (NOCC) and the Ovarian Cancer Research Alliance (OCRA) [10]. Another campaign was conducted by Centers for Disease Control and Prevention (CDC) in 2012, "Inside Knowledge: Get the Facts About Gynecologic Cancer" and it covered five types of gynecological cancers [11]. In 2018, Pan American Health Organization (PAHO), in cooperation with WHO, launched a campaign to prevent cervical cancer, "It is Time to End Cervical Cancer" [12]. Yet another campaign was launched in 2018 by the US

Table 1. Description of Polish and American social marketing campaigns

Name of the campaign; main interest	Main goals	Nature of transmitted messages	Means of communication
Polish campaigns			
„She's beautiful because she's healthy" cervical cancer	Education, raising awareness of the importance of preventive gynaecological examinations. Men commitment to fight this cancer	Evoking positive emotions, motivating to take action	Internet Press Advertising spot App Stationary event
„Coalition for Life" ovarian cancer	Multiple network collaboration to create a patient-centered system. 3 requirements: molecular diagnostics for each person with ovarian cancer, improving the quality and accessibility of treatment, and applying early-stage treatment methods in line with EU standards	Causing anxiety, fear, motivating to expand knowledge and take action by increasing interest in the health of the individual	Internet Movies Press and scientific conferences Webinars
„For Her. We can do more" ovarian cancer	Supporting women suffering from gynecological cancers and their relatives. Taming the fear of gynecological cancer diagnostics	Evoking positive emotions, involving personally and close people to take action	Internet Advertising spot Guidance materials
„Do a checkup and live" cervical cancer	Convincing women to preventive examinations and expanding knowledge	Evoking positive emotions, educating through humorous messages, motivating to action, addressing the individual directly	Internet Stationary event Advertising spot Educational film Promotional posters
„Diagnostics of the ovary" ovarian cancer	Consideration of the importance of regular gynaecological visits for the prevention and early detection of gynaecological diseases	Generating negative emotions, fear of the health of the individual, motivates to reflection and take action	Internet Advertising spot Opening conference
American campaigns			
„Our Way Forward" ovarian cancer	Call for action on ovarian cancer to encourage patients, their families and health care workers to rethink their thinking and talk about the cancer through education and support.	Evoking positive emotions, calm messages, motivate action through education and patient stories.	Internet Stationary events Invitations to clinical trials Promotional videos
„Inside Knowledge: Get the Facts About Gynecologic Cancer" 5 types of gynecologic cancer	Awareness raising about 5 gynaecological cancers: cervical, ovarian, uterine, vaginal, and vulvar. Encouraging women to take care of their bodies so they can see warning signs and seek medical help	Positive messages that focus on the general public by clarifying and presenting health statistics	Television Radio Internet Printed materials Public transportation, public places in major US cities Promotional videos
„It is Time to End Cervical Cancer" cervical cancer	Informing the public, including women and girls about ways to prevent cervical cancer through health information. Raising awareness for the early detection of this cancer	Direct messages to individuals that motivate them to take care of their health and improve it. Generate positive emotions by using animated commercials	Internet Printed materials Stationary events Promotional videos Involvement of public institutions
„GO Teal and White" cervical cancer	Raising awareness of cervical cancer prevention. Calling on women in Alabama to continue regular screening for cervical cancer. Highlighting the fact that during the COVID-19 pandemic it is equally important to prevent this disease and save lives through vaccinations, pap tests, and follow-up examinations	Raising concern through direct messages. Motivating to become active and to take an interest in one's own health	Internet Printed materials Television Stationary events Podcast Promotional videos
„Move The Message" 5 types of gynecologic cancer	Call on people from all over the country to join a social movement to raise awareness of five gynaecological cancers: cervical, ovarian, uterine, vaginal, and vulvar	Positive messages that motivate people to act and spread knowledge through exercise (5 minutes for exercising and social media posting #MoveTheMessage)	Internet Printed materials Stationary events Promotional videos

Health Mitchell Cancer Institute, "GO Teal and White" [13]. The last campaign subject to analysis was "Move The Message" carried out in 2021 by the Foundation for Women's Cancer on the occasion of the month of gynecological cancers, and it focused on five gynecological cancers: cervix, ovary, endometrium, vagina and vulva cancer [14].

Online resources offer many more opportunities to find information about campaigns carried out in the United States than in Poland. Campaigns in Poland focused on single types of cancer: 3 out of 5 campaigns focused on ovarian cancer, and 2 out of 5 were dedicated to cervical cancer. Some US campaigns focused on all types of gynecological cancer (2 out of 5 campaigns), one campaign focused on ovarian cancer, and one was dedicated to cervical cancer.

The aim of most of the analyzed campaigns was widely understood prevention, encouraging the society to think about their health and educating society about gynecological cancers. Both Polish and American campaigns used direct messages which addressed an individual recipient. The goal of the message usually was to evoke positive emotions (3 out of 5 Polish campaigns, and 4 out of 5 American campaigns), and encourage women to participate in preventive examinations and increase their knowledge about gynecological cancers. Two out of five Polish campaigns and one American campaign were characterized by a negative overtone and included messages created to cause anxiety and lead to emotions such as fear. The goal of such campaigns is to encourage the rejection of negative behaviors, such as avoiding cytological examinations among young women.

Each of the analyzed Polish and American campaigns had its own website. Two Polish campaigns offered free medical tests and vaccinations, and only one campaign in the USA promoted an event with free vaccinations. Creative methods that were frequently used were educational films and short advertising spots. Two American campaigns involved charity runs for women and their relatives. Most of the USA campaigns were based on printed materials in the form of informational and educational leaflets or promotional posters. Unlike in the USA, public figures, such as actors and artists, appeared as the faces of two campaigns in Poland, which offered a great opportunity for promotion due to the huge number of their followers and the possibility of using social media to promote the campaigns. Faces of the campaign were frequently women who were patients or who had managed to win over a gynecological cancer (2 out of 5 Polish campaigns, and 3 out of 5 American campaigns). Promotional spots and other films created for the campaigns featured also doctors and specialists, who have authority among the campaign recipients due to their knowledge and experience. Two out of five USA campaigns did not have the face of the campaign.

The most frequently used means of communication, both in Polish and American campaigns, were the Internet, advertising spots and educational films. Four campaigns in Poland and four campaigns in the USA involved stationary events (campaign inaugurations, charity runs). Two of the Polish campaigns used the press and printed materials for promotion. Contrary to Polish campaigns, 2 out of 5 American campaigns used television and radio as the means of communication. The following social media platforms were used in the analyzed campaigns: Instagram, Facebook, Twitter and YouTube. Facebook was the most frequently chosen social media platform among Internet users and campaign organizers. A total of 62.4% of all persons following the profiles of social campaigns in the USA and 78.9% of all persons following the campaigns in Poland had a Facebook account. Regarding the posted content, Facebook was the most popular, too, with about 270 posts uploaded by American organizations and about 210 posts uploaded by Polish organizations. Over 8.5 million (2.6% of the US population) people in the United States and almost 25 thousand (0.07% of the Polish population) people in Poland followed social media profiles of the campaigns that were subject to analysis in this study.

DISCUSSION

Most social campaigns are organized by non-governmental organizations and few of them are dedicated to gynecological cancers. Polish governmental organizations should follow the example of the United States and start to participate in the organization of creative social campaigns in order to target as many people as possible and stop the downward trend in patients' participation in preventive programs.

Social media make it possible for their users and social campaign organizers to quickly spread information with "one click" and "share" buttons. It is worth improving this means of communication as almost everyone has a smartphone these days, and social media are likely to be used more and more frequently by the whole society.

Taking into consideration the fact that that social marketing is a new field in Poland, there is no other study on social campaigns dedicated to gynecological cancer prevention. The structure of the analysis of social campaigns was inspired by the division presented in the book "Social campaigns on health issues - analysis of the content and forms of communication" [15]. Joanna Sułkowska and Robert Seliga [16] discussed the implementation of social marketing in health prevention in their study "Social marketing in health prevention", which is a case study based on three social campaigns on health issues and includes an analysis of the campaigns' main goals, ranges, organizers, and the media used.

The main conclusion of the study is that social marketing improves the effectiveness of health prevention activities. The effectiveness of social marketing was also proved in "Putting social marketing into practice" by Gerard Hastings and Laura McDermott [17], who focused on a television social campaign designed to increase oncological awareness. This campaign resulted in a significant increase in the number of patients reporting to medical facilities, and thus an increase in the detection of cancer cases. The authors proved the effectiveness of using social marketing tools in health care and the increased interest in this marketing tool in their country [17].

It should be emphasized that numerous difficulties were encountered in finding social campaigns in the narrow field of gynecological cancer prevention. Only a small number of social campaigns in the relevant area have been registered in Poland and in the USA. This creates a wide variety of opportunities for future research and discussions on the importance of health prevention and ways of promoting. This study leads to a reflection on the current state of social marketing and future possibilities to ameliorate its implementation in gynecological cancer prevention.

CONCLUSIONS

Social marketing tools are underutilized in gynecologic cancer prevention in both Poland and the United States, leaving ample room for future improvement in its use. It is problematic to find Polish social campaigns dedicated to gynecological cancer prevention, which might be related to the fact that gynecologic oncology is a relatively new field in Poland, and it is continuously modified. The analysis showed that American state organizations are more strongly involved in social campaigns than their Polish counterparts and they show a more modern approach to the gynecological cancer prevention. It is worth noticing that neither of the countries can fully use the potential of social media. More than 60% of the Internet users in Poland have their accounts on social media platforms. This offers a great opportunity to reach to the whole society at a small expense, and it can be of a substantial benefit to non-governmental organizations, which usually have a limited budget. It can be observed that the number of new social campaigns in Poland that are dedicated to the specialist field of gynecological cancers prevention is still small. As opposed to the United States, Poland has not yet created a campaign covering all types of gynecological cancers.

The main problem in Poland is the lack of access to free preventive medical examinations. In addition, population surveillance technologies are outdated and there is no universal database or integration with software that is used by medical professionals. For the implementation of preventive activities based on social marketing, it is of key importance to convince decisive persons and doctors to use preventive activities, and to teach patients about the idea of cancer prevention and its benefits.

A general assessment of the use of social marketing in the prevention of gynecological cancer seems to show that the social marketing tools are more effectively used in the United States than in Poland. There are more foundations, governmental and non-governmental organizations that undertake preventive activities in the USA. Due to the lack of study materials, two campaigns organized by the same foundation were included in the analysis of the Polish campaigns. Many more American campaigns can be found online, which can be related to the fact that the history of social marketing in the USA is much longer than in Poland.

Article information and declarations

Author contributions

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REFERENCES

1. Kotler P, Zaltman G. Social marketing: an approach to planned social change. J Mark. 1971; 35(3): 3–12, indexed in Pubmed: 12276120.
2. NIH. Cancer Stat Facts. https://seer.cancer.gov/statfacts/.
3. Dwilewicz-Trojaczek J, Gawrychowski K, Jarząb B, et al. Aktualne zasady postępowania diagnostyczno-terapeutycznego w onkologii. CMKP 2011: 83–94.
4. Bieńkowska I, Fajfer-Kruczek I, Kitlińska-Król M, et al. Profilaktyka w przestrzeni publicznej. Scriptum. 2013: 220.
5. Główny Urząd Statystyczny. Zdrowie i ochrona zdrowia w 2019 r. GUS, Warszawa, Kraków 2020: 135.
6. Kwiat Kobiecości. O nas. https://www.kwiatkobiecosci.pl/o-nas/.
7. Polskie Amazonki Ruch Społeczny. Kim jesteśmy? https://www.ruch-spoleczny.org.pl/o-nas/.
8. Medistica. Profilaktyka Raka Szyjki Macicy. https://medistica.com.pl/ginekologia-plodnosc/rsm/.
9. Gośliński J. „Dla Niej. Możemy więcej". Kampania edukacyjna na temat nowotworów strefy intymnej. https://www.zwrotnikraka.pl/dla-niej-mozemy-wiecej-kampania-edukacyjna-na-temat-nowotworow-strefy-intymnej/.
10. GSK. Our Way Forward. https://www.ourwayforward.com.
11. CDC. Inside Knowledge About Gynecologic Cancer Campaign. https://www.cdc.gov/cancer/gynecologic/knowledge/about.htm.
12. PAHO. PAHO launches campaign to prevent cervical cancer. https://www3.paho.org/hq/index.php?option=com_content&view=ar

ticle&id=14818:paho-launches-campaign-to-prevent-cervical-cancer&Itemid=0&lang=en#gsc.tab=0.
13. McPhail C. GO Teal and White campaign to raise awareness about cervical cancer. https://www.usahealthsystem.com/news/go-teal-and-white-campaign-1.
14. FFWC. Know The 5 Gynecologic Cancers. Take steps today to protect your tomorrows. https://www.foundationforwomenscancer.org/movethemessage.
15. Daszkiewicz M. Kampanie społeczne o tematyce zdrowotnej- analiza treści i form przekazów komunikacyjnych. UEW 2019.
16. Sułkowska J, Seliga R. Wykorzystanie marketingu społecznego w profilaktyce zdrowotnej. Zeszyty Naukowe SGGW w Warszawie. Polityki Europejskie, Finanse i Marketing. 2013; 10: 59.
17. Hastings G, McDermott L. Putting social marketing into practice. BMJ. 2006; 332(7551): 1210–1212, doi: 10.1136/bmj.332.7551.1210, indexed in Pubmed: 16710004.

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Current status and outlook of minimally invasive treatment for leiomyomas

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ABSTRACT

Objectives: Leiomyomas are benign, highly prevalent gynecologic conditions that can cause abnormal uterine bleeding, pelvic pain, urinary difficulties, and/or bladder or rectal obstruction. With advances in medical technology, women are increasingly interested in treatments that avoid surgery and/or preserve the uterus, which has undoubtedly contributed to the development of minimally invasive approaches. This article reviews the literature and evaluates the effectiveness and safety of minimally invasive approaches for the treatment of leiomyomas and describes the current state of development of minimally invasive treatment modalities for leiomyomas.

Material and methods: Web of Science and PubMed were systematically evaluated using the following keywords: uterine artery embolization, high-intensity focused ultrasound, microwave ablation, radiofrequency ablation, myomectomy, hysterectomy, leiomyomas, fertility. English abstracts relevant to the topic were selected and full-text articles were carefully analyzed.

Results: Uterine artery embolization is an effective treatment modality that has been widely validated, and the remaining means each have their distinct advantages in clinical practice, but more practical and comparative studies are needed. Minimally invasive myomectomy and minimally invasive hysterectomy are technically advanced compared to classical open surgery and are widely used due to the completion of practical experience, but a continuous interest in non-invasive minimally invasive treatment modalities is retained.

Conclusions: Minimally invasive treatment modalities for leiomyomas have emerged as an important treatment option when considering patient requirements, and further research and practice are needed to support their development into a mainstream modality for the treatment of leiomyomas.

Keywords: leiomyomas; minimally invasive surgical procedures; treatment outcome; fertility

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INTRODUCTION

Leiomyomas are benign lesions or tumors of the uterus, consisting of smooth muscle cells and fibroblasts enriched with extracellular matrix (ECM). Leiomyomas appear to develop and regulate gene expression in response to the menstrual cyclicity of gonadal steroids (mainly estrogen and progesterone), developing between menarche and menopause. Leiomyomas are common, occurring in more than 70% of women. However, leiomyomas can be asymptomatic, with 25–50% of women having clinical symptoms. Common symptoms include menstrual bleeding, urinary or pelvic discomfort, dysmenorrhea, painful disorders, infertility, and recurrent miscarriages, severely affecting the quality of life of the patient. The main risk factors for leiomyosarcoma include age and race, it can begin to develop during adolescence, and black women are two to three times more likely to develop the disease than white women [1].

After years of exploration, the treatment options for leiomyomas have become very mature and diversified. The classic treatment options are abdominal myomectomy or hysterectomy, but due to the long recovery time, scarring, and greater harm of these approaches, women's strong need to avoid surgery and to preserve the uterus and fertility has also strongly promoted the development of minimally invasive treatment for leiomyomas [2]. Minimally invasive treatment options are less invasive and less harmful. The advantages of minimally invasive treatment options are undeniable, as they are less invasive and have a faster recovery after surgery. At the same time, however, a significant number of treatment options are still at a stage where their

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safety and efficacy need to be monitored and larger-scale practice is needed to confirm their effectiveness or optimize their procedures.

UTERINE ARTERY EMBOLIZATION (UAE)

This technique achieves reduction of leiomyomas by injecting microspheres into the uterine artery. Routine preoperative preparation of the patient includes fasting for at least six hours, premedication for documented history of allergy to contrast agents, and laboratory assessment of coagulation parameters and renal function. New techniques for uterine artery embolization are flourishing with the development of medical treatments, such as the injection of lidocaine with embolic pellets [3], the development of unilateral trans-radial access, *etc.* [4]. Compared to conventional myomectomy, although it may require additional surgical intervention, its advantages such as short hospital stay, minimally invasive, rapid postoperative recovery, local anesthesia only, and reproducibility are evident, which is why its acceptance by patients and the percentage of procedures is increasing year by year [5]. This is why its acceptance by patients and the percentage of surgical procedures are increasing year by year.

HIGH INTENSITY FOCUSED ULTRASOUND (HIFU)

High-intensity focused ultrasound is a technique that concentrates an ultrasound beam to a point so that the energy at that point is maximized. Its treatment principle is to heat, cavitate, and damage blood vessels by concentrating energy on the target location causing blood supply disruption. Magnetic resonance imaging guided high intensity focused ultrasound (MRgFUS) is one of the most effective methods of treatment, using focused high-energy ultrasound waves guided by magnetic resonance imaging to instantaneously destroy tissue. The high-energy ultrasound heated the target site to 55°C to 85°C, resulting in coagulation necrosis and cell death. MRI images' high contrast, spatial resolution, and multidimensional capabilities provide optimal tissue localization, and MRI thermometry provides real-time thermal imaging of the ablated area [6]. The MRgFUS is also capable of providing real-time thermal imaging of the ablated area. A series of tests, such as evaluation of symptoms and examination of standard contraindications to MRI, is required before deciding whether to use MRgFUS. The best results have been obtained with less than 4 fibroids or less than 50 mL fibroids, with a higher safety profile for fibroids located in the submucosa [7]. It is safer to treat myomas located in the submucosa. To achieve a complete treatment, the distance of the myoma from the anterior abdominal wall must be less than 12 cm.

In general, the patient's symptoms improve significantly after surgery and are accompanied by a reduction in the size of the uterus [8]. Tracking the proportion of patients requiring re-intervention at different time points after surgery shows that the proportion increases with time from 12–48 months and also indicates that older age at treatment tends to mean a lower risk of re-intervention [9]. The study also noted that older treatment age tended to mean a lower risk of reintervention. Compared to uterine artery embolization (UAE), the effectiveness of treatment and post-treatment effects on fertility are similar, but patients receiving MRgFUS after a longer period (60 months) have a poorer quality of life and require less re-intervention than those receiving UAE, with longer recovery times and more medications, and require additional attention to the potential for high-energy sound waves to cause burns and intestinal damage. The MRg is a very good candidate for the UAE. Due to these limitations, MRgFUS is still not a widely used treatment for leiomyomas, but it still offers an effective and reliable option for the non-invasive treatment of fibroids and has great potential for development [10].

Another more widely used treatment is ultrasound-mediated high-energy focused ultrasound (USgHIFU), which, as the name implies, is guided by ultrasound images. After 918 patients were treated, the fibroids were significantly reduced in size, with only 4.6% experiencing symptomatic recurrence [11]. A survey of the fertility status of patients treated with USgHIFU showed that the mean time to pregnancy after HIFU treatment was 5.6 ± 2.7 months, with 88.75% of patients having normal deliveries (including cesarean section). All patients had well-developed fetuses during pregnancy and childbirth without uterine rupture or perinatal and postpartum complications [12]. Thus, USgHIFU is a very friendly treatment option for patients with leiomyomas who wish to have children and can significantly shorten the postoperative period of pregnancy preparation.

Patients who have undergone USgHIFU treatment tend to have a better quality of life and health than laparoscopic myomectomy, mainly because of its non-invasive, minimally invasive advantages. Compared to MRI-guided high-energy focused ultrasound treatment, it is also able to detect and fully ablate myomas up to one centimeter in diameter, despite its slightly less accurate imaging, in addition to the advantages of shorter imaging time, higher treatment efficiency, higher ablation rate, and shorter treatment time. Years of application have also made the technique more stable and mature.

RADIOFREQUENCY ABLATION (RFA)

Radiofrequency ablation (RFA) is a type of hyperthermic ablation, similar to high-energy focused ultrasound, which also causes tissue destruction through high temperatures, although the method of generating high temperatures is slightly different, as the energy is generated in the radio

frequency range (between 3 kHz and 300 GHz) in the form of alternating current (AC) [13]. The coagulation necrosis caused by RF energy results in a reduction in the size of the myoma and enhances the patient's quality of life. the RFA system includes a multi-needle electrode array with thermocouple technology that allows real-time temperature feedback to maximize ablation volume while minimizing needle puncture points. The addition of paired real-time ultrasound to the RFA allows for more precise localization of fibroids [14].

Trans-laparoscopic radiofrequency ablation is effective in small and non-irritating symptomatic leiomyomas. After treatment, the patient's symptoms will remain improved for a long time with a significant improvement in quality of life (including reduction in fibroid size, menstrual bleeding, *etc.*) and a low rate of re-intervention [15]. Transcervical radiofrequency ablation, performed under local anesthesia only, with short operative time and rapid postoperative recovery, is indicated for the treatment of small, solitary or superficial leiomyomas. It offers less surgical trauma and lower surgical risk than trans-laparoscopic radiofrequency ablation, but its treatment outcome may be inferior to that of trans-laparoscopic radiofrequency ablation. The new staging method for leiomyomas developed by the International Federation of Obstetrics and Gynecology provides an important basis for choosing laparoscopy or hysteroscopy in clinical practice (FIGO types 2–5, and 6 are suitable for laparoscopic procedures, FIGO types 1–5, and 6 are suitable for hysteroscopic procedures, and FIGO types 7 and 8 are not suitable due to their anatomical location and risk of producing thermal injury (using these two therapies) [14] and can make an assessment of the difficulty of the procedure.

In a comparative study by Melody Taheri et al. [16] on RAF, UAE, and FUS, it was noted that the treatment effect of RFA was striking among these three minimally invasive treatments (70%, 54%, and 32% reduction in myoma volume for the three, respectively). In terms of impact on fertility, from the available data, the majority of patients treated with RFA delivered at full term with no neonatal complications [17]. Therefore, RAF treatment may be a preferable option for those patients who wish to preserve their fertility.

MICROWAVE ABLATION (MWA)

Microwave ablation (MWA) is a treatment method that uses high-frequency microwave heat to destroy tumor tissue. From the treatment data of microwave ablation (344 patients from eight treatment centers in China), the average ablation rate of myoma after (MWA) treatment was 86.6% (54–100%), and no serious complications occurred [18].

Compared to HIFU, both are safe and effective treatment modalities, however, MWA benefits from a different treatment mechanism (energy decay during the propagation of ultrasound, significant cooling due to blood flow during HIFU treatment) and can produce higher instantaneous temperatures and a wider power field. Therefore, MWA is more suitable for the treatment of large and multivessel fibroids, while HIFU is more suitable for small fibroids and less vascular fibroids, but MWA treatment requires hospitalization and general anesthesia, while HIFU therapy does not [19]. There is no significant difference in treatment outcome or improvement in quality of life compared to UAE, but MWA has a lower risk of embolic complications, is better tolerated, and is less costly [20]. However, MWA has a lower risk of embolic complications and is better tolerated and uses fewer medical resources. Overall, MWA, RFA, and HIFU are all thermal ablation therapies, and further high-quality, multicenter, large sample randomized controlled trials are needed for MWA therapy.

UTERINE FIBROID REMOVAL

Minimally invasive myomectomy has been developed in various ways today, such as laparoscopic myomectomy (LM) and hysteroscopic myomectomy (HM). Compared to cesarean surgery, LM has advantages in terms of reduced bleeding, postoperative complications, and hospitalization. However, this does not mean that LM is free from complications and contraindications, and the size of the fibroids may make the procedure more difficult and increase the risk of intraoperative and postoperative complications [21]. Laparoscopic myomectomy is slightly less time-consuming than cesarean surgery, taking about 70 minutes on average, but the risk of bleeding events is significantly higher with cesarean surgery [22]. The former patients had a higher quality of life compared to those treated with HIFU, which may be attributed to the fact that HIFU is a non-invasive treatment modality. In addition, the size of the fibroids may affect the pregnancy rate in patients after laparoscopic myomectomy. The number and type of myomas do not affect postoperative pregnancy rates or pregnancy outcomes. Postoperative pregnancy interval does not affect pregnancy outcome, placental adhesions during pregnancy, and postpartum hemorrhage [23]. Therefore, the pregnancy rate can be improved by shortening it according to the patient's condition.

In recent decades, thanks to advances in equipment, HM has become a highly recognized minimally invasive treatment for leiomyomas. The size of fibroids treated with the HM method is under 4 cm, since the operating instruments are in the operating scope of about 1 cm. For fibroids larger than 4 cm, additional treatment is needed to reduce the size of the fibroids before using HM. Pre-treatment with gonadotropin-releasing analog (GnRH-a) or the HIFU method is commonly used, and the HIFU method of management often brings advantages in terms of operative time and intraoperative bleeding. There was no significant difference in

Table 1. Advantages and disadvantages of minimally invasive treatment modalities for leiomyomas

Treatment modality	Advantages	Disadvantages
UAE	No surgical incision required; reduced postoperative pain and recovery time; preservation of the uterus	Some treatment limitations; may require multiple treatments; some complications may occur
MRgFUS	Non-invasive; preservation of the uterus and fertility; no anesthesia or hospitalization required; high precision	Indication limitations; longer time required; may require multiple treatments; complications from burns and intestinal injuries
USgHIFU	Non-invasive; easy to undergo; reduced complications; preservation of uterus and fertility	Restricted treatment depth; low precision; takes longer time
RFA	Less trauma and bleeding; preservation of the uterus and fertility; less risk of complications	Professional equipment and technology required; may require multiple treatments; requires surgery under anesthesia
MWA	Fast, effective treatment; less risk of complications; for larger fibroids; preservation of uterus and fertility	Requires specialized equipment and techniques; some complications may occur; requires surgery under anesthesia
Myomectomy	Preservation of the uterus; complete removal of the fibroids	Larger bleeding volume and trauma; longer recovery time; possible postoperative complications and scar formation
Hysterectomy	Complete removal of fibroids and uterus	Greater trauma and bleeding; requires general anesthesia and longer recovery time; not suitable for reproductive needs

UAE — uterine artery embolization; MRgFUS — intensity focused ultrasound; USgHIFU — ultrasound-mediated high-energy focused ultrasound; RFA — radiofrequency ablation; MWA — microwave ablation

the rate of intraoperative complications and one-time resection of leiomyomas between the two groups ($p > 0.05$) [24].

The complications of HM therapy are difficult to ignore and include uterine perforation, bleeding, adhesions, incomplete resection, infection, intravenous infiltration/hysterectomy with intravascular absorption (OHIA) syndrome, and venous air embolism [25, 26]. These can be very critical and even life-threatening, so other treatment options should be used in cases where the risk of HM is known to be high [26].

HYSTERECTOMY

Hysterectomy includes total hysterectomy, which removes both the uterus and the cervix, and subtotal hysterectomy, which removes only the uterus but leaves the cervix intact, for cases where the cervical examination is normal and the patient requests to keep the cervix or where cervical removal is difficult. With the development of surgical techniques, minimally invasive surgical methods have been developed for hysterectomy: total laparoscopic hysterectomy (TLH), total vaginal hysterectomy (TVH), *etc.* [27], which are essentially variations of laparoscopic hysterectomy and vaginal hysterectomy. In general, removal of the uterus means loss of reproductive function and cessation of menstruation, which may also have some endocrine effects. However, patients will have to resort to hysterectomy when other treatment modalities have serious sequelae or are not effective.

In contrast, the laparoscopic route (TLH) is more popular with patients because of its less pain, less blood loss, and quicker recovery. TVH has the shortest multisite procedure time, but TLH has a lower complication rate, which may explain the increasing popularity of TLH with patients [28]. Women who have a hysterectomy appear to have a greater improvement in health-related quality of life than women who have a myomectomy, but this is limited to those who have a minimally invasive procedure. Such a difference is not surprising given that hysterectomy eliminates the possibility of myoma-specific symptoms and dysfunctional uterine bleeding [29].

The most common complication of benign hysterectomy is urinary tract infection, and the use of minimally invasive means has greatly reduced this possibility. It is also worth mentioning that some ethnic differences were demonstrated among patients who underwent hysterectomy. Due to the large sample taken, the varying levels of hospitals, and the different ages of the patients, body mass index, and other various indicators, there are no strict limits on the criteria for comparison, but the results can still serve as an important reference.

SUMMARY AND OUTLOOK

Table 1 summarizes the minimally invasive treatment modalities for leiomyomas described in this article. Uterine artery embolization is a widely validated treatment modality for the minimally invasive treatment of leiomyomas, while high-energy focused ultrasound, microwave ablation, and radiofrequency ablation require larger randomized controlled trials to confirm their practice results. The development of myomectomy and hysterectomy in the minimally invasive direction is more dependent on the overall technological advances in surgery, and both will be further revolutionized when new techniques become available. In addition to surgical treatments, pharmacological treatments are also evolving, such as selective progesterone receptor modulators (SPRM), gonadotropin-releasing hormone analogs (GnRH).

In addition, it should be noted that some malignant tumors different from fibroids, may also be asymptomatic

at first, and blind use of minimally invasive modalities may cause them to metastasize and spread, therefore, after the tissue biopsy is completed, the appropriate modality should be chosen to address them in the shortest possible time according to the situation. In conclusion, in the current fast-paced life, minimally invasive treatment modalities for leiomyomas with short treatment time and quick postoperative recovery are becoming the first choice for more and more people, and minimally invasive treatment (except hysterectomy) is also a better choice for patients who wish to preserve their uterus while remaining fertile. With the huge demand, minimally invasive treatment needs to be accelerated and developed rapidly.

Article information and declarations

Author contributions

As the first author and corresponding author, (Bin Meng) was responsible for the conceptual design and experimental planning of the study, performed the main experimental work, conducted the data analysis and interpretation, and undertook the main writing and revision of the paper. (Ning Liu) was responsible for the execution and data collection of part of the experiment. (Xiaotao Wang and Zhe Geng) participated in the data analysis. (Mingmin Xu and Qian Li) provided expertise and technical support, participated in research discussions and interpretation of results. All authors participated in the final review and approval of the paper.

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Conflict of interest

All authors declare no conflict of interest.

REFERENCE

1. Stewart EA, Laughlin-Tommaso SK, Catherino WH, et al. Uterine fibroids. Nat Rev Dis Primers. 2016; 2: 16043, doi: 10.1038/nrdp.2016.43, indexed in Pubmed: 27335259.
2. Krzyzanowski J, Wozniak S, Szkodziak P, et al. Minimally invasive treatment options for uterine fibroids — state-of-the art 2021. Ginekol Pol. 2022; 93(3): 242–247, doi: 10.5603/GP.a2021.0202, indexed in Pubmed: 35106750.
3. Noël-lamy M, Simons M, Mironov O, et al. Effectiveness of intra-arterial lidocaine for pain control after uterine artery embolization: a prospective randomized study. J Vasc Interv Radiol. 2016; 27(3): S17–S18, doi: 10.1016/j.jvir.2015.12.059.
4. Resnick NJ, Kim E, Patel RS, et al. Uterine artery embolization using a transradial approach: initial experience and technique. J Vasc Interv Radiol. 2014; 25(3): 443–447, doi: 10.1016/j.jvir.2013.11.010, indexed in Pubmed: 24581468.
5. Manyonda I, Belli AM, Lumsden MA, et al. FEMME Collaborative Group. Uterine-Artery embolization or myomectomy for uterine fibroids. N Engl J Med. 2020; 383(5): 440–451, doi: 10.1056/NEJMoa1914735, indexed in Pubmed: 32726530.
6. Coakley FV, Foster RF, Farsad K, et al. Pelvic applications of MR-guided high intensity focused ultrasound. Abdom Imaging. 2013; 38(5): 1120–1129, doi: 10.1007/s00261-013-9999-2, indexed in Pubmed: 23589077.
7. Trumm CG, Stahl R, Clevert DA, et al. Magnetic resonance imaging-guided focused ultrasound treatment of symptomatic uterine fibroids: impact of technology advancement on ablation volumes in 115 patients. Invest Radiol. 2013; 48(6): 359–365, doi: 10.1097/RLI.0b013e3182806904, indexed in Pubmed: 23385396.
8. Silberzweig JE, Powell DK, Matsumoto AH, et al. Management of uterine fibroids: a focus on uterine-sparing interventional techniques. Radiology. 2016; 280(3): 675–692, doi: 10.1148/radiol.2016141693, indexed in Pubmed: 27533290.
9. Gorny KR, Borah BJ, Brown DL, et al. Incidence of additional treatments in women treated with MR-guided focused US for symptomatic uterine fibroids: review of 138 patients with an average follow-up of 2.8 years. J Vasc Interv Radiol. 2014; 25(10): 1506–1512, doi: 10.1016/j.jvir.2014.05.012, indexed in Pubmed: 24998103.
10. Sridhar D, Kohi MP. Updates on mr-guided focused ultrasound for symptomatic uterine fibroids. Semin Intervent Radiol. 2018; 35(1): 17–22, doi: 10.1055/s-0038-1636516, indexed in Pubmed: 29628611.
11. Lee JS, Hong GY, Lee KH, et al. Safety and efficacy of ultrasound-guided high-intensity focused ultrasound treatment for uterine fibroids and adenomyosis. Ultrasound Med Biol. 2019; 45(12): 3214–3221, doi: 10.1016/j.ultrasmedbio.2019.08.022, indexed in Pubmed: 31563479.
12. Zou M, Chen L, Wu C, et al. Pregnancy outcomes in patients with uterine fibroids treated with ultrasound-guided high-intensity focused ultrasound. BJOG. 2017; 124 Suppl 3: 30–35, doi: 10.1111/1471-0528.14742, indexed in Pubmed: 28856864.
13. Lee BB, Yu SP. Radiofrequency ablation of uterine fibroids: a review. Curr Obstet Gynecol Rep. 2016; 5(4): 318–324, doi: 10.1007/s13669-016-0183-x, indexed in Pubmed: 27917310.
14. Baxter BL, Seaman SJ, Arora C, et al. Radiofrequency ablation methods for uterine sparing fibroid treatment. Curr Opin Obstet Gynecol. 2022; 34(4): 262–269, doi: 10.1097/GCO.0000000000000801, indexed in Pubmed: 35895970.
15. Lin L, Ma H, Wang J, et al. Quality of life, adverse events, and reintervention outcomes after laparoscopic radiofrequency ablation for symptomatic uterine fibroids: a meta-analysis. J Minim Invasive Gynecol. 2019; 26(3): 409–416, doi: 10.1016/j.jmig.2018.09.772, indexed in Pubmed: 30253997.
16. Taheri M, Galo L, Potts C, et al. Nonresective treatments for uterine fibroids: a systematic review of uterine and fibroid volume reductions. Int J Hyperthermia. 2019; 36(1): 295–301, doi: 10.1080/02656736.2018.1564843, indexed in Pubmed: 30676099.
17. Polin M, Hur HC. Radiofrequency ablation of uterine fibroids and pregnancy outcomes: an updated review of the literature. J Minim Invasive Gynecol. 2021; 28(11): S23, doi: 10.1016/j.jmig.2021.09.335.
18. Liu H, Zhang J, Han ZY, et al. Effectiveness of ultrasound-guided percutaneous microwave ablation for symptomatic uterine fibroids: a multicentre study in China. Int J Hyperthermia. 2016; 32(8): 876–880, doi: 10.1080/02656736.2016.1212276, indexed in Pubmed: 27405972.
19. Zhao WP, Han ZY, Zhang J, et al. A retrospective comparison of microwave ablation and high intensity focused ultrasound for treating symptomatic uterine fibroids. Eur J Radiol. 2015; 84(3): 413–417, doi: 10.1016/j.ejrad.2014.11.041, indexed in Pubmed: 25572326.
20. Jonsdottir G, Beermann M, Lundgren Cronsioe A, et al. Ultrasound guided microwave ablation compared to uterine artery embolization treatment for uterine fibroids - a randomized controlled trial. Int J Hyperthermia. 2022; 39(1): 341–347, doi: 10.1080/02656736.2022.2034991, indexed in Pubmed: 35134317.
21. Marín-Buck A, Karaman E, Amer-Cuenca JJ, et al. Minimally invasive myomectomy: an overview on the surgical approaches and a comparison with mini-laparotomy. J Invest Surg. 2021; 34(4): 443–450, doi: 10.1080/08941939.2019.1642422, indexed in Pubmed: 31322011.
22. Garneau AS, Lababidi SL, Akin JW. Comparison of operative outcomes for abdominal and laparoscopic myomectomies. Fertility and Sterility. 2018; 110(4): e397–e398, doi: 10.1016/j.fertnstert.2018.07.1112.
23. Lu B, Wang Q, Yan L, et al. Analysis of pregnancy outcomes after laparoscopic myomectomy: a retrospective cohort study. Comput Math Methods Med. 2022; 2022: 9685585, doi: 10.1155/2022/9685585, indexed in Pubmed: 35607646.
24. Liao P, Jiang J, Zeng YH, et al. Comparison of outcomes of hysteroscopic myomectomy of type 2 submucous fibroids greater than 4 cm in diameter via pretreatment with HIFU or GnRH-a. Int J Hyperthermia.

2021; 38(1): 183–188, doi: 10.1080/02656736.2021.1874546, indexed in Pubmed: 33573453.
25. Piecak K, Milart P. Hysteroscopic myomectomy. Menopausal Rev. 2017; 16(4): 126–128, doi: 10.5114/pm.2017.72757, indexed in Pubmed: 29483854.
26. Ciebiera M, Łoziński T, Wojtyła C, et al. Complications in modern hysteroscopic myomectomy. Ginekol Pol. 2018; 89(7): 398–404, doi: 10.5603/GP.a2018.0068, indexed in Pubmed: 30091451.
27. Baxi RP, MacKoul PJ, Danilyants N, et al. A value-based approach to hysterectomy: comparison of minimally invasive hysterectomy techniques. J Minim Invasive Gynecol. 2017; 24(7): S147–S148, doi: 10.1016/j.jmig.2017.08.422.
28. Luchristt D, Brown O, Kenton K, et al. Modern trends in operative time and outcomes in minimally invasive hysterectomy. J Minim Invasive Gynecol. 2020; 27(7): S1, doi: 10.1016/j.jmig.2020.08.023.
29. Wallace K, Zhang S, Thomas L, et al. Comparative effectiveness of hysterectomy versus myomectomy on one-year health-related quality of life in women with uterine fibroids. Fertil Steril. 2020; 113(3): 618–626, doi: 10.1016/j.fertnstert.2019.10.028, indexed in Pubmed: 32192594.

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RECOMMENDATIONS

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Polish Society of Gynecologists and Obstetricians (PTGiP) and Polish Society of Sports Medicine (PTMS) recommendations on physical activity during pregnancy and the postpartum period

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INTRODUCTION

Regular physical activity during pregnancy brings numerous health benefits for both the mother and her child [1–3]. Such behavior is safe for most patients without specific contraindications to physical activity. Therefore, exercise is currently perceived as a key lifestyle component that supports the normal development of pregnancy and reduces the incidence of pregnancy complications.

Women with uncomplicated pregnancies are advised to engage in at least 150 minutes of moderate-intensity physical activity per week (*e.g.*, brisk walking, swimming, resistance training/body toning exercises, gardening) throughout their pregnancy, accumulated over three or more days per week [3–5]. If failing to achieve this goal they should be encouraged to do any physical activity each day to minimize sedentary behavior [3, 5].

Regular physical activity is associated with improved cardiorespiratory fitness and reduced risk of pregnancy-induced hypertension, preeclampsia, gestational diabetes, and excessive weight gain in healthy pregnant women. Those who engage in regular physical activity are significantly more likely to give birth by vaginal delivery, are less likely to suffer from urinary incontinence or depression and find it easier to return to their pre-pregnancy body weight after delivery [2, 6]. There is also strong scientific evidence that moderate-intensity physical activity during pregnancy is not associated with pregnancy loss, miscarriage, preterm delivery, premature rupture of membranes, neonatal death, low birth weight, perinatal damage to the mother or the incidence of labor induction [2, 5]. In addition, exercise during pregnancy can be a preventive measure for both the mother and her child against chronic conditions such as obesity, type 2 diabetes and cardiovascular diseases [6–9].

Importantly, women become less physically active with every subsequent pregnancy, failing to observe the recommended volumes and frequency. The most common reasons for this are feeling unwell, feeling tired, having too little time available or low motivation to exercise, and being uncertain of whether exercise is safe for the mother and

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child. In addition, women often report that their pregnancy care providers do not offer enough information on physical activity. This may be due to the latter having insufficient knowledge on the subject and their concern that exercise may be detrimental to the mother and fetus [2]. Hence, it is extremely important to adequately educate both pregnant patients and the personnel responsible for pregnancy care provision.

ANATOMICAL AND PHYSIOLOGICAL ADAPTATIONS TO PREGNANCY IN THE CONTEXT OF PHYSICAL ACTIVITY

Pregnancy is associated with anatomical and physiological changes that must be considered when planning physical activity during this period. The most significant anatomical changes are weight gain, anterior displacement of the center of gravity with an increased lumbar lordosis, and a loosening of the ligamentous and articular systems. This puts stress on some joints, including the spine — mainly the lumbar segment and the pelvic girdle — and increases the risk of falling. The latter is the most common cause of injury in pregnant women in the second and third trimesters and can lead to negative health consequences for both the mother and child. The risk of falling is higher in women who do not exercise during pregnancy than in those who do [10]. This is most likely due to a poorer posture, worse balance and longer reaction times in non-exercisers [11]. Therefore, it is important to do such exercises during pregnancy that will help reduce the risk of falling. Engaging in new sports or those that impose high technical requirements is not recommended. Women who, prior to their pregnancy, practiced sports entailing the risk of falling or contact sports should modify their training plans to minimize the possibility of sustaining injury [12].

Approx. 50% of pregnant women suffer from lower back and pelvic girdle pain, often causing them to avoid exercise. Many reports have proven that physical activity reduces the severity of these complaints [9, 10]. During the third trimester of pregnancy, the increased weight and stress on the joints implicates considering non-weight bearing activity, such as aquatic or stationary bicycle exercise [11].

The cardiovascular system begins to change in the fifth week into gestation [4]. The heart rate accelerates by an average of 10–15 beats per minute. Peripheral resistance decreases, which can result in lower blood pressure and in symptoms of hypotension when the patient's position changes suddenly (especially from lying to sitting or standing) or when they are standing without moving for a prolonged time. Exercise should not end abruptly, and it is recommended that the intensity in the final part of the exercise session should reduce gradually [13–16]. In the third trimester of pregnancy, the growing uterus can compress the inferior vena cava, mainly in the supine position. Decreased blood pressure or malaise occurring while in the supine position affects 10% of women [4]. This group should avoid remaining supine for longer periods of time. The available research suggests that exercise in the supine position is not associated with negative consequences for the course of pregnancy or the development of the fetus [17]. Nevertheless, those women who are uncomfortable in this position (either in physical or mental terms) should avoid such activity [4]. Tachycardia, jugular venous distention, slight shin edema, leftward displacement of the apex beat, and systolic heart murmur along the left side of the sternum are physiological occurrences during an examination of pregnant patients lying in the supine position [15].

The fetus produces additional heat that must be removed. In addition, fetal temperature maintenance is dependent entirely on the mother's management of her own temperature. The pregnant woman dissipates heat more easily by way of increased blood flow through the skin, elevated respiratory rate, and more abundant perspiration, which is associated with a resetting of the thermoregulatory center [18]. Elevated temperature (> 39°C) during pregnancy may be associated with abnormal embryogenesis and fetal congenital defects. Its impact on neural tube formation is of particular significance [18]. Recommendations as to the conditions of physical activity, its duration and its effects on fetal temperature are provided in the following chapters.

Diastasis recti abdominis is a separation of the linea alba found in 66–100% of women in the third trimester of pregnancy and 39% of patients 6 months after delivery [19, 20]. To date, there has been no consensus among researchers as to what width of the linea alba should be considered a pathology and require intervention [21, 22]. Recommendations as to abdominal muscle exercise in pregnancy are provided in the following chapters.

ASSESSING THE PREGNANT WOMAN AND FETUS

At her first visit during pregnancy, each patient should be notified about the benefits of physical activity in pregnancy. In the absence of complications or obstetric or general medical contraindications, exercise in pregnancy is safe and desired, while pregnant women should be encouraged to continue or commence safe physical activity. The intensity and type of exercise should be individualized. In order to be able to discuss the scope of safe exercise with the patient, the risks to her pregnancy should be assessed first. Particular caution should be maintained with regard to women with high-risk pregnancy, where the choice of the type and intensity of exercise must be made under the supervision of specialists.

Table 1. Pregnancy risk assessment based on the patient's history and medical examination. (Modified from the perinatal care standard provided for in the Health Minister's Order of 16 August 2018 on the organizational standard for perinatal care. Identification of risk factors for perinatal complications) [26]

The risk factors identified through the patient's medical history taken during pregnancy and prior to delivery include, in particular:
1. Her conditions, in particular cardiovascular diseases, blood hypertension, kidney diseases, neurological diseases, mental and behavioral disorders, liver diseases, diabetes mellitus, coagulation defects, thrombophilia, antiphospholipid syndrome, and obesity
2. Active HIV or HCV infections
3. Status post fertility treatment, at least two consecutive spontaneous abortions, or preterm labor
4. Previous stillbirth or delivery of a neonate with severe birth asphyxia
5. Previous delivery of a neonate weighing more than 4 000 g, or contrary — with a very low or extremely low birth weight
6. Multiple pregnancy
7. Bleeding prior to delivery, status post such complications as placenta previa or placental abruption
8. Status post uterine surgery or surgery of the lower segment of the reproductive system, birth canal injuries, uterine atony, postpartum hemorrhage, convulsions, thromboembolic conditions or uterine inversion
9. Where the pregnant patient is a multigravida of over 40 years old or a multigravida having delivered 4 children
10. Chronic infection (also suspected) in the pregnant woman or a body temperature exceeding 38°C more than once during pregnancy
11. Use of psychoactive substances, medicinal products, alcohol or nicotine during pregnancy and in the period immediately preceding pregnancy
The factors identified during pregnancy and prior to delivery based on an examination include, in particular:
1. Systolic pressure exceeding 140 mmHg and diastolic pressure exceeding 90 mmHg, proteinuria higher than 0.3 g/24 h
2. Weight gain of more than 500 g per week in the last trimester
3. Pyelonephritis
4. Anemia
5. Diabetes mellitus
6. Previous or ongoing vaginal bleeding
7. Blood type incompatibility between the mother and the fetus
8. Inadequacy of the size of the uterus or the size of the baby in relation to the duration of pregnancy (problems in determining the precise due date, fetal growth restriction, fetal macrosomia, polyhydramnios, oligohydramnios, myomas, multiple pregnancy, cephalopelvic disproportion)
9. Threatened preterm labor (premature uterine contractions, incompetent cervix)
10. Abnormal location of the placenta
11. Multiple pregnancy with fetuses in abnormal positions
12. Pregnancy past the 41st week, or uncertain due date

HIV — human immunodeficiency virus; HCV — hepatitis C virus

Such pregnancies are classified as either low- or high-risk. The pregnancy risk assessment must follow the perinatal care standards (Tab. 1) [23]. Based on medical history and examination, the obstetrician-gynecologist/perinatologist may issue a pregnancy risk certificate — a template is shown in Figure 1.

The management of an uncomplicated pregnancy in a healthy patient engaged in moderate-intensity sports should not differ in any way from the recommended standard of perinatal care in Poland. However, patients engaged in vigorous sports should have an additional ultrasound done between 28–32 weeks' gestation and the due date. An examination at 35–37 weeks' gestation is suggested to assess fetal growth. Three meta-analyses showed that differences in birth weight were minimal or nonexistent between women who exercised during pregnancy and the non-exercising control group. However, women who continued to exercise intensely during the third trimester of pregnancy were more likely to deliver babies weighing 200–400 g less, although there was no increased risk of fetal growth restriction [24–26].

There is currently no reliable data available on what supervision over pregnant patients engaged in competitive sports should look like. Studies evaluating umbilical artery blood flows, the fetal heart rate and the fetal biophysical profile before and after vigorous exercise in the second trimester, have shown that 30 minutes of vigorous exercise is well tolerated. Therefore, individualized exercise recommendations may be warranted in pregnant women engaged in competitive sports, but only if intensive supervision of fetal well-being, which should primarily include assessment of fetal growth and vascular flows, is ensured. Pregnant women

First name	Last name		Date of birth	PESEL [personal identity number]
Obstetric diagnosis				
Concurrent diseases				
Additional information (past injuries)				
Low-risk pregnancy				
High-risk pregnancy				
Doctor's first and last names			Stamp	

Figure 1. Template of the pregnancy risk assessment certificate issued by the obstetrician-gynecologist/perinatologist — valid until the date of the subsequent appointment scheduled according to the perinatal care standard or an earlier appointment if recommended by the doctor

continuing their competitive sports regime should be aware that there is insufficient data available on the safety of intense physical activity for fetal well-being, the condition of the newborn, and the child's further development and health. Should any signs occur of the risk of preterm labor, vaginal bleeding or placental insufficiency, the pregnant patient should significantly reduce her sport participation.

If there are complications of pregnancy that may constitute an absolute contraindication to exercise during pregnancy (*e.g.*, significant risk of preterm labor or severe preeclampsia, or placenta previa with episodes of bleeding), continuing normal daily activities is permissible, but participation in more strenuous exercise or activities must be given up [4, 15]. Women with relative contraindications (*e.g.*, a history of preterm labor) should discuss the advantages and disadvantages of moderate- to high-intensity physical activity with their obstetrician-gynecologist/perinatologist.

In summary, healthy women with low-risk pregnancy should always be informed about and encouraged to engage in physical activity. In the case of women with complications of pregnancy, the degree of their recommended physical activity should be individually adjusted according to their type of obstetric-medical restriction. In addition, it would be advisable to avoid putting complete ban on physical activity and preventing the pregnant woman from undertaking any physical activity.

Absolute pregnancy-related contraindications to physical activity

In 2020, ACOG experts removed the list of absolute and relative contraindications to exercise during pregnancy. Instead, they recommend consulting a specialist (*i.e.*, an obstetrician-gynecologist, a maternal-fetal medicine specialist, a doctor of another specialty) should there be doubts regarding exercise safety [5, 27]. With concurrent obstetric diseases or general medical conditions, the exercise regimen should be individualized with the safety of the patient and fetus in mind. Limiting activity in the prevention of primary preeclampsia or preterm birth is also discouraged, which was a common practice in obstetric care (Tab. 2).

Table 2. Obstetric conditions requiring specialist consultation to individualize physical activity and ensure safety for the mother or fetus

Incompetent cervix, cervical cerclage, the pessary
Multiple pregnancy at risk of premature birth
Persistent bleeding in the second or third trimester of pregnancy
Placenta previa after 26 weeks' gestation
Threatened preterm labor
Ruptured membranes
Preeclampsia
Intrauterine growth restriction in the current pregnancy

Absolute non-pregnancy related contraindications to physical activity

Pregnant women with chronic diseases may require modification of their physical activity, but not cessation of it. Therefore, in their case, it is necessary to consult their doctor providing prenatal care and determine further management. Conditions of particular significance here are cardiovascular diseases, poorly controlled asthma, diabetes mellitus, hypertension, severe anemia, uncompensated thyroid diseases, malnutrition, morbid obesity, an extremely sedentary lifestyle, and heavy smoking [18].

EXERCISE PLAN FOR PREGNANT WOMEN

The main assumption of targeted physical activity for pregnant women should be to select exercises in such a way that they are not only safe for the mother and fetus but also bring as many health benefits to the women as possible [28]. In order to be able to respond to the needs of all the participants in group classes, different versions of exercise should be proposed considering the trimester of pregnancy and how it has been developing, and the women's level of skills and psychophysical capabilities. They should be informed both of what the correct technique is for each exercise and how to modify it in case of discomfort or a pregnancy-related complaint [29].

For the general population, a health-promoting exercise program includes endurance exercises (usually aerobic), resistance exercises — to increase muscle strength, stretching exercises, and neuromotor exercise training [30]. For pregnant women, pelvic floor training and labor preparation exercises should be added [31–33]. Pregnant patients fall into the healthy adult category, although they are considered a so-called special population [4]. Thus, the planning and implementation of exercise programs for pregnant women should be guided by the same principles as for other adult populations, sometimes perhaps including slight modifications. The bottom line is to select training components appropriately (Tab. 3 [34]):

- frequency (how many exercise sessions per week?);
- intensity (how intense or tiring are the exercises?);
- time (how long does each exercise session last?);
- type of exercise (what exercises are performed?);
- volume (how many individual exercises are performed, most often per week — as a resultant of the intensity, number of sessions and their duration?);
- progression or modification (how to make progress/ /or how to adjust exercise to the course of pregnancy).

Previously inactive women

The exercise program for pregnant women without previous exercise experience should start with low-intensity activities, such as walking or swimming, initially performed in short sessions (*e.g.*, 15 minutes long). It should be gradually extended to reach the minimum level of physical activity recommended for pregnant women, *i.e.*, 150 minutes per week of at least moderate-intensity exercise [4].

Previously active women

According to World Health Organization and American College of Obstetricians and Gynecologists (ACOG) experts, women who were physically active before pregnancy or regularly participated in higher-than-moderate intensity physical activity may continue to do so, provided that the pregnancy is uncomplicated and there is no discomfort during exercise [3, 4].

Table 3. Elements of recommended physical activity for pregnant women (based on Santos-Rocha et al. [34])

Type of exercise	Intensity	Duration/volume	Frequency	Progression or modification
Endurance exercises				
Exercises that activate large muscle groups in a rhythmic and continuous manner, for example: walking, riding a stationary bicycle, dancing, aerobics, aquatic exercise. Many previous activities can be continued during pregnancy, with some modifications Contact sports carrying a high risk of abdominal injury are not recommended. Similarly, sports entailing a high risk of falling are not recommended Underwater diving is not recommended during pregnancy, either	At least moderate to high, monitored using, for instance, the Borg Rating of Perceived Exertion (RPE)*, the talk test** or heart rate values*** Women with no or very limited previous exercise experience are advised to start with low-intensity exercise and gradually increase intensity to reach the moderate level Women with previous exercise experience can participate in vigorous physical activity, provided that the pregnancy develops normally and is monitored continuously There is no conclusive data on the impact of maximum effort activity or exercises at more than 90% of the maximum heart rate on pregnancy	At least 30 min of moderate-intensity exercise per day, up to a total of at least 150 minutes per week or 75 minutes of high--intensity exercise per week Previously inactive women should start with low-intensity exercise, extending duration gradually from 15 to 30 minutes per day	Previously sedentary women: up to 3 days per week Previously very active women can continue their training programs with the same frequency, provided that the pregnancy develops normally Previously active women: 3–5 days per week, even every day	The patients should avoid activities that pose a risk of falling or injury

→

Table 3 cont. Elements of recommended physical activity for pregnant women (based on Santos-Rocha et al. [34])

Type of exercise	Intensity	Duration/volume	Frequency	Progression or modification
Resistance exercises				
A variety of stationary machines, weight-bearing and non-weight bearing exercises, and bodyweight exercises are well tolerated during pregnancy Exercises involving large muscle groups are recommended	For most pregnant women, appropriate intensity will be one that allows multiple submaximal-effort repetitions (*e.g.*, 8–10 or 12–15 repetitions) to be performed until moderate fatigue At the end of the set of repetitions the woman should feel comfortable and have no pain	1 set for beginners 2–3 sets for intermediate and advanced exercisers It is recommended that the basic program include 8–10 exercises for different muscle groups	2–3 non-consecutive days per week	After 16 weeks' gestation, when exercising in the supine position, it should be assessed whether there is compression of the inferior vena cava — in this position the patient may feel uncomfortable, dizzy or weak A safe alternative is to modify the position of the exercise so that instead of lying on her back the patient should assume a lateral recumbent, sitting, or standing position
Weightlifting or intense isometric exercises with a large number of repetitions should be performed with special care, due to the lack of conclusive scientific data on their safety in pregnancy				
Stretching exercises				
A set of active or passive static or dynamic stretching exercises for each musculotendinous junction	The given stretching exercise should be continued until tension or slight discomfort is felt Exercise should not be perceived as painful	In static exercises, the position should be maintained for 10 to 30 seconds (up to 60 seconds) 2–4 repetitions for each exercise	At least 2–3 to 7 days per week	Excessive strain on the joints should be avoided
Neuromotor exercise training				
Exercises developing motor skills, *e.g.*, balance, agility, coordination, gait), proprioceptive training, and all-around exercise regimes (*e.g.*, pilates, yoga, Tai Chi)	Balance training intensity refers to the degree of difficulty of the positions or technical elements being practiced No recommendations for the minimum intensity (and volume) of neuromotor exercise during pregnancy have been developed	20–30 to 60 minutes per day	At least 2–3 to 7 days per week	They can be included in daily activities In the event of a risk of falling or other safety concerns, the patient should exercise under supervision
When doing neuromotor exercises, one should avoid positions that are uncomfortable or pose the risk of losing balance or falling				
Pelvic floor training — see text below				
Comprehensive pelvic floor muscle training should include both conscious contraction and conscious relaxation exercises	The minimum effective intensity (and volume) of pelvic floor exercises has not been determined	10 to 30 min per day	1 to 7 days per week	Can be performed anywhere, anytime, every day Should be included in any pregnancy exercise program
Proper technique for performing pelvic floor muscle exercises should be ensured, and a specialist contacted if necessary				
A variety of pelvic floor muscle exercises should be performed to improve the speed, strength, endurance and coordination of the pelvic floor muscles and to engage both the fast- and slow-twitch muscle fibers				

*The woman can assess her exertion using the 20-point Borg rating (Tab. 4), *e.g.*, as moderate-intensity between 13 and 14 (somewhat hard), or as high-intensity from 17 onwards (very hard) [5, 35]; **Another simple way to assess and monitor exercise intensity is the 'talk test' [36]. If during her activity the pregnant patient can comfortably hold a conversation but cannot sing her exertion is most probably moderate (so-called aerobic); ***Women with previous experience in heart rate monitor use can continue gauging their exercise intensity in this way, although they need to remember that the resting heart rates in pregnancy are often higher than their pre-pregnancy values. The heart rate ranges for individual exertion scopes were borrowed from Canadian recommendations, while the results were obtained in studies of healthy pregnant populations [18] (Tab. 5)

Table 4. 20-Point Borg Rating of Perceived Exertion [35]

Number	Effort
6	No exertion at all
7	Very, very light
8	Very, very light
9	Very light
10	Very light
11	Fairly light
12	Fairly light
13	Somewhat hard
14	Somewhat hard
15	Hard
16	Hard
17	Very hard
18	Very hard
19	Very, very hard
20	Maximum exertion

Table 5. Heart rate ranges recommended for physical activity during pregnancy [18]

Pregnant woman age	Intensity	Range of heart beats per minute
< 29	Low Moderate High	102–124 125–146 147–169
30+	Low Moderate High	101–120 121–141 142–162
Moderate intensity (40–59% HRR)		
High intensity (60–80% HRR)		

HRR — heart rate reserve

PELVIC FLOOR MUSCLE TRAINING FOR THE PREVENTION OF UROGYNECOLOGICAL DYSFUNCTIONS

Pregnancy and childbirth affect the strength of the pelvic floor muscles, urinary system function, urination, and the women's quality of life [37]. Pelvic floor muscle training (PFMT) is an important element of preparing a pregnant woman both for changes occurring in her body as a result of adaptation to pregnancy and for childbirth. Women who do not show symptoms of pelvic floor muscle dysfunction should be trained in the proper exercise of this muscle group and receive clear and accurate instructions on PFMT, best included in a comprehensive health-promoting exercise program. On the other hand, women with incontinence or other pelvic floor dysfunctions, or patients unable to contract their pelvic floor muscles consciously, should be referred for specialist clinical diagnosis by a specialist in the area of her particular dysfunction (*e.g.*, a gynecologist, urologist, proctologist, *etc.*), and subsequently for functional diagnosis and rehabilitation by a urogynecological physiotherapist [38].

Pelvic floor muscle training during pregnancy and after labor can prevent and treat urinary incontinence. The literature on the subject recommends a training protocol compliant with the principles of strength training, emphasizing contractions close to maximal and lasting at least 8 weeks. Notwithstanding, numerous research papers claim that there is a need for further high-quality randomized trials, especially in postpartum women, to determine the effectiveness of the actions taken. Given the prevalence of urinary incontinence in women and its effect on participation in exercise, PFMT should generally be included as a routine part of women's exercise programs. Several systematic reviews and Cochrane reviews implicate there is high-quality evidence of the effective preventive and therapeutic impact of pelvic floor muscle training in urinary incontinence and pelvic organ prolapse in the lesser pelvis [39]. In addition, intense pelvic floor muscle training during pregnancy prevents urinary incontinence both during pregnancy and after labor. Pelvic floor muscle strength improves significantly after intense pelvic floor muscle training [40, 41]. It is worth mentioning, however, that there is no evidence of the effectiveness of exercise regimens other than pelvic floor muscle training in relieving the symptoms of urinary incontinence [42]. According to available studies, pelvic floor muscle training clearly does not prevent damage to the perineum. Further research is needed to examine various protocols and interventions in this area. However, the largest study of pelvic floor muscle training reported a significant reduction in the duration of the second stage of labor, while this intervention also reduced the incidence of urinary incontinence [43]. In summary, pelvic floor muscle exercises used during pregnancy increase the strength of the pelvic floor muscles, prevent the exacerbation of urinary system symptoms, and affect the quality of life of pregnant women [37]. With concomitant dysfunction in the pelvic floor area, pelvic floor muscle exercises should be conducted by a urogynecological physiotherapist.

LABOR PREPARATION EXERCISES, INCLUDING BREATHING AND BIRTHING POSITION EXERCISES

According to scientific reports, skillful breathing and relaxation techniques, explained to and practiced by pregnant women early-enough, can positively affect their sense of self-efficacy and control over labor. They are also likely to reduce the need for pharmacological support, in particular the use of epidurals, and to affect the experience of labor pain. However, there are no valuable scientific reports showing

the effects of these interventions in relation to the improvement of neonatal outcomes. In addition, the role of providing relevant information and focusing on breathing and relaxation techniques in antenatal education is emphasized in research [44]. Regarding breathing, the most frequently suggested techniques are slow and deep breathing during contractions in the first stage of labor and breathing while pushing in the second [45].

As regards the conduct of active delivery, including the use of birthing positions, it is important that non-weight bearing positions that reduce stress on the sacral region (kneeling, four-point kneeling, lateral recumbent position, squatting, delivery in a birthing chair or stool) shorten the second stage of labor [46]. In the second stage of labor, these positions may also reduce the incidence of operative delivery, instrumental delivery, cesarean section, episiotomy, and severe perineal injuries and severe pain, and shorten the duration of the active pushing phase in the second stage of labor. However, these positions may increase the incidence of mild perineal injury [47].

There is no clear agreement among researchers, however, whether the upright or lying birthing positions are beneficial or detrimental to the patient regarding serious or less serious perineal injury. In turn, labor in the lateral recumbent position or with the use of four-point kneeling correlates with higher incidence of complete perineal protection [48]. Researchers have raised the need to leave certain freedom to the patient in childbirth and encourage her to choose her comfortable childbirth position spontaneously [46].

PHYSICAL ACTIVITY IN PREGNANCY FOR OBESE WOMEN — SPECIAL RECOMMENDATIONS

An obese pregnant patient carries an increased risk of complications of pregnancy, labor and puerperium. In this group, hypertension, diabetes mellitus, fetal macrosomia, cesarean section, perineal damage and poor wound healing are observed more often than in pregnant women with normal body mass index (BMI). For these patients, weight gain limitation during pregnancy is of particular importance. The higher the BMI, the lower the desired weight gain should be. Physical activity decreases as BMI increases, and thus it is extremely important that the pregnant woman should be encouraged to participate in any of the forms of physical activity recommended during pregnancy. For obese pregnant patients, exercise is best commenced with 15-minute sessions, gradually extending their duration to 30 minutes to reach the minimum recommended level of physical activity. The best advantages are derived from daily adherence to exercise. Aquatic exercises tend to be popular with obese pregnant women as they help reduce the feeling of their body weight and the stress associated with exposing their own body to the group's view. Moderate-intensity physical effort is recommended to avoid tachycardia and fatigue in pregnant women with obesity [4, 5, 14, 27].

ABDOMINAL MUSCLE EXERCISES

Properly selected and performed abdominal muscle exercises are known to diminish the risk of postural disorders and back pain. What is more, strong abdominal muscles strengthen the abdominal prelum, and thus support the pushing mechanism necessary during natural labor [43]. There is no consensus on which abdominal muscle exercises are most effective in preventing or treating diastasis recti abdominis. Until a standard for the prevention and therapy of diastasis recti abdominis is established, pregnant and postpartum women are recommended to perform abdominal exercises applying the correct technique requiring that abdominal muscle contractions be accompanied by an exhalation, the correct body position (including proper trunk stabilization) be maintained, and a conscious contraction of the pelvic floor muscles be performed [49].

Preventive consultation with a specialist is recommended in order to assess the pathological separation between the rectus abdominis muscles and perhaps individualize the exercise regime. Ultrasound is one of the best methods to assess the separation between the rectus abdominis muscles, which can be combined with a standard ultrasound examination assessing how pregnancy is developing.

SYMPTOMS REQUIRING CESSATION OF PHYSICAL ACTIVITY

Symptoms that require immediate cessation of exercise and an appointment with a doctor include:

- chest pain;
- inexplicable shortness of breath before effort;
- dizziness or headache, feeling faint;
- muscle weakness;
- pain in the calf, accompanied by its swelling and possibly redness;
- sudden swelling of the ankles, hands or face;
- bleeding or a leak of amniotic fluid from the birth canal;
- decreased fetal movement sensation;
- uterine contractions, lumbar or pelvic pain (signs indicating preterm birth) [4].

PHYSICAL ACTIVITY FOR WOMEN WITH COMPLICATED PREGNANCY — LIMITED BED REST RECOMMENDATIONS

Bed rest has historically been regarded as a 'remedy for all pregnancy-related ailments. According to current fact-based medical knowledge, routine bed rest is not recommended. The negative health consequences of this practice have

been reported, among them the risk of venous thromboembolism, bone demineralization and deterioration of the pregnant woman's fitness, as well as negative psychosocial effects affecting not only the mother but also the entire family. There are no studies documenting improvements in outcomes in women at risk of preterm birth prescribed with reduced activity, including bed rest. Based on the available evidence from Cochrane reviews, it is believed that recommending bed rest to treat pregnancy complications may be considered as an unethical approach [50–52].

POSTPARTUM ACTIVITY

In the first hours after labor, the mother should be instructed on how to exercise to assist her postpartum convalescence and, in the absence of medical contraindications, perform lower extremity edema exercises as part of antithrombotic prophylaxis that includes activating the distal parts of the legs, exercises preparing for regaining a full upright position, those that facilitate regaining and maintaining the correct body posture, and breathing and functional exercises, including for instance instruction in lifting and putting her baby back to bed. It is recommended that simple exercises should be done while still in the hospital. These are, *e.g.*, hand, arm, trunk, hip and foot circles, and exercises for individual parts of the body in the supine position on the bed. The selection of these exercises, as well as their intensity and range of motion, should consider how the labor progressed, whether there were any complications thereof, and whether the postpartum woman has any functional and health limitations, *e.g.*, ones related to cesarean section, episiotomy or perineal tear.

In order to prevent pelvic floor muscle dysfunction, in the absence of medical contraindications the patient should commence exercising this muscle group as soon as possible [5, 31]. The woman is allowed to continue to exercise the pelvic floor muscles with the same volume, frequency and intensity as those recommended for pregnant patients, if there are no contraindications related to how the labor progressed or associated with the surgical treatment of the perineum that she received [53]. Women with no previous pelvic floor muscle exercise experience should receive appropriate instruction in how this should be done. A preventive appointment with a urogynecological physiotherapist is recommended to exclude dysfunction of this muscle group and individualize the exercise regime. Ideally, the first consultation assessing the pelvic floor with a qualified specialist should take place in the maternity ward before leaving the hospital following childbirth, and subsequently continue in the postpartum period and, if necessary, also after its completion.

If there are no medical contraindications after returning from the hospital following childbirth, the woman should gradually return to physical activity in order to accumulate a minimum of 150 minutes of moderate-intensity exercise per week as soon as this becomes possible [4]. The time to commence the exercise, as well as its intensity and frequency, are determined by the woman's well-being and health [54]. As a rule, those women who were active during pregnancy will be quicker to return to their pre-pregnancy or antenatal activity levels compared to those who did not exercise during gestation. Due to the high probability of pelvic floor muscle dysfunction, including in particular stress urinary incontinence, it is recommended that in the first 4–6 weeks after childbirth the mother should participate in the so-called low biomechanical load activities, such as walking, Nordic walking, dancing, inline skating, cycling (after the perineum has healed), and resistance exercises. The patient's return to more dynamic forms of activity that entail running or jumping, such as jogging, running, tennis and team games, should be adjusted to how the postpartum convalescence is progressing, and be contingent upon full recovery of pelvic floor and abdominal muscle function, as well as complete healing of the C-section or episiotomy or other perineal wound.

After returning from the hospital, women in an uncomplicated postpartum period can gradually return to resistance exercises they participated in prior to pregnancy. It is recommended to do sessions of at least 5 to 10 minutes between 3 to 5 times per week. The sessions are supposed to be performed alternately (it is wrong to limit oneself to, for example, abdominal muscle exercise). The exercises are to be performed in sets, starting from 1–2 sets of, *e.g.*, 4–6 repetitions, increasing to 2–3 sets of, *e.g.*, 12–16 repetitions. Any progression of difficulty and volume will depend on the characteristics of the patient's physical activity during pregnancy, as well as her well-being and individual needs.

If the woman had a C-section, the recommendation is that the exercise program should be individualized, preferably with the support of a physiotherapist, considering the size of the wound and how it has been healing. The program should start with low-intensity exercises and with a very small range of motion, so that no discomfort or pain is caused in the area of the post-operative wound. Exercise intensity, volume and range of motion should be gradually increased, depending on the woman's well-being.

The exercise sessions for breastfeeding mothers must consider their lactation needs and the child feeding times. It is recommended that the baby should be fed, or milk extracted before physical activity is undertaken to avoid breast soreness during dynamic movements. The woman should ensure she wears an appropriate supportive bra and follows proper hygiene of her breasts, also by using nursing pads. Physical activity, including its intense forms, has no adverse effect on the quantity and quality of breast milk [55].

HIGH-INTENSITY PHYSICAL ACTIVITY FOR PREGNANT WOMEN WITH PREVIOUS HIGH-INTENSITY EXERCISE EXPERIENCE AND FOR PROFESSIONAL ATHLETES

We do not establish separate recommendations for intense exercisers, since there are no large studies available exploring their case. Rather, the only source at hand is scientific reports, which is why the decision is always up to the doctor providing prenatal care, the coach, and the pregnant athlete herself. We make sure to carefully emphasize for which activities there is insufficient data to ensure full safety, as it is in the case of, for instance, weights in strength sports. Our recommendations on these issues are consistent with those of other world societies.

Female athletes, especially those involved in endurance sports, exercise at least 10 times longer per week (700–800 minutes of at least increased-intensity training) than specified in the recommendations for pregnant women who do not exercise on a professional basis. In addition, their training regimes often include at least 2 strength exercise sessions, or 100–120 minutes, per week [56].

The most active period in a female athlete's sports career often coincides with her best reproductive years. Therefore, it frequently becomes necessary to reconcile the expectations and objectives she will have in both these areas. A prolonged sports career requires an adaptation of the training plan allowing the athlete to successfully compete during pregnancy, as long as that is found to be safe, then give birth to a healthy child, and finally return to full competitive activity after labor.

The available literature presents a number of well-documented data on endurance training for pregnant women. There is little data on strength training, though.

Basic recommendations are presented below.

Avoid hyperthermia — body temperature above 39°C

Only 25% of the energy consumed by muscles is used for their effective contraction, while the remaining 75% is a by-product in the form of heat that the body needs to dissipate (through perspiration) to prevent hyperthermia. The latter is especially dangerous in the first six weeks of pregnancy (while the woman may be unaware of being pregnant) when the neural groove forms and converts into the neural tube. During this time, body temperature ≥ 39°C poses a risk of nervous system defects (such as myelomeningocele) [57–62].

One should:

- limit duration of swimming sessions to 45 minutes if water temperature is ≤ 33.4°C;
- limit high-intensity physical activity at up to 90% VO_{2max} to 35 minutes if the ambient temperature is 25°C with 45% humidity;
- limit sitting up in a bath (40°C) or hot and dry sauna at temperatures up to 70°C, with humidity up to 15% to no more than 20 minutes.

High-intensity effort at > 90% of maximum exercise capacity

There is no clear evidence in the available literature on whether high-intensity workout at > 90% of the maximal aerobic capacity (VO_{2max}) or the maximum heart rate (HR_{max}) is safe for the mother and fetus. Studies conducted on female athletes have shown that performing three to five submaximal running intervals, with an exertion level of up to 90% VO_{2max}, had no adverse effect on fetal heart function. Temporary bradycardia and a decreased uterine artery pulsatility index were found in fetuses whose mothers exceeded the exertion level of 90% VO_{2max}. However, fetal parameters quickly normalized after the mother interrupted her exercise [63]. In another paper, Anderson et al. assessed maternal-fetal flows and fetal heart rate in a single interval training session with an exertion level of 80–90% of the maternal maximum heart rate. The fetal parameters remained normal throughout the session [64]. Ong et al. [65] analyzed the effectiveness of a single interval session in a group of women in the third trimester engaged in an average level of activity before and during pregnancy. They observed that adding six 15-second intervals of perceived maximum exertion to traditional continuous moderate-intensity training increased its energy expenditure by 28%. In addition, the authors found that the intense intervals increased the women's exercise satisfaction [65]. Despite the growing body of evidence of the health benefits to be derived from well-planned and monitored high-intensity physical activity in pregnancy [66], the safe training intensity threshold is unknown [67–69]. It is not known how brief, frequently repeated bradycardia and reduced placental flow affect the fetus, which is why special care should be taken until the studies that are currently ongoing can confirm the safety of exercise with an intensity of more than 90% of the mother's maximum exercise capacity.

Training volume adjustment to the stage of pregnancy (and time since labor)

According to clinical data, a pregnant competitive athlete's training intensity (in any trimester) that does not exceed > 90% of her maximum exercise capacity during pregnancy is safe for the mother and fetus. The first trimester of gestation (with the mother not always aware of her pregnancy) is the one where the mother has physiologically

the greatest exercise capacity. Many female athletes have achieved their best results in the first weeks of pregnancy — either when they were unaware of their status (athletes with menstrual disorders) or when their pregnancy was scheduled for doping purposes (female athletes from the GDR). In cases of expected and planned pregnancy, female athletes tend to reduce their training load (volume) to, for example, 80% of the pre-pregnancy values, with particular attention to avoiding hyperthermia. Most female athletes return to their training regime already during the postpartum period. The training load should increase gradually after childbirth [55, 62–70].

Suggestions for training volume adjustment in pregnancy:

- first trimester = up to 80% of the pre-pregnancy values;
- second trimester = up to 90% of the pre-pregnancy values;
- third trimester = up to 50% of the pre-pregnancy values.
- suggestions for training volume adjustment after labor:
- first quarter after labor (0–3 months) = up to 40–50% of the pre-pregnancy values;
- second quarter after labor (4–6 months) = up to 90% of the pre-pregnancy values;
- third quarter after labor (beyond 6 months) = full training volume from before pregnancy.

The above values of training loads are only proposals. The female athlete will adjust the training to her health status, the way her pregnancy and labor progressed, her capacity, her well-being, and the competition timetable [71–73].

Strength training load adjustment during pregnancy

During strength training, especially bench pressing, blood pressure increases significantly, with systolic pressure reaching up to 300 mmHg, diastolic pressure up to 150 mmHg, and intra-abdominal pressure up to 150 mmHg [74]. There is little evidence to indicate how these changes in blood pressure can affect the well-being of the pregnant female athlete and the course of her pregnancy, and whether they pose any potential risk. Prevett et al. studied a group of 679 pregnant women who continued weight-lifting training with at least 80% of their maximum load [75]. Their pregnancy complication rates were not different from those of the average population of pregnant women. In the light of the available studies, the length of strength training and the numbers of repetitions need not be limited. However, in individual cases, it will be necessary to reduce the external load applied, also considering the weight gained in pregnancy. The alternative is to use resistance bands instead of weights. To date, there is no accurate data available determining the safe load values in strength training for pregnant women [56–70].

Nutrition and feeding

During pregnancy, starting from the second trimester, the demand for calories and proteins increases:

- in the second trimester, the intake of an additional 10 g/d of proteins and 300 kcal/d (compared to the pre-pregnancy values) is recommended;
- in the third trimester, the intake of an additional 15 g/d of proteins and 450 kcal/d (compared to the pre-pregnancy values) is recommended.

In addition, from the beginning of pregnancy, folic acid and vitamin D should be provided as supplements and the iron balance should be controlled (or iron supplemented, if needed). Exercising pregnant women can and should breastfeed. With proper nutrition, intensive training does not reduce the amount or impair the quality of their milk. The recommended nutrition throughout the breastfeeding period is the same as in the third trimester of pregnancy [62, 76].

Training under hypoxic conditions

There is no data on the safety of altitude training for competitive female athletes. Canadian experts recommend that women living in lowland areas (*i.e.*, below 2,500 m above sea level) should avoid physical activity at high altitudes (> 2,500 m above sea level) [4]. A review of the literature shows that most of the research on physiological responses under altitude conditions has so far concerned pregnant women leading a sedentary or hardly active lifestyle [77]. Therefore, there is a need for research that will allow for establishing recommendations for competitive female athletes regarding altitude training both under natural (in mountainous areas) and simulated (normobaric hypoxia) conditions.

SUMMARY

Physical activity during pregnancy is associated with benefits for both the mother and the developing fetus. In the absence of medical and obstetric contraindications, physical activity during pregnancy does not carry risks and should be performed regularly throughout the entire period of pregnancy. Some modifications to the exercise routine may be necessary to account for the pregnancy adaptations of the woman's body and the needs for the fetus. Physical activity is also crucial for the woman's health after labor. It is necessary that women be motivated to continue or commence physical activity during pregnancy and in the postpartum period. This is the responsibility of doctors, midwives, coaches, and physiotherapists. Cooperation with qualified instructors, coaches, and pregnancy and postpartum physiotherapists is recommended so that specialized exercise programs can be pursued in an effective manner. Both exercising and non-exercising pregnant patients should undergo routine gynecological and obstetric follow-ups in accordance with the accepted standards.

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Conflict of interest

The authors declare no conflict of interest.

REFERENCES

1. Díaz-Burrueco JR, Cano-Ibáñez N, Martín-Peláez S, et al. Effects on the maternal-fetal health outcomes of various physical activity types in healthy pregnant women. A systematic review and meta-analysis. Eur J Obstet Gynecol Reprod Biol. 2021; 262: 203–215, doi: 10.1016/j.ejogrb.2021.05.030, indexed in Pubmed: 34058612.
2. Yang X, Li H, Zhao Q, et al. Clinical practice guidelines that address physical activity and exercise during pregnancy: a systematic review J Midwifery Womens Health. 2022; 67(1): 53–68, doi: 10.1111/jmwh.13286, indexed in Pubmed: 34841649.
3. WHO. WHO guidelines on physical activity and sedentary behaviour. World Health Organization, Geneva 2020.
4. Mottola MF, Davenport MH, Ruchat SM, et al. 2019 Canadian guideline for physical activity throughout pregnancy. Br J Sports Med. 2018; 52(21): 1339–1346, doi: 10.1136/bjsports-2018-100056, indexed in Pubmed: 30337460.
5. Physical activity and exercise during pregnancy and the postpartum period: ACOG committee opinion, number 804. Obstet Gynecol. 2020; 135(4): e178–e188, doi: 10.1097/AOG.0000000000003772, indexed in Pubmed: 32217980.
6. Dipietro L, Evenson KR, Bloodgood B, et al. 2018 Physical Activity Guidelines Advisory Committee*. Benefits of physical activity during pregnancy and postpartum: an umbrella review. Med Sci Sports Exerc. 2019; 51(6): 1292–1302, doi: 10.1249/MSS.0000000000001941, indexed in Pubmed: 31095086.
7. Nagpal TS, F Mottola M. Physical activity throughout pregnancy is key to preventing chronic disease. Reproduction. 2020; 160(5): R111–R118, doi: 10.1530/REP-20-0337, indexed in Pubmed: 32805707.
8. https://www.who.int/publications/i/item/9789240015128.
9. Yang X, Li H, Zhao Q, et al. Clinical practice guidelines that address physical activity and exercise during pregnancy: a systematic review. J Midwifery Womens Health. 2022; 67(1): 53–68, doi: 10.1111/jmwh.13286, indexed in Pubmed: 34841649.
10. Barraco RD, Chiu WC, Clancy TV, et al. EAST Practice Management Guidelines Work Group. Practice management guidelines for the diagnosis and management of injury in the pregnant patient: the EAST Practice Management Guidelines Work Group. J Trauma. 2010; 69(1): 211–214, doi: 10.1097/TA.0b013e3181dbe1ea, indexed in Pubmed: 20622592.
11. Brewin D, Naninni A. Women's perspectives on falls and fall prevention during pregnancy. MCN Am J Matern Child Nurs. 2014; 39(5): 300–305, doi: 10.1097/NMC.0000000000000064, indexed in Pubmed: 25137078.
12. Bø K, Artal R, Barakat R, et al. Exercise and pregnancy in recreational and elite athletes: 2016/2017 evidence summary from the IOC expert group meeting, Lausanne. Part 5. Recommendations for health professionals and active women. Br J Sports Med. 2018; 52(17): 1080–1085, doi: 10.1136/bjsports-2018-099351, indexed in Pubmed: 29895607.
13. Davenport MH, Marchand AA, Mottola MF, et al. Exercise for the prevention and treatment of low back, pelvic girdle and lumbopelvic pain during pregnancy: a systematic review and meta-analysis. Br J Sports Med. 2019; 53(2): 90–98, doi: 10.1136/bjsports-2018-099400, indexed in Pubmed: 30337344.
14. Bagwell JJ, Reynolds N, Smith JoA, et al. An exploratory analysis of gait biomechanics and muscle activation in pregnant females with high and low scores for low back or pelvic girdle pain during and after pregnancy. Clin Biomech (Bristol, Avon). 2022; 97: 105705, doi: 10.1016/j.clinbiomech.2022.105705, indexed in Pubmed: 35763890.
15. RANZCOG. Exercise in Pregnancy The Royal Australian and New Zealand College of Obstetricians and Gynaecologists 2020.
16. Kazma JM, van den Anker J, Allegaert K, et al. Anatomical and physiological alterations of pregnancy. J Pharmacokinet Pharmacodyn. 2020; 47(4): 271–285, doi: 10.1007/s10928-020-09677-1, indexed in Pubmed: 32026239.
17. Mottola MF, Nagpal TS, Bgeginski R, et al. Is supine exercise associated with adverse maternal and fetal outcomes? A systematic review. Br J Sports Med. 2019; 53(2): 82–89, doi: 10.1136/bjsports-2018-099919, indexed in Pubmed: 30337348.
18. Dervis S, Dobson KL, Nagpal TS, et al. Heat loss responses at rest and during exercise in pregnancy: A scoping review. J Therm Biol. 2021; 99: 103011, doi: 10.1016/j.jtherbio.2021.103011, indexed in Pubmed: 34420641.
19. Benjamin DR, van de Water ATM, Peiris CL. Effects of exercise on diastasis of the rectus abdominis muscle in the antenatal and postnatal periods: a systematic review. Physiotherapy. 2014; 100(1): 1–8, doi: 10.1016/j.physio.2013.08.005, indexed in Pubmed: 24268942.
20. Mota P, Pascoal AG, Carita AI, et al. Normal width of the inter-recti distance in pregnant and postpartum primiparous women. Musculoskelet Sci Pract. 2018; 35: 34–37, doi: 10.1016/j.msksp.2018.02.004, indexed in Pubmed: 29494833.
21. Boissonnault JS, Blaschak MJ. Incidence of diastasis recti abdominis during the childbearing year. Phys Ther. 1988; 68(7): 1082–1086, doi: 10.1093/ptj/68.7.1082, indexed in Pubmed: 2968609.
22. Bø K, Hilde G, Tennfjord MK, et al. Pelvic floor muscle function, pelvic floor dysfunction and diastasis recti abdominis: Prospective cohort study. Neurourol Urodyn. 2017; 36(3): 716–721, doi: 10.1002/nau.23005, indexed in Pubmed: 27037746.
23. https://isap.sejm.gov.pl/isap.nsf/download.xsp/WDU20180001756/O/D20181756.pdf.
24. Kramer MS, Kramer MS. Regular aerobic exercise during pregnancy. Cochrane Database Syst Rev. 2000(2): CD000180, doi: 10.1002/14651858.CD000180, indexed in Pubmed: 10796173.
25. Lokey EA, Tran ZV, Wells CL, et al. Effects of physical exercise on pregnancy outcomes: a meta-analytic review. Med Sci Sports Exerc. 1991; 23(11): 1234–1239, indexed in Pubmed: 1837326.
26. Leet T, Flick L. Effect of exercise on birthweight. Clin Obstet Gynecol. 2003; 46(2): 423–431, doi: 10.1097/00003081-200306000-00021, indexed in Pubmed: 12808392.
27. ACOG. Physical activity and exercise during pregnancy and the postpartum period. The American College of Obstetricians and Gynecologists (ACOG). 2015; Committee Opinion No. 650.
28. de Castro R, Antunes R, Mendes D, et al. Can group exercise programs improve health outcomes in pregnant women? an updated systematic review. Int J Environ Res Public Health. 2022; 19(8), doi: 10.3390/ijerph19084875, indexed in Pubmed: 35457743.
29. Szumilewicz A, Worska A, Rajkowska N, et al. Summary of guidelines for exercise in pregnancy — are they comprehensive enough for designing the contents of a prenatal exercise program? Current Women s Health Reviews. 2015; 11(1): 3–12, doi: 10.2174/1573404811011509142008838.
30. Garber CE, Blissmer B, Deschenes MR, et al. American College of Sports Medicine. American College of Sports Medicine position stand. Quantity and quality of exercise for developing and maintaining cardiorespiratory, musculoskeletal, and neuromotor fitness in apparently healthy adults: guidance for prescribing exercise. Med Sci Sports Exerc. 2011; 43(7): 1334–1359, doi: 10.1249/MSS.0b013e318213fefb, indexed in Pubmed: 21694556.
31. Davenport MH, Nagpal TS, Mottola MF, et al. Prenatal exercise (including but not limited to pelvic floor muscle training) and urinary incontinence during and following pregnancy: a systematic review and meta-analysis. Br J Sports Med. 2018; 52(21): 1397–1404, doi: 10.1136/bjsports-2018-099780, indexed in Pubmed: 30337466.
32. Miquelutti MA, Cecatti JG, Makuch MY. Developing strategies to be added to the protocol for antenatal care: an exercise and birth preparation program. Clinics (Sao Paulo). 2015; 70(4): 231–236, doi: 10.6061/clinics/2015(04)02, indexed in Pubmed: 26017787.
33. Akca A, Corbacioglu Esmer A, Ozyurek ES, et al. The influence of the systematic birth preparation program on childbirth satisfaction. Arch Gynecol Obstet. 2017; 295(5): 1127–1133, doi: 10.1007/s00404-017-4345-5, indexed in Pubmed: 28303340.
34. Santos-Rocha R, Corrales Gu, Szumilewicz A, Pajaujiene S. Exercise testing and prescription in pregnancy. In: Santos-Rocha R. ed. Exercise and Physical Activity During Pregnancy and Postpartum Evidence-Based Guidelines. 2 ed. Springer Nature Switzerland AG, Cham, Switzerland 2022: 219–274.

35. Borg GA. Psychophysical bases of perceived exertion. Med Sci Sports Exerc. 1982; 14(5): 377–381, indexed in Pubmed: 7154893.
36. Persinger R, Foster C, Gibson M, et al. Consistency of the talk test for exercise prescription. Med Sci Sports Exerc. 2004; 36(9): 1632–1636, indexed in Pubmed: 15354048.
37. Kahyaoglu Sut H, Balkanli Kaplan P. Effect of pelvic floor muscle exercise on pelvic floor muscle activity and voiding functions during pregnancy and the postpartum period. Neurourol Urodyn. 2016; 35(3): 417–422, doi: 10.1002/nau.22728, indexed in Pubmed: 25648223.
38. Woodley SJ, Hay-Smith EJ. Narrative review of pelvic floor muscle training for childbearing women-why, when, what, and how. Int Urogynecol J. 2021; 32(7): 1977–1988, doi: 10.1007/s00192-021-04804-z, indexed in Pubmed: 33950309.
39. Martín-Rodríguez S, Bø K. Is abdominal hypopressive technique effective in the prevention and treatment of pelvic floor dysfunction? Marketing or evidence from high-quality clinical trials? Br J Sports Med. 2019; 53(2): 135–136, doi: 10.1136/bjsports-2017-098046, indexed in Pubmed: 29038216.
40. Mørkved S, Bø K. Effect of pelvic floor muscle training during pregnancy and after childbirth on prevention and treatment of urinary incontinence: a systematic review. Br J Sports Med. 2014; 48(4): 299–310, doi: 10.1136/bjsports-2012-091758, indexed in Pubmed: 23365417.
41. Mørkved S, Bø K, Schei B, et al. Pelvic floor muscle training during pregnancy to prevent urinary incontinence: a single-blind randomized controlled trial. Obstet Gynecol. 2003; 101(2): 313–319, doi: 10.1016/s0029-7844(02)02711-4, indexed in Pubmed: 12576255.
42. Jacomo RH, Nascimento TR, Lucena da Siva M, et al. Exercise regimens other than pelvic floor muscle training cannot increase pelvic muscle strength-a systematic review. J Bodyw Mov Ther. 2020; 24(4): 568–574, doi: 10.1016/j.jbmt.2020.08.005, indexed in Pubmed: 33218562.
43. Gomes Lopes L, Maia Dutra Balsells M, Teixeira Moreira Vasconcelos C, et al. Can pelvic floor muscle training prevent perineal laceration? A systematic review and meta-analysis. Int J Gynaecol Obstet. 2022; 157(2): 248–254, doi: 10.1002/ijgo.13826, indexed in Pubmed: 34270799.
44. Leutenegger V, Grylka-Baeschlin S, Wieber F, et al. The effectiveness of skilled breathing and relaxation techniques during antenatal education on maternal and neonatal outcomes: a systematic review. BMC Pregnancy Childbirth. 2022; 22(1): 856, doi: 10.1186/s12884-022-05178-w, indexed in Pubmed: 36402944.
45. Heim MA, Makuch MY. Breathing Techniques During Labor: A multinational narrative review of efficacy. J Perinat Educ. 2023; 32(1): 23–34, doi: 10.1891/JPE-2021-0029, indexed in Pubmed: 36632511.
46. Berta M, Lindgren H, Christensson K, et al. Effect of maternal birth positions on duration of second stage of labor: systematic review and meta-analysis. BMC Pregnancy Childbirth. 2019; 19(1): 466, doi: 10.1186/s12884-019-2620-0, indexed in Pubmed: 31801479.
47. Zang Yu, Lu H, Zhao Y, et al. Effects of flexible sacrum positions during the second stage of labour on maternal and neonatal outcomes: A systematic review and meta-analysis. J Clin Nurs. 2020; 29(17-18): 3154–3169, doi: 10.1111/jocn.15376, indexed in Pubmed: 32531856.
48. Edqvist M, Blix E, Hegaard HK, et al. Perineal injuries and birth positions among 2992 women with a low risk pregnancy who opted for a homebirth. BMC Pregnancy Childbirth. 2016; 16(1): 196, doi: 10.1186/s12884-016-0990-0, indexed in Pubmed: 27473380.
49. Szumilewicz A, Santos-Rocha R. Exercise selection and adatations during regnancy. In: Santos-Rocha R. ed. Exercise and Physical Activity During Pregnancy and Postpartum Evidence-Based Guidelines. 2 ed. Springer Nature Switzerland AG, Cham, Switzerland 2022: 275–361.
50. Sosa CG, Althabe F, Belizán JM, et al. Bed rest in singleton pregnancies for preventing preterm birth. Cochrane Database Syst Rev. 2015; 2015(3): CD003581, doi: 10.1002/14651858.CD003581.pub3, indexed in Pubmed: 25821121.
51. Aleman A, Althabe F, Belizán J, et al. Bed rest during pregnancy for preventing miscarriage. Cochrane Database of Systematic Reviews. 2005; 2010(10), doi: 10.1002/14651858.cd003576.pub2.
52. da Silva Lopes K, Takemoto Yo, Ota E, et al. Bed rest with and without hospitalisation in multiple pregnancy for improving perinatal outcomes. Cochrane Database Syst Rev. 2017; 3(3): CD012031, doi: 10.1002/14651858.CD012031.pub2, indexed in Pubmed: 28262917.
53. Szumilewicz A, Kuchta A, Kranich M, et al. Prenatal high-low impact exercise program supported by pelvic floor muscle education and training decreases the life impact of postnatal urinary incontinence: A quasiexperimental trial. Medicine (Baltimore). 2020; 99(6): e18874, doi: 10.1097/MD.0000000000018874, indexed in Pubmed: 32028397.
54. Santos-Rocha R, Szumilewicz A. Exercise rescrition and adatations in early ostartum. In: Santos-Rocha R. ed. Exercise and Physical Activity During Pregnancy and Postpartum Evidence-Based Guidelines. 2 ed. Springer Nature Switzerland AG, Cham, Switzerland 2022: 363–395.
55. Cary GB, Quinn TJ. Exercise and lactation: are they compatible? Can J Appl Physiol. 2001; 26(1): 55–75, doi: 10.1139/h01-004, indexed in Pubmed: 11173670.
56. Sundgot-Borgen J, Sundgot-Borgen C, Myklebust G, et al. Elite athletes get pregnant, have healthy babies and return to sport early postpartum. BMJ Open Sport & Exercise Medicine. 2019; 5(1): e000652, doi: 10.1136/bmjsem-2019-000652.
57. Chambers CD. Risks of hyperthermia associated with hot tub or spa use by pregnant women. Birth Defects Res A Clin Mol Teratol. 2006; 76(8): 569–573, doi: 10.1002/bdra.20303, indexed in Pubmed: 16998815.
58. Davenport MH, Yoo C, Mottola MF, et al. Effects of prenatal exercise on incidence of congenital anomalies and hyperthermia: a systematic review and meta-analysis. Br J Sports Med. 2019; 53(2): 116–123, doi: 10.1136/bjsports-2018-099653, indexed in Pubmed: 30337347.
59. Graham J. Update on the gestational effects of maternal hyperthermia. Birth Defects Research. 2020; 112(12): 943–952, doi: 10.1002/bdr2.1696.
60. Dervis S, Dobson K, Nagpal T, et al. Heat loss responses at rest and during exercise in pregnancy: A scoping review. Journal of Thermal Biology. 2021; 99: 103011, doi: 10.1016/j.jtherbio.2021.103011.
61. Smallcombe JW, Puhenthirar A, Casasola W, et al. Thermoregulation during pregnancy: a controlled trial investigating the risk of maternal hyperthermia during exercise in the heat. Sports Med. 2021; 51(12): 2655–2664, doi: 10.1007/s40279-021-01504-y, indexed in Pubmed: 34165763.
62. Ravanelli N, Casasola W, English T, et al. Heat stress and fetal risk. Environmental limits for exercise and passive heat stress during pregnancy: a systematic review with best evidence synthesis. Br J Sports Med. 2019; 53(13): 799–805, doi: 10.1136/bjsports-2017-097914, indexed in Pubmed: 29496695.
63. Salvesen KÅ, Hem E, Sundgot-Borgen J. Fetal wellbeing may be compromised during strenuous exercise among pregnant elite athletes. Br J Sports Med. 2012; 46(4): 279–283, doi: 10.1136/bjsm.2010.080259, indexed in Pubmed: 21393257.
64. Anderson J, Pudwell J, McAuslan C, et al. Acute fetal response to high-intensity interval training in the second and third trimesters of pregnancy. Appl Physiol Nutr Metab. 2021; 46(12): 1552–1558, doi: 10.1139/apnm-2020-1086, indexed in Pubmed: 34433004.
65. Ong MJ, Wallman KE, Fournier PA, et al. Enhancing energy expenditure and enjoyment of exercise during pregnancy through the addition of brief higher intensity intervals to traditional continuous moderate intensity cycling. BMC Pregnancy Childbirth. 2016; 16(1): 161, doi: 10.1186/s12884-016-0947-3, indexed in Pubmed: 27417194.
66. Szumilewicz A, Santos-Rocha R, Worska A, et al. How to HIIT while pregnant? The protocol characteristics and effects of high intensity interval training implemented during pregnancy – a systematic review. Baltic Journal of Health and Physical Activity. 2021; 14(1): Article-1, doi: 10.29359/bjhpa.14.1.01.
67. Holt EL, Holden AV. A risk-benefit analysis of maintaining an aerobic-endurance triathlon training program during pregnancy: a review. Science & Sports. 2018; 33(5): e181–e189, doi: 10.1016/j.scispo.2016.09.010.
68. Sigurdardottir T, Steingrimsdottir T, Geirsson R, et al. Do female elite athletes experience more complicated childbirth than non-athletes? A case–control study. Br J Sports Med. 2018; 53(6): 354–358, doi: 10.1136/bjsports-2018-099447.
69. Beetham KS, Giles C, Noetel M, et al. The effects of vigorous intensity exercise in the third trimester of pregnancy: a systematic review and meta-analysis. BMC Pregnancy Childbirth. 2019; 19(1): 281, doi: 10.1186/s12884-019-2441-1, indexed in Pubmed: 31391016.
70. Kimber ML, Meyer S, McHugh TL, et al. Health outcomes after pregnancy in elithe athletes: a systematic review and meta-analysis. Med Sci Sports Exerc. 2021; 58(10): 1739–1747, doi: 10.1249/MSS.0000000000002617, indexed in Pubmed: 33560776.
71. Bø K, Artal R, Barakat R, et al. Exercise and pregnancy in recreational and elite athletes: 2016/2017 evidence summary from the IOC expert group meeting, Lausanne. Part 5. Recommendations for health professionals and active women. Br J Sports Med. 2018; 52(17): 1080–1085, doi: 10.1136/bjsports-2018-099351, indexed in Pubmed: 29895607.
72. Solli GS, Sandbakk Ø. Training Characteristics During Pregnancy and Postpartum in the World's Most Successful Cross Country Skier. Front

Physiol. 2018; 9: 595, doi: 10.3389/fphys.2018.00595, indexed in Pubmed: 29875693.
73. Almquist NW, Sandbakk Ø, Solli GS. Performance-related physiological and haematological changes during pregnancy and postpartum in a well-trained cyclist performing endurance training. Front Physiol. 2022; 13: 762950, doi: 10.3389/fphys.2022.762950, indexed in Pubmed: 35615680.
74. MacDougall JD, Tuxen D, Sale DG, et al. Arterial blood pressure response to heavy resistance exercise. J Appl Physiol. 1985; 58(3): 785–790, doi: 10.1152/jappl.1985.58.3.785.
75. Prevett C, Kimber ML, Forner L, et al. Impact of heavy resistance training on pregnancy and postpartum health outcomes. Int Urogynecol J. 2023; 34(2): 405–411, doi: 10.1007/s00192-022-05393-1, indexed in Pubmed: 36331580.
76. Dewey KG. Energy and protein requirements during lactation. Annu Rev Nutr. 1997; 17: 19–36, doi: 10.1146/annurev.nutr.17.1.19, indexed in Pubmed: 9240917.
77. McManis BG. Integrative Review of Exercise at Altitude during Pregnancy. Int J Environ Res Public Health. 2021; 18(17), doi: 10.3390/ijerph18179272, indexed in Pubmed: 34501869.

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RECOMMENDATIONS

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Guidelines of the Polish Society of Gynecologists and Obstetricians on the diagnosis and management of pregnancies complicated by prelabor rupture of the membranes

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The guidelines of the Polish Society of Gynecologists and Obstetricians present the current recommendations about management, which may be modified in justified cases and after a thorough analysis of the clinical context, which in turn may constitute grounds for future modifications and updates.

INTRODUCTION

Prelabor rupture of the membranes (PROM), defined as rupture of the amniotic membranes before the onset of regular uterine contractility, may occur at term (≥ 37 + + 0 weeks gestation) or prematurely (< 37 + 0 weeks of gestation). The latter is known as preterm prelabor rupture of the membranes (PPROM), and is responsible for approximately 30–40% of all preterm deliveries. PPROM constitutes the most common, identifiable factor for preterm labor and may cause significant morbidity and mortality, mainly due to prematurity, sepsis, cord prolapse, and pulmonary hypoplasia. Additionally, it is associated with elevated risk for intraamniotic

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infection. The management of patients with PPROM and PROM varies and depends on the gestational age as well as other risk factors, chief among them: intraamniotic infection and/or abnormal findings for fetal wellbeing. A thorough assessment of the gestational age and knowledge about the risk factors are vital to achieve accurate diagnosis and offer adequate care to women with PPROM.

RISK FACTORS

The pathogenesis of prelabor rupture of the membranes remains to be fully elucidated. Various pathological events (*e.g.* subclinical or symptomatic, bleeding) may initiate the cascade of biochemical changes (metalloproteinase activation, oxidative stress) which will result in PROM. The risk factors are similar to those for preterm labor (Tab. 1), but many patients are free of any risk factors. A strong association with PPROM has been confirmed for the following factors: PPROM in previous pregnancy, genital tract infection, bleeding in the first, second, and third trimester, and smoking [1–3].

Table 1. Risk factors for preterm labor/prelabor rupture of the membranes (PROM)

Obstetric/gynecologic history • History of preterm labor/PROM • Cervical interventions (*e.g.* conization) • Numerous dilation and curettage procedures • Anatomical defects of the uterus
Maternal demographic characteristics • Age < 17 or > 35 years • Low level of education • Single parenthood • Low socioeconomic status • Short < 18 months interval between pregnancies • Other socioeconomic factors — *e.g.* access to medical care, disability
Nutritional status/physical activity • BMI < 18.5 kg/m^2 • 80+ hour work week • Heavy physical labor
Medical history for the current pregnancy • Assisted reproduction technology methods • Multiple gestation • Fetal factors (chromosomal abnormalities, structural defects, fetal growth restriction, fetal demise) • Bleeding from the genital tract — including placenta previa, placental abruption • Polyhydramnios or oligohydramnios • Chronic maternal conditions — hypertension, diabetes, thyroid diseases, connective tissue disorders • Surgical interventions in the abdominal cavity during pregnancy • Psychogenic factors — stress, depression, mood disorders • Stimulants — tobacco, alcohol, psychoactive substances • Infections — bacterial vaginosis, trichomoniasis, chlamydia, gonorrhea, syphilis, urinary tract infections, intraamniotic infection • Cervical length of < 25 mm between 14–28 weeks of gestation • High concentration of fetal fibronectin between 22 and 34 weeks of gestation • Uterine contractility

BMI — body mass index

DIAGNOSTICS

The diagnosis of PPROM is based on the characteristic findings in patient medical history and physical examination: the patient presents with symptoms of amniotic fluid leakage and amniotic fluid pooling in the posterior fornix of the vagina is observed during the sterile speculum exam — which remains the gold standard. If the amniotic fluid pooling is not visible at the time of the exam, pressure should be applied to the uterine fundus and the patient should be instructed to cough and lean forward, which might increase the leakage of the amniotic fluid, thus confirming the diagnosis.

When in doubt whether the fluid is indeed amniotic, fluid pH may be checked using a litmus paper. Normal vaginal fluid pH ranges from 3.8 to 4.5 (litmus paper will turn yellow), while amniotic fluid pH is typically 7.1–7.3 (litmus paper will turn dark blue). False positive results of the strip test may be found if the sample is contaminated by blood, semen, alkaline antiseptics, some lubricants or bacterial vaginosis (BV).

If the amniotic fluid leakage cannot be conclusively diagnosed, tests for the presence of insulin growth factor binding protein-1 (IGFBP-1) or placental alpha microglobulin-1 (PAMG-1) in cervical discharge might be considered, if available. Studies on these biochemical markers have demonstrated their high sensitivity and specificity for the diagnosis of PPROM [4, 5].

Fetal fibronectin measurement is a sensitive, non-specific test used to confirm amniotic fluid leakage. A negative test is highly predictive of intact fetal membranes but a positive test result is not fully diagnostic. Therefore, fetal fibronectin should not be routinely used in the diagnostic process for PPROM.

Oligohydramnios or anhydramnios on ultrasound may be helpful when attempting to confirm the clinical diagnosis of PPROM but they are not diagnostic.

MANAGEMENT

Management of patients with PPROM remains to be one of the most controversial topics in perinatal medicine. The following issues are the main causes for debate:

- accurate diagnosis in ambiguous cases,
- expectant management versus intervention,
- use of tocolytics,
- duration and type of antibiotic prophylaxis,
- rationale behind corticosteroid therapy,
- testing methods for maternal/fetal infection,
- timing of delivery.

Hospitalization

In patients with PPROM, hospitalization and periodic monitoring of maternal and fetal wellbeing are advised.

Gestational age should be determined in all women with PPROM, with additional assessment of fetal presentation and wellbeing in pregnancies > 22 + 6 weeks of gestation. It is vital to be vigilant for symptoms of chorioamnionitis or placental abruption.

In expectant management, it is important to monitor the mother's well-being based on daily values of clinical parameters (heart rate, blood pressure, body temperature). Laboratory parameters should be measured at baseline, *i.e.* upon admission to hospital, and then checked at least twice weekly, depending on clinical results (WBC, CRP, coagulation test and procalcitonin (PCT) if available).

4–6 hours after administration of antibiotics, WBC and CRP should be monitored. If the patient's clinical condition is stable and inflammatory markers do not indicate progression, peripheral blood leukocyte counts and C-reactive protein should be monitored at least twice weekly. In the case of increased levels of inflammatory markers, treatment should be modified accordingly (administration of other antibiotics/antibiotics with a broader spectrum of action and/or planned delivery should be considered).

Infection leading to intraamniotic infection (intrauterine infection) is one of the major threats associated with PPROM.

According to Gibbs, the clinical symptoms of intraamniotic infection are as follows:

- fever (> 38°C),
- leukocytosis (> 15 G/L),
- maternal tachycardia (heart rate > 100 BPM),
- fetal tachycardia (heart rate > 160 BPM),
- uterine tenderness,
- foul-smelling amniotic fluid.

The clinical diagnosis of **chorioamnionitis** may be made if two of the abovementioned symptoms are confirmed [6].

Symptoms of intraamniotic infection and/or abnormal findings for fetal wellbeing are an indication for elective delivery. In particular, maternal septicemia and symptoms of septic shock are indications for immediate delivery and hysterectomy, if necessary, to remove the source of the infection or bleeding.

During hospitalization, if the uterine cervix is closed, absolute bedrest is not recommended — instead, the patient is advised to restrict physical activity. Bedrest regime does not lower the risk for preterm labor but increases the risk for venous thromboembolism, from 0.8/1000 to 15.6/1000 in patients immobilized for over 3 days. In patients with advanced obstetric status (the risk for umbilical cord prolapse at high cervical dilation), restriction of the physical activity (mix of sedentary behavior and bedrest) is advised — antithrombotic prophylactic treatment is recommended in such cases due to the risk for developing deep vein thrombosis and pulmonary embolism. Compression therapy and/or low-molecular-weight heparin at a prophylactic dose might be considered in patients with low or moderate risk for venous thromboembolism [7].

After hospitalization, ambulatory care may be implemented **in some cases** (< 22 + 6 weeks of gestation). However, such management of patients with PPROM is associated with high risk for maternal infection and **is not recommended**. **Ambulatory care** may be considered after the clinical condition of the patient was evaluated, the patient and her family were made aware of the seriousness of the condition, and written informed request was submitted by the patient. Expectant ambulatory care should include:

- monitoring of the body temperature (twice/day),
- monitoring of the inflammatory markers (twice/week),
- clear instructions how to monitor for worrisome symptoms (*e.g.* abdominal pain, vaginal bleeding, vaginal discharge, fever, chills, flue-like symptoms),
- frequent check-up tests performed by a physician (min. 1/week).

Another hospitalization is recommended after 22 + + 6 weeks of gestation. Hospitalization at a tertiary care center is not required before 22 + 6 weeks of gestation.

Of note, PPROM at this stage of pregnancy is closely correlated with the risk for intraamniotic infection, which in turn might lead to general infection, with septicemia, septic shock, and multiorgan failure. Therefore, it is serious health concern and a life-threatening condition for the mother.

In case of PPROM after 22 + 6 weeks of gestation, the patient needs to be hospitalized at a tertiary care center, whereas women with PPROM after 34 weeks of gestation should be admitted to a secondary care center.

Recommended biochemical and biophysical tests after the diagnosis of preterm prelabor rupture of the membranes (PPROM) — summary
Monitoring of maternal wellbeing (heart rate, blood pressure, body temperature)
WBC, CRP*, clotting test (at baseline — upon admission — followed by twice/week or more), leukocytosis, PCT*, if available
Vaginal and rectal culture for type B streptococci after 22 + 6 weeks of gestation
Vaginal and cervical culture at baseline — upon admission — and later on, depending on patient condition
Cardiotocography (ideally computerized CTG) after 26 weeks of gestation (1/day)
Transabdominal ultrasound

*CRP and PCT do not apply to patients with prelabor rupture of the membranes (PROM) > 37 weeks of gestation; WBC — white blood cell; CRP — C-reactive protein; PCT — procalcitonin

Prophylactic antibiotic therapy

Intraamniotic infection may be the cause of or the consequence of PPROM. The goal of the antibiotic therapy is to lower the incidence of maternal and fetal infections, thus delaying the onset of preterm labor or the need to induce labor. In a Cochrane review about the role of antibiotics in women with PPROM, antibiotic therapy was found to be associated with statistically significantly lower incidence of chorioamnionitis (RR 0.66; 95% CI 0.46–0.96). Statistically significantly lower rates of neonates born within 48 h (RR 0.71; 95% CI 0.58–0.87) and within 7 days (RR 0.79; 95% CI 0.71–0.89) have been reported. Also, lower rates of neonatal infections, the need for surfactant and oxygen therapy, and abnormal ultrasound findings of the neonatal brain before discharge were reported [8].

Reports about the optimal antibiotic therapy and its duration remain conflicting. Various associations of gynecologists and obstetricians recommend different treatments, and the available data are insufficient to determine which antibiotic regimen (drug, dosage, duration) is superior to other antibiotic protocols. According to the guidelines of the **National Medicines Institute**, the following antibiotic therapy is recommended for patients with PPROM (without contraindications for prolonged antibiotic treatment) for 7 days [9]:

- azithromycin 1 g *p.o.* (single dose) + Ampicillin 2 g *i.v.* every 6 hours for 48 hours, followed by Amoxicillin 500 mg *p.o.* every 8 hours for the next 5 days; additionally, Metronidazole 500 mg *i.v.* may also be considered;
- since anaerobic bacteria (*Ureaplasma*, *Gardnerella*, *etc.*) play a significant role in the pathophysiologic mechanism of membrane rupture, it is prudent to include into the protocol a chemotherapeutic agent with high success rate for treating such infections;
- antibiotics used if a patient has an **allergic reaction to penicillin**:
- type I allergic response (anaphylaxis):
  - Azithromycin 1 g *p.o.* (single dose) **+** Clindamycin 900 mg every 8 hours *i.v.* for 48 hours, followed by Clindamycin 300 mg every 8 hours *p.o.* for 5 days,
  - type I allergic response and Group B streptococcus (GBS) resistance to Clindamycin.

Azithromycin 1 g *p.o.* (single dose) **+** Vancomycin 20 mg/kg every 8 hours *i.v.* (max. one-time dose of 2 g for 48 hours).

Further use of antibiotics should be based on the clinical condition of the patient, laboratory test result and culture results (in accordance with the antibiogram).

Corticosteroid therapy

Corticosteroid therapy in patients with PPROM was researched extensively by various clinical trials and was found to lower neonatal mortality rates, respiratory distress, intraventricular hemorrhage, and necrotizing enterocolitis. According to the literature, corticosteroid therapy is not associated with elevated risk for maternal and/or neonatal infection, irrespective of the gestational age. The following regimen is recommended:

- 2 doses of betamethasone (12 mg) i.m. every 24 hours,
- 4 doses of dexamethasone (6 mg) i.m. every 12 hours.

A full-course corticosteroid regimen is recommended in pregnant patients with PPROM without intraamniotic infection, between 24 + 0 and 33 + 6 weeks of gestation.

It may be considered in patients with PPROM who are **at risk for preterm labor within 7 days**, as early as from 23 + + 0 weeks of gestation. In extreme cases (high risk for preterm labor), a single maintenance dose may be administered up to 33 + 6 weeks of gestation, if the previous course was completed at least 14 days earlier. A routine repetition of a full-course corticosteroid regimen is not recommended [10].

According to the guidelines of the World Association of Perinatal Medicine (2022) and the Perinatal Medicine Foundation (2022), a full-course corticosteroid regimen is not recommended between 34 + 0 and 36 + 6 weeks of gestation since its benefits remain unclear. The use of glucocorticosteroids is also not recommended in patients with intrauterine infection. Also, the delivery should not be delayed to administer corticosteroids [10] (Tab. 2).

Of note: transient leukocytosis is observed in pregnant women who received corticosteroids.

Neuroprotection

Randomized studies demonstrated that — administration of magnesium sulphate for fetal neuroprotection before 32 + 0 weeks of gestation lowers the risk for neonatal cerebral palsy (RR 0.71; 95% CI 0.55–0.91) and motor dysfunction (RR 0.6; 95% CI 0.6–0.88) if the delivery is expected within 24 hours. The dosing should be as follows: loading dose of 4 g of magnesium sulphate over 30 minutes, followed by a maintenance dose of 1 g/hour for max. 24 hours. A repeat course at a later time is possible if the delivery did not take place [11].

Irrespective of the protocol, patients with PPROM between 24 + 0 and 32 + 0 weeks of gestation and at high risk for preterm delivery within 24 hours, should receive neuroprotective treatment using magnesium sulphate, which is compliant with the FIGO guidelines [11]. Magnesium

Table 2. Corticosteroid therapy

In patients with PPROM, corticosteroid should be:	
Considered	Between 23 + 0–23 + 6 weeks of gestation
Recommended	Between 24 + 0–33 + 6 weeks of gestation
Not recommended	Between 34 + 0–36 + 6 weeks of gestation

sulphate, min. 4 hours before delivery, should also be administered if elective cesarean section is planned. Magnesium sulphate is contraindicated in patients with myasthenia gravis as it may result in a myasthenic crisis, and in patients with renal disorders, as magnesium is predominantly excreted by the kidneys. If kidney function is normal, there is no need to monitor maternal magnesium levels. However, blood pressure, heart beat, respiratory rate, and tendon reflexes (*e.g.* patellar reflex) need to be monitored every 4 hours [11].

Tocolysis

Routine tocolysis in patients with PPROM is a controversial issue and is not recommended. According to a Cochrane review, tocolysis as compared to placebo in patients with PPROM is associated with mean pregnancy prolongation of 73 hours (95% CI 20–126) and lower rate of deliveries within the next 48 h (RR 0.55; 95% CI 0.32–0.95). Still, it increases the risk for intraamniotic infection. Also, tocolytic therapy was found to be associated with lower Apgar score at birth (Apgar score of < 7 points was more often observed) and more frequent need for mechanical ventilation in the neonates. The conclusion of the review was that there are not enough data to support the use of tocolytics in women with PPROM. Despite the lack of conclusive evidence that tocolytics significantly prolong pregnancy or improve the neonatal outcome, tocolytic therapy may still be taken into consideration in patients with PPROM in active preterm labor to implement the corticosteroids or to transport the mother to a higher level of care perinatal center. As a rule, tocolytics should not be administered for longer than 48 hours. Also, they should not be administered to patients in advanced stages of labor (dilation of > 4 cm) or those presenting with subclinical or manifest symptoms of intraamniotic infection [1–3]. Atosiban is contraindicated in patients with PROM after 30 weeks of gestation.

Amnioinfusion

In certain cases of PPROM before 22 + 6 weeks of gestation, continuous or intermittent amnioinfusion is recommended, as the literature offers an increasing number of reports about high success rates for amnioinfusion. Lack of reliable data prevents such management being introduced into daily obstetric practice [12]. Similar management may also be considered in the third trimester. In a systematic Cochrane review of five studies, amnioinfusion in the third trimester was found to be associated with improved pH in fetal umbilical artery during labor, lower incidence of variable decelerations during labor, as well as lower risk for neonatal death, sepsis, pulmonary hypoplasia, and puerperal sepsis. As some of these benefits were reported for only one study, the authors of the review concluded that further research was necessary before amnioinfusion may be incorporated into routine clinical practice for patients with PPROM in the third trimester [13]. In light of the above, amnioinfusion in PPROM is not recommended at any stage of pregnancy.

The cervical cerclage

There is no conclusive evidence to establish the management standards for patients with PPROM and cervical incompetence treated by cerclage. The findings of retrospective studies remain inconsistent, but the main conclusion is that if the cerclage is left in place for > 24 hours after PPROM, it may indeed prolong the pregnancy, allowing to administer corticosteroid therapy (max. 48 hours) [14]. It is not possible to clearly determine whether the cerclage should be removed in PPROM; it is not a mistake to remove or leave it, the decision should be made individually, depending on the clinical situation.

Delivery

PROM after 37 weeks of gestation

Prelabor rupture of the membranes is observed in approximately 8% of term pregnancies. With expectant management, spontaneous contractile activity within 72 hours develops in 95% of the women. Active management, *i.v.* administration of oxytocin or prostaglandin to induce contractile activity, lowers the risk for maternal inflammatory complications, without increasing the rate of operative delivery. Randomized studies also demonstrated that induced labor was associated with lower demand for antibiotic therapy and fewer admissions to the intensive care unit, for the mother and the neonate. In order to lower the risk for maternal and neonatal complications, induction of labor is recommended in pregnant women with amniotic fluid leakage at > 37 weeks of gestation. Expectant management (up to 48 hours) is also possible in those patients if there are no symptoms of intraamniotic infection. The abovementioned recommendations are compliant with the current guidelines of the Polish Society of Gynecologists and Obstetricians ("Induction of labor", "Induction of labor — clinical algorithms") [15–18].

PPROM between 34 + 0 and 36 + 6 weeks of gestation

According to the guidelines of the Polish Society of Gynecologists and Obstetricians, in patients with PPROM between 34–37 weeks of gestation but with no symptoms of intraamniotic infection, induction of labor is not recommended as it does not lower the risk for systemic infection (neonatal sepsis) and may be associated with higher risk for neonatal respiratory distress. Expectant management, combined with antibiotic prophylaxis, is advised. In case of PPROM with symptoms of intraamniotic infections, delivery (cesarean section or vaginal delivery) is recommended [15, 16].

Management of PROM, depending on gestational age — summary
≥ 37 + 0 weeks of gestation: • delivery (induction of labor or cesarean section, as indicated) • GBS prophylaxis, as indicated
34 + 0 to 36 + 6 weeks of gestation: • expectant management, if there are no symptoms of intraamniotic infection • prophylactic antibiotic therapy • GBS screening test and GBS prophylaxis, as indicated • treatment of intraamniotic infection (if applicable) and delivery
22 + 6 to 33 + 6 weeks of gestation: • expectant management, if there are no symptoms of intraamniotic infection • prophylactic antibiotic therapy • full-course of corticosteroids (24 + 0–33 + 6) • treatment of intraamniotic infection (if applicable) and delivery • vaginal and rectal culture for GBS and GBS prophylaxis, in accordance with the guidelines • magnesium sulphate for neuroprotection (24 + 0–31 + 6), unless contraindicated
< 22 + 6 weeks of gestation: • patient counseling: consultation with neonatology and maternal-fetal medicine team • the patient should be informed about low probability for fetal survival and normal development and high risk for complications (intrauterine infection, septic shock, uterine atony, hemorrhage, death) • management depends on the clinical condition of the patient (presence or absence of intraamniotic infection) and patient wishes: — pregnancy may be continued if there is no threat to maternal health and if informed written maternal decision has been obtained — termination of pregnancy due to the fact that criteria for threat to maternal health and life have been met — if the pregnancy is to be continued: * prophylactic antibiotic regimen; * GBS prophylaxis is not recommended; * corticosteroids are not recommended; * tocolysis is not recommended; * magnesium sulphate for neuroprotection is not recommended; * hospitalization at a tertiary center of perinatal care after 22+6 weeks of gestation.
Irrespective of the nature of maternal decision, written record of the decision — signed by the patient and the obstetrics and gynecology specialist — should always be included in the patient medical records

GBS — Group B streptococcus

PPROM between 22 + 0 and 33 + 6 weeks of gestation

Induction of labor before 34 weeks of gestation is not recommended in patients with PPROM but without symptoms of intraamniotic infection due to high risk for complications of prematurity. Expectant management — combined with a course of steroids, prophylactic antibiotic therapy and neuroprotection (advised <32 weeks of gestation). Elective delivery (cesarean section or vaginal delivery) is recommended to patients with PPROM and symptoms of intraamniotic infection [15, 16].

PPROM before 22 + 6 weeks of gestation

Patients with PPROM before 22 + 6 weeks of gestation should be informed about the risks and benefits connected with expectant management as compared to elective delivery. Of note, long-term amniotic leakage is associated with the risk for systemic intraamniotic infection, which may result in systemic infection (sepsis), septic shock, and maternal death. Also, patient counseling needs to include realistic evaluation of the neonatal outcome, presented by an **obstetric-neonatal team**, who need to supply the patient with the most up-to-date information about the prognosis. Depending on the obstetric status and patient (parents) wishes, either expectant management or induction of a miscarriage need to be offered. Such management is compliant with the current eligibility criteria for induced miscarriage due to a direct threat to maternal health and life.

According to Sklar et al. [19], expectant management at this stage of pregnancy is associated with higher risk for intraamniotic infection, postpartum hemorrhage, admission to the Intensive Care Unit, and hysterectomy. Total maternal morbidity in case of expectant management is approximately two-fold higher as compared to elective delivery (60.2% vs 33%, respectively). Additionally, the survival rate of extremely premature (< 22 + 6 weeks of gestation) neonates has been estimated at 1%.

Although most studies on antibiotic prophylaxis in PPROM focused on patients at > 22 weeks of gestation, we recommend to use broad-spectrum antibiotics to prolong the pregnancy in patients with PPROM and expectant management due to the risk for intraamniotic infection. The antibiotic regimen is the same before and after 22 + + 6 weeks of gestation. Of note, expectant management in patients with amniotic leakage at > 22 + 6 weeks of gestation is associated with the risk for systemic infection, sepsis, and septic shock.

If a patient presents with symptoms of intraamniotic infection and elevated procalcitonin levels (higher risk for systemic infection — sepsis), immediate delivery is necessary, either using pharmacotherapy to induce a miscarriage and, if that proves ineffective or if the maternal condition is deteriorating, using surgical methods (fetal extraction using obstetric instruments or hysterotomy). Progressive symptoms of a septic shock after curettage and despite intensive antibiotic therapy is an indication for immediate hysterectomy to remove the source of the infection. Before 22 + 6 weeks of gestation, the patient **does not need to be hospitalized at a tertiary center for perinatal care.** After 22 + 6 weeks of gestation, hospitalization at a tertiary referral center of perinatal care is recommended.

Article declaration and informations

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Conflict of interests

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Supplementary material

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REFERENCES

1. ACOG practice bulletin no. 80: premature rupture of membranes. Obstetrics & Gynecology. 2007; 109(4): 1007–1020, doi: 10.1097/01.aog.0000263888.69178.1f.
2. Thomson AJ. Royal College of Obstetricians and Gynaecologists. Care of women presenting with suspected preterm prelabour rupture of membranes from 24 weeks of gestation: green-top guideline no. 73. BJOG. 2019; 126(9): e152–e166, doi: 10.1111/1471-0528.15803, indexed in Pubmed: 31207667.
3. National Collaborating Centre for Women's and Children's Health. Preterm Labour and Birth. National Institute for Health and Care Excellence, London 2015.
4. Abdelazim IA. Insulin-like growth factor binding protein-1 (Actim PROM test®) for detection of premature rupture of fetal membranes. Asian Pacific J Reproduct. 2013; 2(1): 25–29, doi: 10.1016/s2305-0500(13)60110-4.
5. Lee SiE, Park JS, Norwitz ER, et al. Measurement of placental alpha-microglobulin-1 in cervicovaginal discharge to diagnose rupture of membranes. Obstet Gynecol. 2007; 109(3): 634–640, doi: 10.1097/01.AOG.0000252706.46734.0a, indexed in Pubmed: 17329514.
6. Drews K, Pieńkowski W. Zakażenie wewnątrzowodniowe — nadal więcej pytań niż odpowiedzi. Ginekologia i Perinatologia Praktyczna. 2016; 1(4): 141–151.
7. Sosa CG, Althabe F, Belizán JM, et al. Bed rest in singleton pregnancies for preventing preterm birth. Cochrane Database Syst Rev. 2015; 2015(3): CD003581, doi: 10.1002/14651858.CD003581.pub3, indexed in Pubmed: 25821121.
8. Kenyon S, Boulvain M, Neilson J, et al. Antibiotics for preterm premature rupture of membranes. Cochrane Database Syst Rev. 2000(2): CD001058, doi: 10.1002/14651858.CD001058, indexed in Pubmed: 10796231.
9. Rekomendacje diagnostyki, terapii i profilaktyki antybiotykowej zakażeń w szpitalu – 2020 pod redakcją: dr n. med. Agnieszki Żukowskiej, prof. dr hab. n. med. Walerii Hryniewicz. Narodowy Program Ochrony Antybiotyków.
10. Dagklis T, Sen C, Tsakiridis I, et al. The use of antenatal corticosteroids for fetal maturation: clinical practice guideline by the WAPM-World Association of Perinatal Medicine and the PMF-Perinatal Medicine Foundation. J Perinat Med. 2022; 50(4): 375–385, doi: 10.1515/jpm-2022-0066, indexed in Pubmed: 35285217.
11. Shennan A, Suff N, Jacobsson Bo, et al. FIGO good practice recommendations on magnesium sulfate administration for preterm fetal neuroprotection. Intern J Gynecol Obstet. 2021; 155(1): 31–33, doi: 10.1002/ijgo.13856.
12. Locatelli A, Vergani P, Di Pirro G, et al. Role of amnioinfusion in the management of premature rupture of the membranes at <26 weeks' gestation. Am J Obstet Gynecol. 2000; 183(4): 878–882, doi: 10.1067/mob.2000.108873, indexed in Pubmed: 11035330.
13. Hofmeyr GJ, Eke AC, Lawrie TA. Amnioinfusion for third trimester preterm premature rupture of membranes. Cochrane Database Syst Rev. 2014; 2014(3): CD000942, doi: 10.1002/14651858.CD000942.pub3, indexed in Pubmed: 24683009.
14. Wu J, Denoble AE, Kuller JA, et al. Management of cerclage in patients with preterm prelabor rupture of membranes. Obstet Gynecol Surv. 2021; 76(11): 681–691, doi: 10.1097/OGX.0000000000000957, indexed in Pubmed: 34854925.
15. Bomba-Opoń D, Drews K, Huras H, et al. Polish gynecological society recommendations for labor induction. Ginekol Pol. 2017; 88(4): 224–234, doi: 10.5603/GP.a2017.0043, indexed in Pubmed: 28509326.
16. Bomba-Opoń D, Drews K, Paszkowski T, et al. Indukcja porodu — algorytmy kliniczne. Wytyczne Polskiego Towarzystwa Ginekologów i Położników. Ginekol Perinatol Prakt. 2018; 3(1): 23–29.
17. Middleton P, Shepherd E, Flenady V, et al. Planned early birth versus expectant management (waiting) for prelabour rupture of membranes at term (37 weeks or more). Cochrane Database Syst Rev. 2017; 1(1): CD005302, doi: 10.1002/14651858.CD005302.pub3, indexed in Pubmed: 28050900.
18. Bond DM, Middleton P, Levett KM, et al. Planned early birth versus expectant management for women with preterm prelabour rupture of membranes prior to 37 weeks' gestation for improving pregnancy outcome. Cochrane Database Syst Rev. 2017; 3(3): CD004735, doi: 10.1002/14651858.CD004735.pub4, indexed in Pubmed: 28257562.
19. Sklar A, Sheeder J, Davis AR, et al. Maternal morbidity after preterm premature rupture of membranes at <24 weeks' gestation. Am J Obstet Gynecol. 2022; 226(4): 558.e1–558.e11, doi: 10.1016/j.ajog.2021.10.036, indexed in Pubmed: 34736914.

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Bilateral fetal hydrothorax accompanying with absent umbilical arterial end-diastolic flow, trisomy 21 and polyhydramnios

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INTRODUCTION

Fetal hydrothorax, which is the result of accumulation of fluid in the foetus's chest cavity, is a rare condition that occurs with incidence ranging from 1/10,000 to 1/15,000 [1]. Accumulation of fluid in the pleural space may result in pulmonary hypoplasia and compression of the oesophagus leading to polyhydramnios [2]. According to the origin, it can be classified as a primary or secondary hydrothorax. Trisomy 21 was found in 4.9–8.9% of cases with fetal hydrothorax [3]. The prognosis is hard to predict and ranges from spontaneous resolution to perinatal death.

Fetal pleural effusion can be classified as primary and secondary fetal hydrothorax. Primary, also known as congenital chylothorax, can result from multiple lymphatic vessel anomalies or thoracic cavity defects caused by external force, a tumor or cardiovascular diseases. It can occur unilaterally or bilaterally and affects males more than females at a ratio of 2:1. It has a perinatal mortality rate of 22% to 53%. Secondary fetal hydrothorax is a feature of immune and non-immune hydrops. Autoimmune conditions include Rh or ABO blood type incompatibility; non-immune factors include chromosomal abnormalities, genetic disorders, infections, congenital cardiac anomalies, congenital lung anomalies, hematologic diseases, metabolic diseases, and noncardiac anomalies. Hydrops is usually bilateral, and is also often associated with ascites, pericardial effusion, subcutaneous edema, hydramnios, and placental thickening. The most common causes of non-immune hydrops are chromosomal anomalies such as Down syndrome and Turner syndrome, which can also be present with additional structural abnormalities.

CASE REPORT

A 41-year-old woman at 31+3 weeks of gestation was admitted due to bilateral fetal pleural effusion and absent end-diastolic flow in the umbilical artery (estimated fetal weight was 1972 g — adequate to gestational age). The patient was previously diagnosed for congenital thrombophilia (factor V Leiden mutation) and hypothyroidism. The patient's obstetric history included seven pregnancies (5 miscarriages, 1 labour at full term and 1 preterm). Her current medications included enoxaparin, acetylsalicylic acid, levothyroxine.

Microbiology tests were run but did not reveal any significant aberrations. Due to the risk of pulmonary hypoplasia, it was decided to perform ultrasound-guided percutaneous placement of bilateral fetal thoraco-amniotic shunts (Fig. 1). Because of increasing and symptomatic polyhydramnios, the procedure was extended to amnioreduction, and 1410 ml of amniotic fluid was drained, the kariotype testing showed a 47, XY, +21. The whole procedure went uneventful.

Three weeks after procedure, premature rupture of membranes and preterm labour occurred. Patient did not agree for vaginal birth after caesarean delivery and according to current recommendations of Polish Society of Gynaecologists and Obstetricians patient was qualified for c-section on a gestational age of 35 weeks and one day. The birth weight was 3350 grams and length 55 centimetres. The assessment in the Apgar scale was respectively 4, 5, 7, 7 points in 1,3,5 and 10 minutes.

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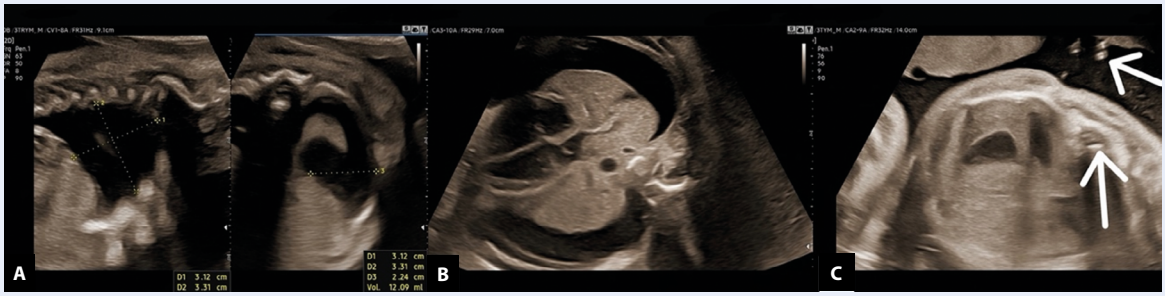

Figure 1. Prenatal ultrasound (US) examination **A.** Hydrothorax in sagittal and transverse section; **B.** Bilateral hydrothorax in transverse; **C.** Condition after placement of bilateral fetal thoraco-amniotic shunts, the ends of shunt showed by arrows

The post-caesarean course was uneventful, and the mother was discharged on the second postoperative day. As for the child, after being born he was intubated, and both chest cavities were drained (80 mL fluid on the right, 40 mL left). Phenotypic features of Down syndrome were present. Moreover, fluid in the abdominal cavity was observed. The examination revealed a significant difference in heart rate between the lower and upper limbs, whereas increased flow rate in the aortic isthmus was seen during the echocardiography. Hence the child was consulted cardiologically for aortic isthmus stenosis and dinoprostone was added to the treatment. On the eighth day of life, the newborn was transferred to the neonatal intensive care unit in University Child Hospital.

CONCLUSIONS

One of the effective forms of diagnosis and treatment of hydrothorax is thoracocentesis or pleural shunt, which increases the chance of prolonging the pregnancy and reduces the risk of respiratory failure in the newborn. Thoracentesis or thoracoamniotic shunting to drain the pleural effusion are considered to improve the perinatal outcomes [3]. According to the literature, thoracoamniotic shunting in fetuses with severe hydrothorax results in an overall survival rate of 59% [4]. In the case of symptomatic polyhydramnios, the procedure can be extended to include amnioreduction. However, it is known in which conditions there is a higher probability of fetal pleural effusion, the causes remain unclear.

Article information and declarations

Conflict of interest

None of the authors reports any conflict of interest.

REFERENCES

1. Cao Li, Du Y, Wang L. Fetal pleural effusion and Down syndrome. Intractable Rare Dis Res. 2017; 6(3): 158–162, doi: 10.5582/irdr.2017.01028, indexed in Pubmed: 28944136.
2. Deurloo KL, Klumper FJ, Oepkes D. Isolated fetal hydrothorax with hydrops: a systematic review of prenatal treatment options. Prenat Diagn. 2007; 27: 893–899.
3. Yumoto Y, Jwa SC, Wada S, et al. The outcomes and prognostic factors of fetal hydrothorax associated with trisomy 21. Prenat Diagn. 2017; 37(7): 686–692, doi: 10.1002/pd.5066, indexed in Pubmed: 28493447.
4. Mallmann MR, Graham V, Rösing B, et al. Thoracoamniotic Shunting for Fetal Hydrothorax: Predictors of Intrauterine Course and Postnatal Outcome. Fetal Diagn Ther. 2017; 41(1): 58–65, doi: 10.1159/000446110, indexed in Pubmed: 27174294.

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Herpes simplex encephalitis in pregnancy

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INTRODUCTION

Herpes simplex encephalitis (HSE) is the most common cause of acute and sporadic viral encephalitis, usually due to the relapse of Herpes simplex (HSV) type 1 infection. It usually presents itself with headache, fever, impaired consciousness, and new onset of seizures [1, 2]. The diagnosis of HSE is mainly based on PCR detection of HSV DNA in cerebrospinal fluid (CSF), but magnetic resonance imaging (MRI) findings have also been found useful in course of differential diagnosis [2].

Treatment with acyclovir *i.v.* should be administered based on the clinical presentation, even before obtaining confirmation of microbial presence, as initiating treatment early increases patient's chances of recovery. Without treatment, mortality reaches up to 70% and even when treated HSE is fatal in 20–30% of patients [3]. More than half of the survivors of HSE experience long-term neurological complications.

CASE PRESENTATION

A 27-year-old woman at 32 + 3 weeks gestation (gravida 1, para 1) presented to the obstetrics department with onset of fever and meningeal signs. She was conscious, but with qualitative disorders of consciousness, auto- and allopsychic disorientation and short-term memory impairment. The day before admission she had experienced three generalized tonic-clonic seizures, nausea, and vomiting. The diagnosis of HSE was based on PCR confirmation of HSV type 1 presence in CSF. Additional MRI (Fig. 1) and electroencephalography (EEG) (Fig. 2) changes were also found. In line with consultations of neurologists and infectious diseases specialists, the patient was administered paracetamol *i.v.*, acyclovir *i.v.*, lamotrigine *p.o.* (changed for levetiracetam *p.o.* in course of hospitalization), dexamethazon *i.v.*, and enoxaparin *s.c.* After two days of treatment, the fever ceased, and the patient regained auto- and allopsychic orientation.

State of the fetus has been strictly monitored — apart from periodic tachycardia and signs of growth restriction no abnormalities have been found and there were no signs of possible premature birth. The patient was discharged at her own request after 25 days of hospitalization, with viable pregnancy,

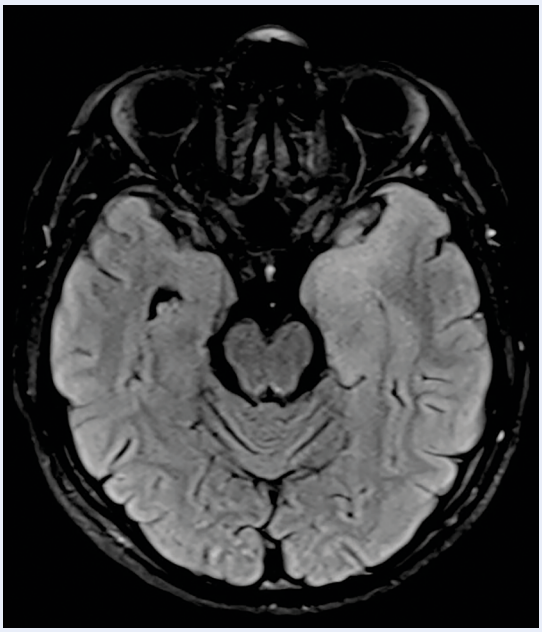

Figure 1. MRI, FLAIR sequence showing hyperintense signal and oedema of the left temporal lobe structures

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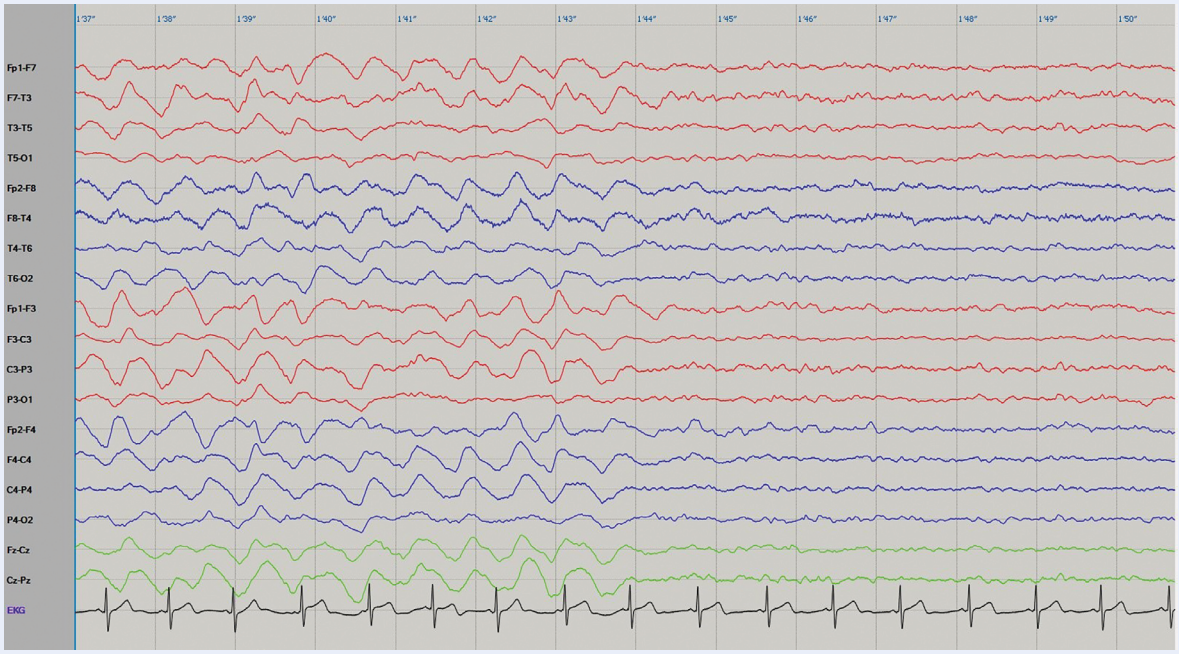

Figure 2. EEG. Frontal intermittent rhythmic delta activity (FIRDA) and mild background slowing

no recurrent seizures and residual bilateral positive Sterling, Jacobsohn, Hoffmann, Babinski and Chaddock signs. In 2-month follow-up no seizures reappeared.

A baby boy was delivered at 37 + 3 weeks' gestation via cesarean section due to the risk of acute perinatal asphyxia and was assessed as small for gestational age (SGA) (birth weight = 2280 g). His CSF tested positive for HSV type 1 antibodies but was negative for HSV DNA. He developed no signs of possible HSV infection.

DISCUSSION

HSE in pregnant patients is an extremely rare finding. It is usually diagnosed during late second and early third trimester, possibly due to the altered immunological response resulting in higher susceptibility to viral infections, which can lead to fetal growth retardation or premature birth. Differential diagnosis should include *e.g.*, eclampsia, cerebral venous thrombosis and metabolic imbalances [1, 4]. Early acyclovir administration is crucial for increasing patient's chances of recovery and its use in pregnancy has been proven to be safe and not associated with an increased rate of birth defects [1, 4]. In case of onset of seizures, anti-epileptic drugs with the highest safety profile for fetus (*e.g.*, levetiracetam and lamotrigine) should be administered in lowest effective doses [1].

Neonatal herpes infections are uncommon and mainly (85% of the cases) acquired during vaginal delivery due to the maternal HSV type 2 infection and presence of herpetic lesions in the maternal genital tract. In utero and postpartum infections are even more sporadic [4].

Article information and declarations

Conflict of interest

All authors declare no conflict of interest.

REFERENCES

1. Dodd KC, Michael BD, Ziso B, et al. Herpes simplex virus encephalitis in pregnancy - a case report and review of reported patients in the literature. BMC Res Notes. 2015; 8: 118, doi: 10.1186/s13104-015-1071-6, indexed in Pubmed: 25888964.
2. Bradshaw MJ, Venkatesan A. Herpes Simplex Virus-1 Encephalitis in Adults: Pathophysiology, Diagnosis, and Management. Neurotherapeutics. 2016; 13(3): 493–508, doi: 10.1007/s13311-016-0433-7, indexed in Pubmed: 27106239.
3. Steiner I, Budka H, Chaudhuri A, et al. Viral meningoencephalitis: a review of diagnostic methods and guidelines for management. Eur J Neurol. 2010; 17(8): 999–e57, doi: 10.1111/j.1468-1331.2010.02970.x, indexed in Pubmed: 20236175.
4. Sellner J, Buonomano R, Nedeltchev K, et al. A case of maternal herpes simplex virus encephalitis during late pregnancy. Nat Clin Pract Neurol. 2009; 5(1): 51–56, doi: 10.1038/ncpneuro0972, indexed in Pubmed: 19129790.

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Usefulness of telemetric cardiotocography in detection of fetal compromise due to the true knot in umbilical cord

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The development of prenatal telemedical systems was accelerated during the COVID-19 pandemic. Pregnant patient seems to be a prime candidate for mobile health applications for prenatal monitoring among which tele-CTG is the most promising [1].

Tele-CTG device enables self-examination at home with an 24/7 access to specialists and unlimited number of tests. Each test is analysed by professional medical staff on-line. The system provides an app for patient's communication with caregiver [1–4].

A 24-year-old patient at 39 weeks of first pregnancy was equipped with tele-CTG device (Carebits system KTG Sigmafon) to monitor fetal heart rate at home after she reported decreased fetal movements during the prenatal visit. The following morning she registered for 30 minutes tele-CTG session (Fig. 1A). The midwife who checked this record asked patient to repeat CTG. As the repeated CTG remained abnormal (Fig. 1B), the patient was asked to go immediately to the nearest hospital and at the same time her doctor received SMS message informing him about this situation.

Within 45 minutes she appeared at the OB/GYN admission ward of the University Hospital No. 4 in Lublin were after initial examination including CTG (Fig. 1C) showing persistent tachycardia,it was determined that she was qualified for immediate cesarean section. A true knot in the umbilical cord (Fig. 1D) was detected during caesarean delivery of a male neonate with a birth weight of 3320 g who received 10 points in Apgar scale.

Tele-CTG proved in this case to be useful in detecting fetal compromise due to true knot in umbilical cord. Although indications for telemetric cardiotocography remain to be defined, patients with post term pregnancy and gravidae with fetal movements abnormalities may be beneficiaries of this technique [5].

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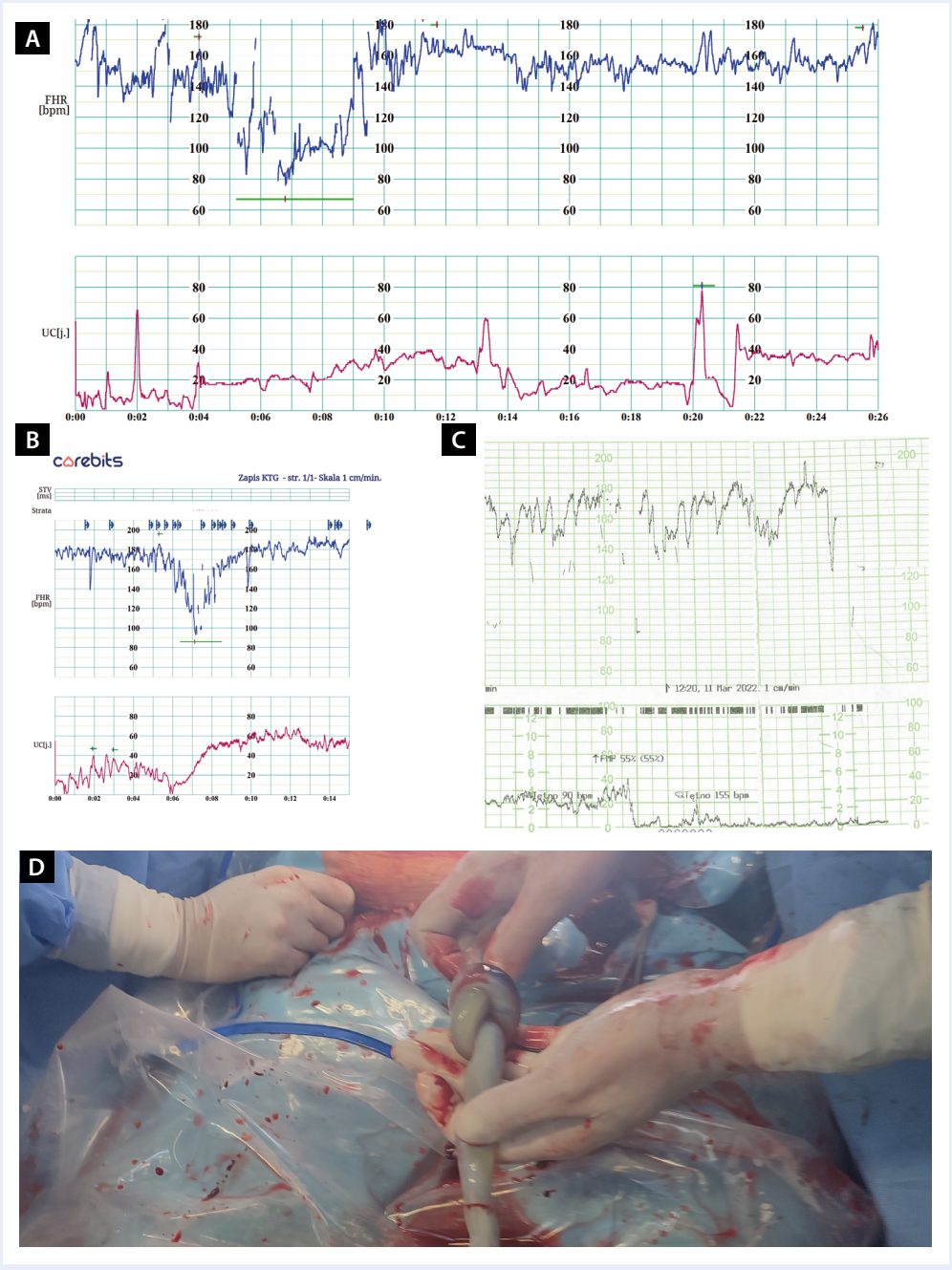

Figure 1. A. 30 minutes tele-CTG session registered in the morning; **B.** Repeated CTG — abnormal; **C.** CTG repeated at the OB/GYN admission ward — showing persistent tachycardia; **D.** True knot in the umbilical cord

REFERENCES

1. Jurgiel J, Graniak A, Jozwik K, et al. Pregnancy and childbirth during the coronavirus pandemic. The cross-sectional study of 1321 participants in Poland. Ginekol Pol. 2022; 93(10): 842–846, doi: 10.5603/GP.a2021.0198, indexed in Pubmed: 35072248.
2. Ghosh AK, Aljallad Z, Badillo-Urquiola K, et al. Carebit: A Privacy-Preserving "Step" Toward Remote Informal Caregiving. Proceedings of the 2018 ACM Conference on Supporting Groupwork. 2018: 154–157, doi: 10.1145/3148330.
3. Gyselaers W, Lanssens D, Perry H, et al. Mobile Health Applications for Prenatal Assessment and Monitoring. Curr Pharm Des. 2019; 25(5): 615–623, doi: 10.2174/1381612825666190320140659, indexed in Pubmed: 30894100.
4. Vermeulen-Giovagnoli B, et al. The development of an obstetric tele-monitoring system. 37th Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBC), Milan, Italy, 2015: 177–180.
5. Stanowisko Ekspertów Polskiego Towarzystwa Ginekologicznego w zakresie zastosowania kardiotokografii w położnictwie. Ginekol Pol. 2014; 85: 713–716.