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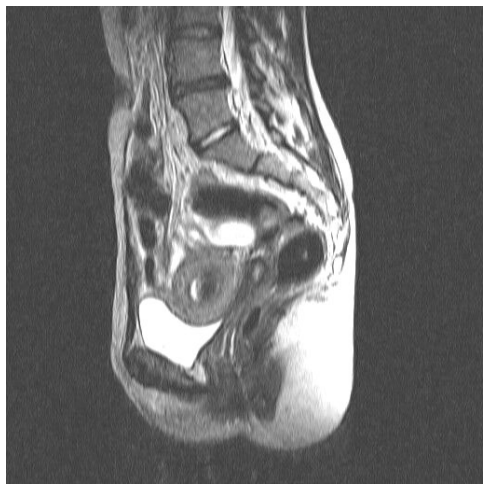

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Transvaginal salpingo-oophorectomy with gasless laparoscopy — an optional pure natural orifice transluminal endoscopic surgery

Tingting Liu, Yinghan Chen, Xinyou Wang

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ABSTRACT

Objectives: To establish the appropriate technique for salpingo-oophorectomy via transvaginal natural orifice transluminal endoscopic surgery (NOTES), under gasless laparoscopy.

Material and methods: Ten patients with clinical indication underwent gasless laparoscopic transvaginal salpingo-oophorectomy with concurrent vaginal hysterectomy. An abdominal-wall lifting device was used after removal of the uterus, and the adnexa was removed trans-vaginally by gasless laparoscopy. The perioperative clinical data, such as operative duration, volume of blood loss, morbidity, intraoperative and postoperative complications, and length of hospital stay, were retrospectively analyzed.

Results: All procedures were successfully done, without any intraoperative or major postoperative complications, and no additional transabdominal ports were required. The salpingo-oophorectomy part of the procedure was completed in approximately 11–40 minutes, with minimal blood loss. All of the patients were discharged, scar-free, 2–4 days after surgery.

Conclusions: Transvaginal NOTES with gasless laparoscopy is a feasible and safe surgical technique in cases involving difficult vaginal salpingo-oophorectomy, which avoids conversion to an abdominal route.

Key words: Transvaginal salpingo-oophorectomy; gasless laparoscopy; natural orifice transluminal endoscopic surgery (NOTES)

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INTRODUCTION

Vaginal hysterectomy is the least invasive of all hysterectomy techniques. It is the preferred route of hysterectomy for benign gynecologic disease [1]. However, salpingo-oophorectomy at the time of vaginal hysterectomy is necessary in some cases, such as for postmenopausal women with atypical endometrial hyperplasia, adnexal mass, or a history of breast cancer. A successful vaginal salpingo-oophorectomy requires appropriate lighting, exposure, and preparation of the operative field at the time of surgery [2]. However, salpingo-oophorectomy at the time of vaginal hysterectomy can occasionally be technically challenging because the ovaries lie above the pelvis and are not readily accessible as a result of local adhesions, difficult visualization, or a less elastic ligament [3, 4]. Even highly skilled vaginal surgeon will occasionally have to convert to an abdominal approach to complete the procedure.

If salpingo-oophorectomy cannot be safely completed vaginally despite using the traditional suture ligation technique or a vessel-sealing device, a transvaginal natural orifice transluminal endoscopic surgery (NOTES) approach can be considered instead of converting to an abdominal route [5–7]. The technique can not only avoid abdominal incision, but also provide excellent access to the target organ and clear visualization of the pelvic cavity. Some investigators have applied transvaginal NOTES in salpingo-oophorectomy following a vaginal hysterectomy [3].

The main limitation of the transvaginal NOTES approach seems to be related to the conflict between instruments, which could be minimized with proper endoscope selection [8, 9]. In addition, devices used to establish and maintain pneumoperitoneum may aggravate the inconvenience of transvaginal operations. Based on our prophase studies [10], we successfully performed transvaginal salpingo-oophorectomy by a simple abdominal wall-lifting instrument under gasless laparoscopy. The technology may reduce the conflict of external instruments and improve operative efficiency. In this study, we aimed to describe the new procedure and

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investigate the safety, feasibility, and effectiveness of this surgical procedure.

MATERIAL AND METHODS

Clinical data

Ten patients underwent transvaginal salpingo-oophorectomy with gasless laparoscopy during vaginal hysterectomy at Shengjing Hospital of China Medical University between March 2017 and December 2018. The patients' characteristics are shown in Table 1. The patients' mean age was 61.7 years (range, 49–72 years). The contraindications to vaginal hysterectomy and subsequent vaginal adnexectomy with gasless laparoscopy are presented in Table 2. All patients provided a written informed consent for surgery. The patients were advised that transvaginal laparoscopic surgery would be performed if operative difficulties were encountered during the operation. All patients consented to possible transvaginal salpingo-oophorectomy with gasless laparoscopy. The study was approved by an institutional review board, and patient confidentiality was always maintained.

Table 1. Characteristics of the women who underwent transvaginal salpingo-oophorectomy with gasless laparoscopy

No.	Age	Gynecological condition
1	69	Postmenopause with uterine prolapse
2	67	Postmenopause with uterine prolapse and hydrosalpinx
3	55	Simple hyperplasia of endometrium with a history of breast cancer
4	52	Complex hyperplasia of endometrium with a history of breast cancer
5	66	Atypical hyperplasia of endometrium
6	60	Atypical hyperplasia of endometrium with pelvic adhesions
7	72	Postmenopause with simple serous ovarian cyst
8	62	Postmenopause with ovarian teratoma
9	49	Symptomatic leiomyomata with tubo-ovarian cyst
10	65	Postmenopause with leiomyomata

Table 2. Contraindications to transvaginal salpingo-oophorectomy with gasless laparoscopy

1. Morbid obesity. Body mass index was greater than 35 kg/m^2
2. A suspicion of malignancy. Ovarian mass was solid or had a solid component
3. History of severe endometriosis or pelvic inflammatory disease
4. Prior open abdominal surgery (more than twice)
5. Severe pelvic adhesions
6. Frozen section was not available
7. Severe medical comorbidities and/or coagulation disorders

Preoperative preparation

All of the patients underwent routine preoperative mechanical and chemical bowel preparation and also received a single dose of prophylactic intravenous antibiotics just before the procedure. Under general endotracheal anesthesia, all patients were placed in the lithotomy position.

Surgical procedure

The uterus was removed using Heaney's technique [11]. In all cases, an effort was made to remove the ovaries vaginally after vaginal hysterectomy. When it was difficult to safely extract or access the adnexa as a result of adhesions, minimal descent, or inadequate exposure after a careful evaluation, transvaginal NOTES was performed under gasless laparoscopy.

An Alexis wound retractor was placed in the vagina. The inner ring was placed through the vagina past the vaginal cuff. The outer ring rested on the perineum (Fig. 1A). There were no umbilical or abdominal ports applied. We used towel forceps as an abdominal wall-lifting device (Fig. 1B). One clamp was placed at the point of the adnexa surface projection on the abdominal wall to establish the operating space, and the other clamp was placed under laparoscopic observation to facilitate gasless surgery, if necessary.

Without using a cannula, a 10 mm endoscope with a 30-degree lens and conventional laparoscopic instruments were directly introduced through the vaginal port. Adhesions were dissected in a similar fashion as conventional laparoscopy when necessary. A vessel-sealing device was

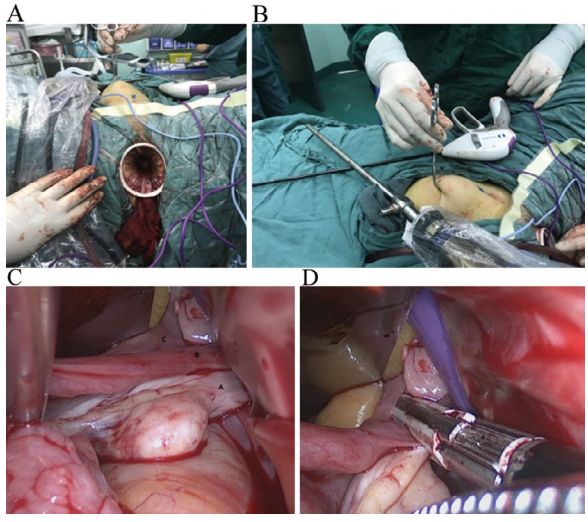

Figure 1. Surgical procedure (A) Alexis wound retractor resting past the vaginal cuff and on the perineum; (B) Towel forceps were used as an abdominal wall-lifting device at the point of adnexa surface projection on the abdominal wall without an abdominal port; (C) Left adnexa from the view of transvaginal laparoscopy; A, Proper ligament of ovary; B, isthmus of fallopian tube; C, infundibulopelvic ligament; (D) Resection of the left adnexa through transvaginal gasless laparoscopy

used to electrosurgically seal and cut the infundibulopelvic ligament and complete the salpingo-oophorectomy under direct visualization (Fig. 1C, D). The specimens were extracted through the vaginal port. After hemostasis was confirmed, the single port was taken out, and the vaginal cuff was sutured by hand in a routine method.

Postoperative management and follow-up

The patients received routine anti-inflammatory therapy for 3 days and rehydration therapy for 1 day after operation. The patients were placed on a semiliquid diet and were allowed to ambulate on postoperative day 1. The vaginal pack was removed 24 hours postoperatively. Patients were followed up during postoperative weeks 1 and 8. Gynecological examinations and pelvic ultrasound were performed.

Observation indicators

Operating time, estimated blood loss, intraoperative complications, postoperative complications, and postoperative hospital stay were recorded. Operating time was defined as the salpingo-oophorectomy procedure time which was started from the placement of the vaginal port and ended when the closure of the vaginal cuff was completed. Pathologic examinations of all salpingo-oophorectomy specimens were recorded.

RESULTS

Until now, only ten patients have taken pure NOTES transvaginal salpingo-oophorectomy with gasless laparoscopy. All the surgical procedures were performed successfully, no additional transabdominal ports were required. The salpingo-oophorectomy procedure time was recorded from the placement of the vaginal port until the closure of the vaginal cuff was completed. The mean operating time was 22.2 minutes (ranging from 11 minutes to 40 minutes), and the blood loss was limited. There were no complications, including intraoperative or major postoperative complications. Postoperative analgesia was routinely administered after vaginal hysterectomy; administration of additional medications was not required. All patients were placed on a semiliquid diet 1 day after the surgery and then to a soft diet after 2 to 3 days. The average postoperative hospital stay was 2.5 days (range, 2–4 days). Pathologic examination of all salpingo-oophorectomy specimens revealed benign results.

All patients were seen on postoperative weeks 1 and 8 and scheduled for follow-up visits. No one required narcotic pain medications after hospital discharge. Only a few outpatients had postoperative complications, including one vaginal cuff granulation tissue repair 2 months after surgery. No febrile episodes or vaginal cuff infections were reported. All of the sexually active patients returned to normal sexual activity after the surgery.

DISCUSSION

Transvaginal NOTES may be valuable when vaginal salpingo-oophorectomy is too difficult to perform [2, 12]. The salpingo-oophorectomy can then be completed under direct visualization using conventional laparoscopic instruments through the vaginal port. Here, we applied the novel approach when ovarian descent was absent or adhesions were discovered intraoperatively following concurrent transvaginal hysterectomy. Using this technique, conversion to an abdominal approach was prevented, achieving clear visualization and excellent cosmetic results [7, 13]. In addition, transvaginal NOTES provides ideal aesthetic effects, can reduce wound complications, shorter hospital stay, with good psychological effects, since there was no trauma is inflicted on the body surface [8, 14]. In our initial series, the pure NOTES transvaginal salpingo-oophorectomy proved the feasibility and safety.

However, only a narrow manipulation space is available, which is the main inherent obstacle to performing pure transvaginal NOTES surgery [9, 15]. Most of the surgical instruments can cause crowding, and frequent collisions are also noted extracorporeally [16]. In conventional pneumoperitoneum, the devices were used to establish and maintain pneumoperitoneum and to reduce the operative space in the vagina, which aggravated the inconvenience. On the basis of our previous animal experiments and preliminary study [10], we developed transvaginal salpingo-oophorectomy using a simple abdominal under gasless laparoscopy wall-lifting instrument, in an attempt to overcome the space obstacle. The novel approach creates more operational space and minimizes conflict between instruments given the lack of need for a pneumoperitoneum device, trocars, or other special instruments in the gasless operation.

The vaginal-incision gas leak is another inherent limitation of pure transvaginal NOTES due to a floppy and weak vaginal cuff. The gas leak of vaginal incision affects the outcomes of pure transvaginal NOTES performed under conventional pneumoperitoneum seriously [17]. The self-constructed vaginal glove port with wound retractor or a commercial port for laparoendoscopic single-site surgery alleviate gas leaks to some extent [3, 18]. However, surgeons typically must choose a medium-sized retractor to avoid excessive traction on the vaginal cuff. Thus, the situation of gas leak inevitably exists. In this study, the abdominal lifting device without pneumoperitoneum was sufficient to provide adequate visibility to perform pure transvaginal salpingo-oophorectomy. Thus, we were able to eliminate concerns about gas leaks and fluently operate without worrying about the effects of intraperitoneal pressure.

Positive-pressure pneumoperitoneum was more optimal than abdominal wall lift technique for operative field and workspace due to the "tenting" effect [19]. However, the technique we used actually showed us satisfactory

exposure and an easy access approach for pure NOTES salpingo-oophorectomy. Two factors may account for this finding. The position of the target organ (the adnexa) is near the operation pathway (the vagina), and this procedure is relatively simple. In addition, two towel forceps are used in our technique to form a parallel double-line suspension, which made it possible to provide adequate and flexible exposure in the pelvis. The first clamp is placed at the point of the adnexa surface projection on the abdominal wall; the second one is placed under laparoscopic observation to make the exposure as wide as possible, which would provide enough space. The surgical assistant adjusts the force and angle of the lifting clamps during the operation to expose the view. Meanwhile, only the appropriate patients should be included for this technique (not including those with morbid obesity or severe adhesions). Careful preoperative evaluation of each patient is very important.

Gasless laparoscopy has other advantages as well. It avoids the occurrence of complications of carbon dioxide pneumoperitoneum, such as subcutaneous or mediastinal emphysema, hypercapnia, air embolism, cardiopulmonary dysfunction, and hemodynamic changes [20]. Since most patients who agree to undergo salpingo-oophorectomy are older postmenopausal women [21], the gasless method is more significant. In addition, there is no need to use a classic commercialized abdominal wall-lifting system, expensive special port, and trocar [22]. Our lifting method is simple, convenient, time saving, and cost-effective.

Although salpingo-oophorectomy via transvaginal NOTES with gasless laparoscopy has the aforementioned advantages. It is technically difficult to perform, mainly due to an unfamiliar and disoriented transvaginal view compared with a traditional abdominal laparoscopic view. Severe adhesions, severe local inflammation, or morbid obesity still remain the technical bottlenecks of this novel approach [23]. We are aware that this is a preliminary work and more practice and experience in this field is required. In addition, the novel approach must be further investigated and validated to assure safety and efficacy.

In this study of ten consecutive patients, we performed gasless laparoscopy for transvaginal salpingo-oophorectomy for the first time and achieved the desired results. The need to convert to an abdominal route could be avoided with this technique; hence, this technique may be a simple minimal-access surgical option when these areas are not easily accessible at the time of vaginal hysterectomy. Additional studies must be performed to validate the safety and efficacy of the new surgical technique.

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Adjuvant therapy for early endometrial cancer — who benefits the most from a radiation therapy?

Marcin Michalak, Zaneta Warenczak-Florczak, Agnieszka Staszewska-Nowak, Andrzej Roszak

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ABSTRACT

Objectives: Since 1990s the number of patients diagnosed with endometrial cancer (EC) has doubled. The standard treatment method for treating early endometrial cancer is surgery. Some patients require a subsequent adjuvant therapy. In early endometrial cancers its application is limited to the populations with a high risk of recurrence.
The aim of this study was to assess the effectiveness of early endometrial cancer treatment based on an analysis of 5-year follow up of EC patients.

Material and methods: The analysis consisted in a retrospective non-randomized interventional study of patients treated for early endometrial cancer (FIGO stage IA, IB, II). Its end point was either local (small pelvis) or distant recurrence of the disease. Intervention involved an adjuvant treatment applied in selected patients according to the current guidelines for EC treatment. There was no randomization for adjuvant and non-adjuvant EC treatment. The study included a total of 419 patients treated for EC from 2010 to 2012.

Results: The analysis revealed that 108 patients (25.8%) were diagnosed with the recurrent disease. Out of 112 patients treated for stage IA endometrial cancer 32 (28.6%) experienced recurrence. Out of 216 patients at FIGO Stage IB, recurrence was diagnosed in 38 (17.6%). In the group of 91 patients treated for FIGO stage II, EC the recurrence was diagnosed in 38 (41.2%) cases.

Conclusions: Early EC treatment results were unsatisfactory and should be improved. The best outcomes were achieved in patients with IA stage of EC who received a radiation therapy.

Key words: early endometrial cancer; adjuvant therapy; Treatment Effectiveness Assessment

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INTRODUCTION

The endometrial cancer morbidity is on the increase, with a peak rate between 55 and 59 years of age. Since 1990s, the number of patients diagnosed with EC has doubled. In 1990 and 2010, 2540 and 5125 new EC cases were registered, respectively.

However, an increase of mortality rate is not as dynamic, with 763 and 1042 patient deaths due to EC in 1990 and 2010, respectively. The difference between mortality and morbidity rate is due to early symptoms of the disease that enable early diagnosis and treatment [1–3].

The standard method for treating early endometrial cancer is surgery. Total hysterectomy with bilateral salpingo-oophorectomy, either open or laparoscopic is recommended.

In selected cases of EC (grade 3), pelvic and aortic lymph nodes should be removed. This procedure has a proven prognostic but not therapeutic value [4]. According to current guidelines, selected patients require subsequent adjuvant therapy. The aim of the adjuvant treatment (either radiation therapy or chemotherapy + radiation therapy) is to diminish the risk of local recurrence and/or distant metastases [5]. Recommended management of patients at the FIGO stage I is either follow-up or vaginal brachytherapy (VBT) alone or combined with external beam radiotherapy (EBRT). In our study, the patients at IA G1 were in follow up. Those at IA G2 stage were either in follow up or underwent vaginal brachytherapy. Qualification for the brachytherapy was based on pathological examination focused on specific risk factors for recurrence. Patients at IA G3 stage underwent complete radiation therapy (brachytherapy and external beam radiotherapy).

Patients at stage II were qualified for complete radiation therapy (VBT + EBRT). Selected patients at II G3 stage were qualified for complete radiation therapy and chemotherapy

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if defined risk factors were present in the pathological report (high risk patients).

As both radiotherapy and chemotherapy cause side effects, their application must be reasonable and based on firm evidence. Randomized clinical trials PORTEC-1 and PORTEC-2 revealed that only high risk patients benefited from the adjuvant radiotherapy [6–8]. Recognized high risk factors included age (the older the worse), Grade 3 tumors, deep myometrial invasion, lymph nodes positive for metastases and lymphovascular space invasion [5, 9–11].

Aim of the study

The aim of this study was the Treatment Effectiveness Assessment (TEA) of early endometrial cancer based on the analysis of 5-year follow up of EC patients.

MATERIAL AND METHODS

The analysis was a retrospective interventional non-randomized study of patients treated for early endometrial cancer (FIGO stage IA, IB and II). Its end point was either local (small pelvis) or distant recurrence of the disease. Intervention included an adjuvant treatment applied in selected patients according to the current guidelines for EC treatment. There was no randomization for adjuvant and non-adjuvant EC treatment. The study included a total of 419 patients treated for EC from 2010 to 2012.

All the patients were thoroughly analyzed for prognostic factors of population-based, clinical, and therapeutic nature and classified into two groups. The first group included the patients diagnosed with the recurrent disease, and the second those with no symptoms of the disease (controls).

Analysis of clinical data (medical history) revealed no significant differences between the patients. Detailed analysis is presented in Table 1.

All the patients underwent surgical treatment and qualification for subsequent adjuvant treatment was based on the final pathological examination. The patients received external beam radiation therapy (EBRT) with brachytherapy (VBT) or brachytherapy alone as a part of adjuvant treatment. EBRT was applied with Intense Modulate Radiation Therapy (IMRT) method in all cases. The range of physical dose of teleradiotherapy to the tumor and lymph node region was 45–50 Gy. Vaginal applications were given with High Dose Rate (HDR) brachytherapy. Dose distribution in applicators was 0.5 cm out of the first and half of the second segment of the vaginal cylinder. The range of physical dose of VBT was 18–37.5 Gy (Tab. 2).

The patients diagnosed with the recurrent disease received adequate treatment as per current radiotherapy and/or chemotherapy guidelines.

Time frame of the analysis was limited to the years 2010 – 2012 due to: a) modification of FIGO staging system (introduced in 2009) and b) 5-year follow up (completed in 2017).

Statistical analysis

Differences between the groups were analyzed using Statistic 6.0 (StatSoft, USA). t-Student test was used for comparison of means (data sets with parametric distribution). Mann-Whitney test was used for comparison of medians (data sets with non-parametric distribution). The chi-squared test with Yates continuity correction was employed to determine the significance of differences between variable frequencies of the analyzed groups. Assumed level of significance was $p < 0.05$.

RESULTS

The analysis showed that 108 (25.8%) out of 419 patients were diagnosed with the recurrent disease. Among 112 patients treated for stage IA EC, 32 (28.6%) experienced the recurrence. Out of 216 patients at FIGO Stage IB, 38 (17.6%) were diagnosed with the recurrent disease. In the group of 91 patients treated for FIGO stage II EC 38 cases (41.2%) of recurrence were diagnosed. Summarized data are presented in Table 3.

Some parameters describing treatment effectiveness based on the data outlined in Table 2 were analyzed and are discussed below.

Application of the adjutant treatment reduced relative risk of recurrence in patients at IA G1 stage of EC by over eight times (Tab. 4). Meanwhile, 88% of patients who received adjuvant treatment avoided recurrence at this stage of the disease. The adjuvant treatment reduced the relative risk of recurrence in patients at II G1 stage by only 2.9 times. This means that 66% of patients who received the adjuvant treatment avoided recurrence. The adjuvant treatment was also effective in patients at IB G2 stage, as 10 for every 12 patients who received it avoided recurrence. In other words, the adjuvant treatment at this stage of the disease reduced the relative risk of recurrence by approximately six times and 83% of the treated patients remained disease-free (Tab. 4).

Furthermore, the analysis of therapeutic methods (Tab. 2) showed that the addition of vaginal brachytherapy in FIGO IA patients significantly (8.3 times) reduced the risk of recurrence. More detailed data is presented in Table 5.

Median progression free survival (PFS) for all the patients included in the study was 28 months (2–125 months). A more detailed analysis revealed that in the group of patients at FIGO stages IA, IB and II the median PFS was 18 months (2–125), 28 months (3–120), and 32 months (2–125), respectively.

The analysis also included the localization of the recurrence. In the group of 108 recurring patients, in 44 cases

Table 1. Clinical characteristics of Patients included into the study

Stage		Recurrent disease	Control	p
FIGO I A	Number of patients	32	79	–
	Age [Years]	62 (52–82)	62 (45–82)	0.618*
	BMI [kg/m^2]	31.2 ± 7.3	32.9 ± 7.4	0.272**
	FMP [Years]	14 (10–17)	14 (10–18)	0.165*
	Menopause [Years]	49.5 (43–57)	50 (41–50)	0.120*
	Labour/Delivery	2 (0–2)	2 (0–6)	0.816*
	Still birth	2 (6.25%)	17 (21.5%)	0.098***
	Hypertension	21 (65.6%)	49 (62.0%)	0.889***
	Diabetes mellitus	9 (28.1%)	15 (18.9%)	0.421***
	Coronary artery disease	6 (18.7%)	7 (8.9%)	0.253***
	Stroke	1 (3.1%)	3 (3.8%)	0.697***
	Hypothyreosis	4 (12.5%)	5 (6.3%)	0.487***
	Glaucoma	1 (3.1%)	1 (1.3%)	0.904***
	Varicose veins	3 (9.4%)	5 (6.3%)	0.875***
FIGO I B	Number of patients	38	178	–
	Age [Years]	66 (54–84)	63 (46–85)	0.822*
	BMI [kg/m^2]	30.6 ± 6.4	31.9 ± 5.6	0.191**
	FMP [Years]	14 (11–17)	14 (10–18)	0.918*
	Menopause [Years]	51 (40–56)	51 (35–59)	0.765*
	Labour/Delivery	2 (0–9)	2 (0–6)	0.657*
	Still birth	5 (13.1%)	39 (21.9%)	0.321***
	Hypertension	22 (57.9%)	112 (62.9%)	0.692***
	Diabetes mellitus	8 (21.0%)	42 (23.6%)	0.900***
	Coronary artery disease	4 (10.5%)	18 (10.1%)	0.826***
	Stroke	1 (2.6%)	4 (2.2%)	0.652***
	Hypothyreosis	3 (7.9%)	11 (6.2%)	0.979***
	Glaucoma	1 (2.6%)	7 (18.4%)	0.930***
	Varicose veins	4 (10.5%)	11 (6.2%)	0.545***
FIGO II	Number of patients	38	51	–
	Age [Years]	60 (46–81)	63 (40–78)	0.084*
	BMI [kg/m^2]	32.3 ± 6.9	31.7 ± 6.3	0.771**
	FMP [Years]	14 (9–18)	12 (11–20)	0.277**
	Menopause [Years]	50 (46–54)	51 (45–58)	0.307**
	Labour/Delivery	2 (0–6)	3 (0–5)	0.001**
	Still birth	6 (15.8%)	9 (17.6%)	0.956***
	Hypertension	16 (42.1%)	26 (50.9%)	0.538***
	Diabetes mellitus	5 (13.1%)	11 (21.6%)	0.457***
	Coronary artery disease	6 (15.8%)	7 (13.7%)	0.975***
	Stroke	1 (2.6%)	1 (1.9%)	0.609***
	Hypothyreosis	4 (10.5%)	6 (11.8%)	0.876***
	Glaucoma	1 (2.6%)	2 (3.9%)	0.795***
	Varicose veins	7 (18.4%)	2 (3.9%)	0.059***

FMP — Firs Menstrual Period; BMI — Body Mass Index; *Mann Whitney Test; **t-Student test; ***χ^2 Test with Yates Continuity Correction

(41%) the recurrence was localized in small pelvis and in 64 cases (59%) metastases were detected either in paraaortic lymph nodes or in other distant localizations. The patients at FIGO stage IA experienced recurrences in small pelvis in

Table 2. Characteristics of Patients included into the study — focus on radiation therapy doses

Stage		Recurrent disease	Control	p
FIGO I A	Number of patients	32	79	–
	Dose of Teletherapy [Gy]	0 (0–45)	0 (0–45)	0.857**
	Dose of Brachytherapy [Gy]	0 (0–30)	28 (0–37.5)	0.00006**
FIGO I B	Number of patients	38	178	–
	Dose of Teletherapy [Gy]	45 (0–45)	45 (0–50)	0.563**
	Dose of Brachytherapy [Gy]	18 (0–35)	18 (0–30)	0.964**
FIGO II	Number of patients	38	51	–
	Dose of Teletherapy [Gy]	45 (0–50)	45 (0–50)	0.987**
	Dose of Brachytherapy [Gy]	18 (0–20)	18 (18–30)	0.415**

*Mann Whitney Test; **t–Student test; ***χ^2 Test with Yates Continuity Correction

Table 3. General juxtaposition of the results – recurrence rate of early Endometrial Cancer

Stage (FIGO)	Recurrence rate
IA	28.6%
IB	17.6%
II	41.2%

19 cases (59%) and distant metastases in 13 cases (41%). Among the patients at IB stage, 11 (29%) recurrences were found in small pelvis and distant metastases were diagnosed in 27 cases (71%). For the patients at stage II, these values were 14 (37%) for small pelvis and 24 (63%) for distant metastases.

Detailed analysis of metastasis localization revealed a correlation between the cancer grade and metastasis pattern. The more aggressive the cancer was (G1 -> G3), the more likely distant metastases were diagnosed. The patients with well differentiated tumors (G1) at FIGO stage IA were at risk of a local recurrence (vaginal vault), while those with poorly differentiated tumors were at risk of distant metastases. In the group of patients at FIGO stages IB and II, the recurrence pattern was different. All the patients were at risk of distant metastases, and the risk was increasing with the cancer grade (Tab. 6).

Contrary to the group who received the adjuvant treatment, the number of patients who **did not** receive it was relatively small and unequivocal conclusions could not be drawn (Tab. 7).

The analysis of population-based factors such as age, BMI, age of the first menstrual period, number of births and miscarriages, or presence of concomitant diseases did not reveal any significant differences between controls and patients diagnosed with EC (Tab. 1).

DISCUSSION

Early endometrial cancer is considered a well differentiated malignant disease with relatively good prognosis that reflects low risk of either local recurrences or distant metastases. On the other hand, EC is a non-homogenous disease that comprises at least two types differing in histology, course of the disease, and treatment. Therefore, despite good prognosis, endometrial cancer patients still suffer from treatment failure and recurrences.

Table 4. Impact of adjuvant treatment on selected parameters

Stage	Grade	RR	RRR	1/RR	PF	NNT
I A	G1	0.12	-0.88	8.30	88%	-2.22
	G2	0.31	-0.69	3.27	69%	-2.52
	G3	–	–	–	–	–
I B	G1	0.24	-0.76	4.25	76%	-2.62
	G2	0.17	-0.83	5.75	83%	-1.21
	G3	–	–	–	–	–
II	G1	0.34	-0.66	2.90	66%	-1.53
	G2	–	–	–	–	–
	G3	–	–	–	–	–

RR — Relative Risk; RRR — Relative Risk Reduction; 1/RR — inverse Relative Risk; PF — Preventive Fraction; NNT — Number Needed to Treat

Table 5. Relation between median PFS and FIGO stage and cancer grade

Stage	Grade	Median time to recurrence [months]	
		Adjuvant treatment	No Adjuvant treatment
I A	G1	11	29 (3–125)
	G2	14 (2–57)	13 (6–46)
	G3	4	–
I B	G1	35 (5–76)	–
	G2	28 (3–120)	13
	G3	25 (9–83)	–
II	G1	34 (11–125)	25 (15–34)
	G2	30 (2–78)	–
	G3	29 (3–54)	–

Table 6. Metastases (localization and rate) in group of early EC patients. who received adequate adjuvant treatment

Stage	Grade	Metastases	Rate %
I A	G1	Local (vaginal vault) Distant	100.0 0.0
	G2	Local (vaginal vault) Distant	43.0 47.0
	G3	Local (vaginal vault) Distant	0.0 100.0
I B	G1	Local (vaginal vault) Distant	33.3 66.7
	G2	Local (vaginal vault) Distant	30.0 70.0
	G3	Local (vaginal vault) Distant	12.5 87.5
II	G1	Local (vaginal vault) Distant	33.3 66.7
	G2	Local (vaginal vault) Distant	12.0 88.0
	G3	Local (vaginal vault) Distant	0.0 100.0

Table 7. Metastases (localization and rate) in group of early EC patients. who did not receive any adjuvant treatment

Stage	Grade	Metastases	
		Lokalization	Rate [%]
I A	G1	Local (vaginal vault) Distant	58 42
	G2	Local (vaginal vault) Distant	60 40
	G3	Local (vaginal vault) Distant	– –
I B	G1	Local (vaginal vault) Distant	– –
	G2	Local (vaginal vault) Distant	100 0
	G3	Local (vaginal vault) Distant	– –
II	G1	Local (vaginal vault) Distant	100 0
	G2	Local (vaginal vault) Distant	– –
	G3	Local (vaginal vault) Distant	– –

The analysis of early EC treatment efficiency provided in this paper revealed 23% recurrence rate. This is not consistent with the outcome of other authors [12, 13]. The higher cancer stage and/or grade were, the higher risk of either local recurrence or distant metastases was.

Our group of patients was not homogeneous in terms of clinical stage of disease, grade and applied treatment. The patients were initially qualified for the surgical treatment and operated on at different centers. This further enhanced intergroup diversity.

The analyzed cohort revealed high recurrence rate in the patients at stage IA G1 (Tab. 8). This group of patients should have had a good prognosis. Thus, if none risk factors for recurrence were present, follow-up after surgery was a recommended procedure. Adjuvant treatment is not recommended, unless any risk factor for recurrence is detected in individual cases. In 2009 FIGO staging system for endometrial cancer changed. The modification shifted patients with former FIGO stage IB (defined as cancer infiltration into myometrium no more than halfway through uterine wall) to the stage IA. Since the new definition of FIGO stage IA had been established, there were two different groups of patients, i.e. the patients with EC limited to the endometrium (with no cancer invasion through basement membrane) and patients with superficial myometrial invasion (less than 50% of the uterine wall). This means that the patients previously treated with VBT, are now disqualified from any adjuvant treatment (if other risk factors are absent). In our analysis, adjuvant brachytherapy applied in this group (FIGO IA G1) significantly reduced the risk of EC recurrence ($p = 0.0006$) (Tab. 2). Similar results were provided by other authors [8, 14–17].

Our analysis also revealed high recurrence rate in the group of patients at FIGO stage II. This means that patients who underwent a complete radical radiation therapy are still at high risk of recurrence. This in turn may suggest that the disease at the time of therapy planning was more advanced than the diagnosis based on histopathological report stated.

One of the most important topics is quality and accuracy of the histopathological report. Boer at al. re-evaluated histopathological reports of the patients included into PORTEC-3 study in England and Norway [18]. The re-evaluation

Table 8. Early Endometrial Cancer recurrence rates. Analysis focused on FIGO Stage. grade and adjutant treatment status (received — Adjuvant treatment. not received — No adjuvant treatment)

		Adjuvant treatment			Recurrence		
Stage	**Grade**	**Altogether**	**Yes**	**No**	**Altogether**	**Adjuvant treatment**	**No adjuvant treatment**
I A	**G1**	53	16	37	20	1	19
	G2	47	40	7	11	7	4
	G3	12	11	1	1	1	0
I B	**G1**	69	68	1	9	8	1
	G2	116	115	1	21	20	1
	G3	31	31	0	8	8	0
II	**G1**	30	29	1	11	10	1
	G2	51	51	0	25	25	0
	G3	10	10	0	2	2	0

revealed modification of at least one assessed factor in 43% of cases. In 34% of cases the type of malignancy changed, in 27% the depth of infiltration, and in 19% the cancer grade [18]. These modifications considerably altered indications for adjuvant treatment, and demonstrated that the patients should have been qualified for this type of therapy [19–23].

The discussed discrepancies in treatment results might be caused by differences in surgical procedures and specimen preparation at different centers and pathology departments (differences in laboratory protocols of specimen preparation). Those differences affected accuracy of the final pathological reports, as described and analyzed by Mitchard and Hirschowitz [24, 25].

The final parameter to be discussed is positive LVSI. Recent studies implied that positive LVSI at early stages of EC is sufficient to recommend a more aggressive treatment, especially in cases of coexisting risk factors. Bosse et al. re-evaluated histopathological data of the patients included into PORTEC-1 and PORTEC-2 study [18]. They found out that positive LVSI was an independent negative prognostic factor for local recurrence, distant metastases and overall survival [26]. They also concluded that histopathological examinations should be performed at referential centers [27–33].

For a long time, European scientific organizations engaged in EC treatment would not agree on the guidelines on EC management. In 2016, European Society of Gynecological Oncology (ESGO), European Society for Radiotherapy and Oncology (ESTRO) and European Society of Medical Oncology (ESMO) finally published a consensus outlining diagnostics, qualification for treatment and extent of surgery at specific stages of the disease. They also provided detailed guidelines for adjuvant treatment and post treatment follow up. There is still place for immune therapy and targeted therapy in EC that will hopefully have positive impact on PFS and OS [34, 35].

The next step should be an evaluation of patients treated for recurrence that were exposed to radiation and/or chemotherapy.

CONCLUSIONS

Early EC treatment outcomes were unsatisfactory and should be improved. High rate of recurrence in early endometrial cancer reported recently encouraged us to investigate the factors responsible for the treatment failure. In patients at IA G1 stage brachytherapy seems justified even though studies suggest only careful follow-up. Brachytherapy introduced in the analyzed group significantly reduced local recurrence.

In patients at this stage, the adjuvant treatment (vaginal brachytherapy alone) seemed reasonable. The women who underwent this treatment scored better than those who did not receive any adjuvant therapy, and we concluded that vaginal brachytherapy dramatically improved locoregional control of the disease.

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Principal component analysis and internal reliability of the Polish version of MESA and UDI-6 questionnaires

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ABSTRACT

Objectives: Urinary incontinence (UI) can affect up to 50% of the population of women over the age of 50. In order to objectively assess discomfort in women with UI prior to initiating treatment and monitoring the outcomes of the treatment, validated questionnaires need to be used to examine the impact of UI on health-related quality of life (HR-QoL). The Urogenital Distress Inventory — Short Form (UDI-6) and the Medical Epidemiologic and Social Aspects of Ageing (MESA) questionnaires are used typically.

Assessment of the Polish translation of the MESA and UDI-6 questionnaires.

Material and methods: 155 patients with symptoms of UI were enrolled. Each of the patients completed the MESA and UDI questionnaires prior to being examined. The final diagnosis was made after diagnostic tests were carried out in the patients.

Results: Principle component analysis showed division of the Polish versions of the questionnaires into domains identical to the original version. Analyses of internal consistency reliability revealed high internal consistency for the MESA questionnaire (0.90) and a low reliability of the UDI-6 questionnaire (0.44).

Conclusions: The Polish version of the MESA questionnaire was demonstrated to be a clinically useful diagnostic tool in the studied population, UDI-6 did not reached a sufficiently high reliability in the study group to be recommended as a diagnostic tool.

Key words: urinary incontinence; UDI-6; MESA; health-related quality of life

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INTRODUCTION

Urinary incontinence (UI) can occur in as many as 40–50% of women after the age of 40, and the incidence increases with age [1]. There are four main types of urinary incontinence: urge incontinence due to an overactive bladder (OAB), stress incontinence (SI) due to poor closure of the bladder, overflow incontinence due to either poor bladder contraction or blockage of the urethra and mixed urinary incontinence which aggregate symptoms of OAB and SI. Women with UI are more likely to suffer from depression, and report a reduced enjoyment of sexual activity [2]. Affected women also receive lower scores in health-related quality of life (HRQoL) questionnaires [2], which enable researchers to test the impact of urinary incontinence symptoms on a patient's physical, mental and social functioning. These questionnaires are extremely important in the classification of women suffering from UI in order to provide the best treatment and to establish follow-up measures. A large number of HRQoL questionnaires developed for the assessment of patients with urinary incontinence are described in the literature, however, these tools are usually originally developed in English. To reach the target patient's, the origi-

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nal questionnaire should be translated into the patient's language. After completing the translation of a questionnaire, its validity needs to be assessed objectively.

The Medical, Epidemiologic, and Social aspects of Aging (MESA) questionnaire is a research tool published over 20 years ago [3], but has not yet been validated in Polish. The score obtained in the questionnaire reflects the severity of the patient's ailments, and the impact of these ailments on their quality of life. Numerous studies, the results of which have been published, have demonstrated the value of the MESA questionnaire in assessing both in the diagnosis of UI and the effectiveness of UI and urinary urgency treatment [4]. The MESA questionnaire consists of two parts: the first part contains six questions and is related to UI, the second part contains nine questions and is related to stress UI. The patient evaluates the severity of the symptoms on a four-point scale.

An additional tool for assessing the impact of UI on women is the UDI (Urogenital Distress Inventory) questionnaire. The UDI-6 (Urogenital Distress Inventory — Short Form) questionnaire is a shortened version of the 19-element UDI. The shortened version is less time-consuming for the patient while maintaining the informative value for a clinician. The questionnaire consists of six questions examining three domains: IS — irritative symptoms (questions 1 and 2), SS — stress symptoms (questions 3 and 4), OS — obstructive/discomfort (questions 5 and 6), and each question is assessed by the patient on a four-point scale. The literature shows that these parameters correlate with data from other measures including voiding diaries, urodynamic examination, and sanitary tests, and change as a result of treatment [5].

Objectives

The objective of this study is to validate the Polish translation of two questionnaires examining health-related quality of life — UDI-6 (Urogenital Distress Inventory-Short Form) and MESA (Medical Epidemiologic and Social Aspects of Ageing).

MATERIAL AND METHODS

The study involved 155 Polish-speaking patients with UI problems who were tested for UI in the urodynamic laboratory at the Urology Department of Saint Raphael's Hospital in Czerwona Gora, Checiny, Poland. All patients underwent urodynamic testing using Medtronic's Duet Logic G2. The results of the urodynamic tests were interpreted based on the definitions and units established by the International Continence Society (ISC). Based on the urodynamic tests, the patients were classified into one of five the groups: stress urinary incontinence (SUI), urge urinary incontinence (UUI), overactive bladder without urinary incontinence (OAB), mixed urinary incontinence (MUI) and patients without a urodynamic diagnosis of urinary incontinence (no UI). Each patient completed the UDI — 6 and MESA questionnaires before being tested. The questionnaires were previously translated by two independent translators into Polish and translated back into English by a native speaker, then the questionnaires were completed by 6 patients with SUI. After talking to the patients, there were no major problems with understanding the content. The final version was chosen by the authors. To assess the structure of the questionnaires, we performed a principal component analysis (PCA). Individual groups of urodynamic diagnoses in terms of demographic parameters were compared using the Kruskal-Wallis test due to the lack of fulfilment of assumptions with a distribution close to normal or equal variance, and the qualitative data were compared using the Pearson's chi-squared test. We considered $p < 0.05$ to be a statistically significant difference. In order to assess internal consistency reliability, we calculated the Cronbach's alpha coefficient. We determined the internal consistency reliability to be acceptable for a result > 0.7. We performed statistical analysis using Statistica 13.1 (*StatSoft Polska*) and R (version 3.4.4).

RESULTS

One hundred fifty-five female patients participated in the study. The average age of the respondents was 55.2 [standard deviation (SD) = 11 years], the youngest patient was 19 years old and the oldest 82 years old. The age distribution in the study group was similar to the normal distribution ($p = 0.11$ in the Shapiro-Wilk test). 69% of the patients in the study were postmenopausal. Based on the urodynamic examination, the percentage of definitive diagnoses was as follows: 24.5% no UI, 49.6% SUI, 13.5% MUI, 5.8% UUI, and 6.45% of the patients were diagnosed with OAB without UI. There was no statistically significant difference between the average age of the patients in the individual groups ($p = 0.35$). Patient demographics are shown in Table 1.

Kaiser-Meyer-Olkin measure of sampling adequacy was 0.92 for MESA and 0.56 for UDI-6 questionnaire, indicating that PCA is suitable for the datasets. Bartlett's test of sphericity ($p < 0.005$) for both questionnaires showed that the correlation between specific questions in questionnairee was sufficiently large for PCA.

Results of the PCA for MESA showed that 2 components had eigenvalues greater than 1, based on Kaiser's criterion we rejected rest of components. The first principal component included questions about SUI (questions 7–15), which explained 48.6% of the total variance of the questionnaire. The second component included questions about UUI, explaining 19.42% of the total variance. The cumulative percentage of the explained variance in relation to the separated factor loadings was 68%. Due to the results of the above analysis,

Table 1 Demographic characteristics of patiants in groups

Prarameter	Study group (n = 155)					
	SUI (n = 77)	MUI (n = 21)	UUI (n = 9)	OAB (n = 10)	no UI (n = 38)	
Age (mean ± SD)	56.21 ± 10.41	56.76 ± 8.95	57.33 ± 6.52	52.80 ± 16.59	52.34 ± 12.31	p = 0.35
Postmenopausal, n (%)	57 (74.03%)	18 (85.71%)	7 (77.78%)	5 (50%)	20 (52.63%)	p = 0.03

Table 2. Medians, IQR — interquartile range, sums of points in questionnaire domains

Questionnaire	Domain	SUI		MUI		UUI		OAB		no UI	
		median	IQR	median	IQR	median	IQR	median	IQR	median	IQR
MESA	MESA-UUI	7.00	10.00	10.00	4.00	13.00	6.00	12.00	10.00	8.00	8.00
	MESA-SUI	19.00	8.00	21.00	8.00	14.00	13.00	10.00	13.00	13.50	12.00
	MESA-sum	25.00	15.00	32.00	9.00	24.00	13.00	22.50	25.00	19.00	13.00
UDI-6	UDI-6IS	3.00	4.00	4.00	2.00	5.00	2.00	4.00	1.00	4.00	3.00
	UDI-6SS	5.00	2.00	4.00	1.00	4.00	2.00	3.50	3.00	3.00	3.00
	UDI-6OS	2.00	3.00	2.00	1.00	3.00	2.00	4.00	4.00	3.00	1.00
	UDI-6 sum	9.00	5.00	10.00	3.00	11.00	3.00	10.50	4.00	10.00	4.00

which confirm the specific structure of the questionnaire (consisting of two parts, one of which (6 questions) concerns UUI and the other (9 questions) concerning SUI), we calculated the internal consistency reliability separately for each part as well as for the questionnaire as a whole. The internal consistency reliability in each case was high. Cronbach's alpha was 0.9 in the case of UUI, 0.92 in the case of SUI and 0.90 in the case of the whole questionnaire. We also compared the scores obtained in the questionnaire for the individual groups of urodynamic diagnoses. We obtained a statistically significant difference in the total score between the patients with SUI and UUI in the first part of the questionnaire - questions 1-6 (median = 7 vs 13, p = 0.0014), as well as in the part on SUI — questions 7–15 (median = 19 vs 14, p = 0.00001).

In the dataset obtained from the UDI-6 questionnaire, PCA extracts three principal components based on Kaiser's criterion. The first component includes questions 1 and 2 about the symptoms of overreactive bladder, and explains 31.12% of the total variance. The second component contains questions 3 and 4, largely about SUI symptoms, and explains 29.7% of the total variance. The third component (questions 5 and 6) with questions about signs of discomfort from the lower urinary tract explains 14.73% of the total variance. Question No. 6 was the only question characterized by a low correlation with the corresponding main component (r = 0.24). Based on the above analysis, we calculated the internal consistency reliability coefficient for each of the three dimensions. Cronbach's alpha was 0.61 for questions 1 and 2, 0.60 for questions 3 and 4, and 0.39 for questions 5 and 6. Cronbach's alpha for the entire questionnaire was 0.44. We did not observe a statistically significant difference between the groups of urodynamic diagnoses and the number of points obtained in the questionnaire (Tab. 2).

DISCUSSION

Condition-specific health-related quality of life questionnaires are helpful tools in clinical practice. They provide a subjective assessment of the impact of a disease on a patient's quality of life, and help assess the effectiveness of treatment. In their recommendations from 2017 [6], the European Association of Urology (EAU) suggest using validated questionnaires assessing the quality of life for examining patients for whom standardization of assessment is necessary. Questionnaires translated into a new language should be re-validated for the target population. This allows researchers to assess whether the translation of the questionnaire is linguistically appropriate, has an equivalent structure, and works in new cultural conditions. After proper assessment, validated questionnaires make it possible to compare results between different countries/language groups. We have not found any reports in the literature concerning the validation of the MESA questionnaire in Polish language conditions. The results we obtained indicate undoubtedly indicate its usefulness. The PCA mathematically reflects its language structure, and our findings showed high internal consistency reliability both in individual parts and as a whole. In addition, the summary results obtained in the individual parts differed in patients with UUI and SUI.

In our study, we showed the preservation of the original three-dimensional structure of the UDI — 6 questionnaire in the Polish translation. The internal consistency reliability for the first and second dimensions measured by Cron-

bach's alpha is acceptable, but unacceptable for the third dimension. The third dimension includes questions about difficulty emptying the bladder and pain in the lower abdomen and perineum. Answers to these questions correlated with each other only slightly in our study group. This may indicate a low usefulness of the questionnaire among a heterogeneous group of patients. It is worth noting that Cronbach's alpha in the third dimension of the questionnaire was acceptable (0.62) after performing calculations in a subgroup of patients with UUI, however, the reliability of the entire questionnaire in this group was not greater. We found one report validating the UDI-6 questionnaire in the Polish language conditions in the literature [7]. This research demonstrates a high reliability of the questionnaire in the authors' translation, except for patients diagnosed with MUI.

CONCLUSIONS

The Polish version of the MESA questionnaire is a useful diagnostic tool in the study population. The authors' translation of UDI-6 has not proven to be a sufficiently reliable diagnostic in our study sample, and cannot be recommended as a diagnostic tool in the group of women with UI.

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Comparison of eleven commonly used formulae for sonographic estimation of fetal weight in prediction of actual birth weight

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ABSTRACT

Objectives: The aim of the study is to compare the accuracy of 11 formulas in predicting fetal weight.

Material and methods: The study includes 1072 pregnant women of gestational age from 28 to 42 weeks, who gave birth between January and June 2017. Pregnant women were divided into five groups; group 1, where actual birth weight (ABW) was less than 2500 g, group 2, where ABW was between 2500–4000 g, group 3, where ABW was above 4000 g. Group 4 — newborns with birth weight under 10 percentile and group 5 — newborns with birth weight above 90 percentile. The accuracy of the estimated fetal weight (EFW) was assessed by calculating absolute percentage error (APE) and 'limits-of-agreement'. R Spearman correlation was utilized between EFW and ABW.

Results: The most accurate formula for group 1 is Hadlock3 (MAPE = 7.04%), the narrowest limits of agreement has Combs — [mean (SD): 99.41 g (269.57 g)]. For group 2, the lowest MAPE (5.43%) has Ott, the narrowest limits of agreement belongs to Combs – [mean (SD): -101.36 g (275.88 g)] . For group 3 is Hadlock3 (MAPE = 5.79%), the narrowest limits of agreement has Hadlock5 [mean (SD): -637.32 g (209.59 g)]. For group 4 is Combs (MAPE = 7.72%), the narrowest limits of agreement has Combs [mean (SD): 195.77 g (264.97 g)]. For gr oup 5 is Warsof2 (MAPE = 7.06%), the narrowest limits of agreement has Campbell [mean (SD): 227.81 g (299.26 g)].

Conclusions: Median of absolute percentage error is the most useful parameter to predict birth weight. Each group of fetuses needs different formula to predict the most accurate weight.

Key words: fetal ultrasonography; estimation of fetal weight; Hadlock, SGA; LGA

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INTRODUCTION

Sonographic estimation of fetal weight plays an important role in obstetrics. Meaning of sonograms performed for the purpose of predicting fetal weight is rising from 24 weeks of gestation, the age of viability. Estimated fetal weight (EFW) is an essential parameter which may be helpful in decision-making during perinatal period and it can be calculated using various mathematical methods. There are several mathematical formulas that use different fetal structures to estimate fetal weight such as biparietal diameter (BPD), head circumference (HC), abdominal circumference (AC), and/or femur length (FL). The accuracy of these formulas may vary, nevertheless low values have an impact on physicians' decisions. The performance of formulas may also be different in macrosomic fetuses or low-birth-weight fetuses. Macrosomia refers to growth beyond a specific threshold, regardless of gestational age. Depending on the guidelines, various thresholds are accepted, the most commonly used threshold is weight above 4500 g. Also, weight above 4000 g is accepted as macrosomia. Knowledge about estimated fetal weight is useful at term for decision-making regarding mode of delivery. To identify the preterm macrosomic fetus, weight charts are used, it is established that any fetus weighing above 90th percentile for gestational age is defined as large for gestational age. The most common serious concern connected with fetal macrosomia is shoulder dystocia, which leads to birth trauma, brachial plexus injury, clavicular fracture or asphyxia [1, 2].

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Table 1. Formulae used for fetal weight estimation

First author	Components	Formula
Hadlock1 [6]	HC, AC, FL	Log_{10} BW = 1.326-0.00326 (AC) (FL) + 0.0107 (HC) + 0.0438 (AC) + 0.158 (FL)
Hadlock2 [6]	AC, FL	Log_{10} BW = 1.304 + 0.05281 (AC) + 0.1938 (FL) -0.004 (AC) (FL)
Hadlock3 [6]	HC, BPD, AC	Log_{10} BW = 1.335-0.0034 (AC) (FL) + 0.0316 (BPD) + 0.0457 (AC) + 0.1623 (FL)
Hadlock4 [7]	HC, BPD, AC, FL	Log_{10} BW = 0.3596 + 0.00061 (BPD) (AC) + 0.0424 (AC) + 0.174 (FL) + 0.0064 (HC)-0.00386 (AC) (FL)
Hadlock5 [8]	HC, AC, FL	Log_{10} BW = 1.3596 + 0.006 (HC) + 0.0424 (AC) (FL)
Shepard [9]	BPD, AC	Log_{10} BW = -1.7492 + 0.166 (BPD) + 0.046 (AC)-0.002546 (AC) (BPD)
Campbell [10]	AC	LnBW = -4.564 + 0.0282 (AC)-0.00331 $(AC)^2$
Warsof1 [11]	FL	LnBW = 4.6914 + 0.00151 $(FL)^2$-0.0000119 $(FL)^3$
Warsof2 [11]	AC, FL	LnBW = 2.792 + 0.108 (FL) + 0.0036 $(AC)^2$-0.0027 (FL) (AC)
Combs [12]	HC, AC, FL	BW = 0.23718 $(AC)^2$ (FL) + 0.03312 $(HC)^3$
Ott [13]	HC, AC, FL	Log_{10} BW = -2.0661 + 0.04355 (HC) + 0.05394 (AC)-0.0008582 (HC) (AC) + 1.2594 (FL/AC)

BPD — biparietal diameter; HC — head circumference; AC — abdominal circumference; FL — femur length; BW — birth weight

Low birth weight is defined as less than 2500 g at the first weight determination after birth, it is associated with fetal prematurity or small for gestational age. Small for gestational age (SGA) is defined as infants with a body weight below the 10^{th} percentile for gestational age and comprises infants who are constitutionally normally small and those who are small because of fetal restriction [3]. Infants with fetal of growth restriction are at increased risk for morbidity and mortality [4]. Any stage requires medical intervention, proper time and mode of delivery. Nowadays, estimation fetal weight could be also improved by using three-dimensional ultrasound [5]. The aim of the study was to compare the accuracy of 11 formulas in predicting fetal weight, which are the most widespread between gynecologists.

MATERIAL AND METHODS

The retrospective cohort study included 1072 pregnant women of gestational age from 28 to 42 weeks, who gave birth in Department of Obstetrics and Perinatology JU MC between January and June 2017. The inclusion criteria were: Caucasian, race, singleton pregnancies and the interval between estimation of fetal weight and delivery within 48 hours. Intrauterine fetal deaths and fetuses with lethal defects were excluded. We divided pregnant women into five groups depending on actual birth weight (ABW); group 1 comprising 40 patients,where actual birth weight (ABW) was less than 2500 g, group 2 including 932 patients, where ABW was between 2500–4000 g, group 3 with 100 patients, where ABW was above 4000 g. According to ABW, we have analyzed weight charts. Group 4 includes newborns with birth weight under 10 percentile and group 5 — newborns with birth weight above 90 percentile. Ultrasound examinations were performed by obstetricians who underwent the same training course, with the use of General Electric Voluson ultrasound device with 4–8 MHz transabdominal curvilinear transducer. In cases which the ultrasound examination was repeated, only the last examination before delivery was taken into account. Each fetus was included only once. Birth weight and neonatal weight were obtained within 1h after delivery by the nursing staff. We evaluated 11 widely accepted weight formulas (Tab. 1). Measurement were performed by doctors as a part of diagnostic work-up before delivery, informed consent was obtained from all individuals on admission included in these study. The study was approved by Bioethics Committee of the University.

Statistical analysis

Data were analyzed using *STATISTICA 13.1* statistical analysis software. The accuracy of the EFW was assessed by calculating absolute percentage error (APE): |(EFW - ABW)/ /ABW| x 100% in order to predict accuracy of a formula. Differences between the weight formulas were compared using Wilcoxon's test for median absolute percentage error (MAPE) values at a significance level < 0.05. We chose median due to nonparametric distribution of data.We compared the lowest MAPE and and the other equations. We utilized R Spearman correlation to evaluate the power of relationship between actual birth weight and estimated fetal weight. Accuracy was also determined with the 'limits-of-agreement' method described by Bland and Altman [14]. The overall median difference between fetal weight and birth weight is connected with the systematic error, while the limits of agreement refer to the random error. The 95% limits of agreement show the difference between the birth weight and the EFW that can be expected, and which tendency (to underestimate or overestimate) is found.

Table 2. Maternal characteristics of the study group

	Group 1 (≤ 2500)	Group 2 (2500–4000)	Group 3 (≥ 4000)	Group 4 (< 10 cent.)	Group 5 (> 90 cent.)
Sample size	40	932	100	94	123
Maternal age, years, mean (SD)	31.81 (5.64)	31.69 (4.66)	31.34 (3.88)	32.36 (4.89)	31.70 (4.66)
Mean gestational age the time of ultrasound examination, weeks, median (range)	34.36 (28.00–41.29)	39.14 (33.43–42.00)	40.00 (36.57–41.14)	39.00 (30.57–42.00)	38.86 (28.00–41.00)
Parity, median (range)	0 (0–3)	1 (0–8)	1 (0–2)	0 (0–4)	1 (0–3)
Maternal BMI before pregnancy, median (range)	22.76 (17.21–38.53)	21.77 (14.37– 42.24)	23.05 (18.78–55.10)	21.09 (14.86–34.77)	22.50 (18.17–55.10)

Table 3. The median absolute percentage error (MAPE) (left side) and limits of agreement (right side) between estimated fetal weight (g) and actual birth weight (g) in group 1 for each regression formula in group 1

Regression formula	Median APE [%] (range)	p value	mean [g] (SD)	95% limits of agreement [g]
Hadlock1	56.98 (34.32–182.27)	< 0.05	1262.85 (287.46)	699.44 to 1826.27
Hadlock2	9.54 (0.67–42.10)	> 0.05	50.72 (301.48)	-540.19 to 641.62
Hadlock3	7.04 (0.20–45.32)	–	70.47 (298.17)	-513.95 to 654.89
Hadlock4	8.08 (0.21–40.77)	> 0.05	45.21 (298.44)	-539.73 to 630.14
Hadlock5	56.59 (34.00–182.13)	< 0.05	1256.29 (288.48)	690.86 to 1821.72
Shepard	12.30 (0.90–57.80)	< 0.05	224.76 (362.47)	-485.68 to 935.20
Campbell	10.82 (0.13–48.21)	> 0.05	127.36 (302.65)	-465.83 to 720.55
Warsof1	15.82 (0.07–74.04)	< 0.05	276.91 (460.94)	-626.53 to 1180.35
Warsof2	11.51 (0.34–58.12)	< 0.05	197.64 (366.84)	-521.38 to 916.65
Combs	7.93 (0.48–35.83)	> 0.05	99.41 (269.57)	-428.94 to 627.76
Ott	8.32 (0.54–40.36)	> 0.05	101.36 (287.22)	-461.59 to 664.31

RESULTS

We identified 1072 singleton pregnancies fulfilling the inclusion criteria and divided them into five groups. Each group was separately analyzed in order to find the most accurate formula and show a tendency to underestimate or overestimate. Maternal characteristics of each study group is presented in Table 2.

Group 1 comprises 40 fetuses with ABW under 2500 g, median of weight is 2100 g. Table 3 shows the APE as median values (range). The lowest MAPE is found for the formula Hadlock3 (7.04%). There is a significant difference between it and the other equations ($p < 0.05$), except from the Hadlock2, Hadlock4, Campbell, Combs and Ott ($p > 0.05$) formulas. Hadlock3 has also the highest value of Spearman corrrelation ($R = 0.845$). Following the strongest correlations belong to Hadlock4 ($R = 0.841$) and Ott ($R = 0.838$). Table 3 shows agreement between estimated fetal weight and true birth weight as assessed by limits-of-agreement method. All tested formulas have a tendency to overestimate fetal weight. The narrowest limits of agreement has the EFW calculated with Combs formula. In contrast, the widest range is found for Warsof1 formula.

Group 2 comprises 932 fetuses with ABW between 2500 g and 4000 g, median of weight is 3350 g. The lowest MAPE is found for the formula Ott (5.43%). It differs significantly from the other equations ($p < 0.05$), only the Hadlock4, Campbell and Combs formulas are the exceptions ($p > 0.05$) (Tab. 4). The highest Spearman correlation are for Hadlock4 ($R = 0.686$), Hadlock1 ($R = 0.683$) and Hadlock5 ($R = 0.682$). According to Table 4, all tested formulas, except for Ott, Campbell and Combs tendency to overestimate fetal weight. The narrowest limits of agreement has Combs while the widest range has Warsof1.

Group 3 comprises 100 fetuses with ABW over 4000 g, median of weight is 4165 g. The lowest MAPE has Hadlock3 (5.79%). P value below 0.05 in case of other equations, except from Hadlock2, Shepard and Warsof2, indicates there is significant difference between them and Hadlock3 formula. (Tab. 5). Spearman correlation values are the highest for Hadlock1 ($R = 0.332$), Hadlock5 ($R = 0.329$) and Ott ($R = 0,328$). Table 5 presents that all formulas have a tendency to underestimate fetal weight. The narrowest limits of agreement has Hadlock5, the widest limits of agreement belongs to Shepard.

Table 4. The median absolute percentage error (MAPE) (left side) and limits of agreement (right side) between estimated fetal weight (g) and actual birth weight (g) for each regression formula in group 2

Regression formula	Median APE [%] (range)	p value	mean [g] (SD)	95% limits of agreement [g]
Hadlock1	7.25 (0.01–40.72)	< 0.05	179.17 (318.06)	-444.24 to 802.57
Hadlock2	5.96 (0.03–57.83)	< 0.05	51.05 (301.12)	-539.14 to 641.24
Hadlock3	5.73 (0.02–51.25)	< 0.05	49.63 (294.87)	-528.31 to 627.58
Hadlock4	5.53 (0.00–50.41)	> 0.05	3.18 (286.33)	-559.03 to 563.39
Hadlock5	7.26 (0.00–40.38)	< 0.05	171.95 (317.96)	-451.25 to 795.15
Shepard	8.91 (0.03–64.97)	< 0.05	248.77 (376.25)	-488.68 to 986.22
Campbell	5.51 (0.01–48.27)	> 0.05	-36.95 (283.09)	-591.81 to 517.91
Warsof1	7.14 (0.02–46.74)	< 0.05	48.47 (385.96)	-708.02 to 804.96
Warsof2	7.38 (0.01–65.89)	< 0.05	180.52 (313.78)	-434.48 to 795.53
Combs	5.56 (0.01 –45.91)	> 0.05	-101.36 (275.88)	-642.08 to 439.37
Ott	5.43 (0.01–51.25)	–	-33.84 (282.51)	-587.56 to 519.87

Table 5. The median absolute percentage error (MAPE) (left side) and limits of agreement (right side) between estimated fetal weight (g) and actual birth weight (g) for each regression formula in group 3

Regression formula	Median APE [%] (range)	p value	mean [g] (SD)	95% limits of agreement [g]
Hadlock1	14.00 (9.37–30.00)	< 0.05	-630.43 (209.91)	-1041.84 to -219.01
Hadlock2	6.46 (0.01–30.31)	> 0.05	-233.41 (340.04)	-899.89 to 433.06
Hadlock3	5.79 (0.02–49.91)	–	-237.79 (366.68)	-956.48 to 480.91
Hadlock4	5.81 (0.09–43.02)	< 0.05	-293.74 (344.90)	-969.74 to 382.26
Hadlock5	14.19 (9.59–30.11)	< 0.05	-637.32 (209.59)	-1048.12 to -226.52
Shepard	7.22 (0.00–70.54)	> 0.05	60.45 (510.42)	-939.96 to 1060.87
Campbell	10.70 (0.38–25.84)	< 0.05	-488.81 (261.88)	-1002.09 to 24.47
Warsof1	13.99 (3.36–37.09)	< 0.05	-616.34 (311.22)	-1226.34 to -6.34
Warsof2	5.80 (0.08–29.33)	> 0.05	-90.70 (379.93)	-835.37 to 653.98
Combs	9.69 (0.15–29.25)	< 0.05	-473.20 (300.00)	-1061.20 to 114.81
Ott	7.52 (0.17–28.15)	< 0.05	-365.07 (311.49)	-975.59 to 245.45

Group 4 includes 94 SGA babies with actual birth weight under 10 centile, median of weight is 2679 g. The lowest MAPE has Combs (7.72%). There is a significant difference between it and other equations ($p < 0.05$) except from Campbell formula (Tab. 6). Hadlock1, Hadlock5 and Ott formulas have the highest value of Spearman correlation. R equals 0.727 for each of them. Table 6 shows that all formulas have a tendency to overestimate predicting weight. The narrowest limits of agreement has Combs, while the widest range has Warsof 1.

Group 5 comprises 123 LGA babies with actual birth weight above 90 centile, median of weight is 4090 g. The lowest MAPE has Warsof 2 (7.06%). It differs significantly from the other equations ($p < 0.05$) except from Hadlock3, Hadlock2 and Shepard (Tab. 7). The strongest correlation values are for Ott ($R = 0.537$), Hadlock5 ($R = 0.536$), Hadlock1 ($R = 0.532$). All tested formulas have a tendency to underestimate actual birth weight, except for Shepard (Tab. 7). Also Shepard formula has the widest limits of agreement. In contrast, the narrowest range is found for Campbell formula.

DISCUSSION

In our study we formed five groups, each of them should be analyzed separately.

For fetuses with ABW under 2500 g, the most accurate formula is Hadlock3 (MAPE = 7.04%). Hadlock3 has also the highest value of Spearman correlation ($R = 0.845$). According to other Hadlock formulas, all of them have high accuracy. It indicates that Hadlock formulas are stable. Esinler et al. [15] collated the performance of 18 different formulas for prediction of fetal weight. They compared formulas in the whole study population and subgroups by using percentage error (PE), absolute percentage error (APE) and Cronbach's alpha value. They reported that the lowest three mean APE values were associated with Hadlock4 (9.1%), Hadlock1 (9.2%) and Ott (9.8%). Choi Wah Kong et al. [16] assesed the accuracy

Table 6. The median absolute percentage error (MAPE) (left side) and limits of agreement (right side) between estimated fetal weight (g) and actual birth weight (g) for each regression formula in group 4

Regression formula 10 cent	Median APE [%] (range)	p value	mean [g] (SD)	95% limits of agreement [g]
Hadlock1	28.78 (13.11 - 164.33)	< 0.05	828.13 (279.56)	280.20 to 1376.06
Hadlock2	11.12 (0.15 - 57.83)	< 0.05	284.29 (340.19)	-382.47 to 951.06
Hadlock3	10.09 (0.39 - 51.25)	< 0.05	280.10 (316.63)	-340.50 to 900.70
Hadlock4	8.75 (0.38 - 50.41)	< 0.05	238.94 (303.56)	-356.04 to 833.92
Hadlock5	28.49 (12.88–163.95)	< 0.05	820.72 (279.74)	272.42 to 1369.01
Shepard	14.33 (0.90–59.49)	< 0.05	398.16 (357.51)	-302.56 to 1098.88
Campbell	9.26 (0.06–48.27)	> 0.05	227.81 (299.26)	-358.75 to 814.37
Warsof1	22.61 (0.07–74.04)	< 0.05	525.55 (395.80)	-250.21 to 1301.32
Warsof2	17.22 (0.09–65.89)	< 0.05	460.00 (368.24)	-261.75 to 1181.74
Combs	7.72 (0.20–45.91)	–	195.77 (264.97)	-323.56 to 715.10
Ott	9.16 (0.54–51.25)	< 0.05	237.07 (284.83)	-321.19 to 795.34

Table 7. The median absolute percentage error (MAPE) (left side) and limits of agreement (right side) between estimated fetal weight (g) and actual birth weight (g) for each regression formula in group 5

Regression formula 90 cent	Median APE [%] (range)	p value	mean [g] (SD)	95% limits of agreement [g]
Hadlock1	12.43 (1.11–75.24)	< 0.05	-485.49 (374.14)	-1218.80 to 247.82
Hadlock2	7.16 (0.01–30.31)	> 0.05	-207.45 (347.47)	-888.48 to 473.59
Hadlock3	7.13 (0.02–49.91)	> 0.05	-211.09 (371.36)	-938.96 to 516.78
Hadlock4	7.58 (0.09–43.02)	< 0.05	-266.99 (349.24)	-951.50 to 417.51
Hadlock5	12.59 (1.11–75.24)	< 0.05	-492.40 (374.15)	-1225.74 to 240.93
Shepard	7.26 (0.03–70.54)	> 0.05	77.32 (501.22)	-905.06 to 1059.70
Campbell	9.27 (0.28–30.20)	< 0.05	-414.08 (289.73)	-981.96 to 153.80
Warsof1	12.77 (0.12–37.09)	< 0.05	-553.68 (369.94)	-1278.76 to 171.41
Warsof2	7.06 (0.08–29.33)	–	-72.07 (383.22)	-823.19 to 679.04
Combs	10.33 (0.22–29.25)	< 0.05	-433.57 (308.83)	-1038.88 to 171.74
Ott	8.29 (0.17–28.59)	< 0.05	-332.56 (316.72)	-953.33 to 288.22

of INTERGROWTH-21 formula with the traditional Hadlock1 and Shepard formula. INTERGROWTH-21 had a higher mean of the APE (9.72%) than Hadlock1 (6.93%) or Shepard (8.96%). According to newer technology, perhaps 3D methods might improve accuracy of estimation fetal weight [5]. Hasenoehrl et al. showed that the lowest mean absolute percentage error in birth weight estimation for fetuses under 2500 g belongs to 3D Schild formula (7.0%) compared to Hadlock4 (8.0%). The disadvantage of 3D ultrasonography is that it is time consuming method, it lasts longer, especially at the beginning of learning these technic.

Our analysis for fetuses between 2500 g and 4000 g shows that the most accurate formula is Ott (mean APE is 5.43%). Although, the highest Spearman correlations belong to Hadlock formulas. Hoopmann et al. [17] compared 35 formulae in 3416 fetuses with weight between 2500 g and 4000 g. They determined and compared the mean percentage error, the mean absolute percentage error, also the proportions of estimates within the error ranges of 5, 10, 20 and 30%. In addition, separate regression lines were calculated for the relationship between estimated and actual birth weight.. Halaska formula had the best value of mean absolute percentage error (6.6%). 20 formulae (Halaska, Schild I, Shinozuka, Sabbagha, Hadlock III, Hadlock I, Ott, Hadlock V, Combs, Hadlock II, Merz I, Rose-McCallum, Shepard, Warsof, Ferrero, Hadlock VI, Campbell, Persson, Hansmann, Jordaan) exhibited MAPE values of ≤ 10%. In our study, estimation of fetal weight with Campbell, Combs and Ott formulae have a tendency to underestimate fetal weight, other 8 formulae overestimate fetal weight. These results contrast with Hoopmann et al. study [17], where the majority of the tested formulae gave underestimations of the

Table 8. R Spearman correlation for groups from 1 to 5

Regression formula	R Spearman correlation				
	Group 1	Group 2	Group 3	Group 4	Group 5
Hadlock1	0.834	0.683	0.332	0.727	0.532
Hadlock2	0.820	0.661	0.312	0.709	0.527
Hadlock3	0.845	0.680	0.305	0.706	0.527
Hadlock4	0.841	0.686	0.319	0.719	0.531
Hadlock5	0.834	0.682	0.329	0.727	0.536
Shepard	0.814	0.648	0.195*	0.659	0.464
Campbell	0.775	0.630	0.229	0.691	0.483
Warsof1	0.674	0.375	0.218	0.563	0.354
Warsof2	0.742	0.640	0.305	0.659	0.527
Combs	0.833	0.671	0.326	0.725	0.526
Ott	0.838	0.676	0.328	0.727	0.537

actual birth weight. Analysis of 3D formulas [5] shows higher accuracy of 3D Schild formula compared to Hadlock4 in group of fetuses between 2500g and 3000g (mean absolute percentage error 5.3% vs 7.8%) and those between 3500 g and 4000 g (4.8% vs 9.6%).

Group 3 comprises fetuses with ABW over 4000g, the most accurate formula is Hadlock3 (MAPE = 5.79%). The highest correlation value has: Hadlock1 (R = 0.332). There is a visible relation (Tab. 8); the Spearman correlation, power of relationship, decreases with actual birth weight. According to factors affecting the accuracy of fetal weight, some older studies claim that maternal BMI [18] or fetal sex [19] are apparently not a significant influence on measurement error. Esinler et al. [15] showed that the lowest mean APE in these group were associated with Merz II (4.8%), Hadlock3 (5.6%), Hadlock4 (5.8%) formulae. Hart et al. [20] developed formula, which includes AC, HC, FL and also maternal weight. They showed that new formula compared to seven formulas allows to estimate better weight in macrosomic fetuses. Mean APE for Hart formula was 3.69%. Unfortunately, maternal weight during USG examination is not routinely asked, that is why we can not use these formula in our study. Also, appliance of 3D Schild formula could improve accuracy of estimation fetuses over 4000 g [5]. There is an evident problem with underestimation fetuses with ABW over 4000 g in our and others study [21].

For SGA babies the most accurate formula is Combs (MAPE = 7.72%). Our study confirms that nontargeted formulas have a tendency to overestimate the weight of SGA fetuses. The drawback of our study is lack of specific targeted formulas for SGA fetuses. Melamed et al. [22] shows that the best performing model is targeted model of Scott et al [23]. Although, Hadlock formulae reaches one of the highest accuracies in these study. The accuracy of fetal weight estimation is different in specific subgroups of SGA fetuses: early versus late SGA, asymmetric versus symmetric, and presence of Doppler abnormalities. Usefulness of Hadlock formulae was shown by Shen et al. [24]. These study reveals high sensitivity and high specificity of Hadlock formulae.

The most accurate formula for LGA is Warsof2 (MAPE = 7.06%), following formulae with the lowest MAPE are Hadlock3 (7.13%) and Hadlock2 (7.16%). The formula with the highest correlation between EFW and ABW is Ott (R = 0.537). Aviram et al. [25] shows that there is a wide variation in EFW formulas performance for detecting LGA. To the most accurate belong those, which contain abdominal circumference (AC), femur length (FL) and biparietal diameter (BD). Hadlock formulae have the lowest Euclidean distance. Rosati et al [26] claims that similarly to our study, Warsof2 formula is the most accurate (the lowest mean percentage error). These study shows the best ability to identify fetal macrosomia with formulas based only on abdominal measurement (Warsof2, Hadlock1, Campbell). There is a problem in understanding definitions of macrosomia [weight — (grams)] and large-for-gestational age (centile) in many studies.

CONCLUSIONS

Our study shows that various formulas have an impact of accuracy of estimated fetal weight in different weight ranges. Especially, when SGA or LGA is suspected. It is important to use different formulas, because it predicts better actual birth weight and helps in clinical decisions. In everyday clinical practice, median of absolute percentage error (MAPE) seems to be the easiest and the most useful parameter. To conclude, the most accurate formula for fetuses under 2500 g is Hadlock3, for fetuses between 2500 g and 4000 g is Ott, for fetuses above 4000 g is Hadlock3, for suspected SGA babies is Combs and for suspected LGA babies is Warsof2. In future, we could extend our work and

analyze fetal 3D ultrasonography. Every year, new formulae and technologies are introduced, however we can rely on accuracy of those we have known and used for years [27].

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Antenatal depression and anxiety in primiparous Polish mothers and fathers

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ABSTRACT

Objectives: Mood disturbances are the most prevalent mental health problems in expectant parents. The knowledge about the factors which increase the risk of perinatal depression is insufficient, especially in fathers. The aims of the present study were to estimate the prevalence and to compare mean levels of antenatal depression and anxiety as well as to examine the relationship between the risk for depression and anxiety in primiparous Polish parents.

Material and methods: 250 parental couples participating in antenatal classes took part in the study. Depression and anxiety were measured with the Edinburgh Postnatal Depression Scale (EPDS) and the State-Trait Anxiety Inventory (STAI), respectively. Paired t-test with bootstrapping was applied to compare parental EPDS, as well as STAI raw scores. Pearson correlation coefficients were calculated for depression and anxiety scores for women and men separately. The factors predictive for the increased risk of depression were investigated with the use of a multivariate logistic regression analysis.

Results: 10% of women and 4% of men were at risk of depression. High level of state anxiety was found in 7.7% of expectant mothers and 10% of fathers, whereas elevated state anxiety was found in 19% of both parents. EPDS scores correlated moderately with anxiety. The risk of depression was increased by state anxiety in the case of mothers and by trait anxiety in the case of fathers.

Conclusions: High level of anxiety increases the risk of antenatal depression. Both parents should be screened for depression and anxiety in the prenatal period.

Key words: antenatal depression; antenatal anxiety

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INTRODUCTION

While becoming a competent and sensitive caregiver involves a series of changes in many aspects of the new parents' lives, pregnancy is an adaptive time of psychological transformation and adjustment [1]. Transition to parenthood, however, is also a challenging period of disequilibrium and increased psychological distress [2, 3]. A vast body of research confirms the perinatal period as associated with heightened vulnerability to mental health concerns [4–8]. Depression and anxiety are widely recognized as the most prevalent mood disturbances in expectant and new mothers and fathers [5, 9, 10]. According to available data, perinatal depression affects approximately 10–23.8% of women and 2–10% of men, whereas up to 28% of mothers and 14% of fathers suffer from anxiety [9–13]. It is also known that maternal and paternal depression is significantly correlated. The increase in one parent's symptomatology corresponds with the worsening of the other partner's mental health [12, 14].

Despite a growing number of research in the field of perinatal psychopathology, prevalence and trajectories of antenatal depression and anxiety were investigated to a lesser extent as compared to parental postnatal mood disorders [13]. It was proved, however, that prenatal mental health difficulties are a predictor and a risk mechanism for the postnatal psychopathology [15–17]. This is of special clinical and public health importance, as impaired parental mental well-being during pregnancy is significantly associated with perinatal as well as long-term adversity. Numerous studies evidenced that maternal perinatal mood disorders may lead to such detrimental consequences as obstetric complications, postpartum mental health disorders, disturbances in mother-infant interactions and caregiving, alternations in child development and child developmental outcomes [9, 18–20].

The analogous knowledge about men is relatively less extended and partially inconsistent [14, 21]. Existing literature on antenatal emotional well-being in men documents

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that, similarly to maternal psychopathology, paternal perinatal depression is significantly associated with impaired fathers' parenting and father-child interactions, long-term psychological problems in children and emotional well-being of spouses [21–23]. However, the paternal vulnerability to depression and anxiety as well as the prevalence and course of mental health problems in perinatal period in men remain unclear. For instance, Teixeira and colleagues [9] found higher rates of depression and anxiety in mothers. Their study results also revealed different patterns of mood disturbances throughout pregnancy: decrease in depression and increase in anxiety in both mothers and fathers. Increase in anxiety was not confirmed by Leach and the team [5]. According to systematic review carried out by the researchers, paternal anxiety was common in perinatal period and remained stable across the pregnancy. Korja et al. [13], on the other hand, reported low levels of depression and anxiety symptoms during the whole pregnancy in both mothers and fathers as well as similar and not gender-specific trajectories of perinatal mood disturbances.

Regardless of gender differences, parental antenatal depression is a well-documented risk factor for postnatal depression. Multiple studies showed the continuity of mood disorders throughout the perinatal period in both mothers and fathers [15]. A large number of studies also confirmed the link between parental perinatal mood disorders and developmental abnormalities in children [24]. In some longitudinal studies antenatal maternal depression was found to be associated with child's difficult temperament in infancy [18, 25], emotional and behavioral problems in childhood [26], and mental health problems in adolescence [27]. According to publications from the Avon Longitudinal Study of Parents and Children (ALSPAC) maternal prenatal depression was linked to developmental delays in toddlers at 18 months of age [28], whereas paternal antenatal depression was associated with behavioral problems in 42-month-old children as well as with psychiatric diagnosis in 7-year-olds [22]. Additionally, the risk of developmental problems was higher when fathers were depressed both pre- and postnatally. Still, further investigation is needed to widen the knowledge about the factors predicting prenatal depression in both mothers and fathers.

Objectives of the current study

Perinatal mental health in parents, and especially in fathers, needs further exploration [14]. There is scarce research on the prevalence of antenatal mood disorders in the group of Polish primiparous parents. Thus, the aims of the present study were 1) to estimate the prevalence of antenatal depression and anxiety (state and trait) in both expectant mothers and fathers, 2) to compare mean levels of depression, state anxiety and trait anxiety between the sexes, and 3) to examine the relationship between the risk for antenatal depression and anxiety in the group of primiparous mothers as well as fathers. Additionally, models of variables, which could explain an increased risk for antenatal depression in mothers and fathers, were sought for.

MATERIAL AND METHODS

The subjects

Two hundred and fifty pairs of expectant parents (mothers and fathers) were invited to take part in the study. The inclusion criteria comprised: 24^{th}–37^{th} week of gestation, primiparity, no major pregnancy complications, participation in typical forms of antenatal education. All parents gave written informed consent for their participation. The study was conform to the Declaration of Helsinki.

Eventually, 229 women and 181 men who met the required criteria were enrolled. The participants were recruited over a period of 12 months via antenatal classes, which were organized at four different obstetric units in a capital city with the population of around 2 million. The sample consisted of subjects with predominantly higher education (at least Bachelor's degree in 91% of women and 80% of men), within an age range of 21 to 40 years in the case of women (M = 29, SD = 3.3.), and 23 to 42 years in the case of men (M = 30, SD = 3.55). The mean week of gestation was 30.47 (SD = 2.95), the median value was 31 weeks, whereas the minimum and the maximum values were, as assumed, 24 and 37 weeks, respectively. Around 40% of participants were examined during the spring/summer courses, whereas the remaining 60% during the autumn/winter courses.

Procedure and measures

Correlational study design was used. The subjects were asked to complete a set of questionnaires on a single occasion during the third trimester of pregnancy, after an antenatal class meeting. Depression and anxiety were measured with self-report questionnaires, the Edinburgh Postnatal Depression Scale (EPDS) [29] and the State-Trait Anxiety Inventory (STAI) [30], respectively. In addition, the subjects were also asked to complete a brief demographic survey with questions concerning their sex, age, education, socioeconomic status, obstetric factors (*e.g.* gestational age, previous history, etc.), their unborn baby's sex (if known), and the number of times the baby was seen on the ultrasound. The final task was writing a short description of the unborn child (up to 3–5 sentences). This was a qualitative part of the study and its results are not to be reported here.

Data analytical approach

Statistical analyses were conducted with IBM SPSS Statistics 24.0 (Predictive Solutions) and STATISTICA 13 (Statsoft). *Descriptive statistics* were used to describe the basic features of the data. Paired t-test with bootstrapping was

used to compare maternal and paternal EPDS, as well as STAI raw scores. As depression can be a seasonal phenomenon, the effect of the measurement timing (autumn/winter vs spring/summer) was controlled for. In addition, Pearson correlation coefficients were calculated for EPDS and STAI scores for women and men separately. A multivariate logistic regression analysis was undertaken to investigate the factors predictive for the increased risk of depression. Generalized Linear/ Nonlinear Model analysis in STATISTICA 13 was used, and specifically Binomial Linear Model with Logit link function. Backward stepwise procedure was used with 5% criterion of significance for adding, and 10% for removing a variable.

RESULTS

Increased risk of depression (EPDS score of 12 points and more) was observed in almost 10% of 229 women and 4% of 181 men who took part in the study. Complete data from both of the partners were obtained for 169 pairs. Out of these, in the case of 85.8% of couples neither of the partners had an elevated risk of depression, in 1.2% of couples both partners had an elevated risk of depression, in 10% of couples only the woman had an elevated risk of depression, and in 3% of couples increased risk of depression was observed in the man only. Significant differences were found between the raw scores of women and men in EPDS, with medium effect size ($p < 0.01$; Cohen's $d = 0.497$). No statistically significant results were found in EDPS scores of parents participating in summer versus winter courses (all ps > 0.05).

Table 1. Raw scores of depression risk (based on EPDS), state anxiety and trait anxiety (based on STAI). Results limited to pairs of parents for whom complete data from the questionnaires were obtained

	Expectant mothers n = 169			Expectant fathers n = 169		
	Mean	SD	Range	Mean	SD	Range
Risk of depression	7.16	3.47	0–19	4.484	3.435	0–19
State anxiety	34.73	8.502	19–66	34.286	8.04	17–58
Trait Anxiety	37.78	7.259	23–62	33.948	7.336	20–58

In the study, 4% of women and 4.7% of men had high scores of trait anxiety (at the level of 8-sten score or higher). High level of state anxiety was found in the case of 7.7% of women and almost 10% of men, whereas elevated state anxiety (7-sten score or higher) was found in as many as 19% of both expectant mothers and fathers. Although no statistically significant differences were found in the mean scores of state anxiety between women and men ($p > 0.05$), trait anxiety differentiated the two sexes, with higher raw scores in the case of women ($p < 0.01$; Cohen's $d = 0.355$, small effect size). No effects were found for participants of autumn/winter vs spring/summer courses (all ps > 0.05). Raw scores of EPDS and STAI in both parents are presented in Table 1, whereas the results of paired t-test with bootstrapping in Table 2.

As could be expected, there was a positive moderate correlation between EPDS scores and the level of both state and trait anxiety (Pearson's r for women: 0.525 and 0.54, respectively; Pearson's r for men: 0.555 and 0.632, respectively).

In the next step, a model of variables that could best explain a higher risk of depression, separately for expectant mothers and fathers, was sought for. The risk of depression was treated as a dichotomized variable with two values: "low risk" (EDPS score less than 12 points) and "high risk" (EDPS score equal to or higher than 12 points). The initial set of variables comprised: trait anxiety (raw score), state anxiety (raw score), parental level of education (Bachelor's degree or higher vs secondary education or lower), time of antenatal course (autumn/winter vs spring/summer). For women, the only variable left in the model was state anxiety. The model's goodness of fit was sufficient (Hosmer-Lemeshow test = 7.437, $p = 0.385$; AUC: 0.8145). Each point more in the state anxiety scale increased the risk of depression in women 1.2 times. In addition, having state anxiety at the level of 8 stens and more increased the risk of depression in women 16 times [OR = 16.24, 95% CI = (4.89, 53.88), $p < 0.001$].

As expectant fathers were concerned, the only variable left in the model was trait anxiety. Each point more in the trait anxiety scale seemed to increase the risk of depression in men 1.23 times. What is noteworthy, having trait anxiety at the level of 8 stens and more increased the risk of depression in men 38 times [OR = 38; 95% CI = (5.78, 249.84), $p < 0.001$].

Table 2. Paired t-test with bootstrapping to compare mean results of depression risk, trait anxiety and state anxiety in women and men from the couples under study

Variables		Mean difference	SD	Standard error	Significance (bilateral)	Confidence interval 95%	
						Lower endpoint	Upper endpoint
Pair 1	Risk of depression_M - Risk of depression_F	2,571	-0.00720	0.41427	0.001	1.69514	3.33117
Pair 2	Trait Anxiety_M – Trait Anxiety_F	3,831	0.01748	0.83965	0.001	2.14935	5.44073
Pair 3	State Anxiety_M – State Anxiety_F	0.442	-0.02652	0.89348	0.620	-1.39577	2.10390

M — mother; F — father

AUC value for this model was 0.833, which can be interpreted in terms of a relatively good efficiency of the model to predict low vs high risk of depression in men. At the same time Hosemer-Lemeshow test statistic turned out to be significant ($p < 0.05$), which may indicate that there might be other models, better fitted to the data. Therefore, the results of our model building should be treated with caution.

DISCUSSION

Depression and anxiety are known to be the most common antenatal mental health issues in both mothers and fathers, even though differences have been found in the prevalence of depression and anxiety symptoms depending on ethnic background, parity, or trimester of pregnancy [6–8]. Our results are consistent with a vast body of research, which points to higher levels of depression in expectant mothers as compared to expectant fathers [9]. However, our results are only partially in line with some studies [16], which evidenced mothers as presenting higher ratings of antenatal anxiety. In our study sample differences were found only in the case of trait anxiety. Parents did not differ in the state anxiety level. What is more, gender differences were found in the type of anxiety predictive for antenatal depression. While the state anxiety turned out to be a predictor of maternal depression, the trait anxiety significantly increased the risk of depression in fathers. It can be hypothesized that although preparing for parenthood and the upcoming delivery is stressful for both parents, the anxiety related to pregnancy and childbirth may have greater impact on vulnerability to depression in mothers than fathers. The increased level of anxiety, especially in the last trimester of pregnancy, is often described as a physiological and adaptive phenomenon, as it helps parents to reduce fantasies about the "imagined baby" [2]. Solicitude for and the concentration on the child's health and safe delivery facilitate parental preparations for meeting the real newborn. It can be presumed, however, that the very high level of state anxiety lacks its adaptive functions in mothers and puts them, and thus their expected and new-born babies, at the risk of maladaptation. Fathers, on the other hand, seem to be prone to depression more due to their personality-based predisposition to anxiety. This phenomenon needs further investigation. Quantitative measures of anxiety do not answer the question of the sources and gender-specific themes of parental concerns. Including more complex and qualitative methods to the future research could be beneficial for looking into the specificity of and gender differences in parental antenatal anxiety.

In light of our results, mood disturbances in the last trimester of pregnancy are common among primiparous Polish parents. What is especially surprising, the prevalence of the elevated level of anxiety in both parents turned out to be higher than the prevalence of the risk of depression, which is alarming. Additionally, anxiety (state or trait, depending on the parent's gender) turned out to be a significant risk factor for depression. This points to the strong need to introduce screenings not only for depression, but also for anxiety during the antenatal period. This recommendation is especially noteworthy in light of some studies which indicate that detrimental effects of prenatal depression increase when coupled with anxiety [18, 24]. Our study also reaffirm the notion that an antenatal screening for both depression and anxiety should include fathers. The importance of taking paternal antenatal mental health seriously into account is emphasized by the study of Paulson and colleagues [14], who found stable patterns of occurrence and severity of depressive symptoms between the 3rd trimester and the 6-month postpartum in both mothers and fathers. Additionally, paternal prenatal depression was found to be predictive for worsening maternal emotional well-being [14] and for future developmental problems, including emotional-behavioral difficulties and psychiatric diagnoses in children [22].

A question arises as to the tools used for screening purposes. The Edinburgh Postnatal Depression Scale is commonly implemented in clinical practice as the only screening tool for mood disturbances with the assumption that the anxiety subscale can be distinguished in the total score. However, the specificity of symptoms as well as the pathophysiology of depression and anxiety remain distinct and thus should be examined independently, as recommended in numerous studies on perinatal mental health [13, 31, 32]. The analysis conducted by Brouwers, van Baar and Pop [33] also showed that EPDS anxiety subscale did not measure anxiety accurately. Our results add to this standpoint, as it turned out that different anxiety types are the risk factors for depression depending on parental gender.

Results of our study should be treated with caution due to numerous limitations. First of all, the sample is not representative for Polish primiparous parents as more than 80% of participants had higher education. This was unexpected as all subjects were recruited via antenatal classes, which were free of charge and open to all expectant parents who inhabited the city. It remains unclear whether well-educated parents predominated among the participants of the classes or less educated parents were not interested in participating in the study.

Secondly, gender differences in anxiety found in our study point to the problem of the gender adequacy of tools used to screen for depression in men. Paternal symptoms of perinatal depression have been far less investigated, but it is known that the manifestation of depression differs between the sexes [34]. EPDS, used in the present study, was originally created to assess maternal perinatal mood [29]. Thus, a gender-specific tool, such as The Perinatal Assessment of Paternal Affectivity (PAPA) [35] — a new self-report screening for affective symptoms in fathers during the perinatal period,

would be more proper to assess depression in fathers. This tool, however, is yet in the process of Polish adaptation.

CONCLUSIONS

Anxiety and depression are common mood disturbances among primiparous Polish parents. High level of anxiety increases the risk of depression in both mothers and fathers. There is a strong need to screen for depression and anxiety in both parents in the prenatal period.

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Small invasive technique of Internal Iliac Artery ligation for postpartum haemorrhage

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ABSTRACT:

Objectives: Internal Iliac artery ligation (IIAL) is an effective life-saving method to control obstetric hemorrhage, and a hysterectomy can often be avoided. A standard ligation procedure requires wide tissues dissection: incision in the peritoneum lateral to and parallel with the ureter. That can be traumatic and is difficult in practice what results in a rare use of IIAL in surgical emergency. As an alternative a novel, small invasive technique was used, which protocol is attached to the paper as a video presentation file.

Material and methods: Forty-five women treated by Internal Iliac Artery ligation for postpartum haemorrhage. In 27 patients (Cohort A) standard IIAL procedure by Kelly's method was used. In the remaining 18 patients (Cohort B) a novel, small invasive technique was performed. Time of both surgical procedures of IIAL was measured.

Results: Time of Standard technique of IIAL vs Novel small invasive technique of IIAL: 34 (26–41) min. vs 13 (8–16) min. $p < 0.001$.

Conclusions: The presented novel small invasive technique of Internal Iliac artery ligation can be an easier and safe alternative for standard ligation procedure.

Key words: postpartum hemorrhage; surgery; internal iliac artery

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INTRODUCTION

Internal iliac artery ligation (IIAL) has been a valued method of treating postpartum haemorrhage saving women's fertility [1]. IIAL is an effective life-saving method to control obstetric hemorrhage, and a hysterectomy can often be avoided [2]. Even in the most catastrophic situations, rapid alternatives to hysterectomy are needed for women wishing to preserve their reproductive potential [3, 4]. It has proven that IIAL does not affect the activity of the pelvis minor's organs or fertility and that late complications seem to occur rarely [5, 6]. Complications that may occur include changes in the ovarian blood flow and the loss of ovarian reserve [7]. Kelly H. performed hypogastric artery ligation to control bleeding from pelvic cancer in 1894 [8]. In the modern era, Kellys's technique evolves, but is still considered as a standard. A standard ligation procedure requires wide tissues dissection: incision in the peritoneum lateral to and parallel with the ureter. The bifurcation of the common iliac artery needs to be located in a triangle composed by the infundibulopelvic ligament, the lateral side of the uterus and the ureter [8]. Unfortunately, that procedure can be traumatic and is difficult in practice. That results in the rare use of IIAL in the obstetric wards. As an alternative, the manuscript present the author's own technique which can be it easier for the physicians to learn.

Objectives

Manuscript present a novel, small invasive technique of IIAL for postpartum haemorrhage, with comparison to a standard technique.

MATERIAL AND METHODS

We conducted a prospective cohort study. The study group consisted of 45 women treated by Internal Iliac Artery ligation (IIAL) for postpartum haemorrhage, due to the protocol of Royal College of Obstetricians and Gynaecologists Green-top no. 52 Guideline [9]. In 27 patients (Cohort A) standard IIAL procedure by Kelly's method [8] was used. In the remaining 18 patients (Cohort B) a novel, small invasive technique was performed by the own author's protocol, attached to this manuscript as video presentation. The description of the presented novel protocol is as follows:

1.0 Laparotomy

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1.1 Use the suprapubic transverse surgical incision into the abdominal cavity
2.0 Uterus elevation
2.1 By hand, elevate an uterine Corpus
2.2 Use the traction in the direction of pubic symphysis
2.3 Move up the intestine from the Douglas space
3.0 Identification of anatomical structures of extraperitoneal space of the pelvic minor
3.1 Lateral to the promontory, identify common internal artery
3.2 Follow down to the bifurcation of the common iliac artery
3.3 Lateral to the bifurcation of the common iliac artery find the external iliac artery
3.4 Medially to the bifurcation of the common iliac artery find the internal iliac artery
3.5 Across in front of the common iliac artery identify the ureter
3.6 Ureter pass down posteroinferiorly on the lateral wall of the pelvis and then curve anteromedially to enter the bladder
4.0 Incision of peritoneum
4.1 With the use of tweezers, elevate peritoneum directly above internal iliac artery 2 cm below bifurcation
4.2 Cut the elevated peritoneum with scissors in a transverse direction to the artery
5.0 Preparation of the internal iliac artery
5.1 With the use of Tupfer clean, longitudinal the anterior wall of the internal iliac artery on 2 cm long
6.0 Dissection of the internal iliac artery and the iliac vein
6.1 With the use of blunt dissector separate artery from the vein
6.2 Move the branches of the dissector forward artery bilateral to the wall of artery
6.3 Avoid touching of the vein
6.4 During that maneuver gently elevate the artery
6.5 Repeat it until the artery is completely separated from the vein
7.0 Ligation of the internal iliac artery
7.1 Insert absorbable suture and ligate the internal iliac artery

In order to apply a uniform surgical procedure all the surgeries were performed by the same team using a surgical protocol by Kelly [8] (Cochort A), and own author's one (Cochort B). Time of both surgical procedures of IIAL was measured. All the study participants provided written inform consent. The protocol was acknowledged by the University of Rzeszow Bioethics Committee. The analysis of the convergence of features was made by the chi-squared test. The level of $p < 0.05$ was considered statistically significant.

RESULTS

The results are shown in Table 1.

Table 1. Comparsion of the time of the procedure of standard internal iliac artery ligation and the novel small invasive technique

Analysed	Number of procedures	Time of procedure (min.) [Mediana/95% CI]	P
Standard technique of IIAL	27	34 26–41	< 0.001
Novel small invasive technique of IIAL	18	13 8–16	

DISCUSSION

The effectiveness assessment of IIAL in postpartum haemorrhage treatment is high [9]. However, in practice the use of this technique in obstetrics departments is low [10]. The main reason for the rare implementation of IIAL in the treatment of postpartum haemorrhage is a rather difficult surgery technique with fear of iatrogenic damage to the iliac vessels or the ureter. The presented innovative technique, based on the preparation of the iliac arteries and ureters from access directly on the posterior-lateral wall of the pelvis minor presents an interesting alternative to the classic technique described by Kelly [8]. Especially in cases of bleeding following Cesarean sections, haematomas in parametria are quite frequent, which significantly hinders IIAL using the classic Kelly technique, even for experienced surgeons. The innovative technique presented in this article gets around this problem. Due to the lack of loose connective tissue under the peritoneum of the posterior-lateral wall of the pelvis minor, this area is almost always free from haematomas, which facilitates the identification of anatomical structures, even in difficult situations. The paper proves that presented innovative technique of IIAL allows for a significant reduction in the time of the procedure. In the examined group of 18 women who underwent surgery using the presented innovative own technique and 27 women who underwent surgery using the traditional Kelly technique, the surgeries were performed by the same surgical team. The average time of the surgical procedure after opening the abdominal cavity until occlusion of the internal iliac artery was on average 13 min. vs 34 min. ($p < 0.001$). This indirectly proves the significant simplification of the technique, which makes it easier for the physicians to learn. The weak point of this study was the small study group size, but in the presented innovative own technique of IIAL, despite from the technical simplification, the essential element is the effect of the procedure shortening. In women undergoing the IIAL procedure, usually due to substantial earlier blood loss, haemostatic disorders occur during the surgery [11]. In such cases, along with the reduction in the time of medical procedures, the chances for patients' recovery improves.

CONCLUSIONS

The presented novel small invasive technique of the Internal Iliac artery ligation can be an easier and safe alternative for standard ligation procedure.

Attachment

Video presentation file available on *https://journals.viamedica.pl/ginekologia_polska*

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Human papilloma virus-related premalignant and malignant lesions of the cervix and anogenital tract in immunocompromised women

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ABSTRACT

The number of immunocompromised patients is rising, and immunodeficiency is an independent risk factor for the development of premalignant and malignant lesions of the cervix and anogenital tract. The aim of this review was to summarize and update data on human papilloma virus (HPV) infections and HPV-based anogenital lesions detected in patients who were immunocompromised due to both organ transplantation and human immunodeficiency virus (HIV) infection. The incidence of HPV infections among solid organ recipients and HIV positive females is reported to be significantly higher when compared with age-matched healthy controls- i.e. higher by up to 65% and 46.6% respectively, vs 38% in the controls. These infections are also more often chronic, high risk HPV and multitype. Data suggest that HPV infections in these patients might not only occur more frequently, but that the course of the infection might also lead to faster oncogenesis. However, the treatment options for malignancies are limited; and this implies the need for intense primary and secondary prevention regimens. As infections with HPV types other than 16 and 18 and multitype infections are particularly frequently discovered in immunocompromised patients, they would probably benefit most from a nonavalent vaccine. Gynecological screening should be performed annually, including cervical smears and/ or HPV testing. In the group of non-responders, self-sampling methods should be considered.

Key words: HPV; human papilloma virus; immunocompromise; HIV; transplantation; malignancy

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INTRODUCTION

For years, the greatest concern regarding patients treated with transplantation for end-stage organ failure was to sustain the graft function in order to lengthen patients' life expectancy. Nowadays, solid organ rejections are successfully prevented with maintenance treatment based on combinations of immunosuppressive drugs such as calcineurin inhibitors (cyclosporine, tacrolimus), corticosteroids and adjuvant drugs (mycophenolate mofetil, azathioprine or mammalian target of rapamycin-mTOR inhibitors *e.g.*, sirolimus, everolimus) thus improving patients' survival rates. Recent clinical observations indicate that life expectancy depends more on factors secondary to life-long immunosuppressive therapy and the increasing age of this transplant population, such as cardiovascular diseases or malignancies, and especially those driven by viral infections. It is estimated that in the next decade, mortality due to malignancies will exceed that from cardiovascular diseases in the population of renal transplant recipients [1].

Immunodeficiency is a well-established risk factor for developing *human papilloma virus* (HPV)-related premalignant and malignant lesions of the lower genital tract and anogenital region [2, 3]. HPV infections are frequently observed in the general population, with up to 80% of women reported as experiencing such infections during their lifetime. These infections are however usually transient, and authors estimate that about 70% of immunocompetent individuals are clear of the infection within 12 months, and 91% are clear within 24 months, with the mean duration of the infection between 8 and 13 months [4]. On the other hand, immunocompromised patients are prone to experiencing chronic HPV infections, and the reasons for this persistence are not fully understood.

Immunodeficiency (immunosuppression or immunocompromise) results from any of three main reasons: viral

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infections as in *human immunodeficiency virus* (HIV) positive patients or in patients with acquired immune deficiency syndrome (AIDS); from the use of immunosuppressive drugs by such as solid organ transplant recipients (*e.g.*, renal transplant recipients (RTRs), or liver transplant recipients (LTRs) and/or in patients with connective tissue diseases (*e.g.*, systemic lupus erythematosus, or systemic scleroderma); and also in rare cases of primary immunodeficiency disease. Immunodeficiency in both HIV/AIDS patients and solid organ recipients was proved to be an independent risk factor for developing various malignancies, including HPV-related malignancies [2]. Buell et al. [1] estimated that after 10 years of immunosuppression, the risk of malignancy reaches 20%, which is three- to fivefold higher than in the general population.

Hinten et al. [5], in a review published in 2012, analyzed HPV-related premalignant and malignant lesions of the female anogenital tract in RTRs. In our mini-review, we aimed to combine and update data on HPV infections and HPV-based anogenital lesions detected in immunocompromised patients due to both organ transplantation and HIV infection. To do this, we searched the PubMed database looking for information on "human papilloma virus" or "HPV" and "immunosuppression" or "immunodeficiency" or "transplantation" or "HIV" and "cancer" or "malignancy" or "neoplasia". References included in the articles thus retrieved were also reviewed to identify further articles corresponding with our analysis topic.

HUMAN PAPILLOMA VIRUS (HPV)

Over 200 types of HPV have been discovered so far; and we distinguish between cutaneous subtypes connected with the formation of verrucae and mucosal subtypes that are mostly responsible for the development of lesions in the anogenital region. The latter are further divided into low-risk HPV subtypes (lrHPV: 6, 11, 27, 32, 42, 53, 54, 57, 61, 62, 69, 71, 72, 81, 83, 84, 86, 87, 89, 90, 102, 106), high-risk HPV subtypes (hrHPV: 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66), and HPV subtypes of unknown risk (subtypes 26, 30, 34, 53, 67, 68, 69, 70, 73, 82, 85 and 97) that are further investigated to assess their oncogenic potential and that are usually considered to be potentially high-risk subtypes [6].

The most-studied subtypes that are linked with the creation of anogenital malignancies are hrHPV types 16 and 18, and they are said to be responsible for approximately 70% of cervical cancers and precancerous lesions [7]. Another 20% of cervical cancers are related to hrHPV types 31, 33, 35, 45, 52 and 58 [8]. Studies have shown that HIV infection might influence the carcinogenicity of hrHPV types and therefore, the detection rates of invasive cervical carcinoma attributable to HPV 16 might be lower in HIV-positive females, with concomitantly higher detection rates of cancers attributable to HPV 18. Some authors have claimed that acquisition of HPV 16 is less affected by the CD4 cell count than the acquisition of other hrHPV types; and this might indicate the existence of mechanisms that enable HPV 16 to avoid immune surveillance, and as such, it is something that requires further investigation [8].

INCIDENCE

The incidence of HPV infections among both solid organ recipients and HIV-positive females are reported to be significantly higher than among age-matched healthy controls: up to 65% and up to 46.6% vs 38% respectively [9, 10]. The infections are also more often hrHPV and multitype infections. Data suggest that HPV infections in these patients might not only occur more frequently, but that their course might also lead to faster oncogenesis [11]. It was proved in a study by Adebamowo et al., that HIV-positive females, when compared with HIV-negative subjects presented a significantly higher prevalence of lrHPV and hrHPV and a persistence of hrHPV [12]. These findings are supported by those of the meta-analysis by Looker et al., which proved that in the presence of HIV infection, the risk of HPV acquisition doubles, and for clearance halves, especially with a decline in the CD 4 cell count. A threatening observation is that similarly to other sexually transmitted diseases, HPV infection itself may promote the acquisition of HIV infection [7].

However, some authors found the prevalence of hrHPV infections and genital malignancies to be similar to that in healthy age-matched controls [13, 14] (Tab. 1).

Table 1. High-risk HPV prevalence

Article	Year		Reason for immunocompromise	Number of patients included	hrHPV detected	Most common hrHPV subtype
Adebamowo et al. [12]	2017	original	HIV +	427 (baseline) 321 (after 6 months)	124 (29%) 51 (15.9%) respectively	Type 52 (8.9%/ 5.5%) Type 35 (7.0%/4.4%)
Pietrzak et al. [13]	2012	original	RTRs	60	11 (15%)	—
Origoni et al. [14]	2011	original	RTRs/R&PTRs	48	10.5– 27.7 over 10 years of observation	—
Roensbo et al. [27]	2018	original	RTRs, BMTRs	60	15% (29.4%– BMTRs, 9.3% RTRs)	Type 45 (3.3%)

hrHPV — high risk human papilloma virus; RTRs — renal transplant recipients; R&PTRs — renal and pancreas transplant recipients; BMTR — bone marrow transplant recipients

Another important set of findings that often characterizes HPV, is that in immunodeficient females the related anogenital malignancies are multifocal, and that they may develop synchronously or metachronously. It has recently been suggested that multifocality in these patients might be due to repetitive independent infections with various HPV types. This thesis is supported by the fact that in contrast to the general population, in which such multifocal lesions usually contain identical HPV types, in immunocompromised females, multiple types of HPV are often detected, even including types that are not usually specific for high-grade lesions and the types may vary from lesion to lesion within the same person [11, 15]. Varying hrHPV subtypes between different lesions were reported in 57.1% of patients by Meeuwis et al. [11].

HPV PERSISTENCE

Persistent hrHPV infection is a factor that is necessary for the development and maintenance of dysplastic lesions and their further progression to becoming invasive anogenital cancers [16]. Studies with immunocompromised females show that these chronic infections are partially linked to viral latency. Studies on HIV-positive females have shown a significantly reduced likelihood of HPV infection being cleared when compared with HIV-negative patients; however not all the studies indicating this achieved sufficient statistical significance to make the findings conclusive [17].

Some studies suggest that in HIV-positive patients, there are additional factors, apart from immunosuppression, that contribute to the increased prevalence and persistence of HPV infections. This might be due to direct interactions of the viral genes of HIV and HPV or to changes in reactions of the cytokines in cervical mucus to HPV [12].

RISK FACTORS

The risk for developing malignancies is said to be linked to the dose and duration of immunosuppression treatments [1]. However, some authors suggest that the intensity of a specific immunosuppression treatment might constitute a more important factor in oncogenesis than cumulative doses [18]. A recently published study by Mazanowska et al. [19] suggests that an hrHPV infection's prevalence might also be influenced by the type of immunosuppressants administered. For instance, RTRs treated with mammalian target of rapamycin (mTOR) inhibitors may be less prone to developing cervical cancer than those on regimens that lack these drugs. Therefore, some authors state that graft recipients who are at a particularly high risk of developing malignancies could benefit from including mTOR inhibitors in their therapy [19]. The connection between the use of certain immunosuppressive drugs and the development of malignancies was also studied by Madeleine et al. [20].

LESIONS OF THE CERVIX

Infection with hrHPV is a necessary factor in the development of cervical intraepithelial neoplasia (CIN) and cervical cancer in both immunocompetent and immunocompromised individuals: the hrHPV incidence in squamous cell carcinoma (SCC) of the cervix is reported to be 100%. While the incidence of CIN in RTRs is shown to increase 2- to 14-fold, the incidence of invasive cervical cancer in RTRs, which was previously 3-to-5 times higher than in the general population, is now comparable, due to the implementation of early screening [3, 11].

The progression of abnormal cervical cytology in immunosuppressed females is observed to be more rapid than in healthy controls, while the regression rates in RTRs are significantly lower than in the general population. Tanaka et al. [21] reported 0% spontaneous regressions of CIN 1 and CIN2 in RTRs compared with 68% and 52% respectively in controls.

AIDS patients are defined as individuals who are HIV positive and have either a CD4 cell count below 200/μL and/or an AIDS-defining disease, and in 1993, cervical cancer became one such disease.

The prevalence of CIN among HIV-positive patients is estimated at about 20–40% compared with 3% in the general population [22]. Since 2008, British guidelines recommend offering an HIV test to all patients diagnosed with CIN2 or above.

Data on associations between the risk of developing cervical cancer and levels of immunosuppression as determined by the CD4 cell count, are inconclusive, as some authors observed an increased risk in patients with a lower CD4 cell count and others noted no such relation [23, 24].

The influence of highly active antiretroviral therapy (HAART) on HPV-related malignancies and HPV infection itself is also a matter of controversy. Some authors have reported an increased chance of regression of CIN and clearing of HPV infections other than types 16 and 18, while others observed no such correlation [10, 23].

VULVAR LESIONS

Histopathologically, most invasive vulvar cancers are squamous cell carcinomas (SCC). Together with SCC's preinvasive precursor, vulvar intraepithelial neoplasia (VIN), it may be derived either from an HPV-dependent pathway, or from an independent pathway. Unlike premalignant and malignant lesions of the cervix that are always connected with an hrHPV infection, and premalignant and malignant lesions of the anus in which the hrHPV infection rate is also very high, most vulvar SCC and VIN in the general population are hrHPV-free and are observed in women in their 70s, while HPV-positive vulvar lesions are less common (20–57%) and are observed more frequently among younger females. In contrast, the majority of vulvar SCC and VIN discovered among immunocompromised females are hrHPV-related;

and studies show that these might constitute up to 100% of cases. In this group of patients, the woman's age when vulvar cancer is diagnosed, is significantly lower than in healthy controls: approximately 40 years old; and this is a result of an HPV-dependent etiology [9, 11].

In a study by Meeuwis et al. [3], a 50-fold increased risk for developing vulvar SCC was detected in a cohort of RTRs. The study found that the most common HPV types in vulvar lesions in both immunocompetent and immunocompromised patients were type 16 (60% vs 50% respectively) and 33 (20% vs 17% respectively), while the other types described in vulvar lesions in the general population are 18, 52 and 58. Type 58 also occurred in 17% of the vulvar neoplasms of RTRs in the cohort studied by Meeuwis et al. [11]. Studies have shown that vulvar cancer usually develops between 10- and 20-years following transplantation, which might suggest that its development requires prolonged HPV infection [5].

A meta-analysis study by Grulich et al., comparing the incidence of malignancies between population of HIV/AIDS patients and solid organ recipients, suggested there is a higher risk of developing vulvar cancer in the latter population [2].

Interestingly, the incidence of VIN (but not invasive vulvar cancer) and anal intraepithelial neoplasia (AIN) in organ recipients was observed as increasing in patients who had received a transplant for the second time. The authors also noted a significant rise in the incidence of vulvar cancer in pancreas transplant recipients [20].

VAGINAL LESIONS

The number of vaginal intraepithelial neoplasia (VaIN) is observed to increase. These lesions are often diagnosed simultaneously to VIN and CIN [3].

ANAL LESIONS

Most anal cancers, in both immunocompetent and immunocompromised patients, are SCC. AIN is similar to CIN. Mostly, both invasive and preinvasive anal lesions are HPV-dependent; and therefore, immunocompromised patients are also at a higher risk of their development. In the general population, anal cancer constitutes about 1.5% of cancers, while in the cohort of RTRs studied by Meeuwis et al. [11], the increased risk of this cancer was estimated to be approximately 122-fold. Studies show that risk factors for developing anal cancer are anoreceptive intercourse, previous diagnosis of an HPV-related cervical or vulvar cancer, and condylomata acuminata.

The detection rate for HPV infections in invasive anal cancer is 71–92.2% in the general population [11]. HPV subtype 16 is the most prevalent, and is detected in 66.7% of patients, followed in prevalence by subtypes 18 and 33.

HIV-positive females are said to have a 35-fold higher chance of developing anal cancer when compared with HIV-negative controls. Also, in a meta-analysis by Grulich et al. [2], HIV/AIDS patients proved to be at a significantly higher risk of developing anal cancer when compared with subjects who were immunosuppressed because of solid organ transplantation.

Furthermore, a higher risk of developing anal high grade squamous intraepithelial lesions (HSIL) was observed in HIV positive patients who had undergone solid organ transplantation, regardless of the organ type transplanted or use of T cell depleting medications. No further studies have yet been performed on this group of patients [25].

PRIMARY PREVENTION

As the incidence of HPV infections, and the overall risk of developing HPV-related premalignant and malignant lesions of the anogenital region in immunocompromised females increases, actions should be taken in order to prevent these infections. Patients should be educated on anogenital cancer risk factors and vaccination should be recommended. The effectiveness of vaccination in anogenital cancer prevention in the general population is already well-proven. However, there is limited data on HPV vaccines in immunosuppressed females. The safety and immunogenicity of these vaccinations have already been proved in the population of HIV-1 infected women [26]. Further research is needed to determine whether vaccine-induced immunity against HPV persists in immunocompromised patients in contrast to vaccine-induced hepatitis B immunity which has been reported as declining over time in this group of patients [5]. Recently published data by Cespedes et al., on the response of HIV-1 positive females to a quadrivalent HPV vaccine, are promising. The data suggest that despite the gradual decline in antibody titers, seropositivity was sustained until 72 weeks post-vaccination for all subtypes except for type 18, in a cohort of patients with CD4 $\leq$ 200 cells/mm^3 [6].

Moreover, it is worth noting that as infections with hrHPV types other than subtype 16 and 18 and multitype infections are both discovered particularly frequently in immunocompromised patients, these patients would probably benefit most from the nonavalent vaccine against types 6, 11, 16, 18, 31, 33, 45, 52 and 58 that was approved in 2014 [27]. In a study by Cespedes et al. [6], the nine hrHPV types listed above accounted for 63% of cervical and 64% of anal HPV types detected.

Studies have also been conducted to assess the therapeutic effectiveness of HPV vaccinations in the population of immunosuppressed patients [28].

SECONDARY PREVENTION

Despite a lack of hard evidence, but due to a generally accepted increase in the prevalence of hrHPV infections and the higher risk of developing anogenital malignancies in

immunosuppressed females, both the American Society of Transplantation (in 2000) and the Expert Group on Renal Transplantation (in 2002), recommended annual cervical cancer screening, including Pap smears and pelvic examinations in this group of patients [29, 30]. According to the literature, insufficient annual screenings are being carried out: Kerkhoff et al. [31] described an overall 16% uptake of annual screenings in the Republic of Ireland and that in 26% of RTRs there was no screening at all. Similarly, in the Northern Ireland study by Courtney et al. [32], the overall uptake was 10% and 32% of RTRs had no screening. The uptake of cervical screening in underprivileged countries is clearly even lower. Nega et al. [28] reported a 10% lifetime uptake of cervical screening in Ethiopia among HIV positive females, and 93.4% of those were only screened after the diagnosis of HIV.

Some authors proclaim postponing the implementation of annual screenings until approximately 3 years following transplantation in patients with a normal pretransplantation screening result because most malignancies are detected several years after transplantation (*e.g.*, according to Meeuwis et al. [3], detection is 9 years after RT). This matter requires further investigation.

SELF-SAMPLING

As the participation of immunocompromised patients in gynecological screening has proved to be low, despite recommendations for annual checkups, a novel method of HPV testing based on self-sampling was recently introduced in order to increase the detection of anogenital malignancies. It has been shown that giving nonresponders the opportunity to self-collect the specimen for hrHPV testing has increased their willingness to participate in the screening program. Various self-collection devices were tested, such as tampons, brushes, lavages and swabs. While tampons seem to be the most preferred device (probably as patients are most familiar with them) according to some authors, the self-collection device most researchers recommend is the cervicovaginal brush. These latter have proved to be well-accepted by females, have demonstrated a greater sensitivity for CIN detection than swabs, require less processing than tampons, may be transported and stored in a dry state, in contrast to lavages, and may therefore be delivered by mail, thus expanding the participation possibilities for screening programs [33]. It was proved that the sensitivity of self-collected vaginal samples is comparable with that of cervical samples [34].

TREATMENT

When diagnosing a malignancy in an immunocompromised patient, healthcare providers face additional factors that need to be taken into consideration when planning a therapy. In solid organ recipients the possible therapeutic options are greatly influenced by the need to preserve the graft's function. This relates mostly to surgery and radiotherapy. The location of graft in the pelvis, especially in RTRs, limits both the possibility of radical surgery with extensive lymphadenectomy and of radiotherapy [35]. For these reasons, oncologic treatment of solid organ recipients often has to be limited and therefore, mortality rates among invasive cancer cases are high. This latter emphasizes the need for primary and secondary prevention that enable early stage detection of the malignancy.

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Epidemiology, prevention and management of early postpartum hemorrhage — a systematic review

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ABSTRACT

Early Postpartum Hemorrhage (EPH) is one of the leading causes of postpartum mortality. It is defined as blood loss of at least 500 mL after vaginal or 1000 mL following cesarean delivery within 24 hours postpartum. The following paper includes literature review aimed to estimate the incidence and predictors of early postpartum hemorrhage (EPH). Available prevention and treatment methods were also assessed. The inclusion criteria for the study were met by 52 studies.

The exact frequency of EPH in different populations varies from 1.2% to 12.5%. Maternal, pregnancy-associated, labor-correlated and sociodemographic risk factors seem to be important predictors of EPH. In these cases appropriate prophylaxis should be considered. However, EPH may occur without previous risk factors. The main reason for EPH is uterine atony which contributes to up to 80% of cases of postpartum hemorrhage (PPH). Other common reasons for PPH include genital tract injuries, placenta accreta or coagulopathies. Interestingly, the majority of uterotonics seem to have a similar effect. However, carbetocin seems to be the most effective in certain situations.

Appropriate diagnosis of EPH is the most important issue. The treatment should be causative. The first-line treatment should include uterotonics. Surgical interventions, if required, should be performed without delay, although preoperative uterine tamponade should be considered due to its high effectiveness.

Medical staff training in medical simulation centers is an important factor that improves the outcomes of EPH treatment. It provides adaptation to hospital protocols, team work improvement, self-confidence building, more accurate blood loss evaluation and reduced perception of stress. The implementation of systematic trainings provides better outcomes in the future.

Key words: postpartum hemorrhage; delivery; perinatology; medical simulation

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INTRODUCTION

Early postpartum hemorrhage (EPH) is usually defined as blood loss of at least 500 mL following vaginal delivery (VD) or 1000 mL following a cesarean section (CS) within 24 hours postpartum [1–3]. Late postpartum hemorrhage (LPH) occurs after 24 hours following labor and complicates 0.23% of deliveries. According to the American College of Obstetricians and Gynecologists, EPH may be recognized with the presence of signs of hypovolemia within 24 hours after delivery [4]. EPH may be divided into minor (500–1000 mL), moderate (1001–2000 mL) and severe (> 2000 mL) [3]. This complication significantly impacts global women's health as the most frequent reason for perinatal deaths all over the world [2].

The volume of blood loss is usually estimated visually. However, this method is connected with a high possibility of error. The underestimation occurs in 30 to 50% if it is only visual [1]. To make the assessment more objective it is highly advisable to count utilized medical materials, such as surgical towels and drapes. Estimating weight difference of dry unused materials and those soaked with blood seems to be another effective method. Using a calibrated collector bag is also recommended for a more accurate blood loss estimation. Gravimetric blood loss measurement includes weighing bags after delivery [5]. Modified Brecher`s formula consists in hemoglobin measurement after delivery which makes the evaluation more accurate.

Undiagnosed abnormal postpartum blood loss (UPPBL) is defined as decrease in hemoglobin level of at least 2 g/dL without any symptoms or signs of EPH [6]. Apart from an increased risk of maternal mortality (12 to 17.2%) EPH may lead to further serious complications related to severe

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anemia, such as acute kidney injury (29.3%), hepatic failure, Sheehan Syndrome, adult respiratory distress syndrome (24.6%) and disseminated intravascular coagulopathy (DIC) (11.7%) [2].

The following paper includes a literature review of recent studies regarding PPH. The main aim of the study was to estimate the incidence and predictors of EPH. Available prevention and treatment methods of EPH were also assessed.

MATERIAL AND METHODS

The authors searched PubMed database for articles concerning postpartum hemorrhage published from June 2014 to April 2019. Searching with 'postpartum hemorrhage' query revealed 186 original studies. The inclusion criteria for the study were: a uniform definition of EPH (blood loss of at least 500 mL after VD or 1000 mL following CS within 24 hours postpartum), a study group ≥ 250 patients and the English language of the manuscripts. 52 studies met the inclusion criteria (Fig. 1).

RESULTS

According to the WHO postpartum hemorrhage is one of the leading reasons for postpartum mortality, especially in developing countries of Asia (30.8%) and Africa (33.9%). Conversely, in developed countries the average mortality rate was estimated to 13.4% of all PPHs (1.2–49.6%). The exact frequency of EPH in different populations is shown in Table 1 [6–10] and varies from 0.4% to 33%.

Etiology

The leading cause of EPH is uterine atony which contributes 60 to 80% of those complications and 20–30% of mothers' deaths [10]. Childbirth via CS may also lead to PPH. There are only few papers concerning PPH occurrence after CS in which PPH ratio amounted to 0.3–6% [11]. The prevalence of PPH has increased over the past few years, which may be caused by an increased incidence of uterine atony and CS. The number of emergency hysterectomies (5.8–6.3/10,000 births), blood transfusions, performing B-Lynch sutures (10.7/10,000 births) and uterine artery embolizations are the most correlated with uterine atony. Other common causes of EPH are genital tract injuries or episiotomy (16.7%), placental abnormalities (4 to 36% of retained placenta, abnormal placental implantation or placental abruption) or coagulopathies (e.g. anticoagulant treatment or DIC) (7.4%) [10].

Risk factors

Unmodifiable risk factors of EPH include a history of EPH (OR = 2.3–10.5) and a delivery of a large for gestational age

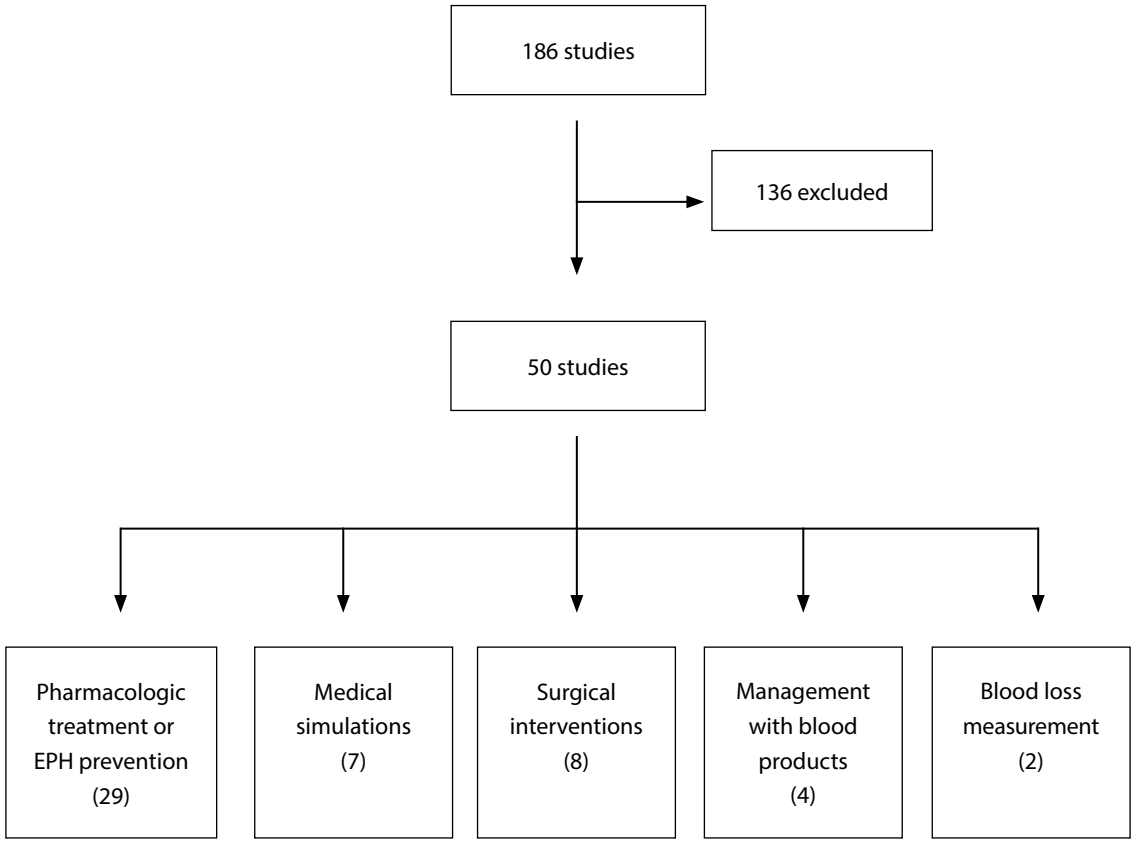

Figure 1. Study flow diagram

Table 1. Frequency of PPH [3, 10, 13, 15, 17–35] identified using a multivariable analysis, were: retained placenta (OR 3.5, 95% CI 2.1–5.8

Country	Years	Population	PPH frequency
Israel	1988–2002	154 311	0.4%
Africa Asia Europe	2008	505 379	Severe EPH: **0.3–3.8%** **2.7%** **5.5%**
Asia, Africa, Middle East, Latin America (data from 28 countries)	2010–2011	274 985	VD**: 1.2%**
WHO	2012		2%
USA	1995–2004	870 000	2.93%
USA	1999–2008	8 500 000	3%
USA	2006–2012	1 339 397	CS**: 2%**
Canada	2003–2010	2 200 000	6.2%
Norway	1999–2004	307 415	Severe EPH: **1.1%**
Norway	2008–2011	43 105	Severe EPH: **2.5%**
United Kingdom	2003–2013	24 230	CS: **12.4%**
France	2004–2006	146 781	6.4%
France	2016	3 917	VD UPPBL: **11%** VD EPH: **11.2%**
Nederland	2000–2008	1 599 867	4.5%
Denmark	2008	147 132	CS: **2.24%** VD: **1.75%**
Ireland	1999–2009	649 019	2.6%
Spain	2017	1 352 691	3%
Brazil	2010	9 555	12.5%
RPA	2012	15 725	2.5%
Nigeria	2014	4 889	3.4%
India	2010–2012	96	CS: **1.8%** VD: **1.3%** Instrumental: **5.3%**
Tunisia	2010–2013	39	Severe PPH included to the study
Japan	2011	1 294	VD: **33%**
German	2010–2013	1 550	8.4%

fetus (> 4000 g) (OR = 1.7–1.9). Uterine abnormalities such as uterine fibroids (OR = 2.0–2.7) also played an important role in the incidence of EPH [6]. Pregnancy complications, such as maternal anemia (hemoglobin level below 9 [g/dL]) (OR = 4.1), hypertensive disorders (OR = 1.6–3.6), gestational diabetes mellitus (OR = 1.6), a multiple gestation (OR = 1.5–3.7), polyhydramnios (OR = 2.6) and preterm delivery (OR = 2.6) were significantly correlated with EPH [12].

Maternal fever (OR = 1.7–2.5), labor induction (OR = 1.5–1.7) and instrumental (OR = 1.2–2.9) or operative delivery (OR = 1.4–5.7) increase the risk of EPH. Retained placenta increase the risk of hemorrhage immediately after delivery (OR = 3.5–4.1) as well as after subsequent pregnancy [12].

Sociodemographic factors, such as obesity [BMI > 35 (kg/m^2)] (OR = 2.3), mother's age over 35 years (OR = 1.5–1.7) and Middle Eastern ethnicity (OR = 1.8) increase the risk of EPH [13]. Conversely, smoking (OR = 0.8) during pregnancy seems to reduce the risk of EPH [6, 13]. All the mentioned risk factors of PPH are shown in Table 2 [6, 10, 14].

Risk factors of UPPBL are similar to those in EPH and include Asian ethnicity (aOR = 2.3), previous cesarean section (aOR = 3.4), episiotomy (aOR = 2.6), primiparity, prolonged labor, instrumental delivery and retained placenta [6].

Prevention

WHO guidelines for the prevention of EPH include a thorough assessment of possible risk factors as the primary prophylaxis of this complication. Moreover, pharmacological prophylaxis includes 10 IU of oxytocin in bolus (intravenously or intramuscularly), 100 µg of carbetocin (intravenously or intramuscularly), misoprostol (400 µg or 600 µg, per os), ergometrine/methylergometrine (200 µg, intramuscularly or intravenously) or oxytocin and ergometrine together (5 IU and 500 µg, intramuscularly) [15]. According to German guidelines 3–5 IU of intravenous oxytocin or 100 µg of intravenous carbetocin should be recommended (Tab. 3.) [1]. Conversely, RCOG suggested 0.5–1 g of intravenous injection of tranexamic acid, carboprost or misoprostol to be superior to oxytocin prophylaxis. However oxytocin and/or ergometrine or 100 µg of intravenous carbetocin is highly advised, similarly to the guidelines of the Society of Obstetricians and Gynaecologists of Canada [3]. RCOG guidelines suggest that the prevention of minor EPH with 5 IU and 10 IU of oxytocin has comparable results [3]. ACOG recommends to prevent EPH by using 10 IU of oxytocin intramuscularly or intravenously as the most effective [4]. An intravenous bolus of tranexamic acid at a dose of 0.5–2 g (15–30 mg/kg BW) should also be considered [2, 3]. Moreover, it could be used as prophylaxis of EPH after VD.

In twin pregnancies carbetocin prophylaxis of EPH after CS seems to be more effective than oxytocin in the prevention of EPH [16]. The authors found several publications concerning a higher efficacy of carbetocin than oxytocin in the 3rd stage of labor. Moreover, in another study carbetocin was a better alternative to traditional oxytocin in the prevention of PPH after vaginal delivery. The most significant adverse effect after drug administration was hypotension with no difference between those two drugs. Pruritus was the only symptom which was more often experienced in carbetocin-treated group. By contrast, the authors of another study reported that carbetocin had the same effectiveness as oxytocin at lower doses and needed less time to be effective. Conversely, misoprostol needed the longest period to reach sufficient uterine contractility [17]. No differences in effectiveness were

Table 2. Risk factors of PPH [10, 15, 17, 21, 22, 25, 27, 30, 36, 41–44] the incidence of severe postpartum hemorrhage (PPH

Risk factors of PPH	OR	95% CI
Mother diseases and pregnancy-associated conditions		
Past history of PPH	2.3–10.5	1.3–10.6
Uterine anomaly in the past	2.4	1.2–5.0
Uterine surgery in the past	3.4	1.6–7.1
Multiple pregnancy	1.5–3.7	1.3–5.3
IVF/ICSI	1.8–2.9	2.2–3.9
Preeclampsia or HELLP syndrome	1.8–3.6	1.6–5.7
Hypertension disorder	1.6–2.0	1.1–3.9
Chorioamnionitis	2.9	2.5–3.4
Delivery < 37 weeks of gestation	2.6	2.3–3.0
Delivery > 41 weeks of gestation	1.6–1.9	1.0–2.8
Fibroids	2.0–2.7	1.8–4.2
Lacerations	2.4	2.0–2.8
Nulliparity	1.1–2.0	1.0–2.6
Third pregnancy	1.3	1.1–1.6
Anemia (Hb ≤ 9.0 g/dL)	4.1	2.8–6.1
GDM	1.6	1.1–2.3
Polyhydramnios	2.6	1.2–5.5
Anticoagulant medication	4.7	2.8–7.7
Placenta previa	3.0–7.0	2.9–7.3
Labour related factors		
Retained placenta	3.5–4.1	2.1–5.8
Placenta accrete	3.3	1.7–6.4
Instrumental delivery	1.2–2.9	0.9–3.5
CS	1.4–5.7	1.2–6.5
CS in the second stage of labor	2.1–3.4	1.2–4.7
Uterine rupture	11.6	9.7–13.8
Labour Induction	1.5–1.7	1.1–2.0
PROM	1.4–1.5	1.0–1.9
Body temperature in labour > 38°C	1.7–2.5	1.1–3.6
Labour induction or augmentation	1.4–2.0	1.1–2.4
LGA	1.7–1.9	1.2–2.6
Sociodemographic		
BMI > 35kg/m^2	2.3	1.3–3.6
Age > 35 years	1.5–5.7	1.1–7.1
Middle Eastern descent	1.8	1.2–2.7
African descent	1.5	1.1–2.2
Smoking	0.8	0.6–1.0

reported for an intravenous administration of 100 µg of carbetocin and 5 IU of oxytocin [18]. Furthermore, no differences in efficacy were found between 10 IU and 30 IU of oxytocin administered intravenously, but the higher dose was effective for a longer period (8–12 vs 2–4 hours) [19].

Table 3. Carbetocin usage

Multiple pregnancy
≥ 4 deliveries in past
≥ 2 cesarean sections in past
Other uterine scare
Large uterine fibroids
PPH or uterine atony in the past
Suspected fetal macrosomia
Polyhydroamnios
Placenta previa
Placenta accreta
BMI > 35 kg/m^2
HCT < 35%
Fibrinogen concentration < 4 g/L
PLT < 100 000

BMI – body mass index; HCT – hematocrit; PLT – platelets

The authors found the advantages of 5 IU of oxytocin administered intramuscularly over 200 µg of sublingual misoprostol. However, misoprostol is more cost-effective, may be stored at room temperature and is easier to use. Therefore, it may be a good alternative to oxytocin. Heat-stable carbetocin compared to oxytocin and 800 µg of rectal misoprostol had a similar effectiveness compared to 10 IU of intramuscular oxytocin in the 3rd stage of labor [20].

Several studies compared the effectiveness of 10 IU of bolus of oxytocin with 600 µg of intramuscular misoprostol in the prevention of EPH, with no significant differences between groups. Furthermore, other authors found that 800 µg of misoprostol seemed to be more effective than the standard dose of oxytocin [21].

A combination of methylergonovine and oxytocin infusion during CS successfully decreased severity of EPH [22]. On the other hand a combination of misoprostol and oxytocin seemed to increase the risk of side effects related to pharmacotherapy, such as fever, nausea and shivering.

Tranexamic acid was effective in reducing the rate of EPH, especially if administered within 3 hours after labor (RR 0.69, 95% CI: 0.5–0.9; p = 0.008) [23]. Another study demonstrated that tranexamic acid did not enhance the anti-hemorrhagic effect in a group of women after oxytocin administration [24]. The supplementation of fibrinogen after EPH in women with normal fibrinogen level also did not improve those results. In contrast to those findings some researchers recommended a routine administration of 3 g of fibrinogen in case of EPH.

Delayed umbilical cord clamping and cord drainage presented a protective effect against EPH.

Treatment

It is important to estimate the occurrence of probable reversible reasons for EPH. An injury of the uterus or the genital tract seems to be the most recognizable factor and requires primary surgical treatment.

The management of retained placenta includes controlled cord traction, Credé maneuver and manual placenta removal [2].

External uterine massage or bimanual uterine compression should be considered as the first-line treatment of uterine atony. The second-line treatment might involve intrauterine tamponade with Foley catheter, or other dedicated intrauterine balloon catheters, which effectiveness reached up to 80–90% [25]. The availability, easy usage and safety are important issues of this method when uterine subatony or undiagnosed focal placenta accreta is present. However, no papers have been found to compare those methods. Early balloon tamponade is effective when used before coagulopathy occurrence.

Another tools utilized in the treatment of uterine subatony are uterine compression sutures (B-Lynch, Cho and Hayman) with effectiveness estimated to 60–75% [26]. However there is insufficient data concerning comparison of different techniques. On the other hand endovascular balloon techniques seem to be more effective (uterine preservation, less blood loss and higher postoperative hemoglobin levels). Several previous studies showed similar effectiveness of compression sutures, intrauterine tamponade and uterine artery ligation. However, intrauterine tamponade should be preferred option because of lower costs and invasiveness as well as faster therapeutic effect. In severe cases combination of aforementioned methods should be considered to preserve female fertility [26].

Obviously, pharmacologic treatment should be introduced simultaneously — intravenous 10–30 IU of oxytocin or 100 µg of intravenous bolus of carbetocin, with similar clinical effectiveness (blood loss, severe postpartum hemorrhage, blood products transfusions). On the other hand few studies has shown higher effectiveness (amount of blood loss and the need for other uterotonics) of 100 µg carbetocin vs 5 IU oxytocin in EPH management [17].

Other vasoconstrictors, such as methylergometrine 0.2–0.4 mg intramuscularly, PGF2α (enzaprost) 1 mg into the uterine muscle, PGE1 (misoprostol) 600–1000 µg per rectum are also used [2].

Total hysterectomy is the last-ditch intervention in case of uterine atony. The incidence of such intervention constitutes 1.1–2.3% of EPH [27] and 0.63 per 1000 childbirths. Over 30 minutes desmopressin infusion 0.3 µg/kg BW should be considered in women with hypovolemic shock [28].

The administration of crystalloids and colloids should be obligatory apart from drugs increasing the contractility of the uterus. In case of massive perinatal bleeding, blood product transfusion (4 or more units of packed red blood cells (RBC), fresh frozen plasma (12–15 mL/kg BW), (25 IU/kg BW) prothrombin complex concentrate and platelets, when platelet count is below $75*10^9$/l) should be considered [2, 3]. One study suggested cell salvage but this procedure is very expensive and not easily available.

1 g of calcium chlorate and the substitution of fibrinogen (30–60 mg/kg BW), rFVIIa (90 µg/kg BW or 15–20 IU/kg BW) or factor XIII should be considered when severe bleeding is present [3].

Late EPH requires vaginal microbiology and subsequent antimicrobial treatment of endometritis if such a diagnosis is confirmed. Ultrasound should be performed to look for placenta retained tissue and subsequent surgical intervention should be planned.

Medical simulations of EPH are important for the improvement of medical staff skills. A reduction in the number of possible errors, easier and faster medical interventions, shortening the time to the preparation of blood products, more appropriate blood loss evaluation, self-confidence and comfort level, practices in surgical and pharmacological management are the main goals of medical simulations [29]. Such courses improve the recognition of EPH and shorten the duration of appropriate medical intervention — uterine massage and the administration of second-line medications. The results showed an improvement of medical skills in that publication from 27.3% to 63.6% ($p = 0.01$) [30]. Another study showed a significant improvement in team cooperation [31]. Some research also showed that such simulations have a positive influence on obstetric outcomes in the future. A subsequent trial showed a higher rate of appropriate EPH evaluation and fundal massage implementation. Another publication proved that one-day simulation caused a significant improvement in medical skills and the effect persisted over the next 3 months (0.4% vs 0.03%, OR 19, 95% CI 2.5–147) [32].

DISCUSSION

An inconsisenst definition of EPH, varying across countries contributes to the publication of non-comparable results and different conclusions concerning EPH. The frequency of EPH was compared in this study and an increasing trend was observed. Furthermore, EPH is the main cause of maternal mortality [32]. Apart from death it is associated with severe maternal condition after childbirth. Therefore, an interest in the subject is not surprising. Risk factors listed in the Results section are one of research areas. Prediction strategy assumes risk factor evaluation before any childbirth. EPH causes may be easier to memorize by remembering

their division in 4Ts: tone, tissue, trauma and thrombin with higher attention to uterine atony as the most frequent cause of EPH [10]. It seems that an increased rate of EPH is caused by an increased level of uterine atony secondary to a higher rate of CSs. Regrettably, EPH occurs in two-thirds of women without any risk factors [28].

It is commonly known that it is better to prevent than to treat possible complications. For that reason, the main attention is paid to preventive methods which consist of uterotonics (oxytocin, carbetocin, enzaprost/carboprost or misoprostol, ergometrine or methylergometrine) and tranexamic acid. Thus, the prophylaxis should include 3–10 IU of oxytocin intravenously or 100 µg of carbetocin intravenously in the 3rd stage of labor and 100 µg of carbetocin intravenously during CS in high risk patients. Economic issues should also be considered because of a higher carbetocin cost. Moreover, an intravenous administration of oxytocin was shown as more effective (due to severe EPH, blood transfusion and admission to a high dependency unit) than intramuscular administration in the 3rd stage of labor [33]. Another trial showed acceptable outcomes of misoprostol in comparison with oxytocin, but a high price of misoprostol was emphasized [34]. Previous studies showed also the efficacy of other uterotonics in the absence of oxytocin and carbetocin. Tranexamic acid should be also considered.

Apart from early prophylaxis, in any case of EPH pharmalological and if severe - surgical treatment should be introduced. Pharmacologic intervention seems to be superior to a surgical one. However, if surgical intervention is necessary, no delay in its performance should occur, especially when regards pelvic vessel occlusion, compression sutures (eg B-Lynch) management or emergency hysterectomy. Hamilton maneuver is the best option in preparation to the surgical procedures.

In case of hypovolemic shock, desmopressin 0.3 µg/kg of BW and other vasoconstrictors like norepinephrine should be considered.

Pelvic packing may be performed in case of the lack of selective arterial embolization, for patient transport to a tertiary care unit or in case of persistent bleeding after hysterectomy [7].

Intravenous infusions of crystalloids and colloids should be obligatory apart from previously mentioned drugs. Moreover, blood transfusion may be necessary [2, 3]. Fibrinogen substitution (30–60 mg/kg BW), which could reach ≥ 2 g/L as well as rFVIIa (90 µg/kg BW or 15–20 IU/kg BW) or factor XIII use could improve the PPH outcomes [3].

Medical simulations of EPH are important for the improvement of medical staff skills, which had an influence on EPH outcomes. Importantly, attention should be paid to becoming familiar with hospital protocols, team work improvement, understanding one's own mistakes, building self-confidence, and reduced perception of stress. Blood loss evaluation is also improved after such trainings. It seems rational that it should be implemented as early as the beginning of medical practice and repeated every 3 months.

No research on the frequency of EPH in the Polish population is currently available. Further studies should also evaluate more accurate blood loss measurement methods and their customization.

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Endometrial microbiota — do they mean more than we have expected?

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ABSTRACT

Low biomass microbiome has an increasing importance in today's fertility studies. There are more and more indications for incorporating upper gynecological tract microbiome content in patients diagnostic and in vitro fertilization process, as doing so may help to evaluate chances for a positive outcome. An abnormal endometrial microbiota has been associated with implantation failure, pregnancy loss, and other gynecological and obstetrical conditions. Furthermore it has been shown, that using molecular methods in addition to routine diagnostics may help diagnose chronic endometritis or even indicate cancerogenic changes. Understanding the significance of microbiome in endometrium may completely change therapeutic approach in treatment of this part of reproductive tract. Next generation sequencing (NGS) has allowed to isolate culturable and unculturable bacteria from female reproductive tract and is a cheaper and quicker alternative for other widely known and used methods.

Key words: endometrium; microbiota; reproductive health; next generation sequencing

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INTRODUCTION

For almost a century gynecologists and scientists were convinced that a healthy uterus is sterile. Henry Tissier, who in early 1930's has isolated bacteria from the stool of healthy breastfed infants, believed that an infant develops in a sterile womb and its first contact with the bacteria occurs during entering the birth canal [1, 2]. Further studies on this subject has shown that meconium is not sterile, and bacteria were also detected in amniotic fluid, umbilical cord and fetal membranes of healthy term babies [3–6]. These findings prompted further research as more proof of nonsterile fetus cast doubt on the assumption of has no commensal microflora in the upper genital tract. The importance of microbiome in the entire fetal life is currently studied by many researchers [7].

UTERINE MICROBIOME

Until very recent, the cervix had been seen as a perfect barrier between the vagina, uterus and the fallopian tubes, which were believed to be sterile. However, some studies have proven, that the changes in relative concentration of mucins present in the cervix, are leading to changes in their aggregation. Such changes dependent on pH variations during menstrual cycle and may allow bacteria passage under certain conditions [8].

In 1995 Moller et al. [9] published a study describing bacterial culture isolated from the cervix and the uterus of 99 patients undergoing a hysterectomy, where main indications for the procedure were persistent vaginal bleeding (n = 29) and fibromyomas of the uterus (n = 34). 26 of the studied patients were culture-negative for all microorganisms based on the samples from the apex of the vagina and the cervical os. The team has managed to isolate bacteria from the uterine cavity samples in 24 out of 99 analyzed cases. The most common pathological organism isolated from the vagina was *G.vaginalis*. It was found in 45.5% of culture-positive women. Other frequently isolated bacteria were *S.agalactiae* and *Enterobacter spp.* found in in 15% of the cases. Among the 24 patients with a positive culture

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from the uterine cavity *G.vaginalis* was isolated in 11 cases and *S.agalactiae* in 5 cases. The team has concluded that the uterine cavity is contaminated with microorganisms in a significant number of patients admitted for hysterectomies. It has been recommended to send the endometrium biopsy samples for histological and microbiological testing prior to the hysterectomy [9].

The result of this and many other studies have shown, that there is a microbiota continuum along the female reproductive tract. The lower third of vagina, and posterior fornix are dominated by *Lactobacillus spp* .(99.99%). However, samples taken from cervical canal contain lower proportion of *Lactobacillus spp.* (97.56%) than the vaginal samples [9, 10]. According to the study by Chen et al., *Lactobacillus spp.* is not a dominant genus in the endometrial samples (30.6%). Bacteria such as *Acinetobacter* (9.07%), *Pseudomonas* (9.09%), *Sphingobium* (5%) and *Vagococcus* (7.29%) form a large portion of endometrial microbiome. At the openings of the fallopian tubes the proportion of these bacteria increases while the median relative amount of *Lactobacillus spp.* is around 1,69%, and peritoneal fluid from the pouch of Douglas contains little to no *Lactobacillus* genus [10–12].

Next generation sequencing (NGS) has enabled a far more global evaluation of bacterial composition of the uterus as it cannot be measured with culture dependent methods. In the year 2000 Drancourt et al. [13], made several recommendations concerning proposed criteria for 16S rDNA gene sequencing as a reference method for bacterial identification. In further studies however it has been observed that the 16S rDNA is not a perfect target for NGS analysis and bacteria identification. Genomic DNA isolated from a sample contains random fragments of bacterial genomes and can be, potentially, contaminated by host DNA or DNA of other organisms present in this sample [14]. 16S RNA amplicon sequencing can be targeted specifically against bacteria. It also does not require the availability of reference genome sequences. Furthermore it can be used in cases where only trace amount or poor quality bacterial DNA templates are accessible [15, 16]. Therefore 16S rRNA sequencing became a standard method in bacterial community profiling.

It is important to highlight that the differences between the endometrial and vagina microbiome have been observed regardless of the method of collection of endometrial samples, which confirms the existence of indigenous endometrial microbiota and shows that the vaginal – cervical canal is a safe route for sampling the uterine cavity for further microbiome analysis [12, 17, 18].

The role of immune system in uterus colonization cannot be forgotten. Studies have shown that the endometrial fluid and the uterine mucosal surface contain infection-controlling molecules, known as antimicrobial peptides (AMPs), with changing levels during the menstrual cycle [19]. AMPs are contributing to female reproductive tract health with implication for fertility and pregnancy [20]. The secretory leukocyte protease inhibitor, which has antiviral and antifungal properties, is present in the uterus. It acts against gram — negative bacteria such as E.coli and gram-positive bacteria such as S. aureus [21]. Givan et al. [22], has shown presence of the lymphocytes in the mucosal layer, ready to act upon pathogen invasion, throughout all stages of the menstrual cycle. We can, therefore, assume that the uterus could offer a safe niche for symbiotic colonization.

Koedooder et al. [23] has proposed semen to be another possible route of introducing microbiota into female reproductive tract. His studies have shown, that the male and female microbiome are influenced by each other and seem to interact [23]. How the two interact is still unknown. Future research could resolve the question of the existence of temporary female-male microbiome forms during post-coital period and its influence on conception.

Current data suggest that the importance and confirmation of natural presence of healthy uterine microbiota need to be assessed by well-setup large cohort studies [24].

INFLUENCE ON REPRODUCTION AND WOMEN'S HEALTH

There are some indications that uterine microbiome might influence endometrial receptivity. Early prospective studies considering the role of endometrial microbial colonization suggested that positive microbiological endometrial culture, obtained from the tip of the transfer catheter in patients undergoing in vitro fertilization, had negative effects on implantation and pregnancy rates. The transfer catheter tip or cervical smear culture positive for bacteria strains such as: *Enterobacteriaceae spp., Streptococcus spp., Staphylococcus spp., Escherichia coli*, was associated with decreased implantation rate and poor pregnancy outcome [25–27]. For example, Selman et al. have designed prospective clinical trial including 152 patients undergoing IVF procedure. Separate samples for microbial examination, were taken during embryo transfer from the vagina, the cervix and culture medium: prior and post-embryo transfer. Of the 152 patients, 133 tested positive for one or more microorganisms, and the remaining 19 patients tested negative in all samples taken. In the positive group the microorganisms identified were as follows: *Enterobacteriaceae* in 99 patients, *Streptococcus spp.* in 43 patients, *Staphylococcus spp.* in 68 patients, *Lactobacillus* in 19 patients and other species such as: *S.agalactiae, G.vaginalis, Ureaplasma urealyticum* and yeast in 28 patients. Pregnancy rates were significantly lower in patients positive with *Enterobacteriaceae* culture and *Staphylococcus* (in compare with negative culture group (22.2% vs 51% and 17.6% vs 43% respectively) [26].

Those results have been confirmed by Moreno et al. [18] study where patients were divided into two general groups: LD (*Lactobacillus* Dominant; > 90%) and NLD (non-*Lactobacillus* Dominant; < 90%). The analysis of endometrial microbiota showed significant differences in the bacterial diversity in the NLD group. This group, in comparison with the LD group, also had significantly lower implantation (23.1% vs 60.7%, p = 0.02), pregnancy (33.3% vs 70.6%, p = 0.03), ongoing pregnancy (13.3% vs 58.8%, p = 0.02), and live birth (6.7% vs 58.8% p = 0.002) rates.

Genus *Lactobacillus* is a very important component in major part of the uterine microbiome studies. However, comparison of the relative abundance of *Lactobacillus* between sequencing reports underline the inconsistency among reports and needs further investigation [28–30]. Fang et al. [31] described higher levels of *Lactobacillus* in the group of women with endometrial polyps or in women with chronic endometriosis coexisting with endometrial polyps, compared with healthy control. By contrast, the work of Moreno et al., reported that high levels of *Lactobacillus* (over 90% as defined by the group) are significantly associated with growing reproductive success in women undergoing IVF. Nevertheless, it has not been determined, which species of *Lactobacillus* may be capable of conferring this benefit [18].

In other studies, the increased reproductive success in women with high level of *Lactobacillus* may have reflected the composition of the vaginal microbiome at the time of embryo transfer [28]. Haahr et al. have tested 130 patients undergoing IVF treatment. PCR analysis for *G.vaginalis, A.vaginae, L. crispatus, L. jensenii, L.gasseri* and *L.iners* were performed. Dominance of *Lactobacillus spp.* was interpreted as normal, whereas bacterial vaginosis was diagnosed if the *G.vaginalis* and/or *A.vaginae* were dominating. Eighty-four patients completed IVF treatment and overall clinical pregnancy rate was 35% (29/84). Interestingly, only 2 of 22 patients with abnormal vaginal microbiota obtained pregnancy (p = 0.004) [30]. Even though the microbial uterine environment plays a role in the implantation and placentation process, it is mainly tightly regulated by female sex hormones.

Therefore Moreno et al. [18] has evaluated IVF catheter tips at two different time points. One sample was taken at the pre receptive phase and the other at the receptive phase of the same menstrual cycle to asses shift in microbiome composition in IVF patients. This study has indicated, that the uterine microbiome was similar at both time points in 9 out of 13 patients sampled, which is similar to the vaginal microbiome changes in the same time window [18, 32].

Recent reports from Moreno et. al demonstrates, that molecular microbiology is a reliable, fast, and cheap diagnostic tool that allows for the detection of culturable and non-culturable bacteria associated with chronic endometritis and has 77% concordance with a combination of the classical diagnostic methods such as histology, hysteroscopy and microbial culture [10]. This is very important information, as chronic endometritis can be asymptomatic, and is found in about 40% of infertile patients, likely causing repeated implantation failure or even recurrent miscarriage [10]. The study includes a small study group (65 patients), which indicates that more research has to be done to confirm those findings.

Pathological changes in endometrial microbiota may play an important role in carcinogenesis [33, 34]. There are some hypothesis that the pelvic inflammatory disease (PID) may result from pathogenic bacteria ascendance through the cervix into the upper genital tract and cause inflammation of the uterus, fallopian tubes and/or ovaries [34, 35]. Carcinogenesis on the other hand may occur when the tumor-associated loss of bacteria function causes increased commensal penetration and inflammation induction, which in turn result in enhance tumor growth. Other possibility is so called: pathobiont-mediated tumorigenesis, by which potentially pathogenic commensal strains are creating tumorigenic environment by secreting mediators [36].

IMPLICATIONS FOR THE FUTURE

If bacteria are naturally present in the womb, their importance not only in terms of fertility, but also in maintenance of the uterus deserves attention.

In the future, the targeted elimination of cancer — associated with microorganisms might provide a new therapy option. It seems to be a very attractive alternative because of its minimal expected side effects and the possibility of its preventive application. Studying the interactions between host and endometrial microenvironment may open new diagnostic possibilities and help to prevent consequences of serious diseases. It may also help us better understand the role of microbiome in implantation process and suggest routes to achieve positive outcome in infertility treatment. Molecular methods are shown to be a very powerful tool in defining the role of endometrial microbiome in women's health.

CONCLUSIONS

Thanks to next generation sequencing (NGS), endometrial microbiome is becoming better characterized and its importance in gynecologic and reproductive health is increasing. However, researchers have not yet reached a consensus, whether an altered microbiome is a cause or an effect of upper gynecological tract diseases. More research is needed to describe and understand the role of endometrial microbiome in endometrial receptivity and the outcome of in vitro fertilization. For optimal success, further studies require well-designed experiments and larger patient groups to explain the interactions between host microbiome and women's health.

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CLINICAL VIGNETTE

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Lack of connection between the uterine cervix and corpus in an adolescent treated in childhood for teratoma of the ovary

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A 19-year-old female patient was admitted to the Clinic because of primary amenorrhea.

In the initial anamnesis, it was learned that at the age of 10, the patient had undergone surgery to remove an immature teratoma of the left ovary at another hospital. Following the operation, adjuvant chemotherapy treatment was administered. The patient underwent surgery six years later. During that operation, an serous ovarian cyst of the right ovary was removed.

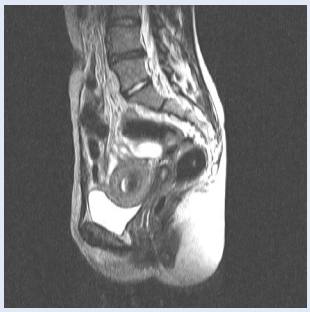

Figure 1. T2-weighted MRI scan showing no connection between the cervical canal and uterine cavity

Given the reason that the patient reported to the clinic, an urography and ultrasound were performed. The result of the former was normal; and the latter indicated grounds for suspecting that the cervix and uterine corpus were not connected.

To either confirm or eliminate this possibility, an MRI of the pelvis was scheduled. That test confirmed the suspected abnormality, indicating the presence of fluid within the uterine cavity possessing a different signal, arranged in horizontal levels. It was confirmed that there seemed to be no connection between the cervical canal and uterine cavity (Fig. 1).

Based on the results of all of the tests, it was decided to operate. After opening the abdominal cavity, it was evident that the uterus and cervix were not connected to each other, nor was the septum between them visible. Thus, during the operation, the connection between the uterus and cervix was reconstructed (Fig. 2).

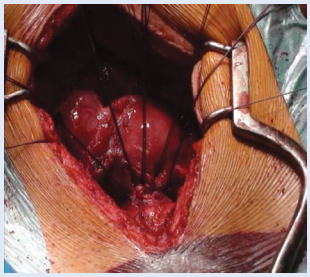

Figure 2. Reconstructed connection between the uterus and cervix

Again, despite her treatments, the patient reported to the hospital on repeated occasions with severe menstrual bleeding and pain. In addition to standard diagnostics, a psychiatric consultation was commissioned because a somatic symptom disorder was suspected; however, it was not confirmed. After repeated consultations and due to the exhaustion of all therapeutic methods to alleviate the patient's pain, a hysterectomy was ordered. The patient intended to have the procedure performed in another hospital, but she delayed making the final decision because of her young age and the possibility of losing her fertility. After several years, in-depth diagnostics was repeated and a presacral tumor was found, which turned out to be a distant metastasis of mature ovarian teratoma.

DISCUSSION

So far, two cases of this defect have been described, however they might be of a different origin [1, 2]. It is very unlikely for such a defect to occur, because the uterus develops ontogenetically from paired ducts (the Müllerian ducts). As the ducts connect at the sagittal plane, the developmental defects described by us at the beginning concern both sides of the uterus. Thus, the formation of a separate corpus and cervix is unlikely. The author of the paper concerning a similar defect believes, that the formation of uterus is bi-directional and the development of uterine corpus and cervix is possible without the middle component [2]. However, both cases described in the literature differ from our patient. In the above cases, connective tissue was found between uterine corpus and cervix, whereas it has not been observed in our patient. Moreover, our patient had an abdominal surgery in her childhood.

Due to the fact that the patient was not diagnosed with a malformation, it was suggested that the cause was iatrogenic. However, there was no confirmation of that assumption in the medical documentation from another hospital. It is probable that, although the presence of this defect was not confirmed during previous operations, it had already been present. However, the internal reproductive organs in young girls are quite small and more attention was paid to removal of neoplasm from the genital organs.

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