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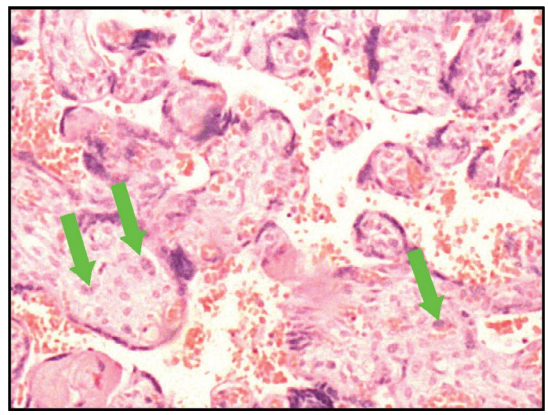

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Evaluation of occult uterine *leiomyosarcomas*

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ABSTRACT

Objectives: To determine the frequency of occult uterine leiomyosarcomas following hysterectomies and myomectomies performed for benign reasons at our clinic and to draw comparisons with similar studies in the literature.

Material and methods: All hysterectomies and myomectomies that have been performed for benign reasons at our clinic between 2010 and 2017 were retrospectively examined via the hospital's information system and the patients that were found to have *leiomyosarcomas* were analysed. The incidence of occult uterine *leiomyosarcoma* per 1000 surgeries at our clinic was calculated using the Wilson score interval.

Results: A total of 6,173 hysterectomies were performed, and occult uterine *leiomyosarcoma* was identified in 5 patients. The incidence of occult uterine *leiomyosarcoma* was calculated to be 0.08% (95% CI 0.03–0.018%). Only 1 of the 771 patients who underwent myomectomy was identified with occult uterine *leiomyosarcoma*, making its incidence in myomectomy 0.12% (95% CI 0.02–0.073%). When all the patients are considered, occult uterine *leiomyosarcoma* was identified in 6 of the 6,944 patients, and the general incidence of occult uterine *leiomyosarcoma* was calculated as 0.08% (95% CI 0.03–0.018%).

Conclusions: In our study, the incidence of occult uterine *sarcoma* following myomectomy and hysterectomy was found to be lower than that reported in the literature. The reason for this lower incidence includes not only genetic causes and racial differences but also preoperative imaging, endometrial and cervical sampling that is performed on every patient.

Key words: *leiomyosarcoma*; hysterectomy; myomectomy; myoma

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INTRODUCTION

Hysterectomy is a commonly performed surgery in gynaecology, and it is reported that approximately 600,000 hysterectomies are performed annually in the South Korea, which is roughly similar to the number of such surgeries performed annually in the United States [1, 2]. A study conducted in Turkey in 2017 on secondary care hospitals affiliated with the Ministry of Health revealed that the total number of hysterectomies performed annually was more than 15,000 [3]. The large majority of hysterectomies are performed for benign reasons worldwide. According to a society-wide study carried out in the United States, the indications for hysterectomy include uterine fibroids in 51.4% of the cases, abnormal uterine bleeding in 41.7%, endometriosis in 30% and uterine prolapse in 18.2% [4]. Another study in the United States determined that approximately 43,000 myomectomies are performed annually due to uterine fibroids, which is the most common reason for hysterectomy, whereas this figure is approximately 9,412 for Turkey [3, 5].

Uterine *sarcomas* reportedly account for 1% of all gynaecological cancers, and 3–7% of uterus-related cancers [6]. According to their histological classification, 40% of uterine sarcomas are *carcinosarcomas*, 40% are *leiomyosarcomas*, 10–15% are endometrial stromal *sarcomas* and 5–10% are undifferentiated *sarcomas* [7]. *Leiomyosarcomas*, listed in this classification, show clinical findings similar to those of uterine fibroids, which leads to certain difficulties in the preoperative diagnosis and treatment of patients [7–9]. Although they are not specific, *leiomyosarcomas* are associated with several risk factors that are different from those associated with uterine fibroids, such as being from the black community, being diagnosed above the age of 60 years, use of tamoxifen or exposure to pelvic radiation, and retinoblastoma in childhood [10–13].

In recent years, there has been an increase in the number of hysterectomies and myomectomies performed worldwide through minimally invasive methods for indications of uterine fibroids, leading to a greater need for the morcella-

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tion of specimens. In this context, the U.S. Food and Drug Administration (FDA) 2014 has drawn attention to the possibility of occult gynaecological cancers, particularly uterine *sarcomas* that are associated with uterine fibroids [14]. Based on the possibility of uncontrolled spread within the abdomen in gynaecological cancers that could not be identified preoperatively, have been conducted following the aforementioned FDA report for determining the frequency of occult uterine *sarcomas*. A review of the literature shows that the frequency of occult uterine *sarcomas* tends to vary in the range of 0–0.89% [5, 15].

Objectives

The present study aimed to determine the frequency of occult uterine *leiomyosarcomas* following hysterectomies and myomectomies performed for benign reasons at our clinic and to draw comparisons with similar studies in the literature.

MATERIAL AND METHODS

All hysterectomies and myomectomies that have been performed at Izmir University of Health Sciences Tepecik Training and Research Hospital between 2010 and 2017 were retrospectively examined via the hospital's information system. The preoperative diagnoses of all patients were examined. The study included patients who were operated for benign reasons, such as pelvic pain, leiomyoma, endometriosis, abnormal uterine bleeding and uterovaginal prolapse. For the past 10 years, our clinic has been collecting cervical smear samples for endometrial sampling purposes from all patients who have planned hysterectomy surgeries, with sample collection being performed at least 1 month before the date of surgery. Therefore, all patients included into the study had their preoperative assessment done according to these principles.

Patients with planned operations for diagnosed gynaecological or non-gynaecological cancers, patients with dysplasia or atypical endometrial hyperplasia, patients with prior surgeries performed for staging purposes, patients with suspicions of malignancy in their medical history and patients with hysterectomies performed for obstetric reasons were excluded from the study. The cases of uterine *sarcomas* that were initially not detected during preoperative examination but were subsequently identified as a result of postoperative histopathological examinations performed following hysterectomy and myomectomy surgeries were classified based on the guidelines of the World Health Organisation [16], and the patients that were found to have *leiomyosarcomas* were analysed.

The information of patients identified with occult uterine *leiomyosarcomas* was examined in detail through the hospital's information system and patient files. An analysis was performed on the patients' demographic characteristics, preoperative findings, primary surgical indication and type, weight of specimen, final pathology results, postoperative conditions and treatments and patient survival. The incidence of occult uterine *leiomyosarcoma* per 1000 surgeries at our clinic was calculated using the Wilson score interval.

Simultaneously, our results on occult uterine *leiomyosarcoma* were compared with those of suitable studies found by performing searches on PubMed using the MeSH terms 'Hysterectomy', 'Myomectomy', '*Adenosarcoma*', '*Leiomyosarcoma*' and '*Carcinosarcoma*'.

Statistical analysis

The data were statistically analysed using SPSS 22.0 (SPSS Inc., Chicago, Illinois) software. The normality distribution of continuous variables was evaluated with a normality test that was suitable to the number of data collected. Mean ± standard deviation or median (min. and max.) were used for descriptive continuous variables. The Mann–Whitney U test was used for the comparison of variables lacking normal distribution, whereas the Student's t-test was used for the comparison of variables with normal distribution. Categorical variables were presented as number of cases and percentages. A value of $p < 0.05$ was considered to be significant. EpiTools epidemiologic calculators (http://epitools.ausvet.com.au) were used for the Wilson score interval.

RESULTS

A total of 6,173 hysterectomies were performed at our clinic over 7 years, and occult uterine *leiomyosarcoma* was identified in 5 patients. The incidence of occult uterine *leiomyosarcoma* was calculated to be 0.08% (95% CI 0.03–0.018%). Only 1 of the 771 patients who underwent myomectomy was identified with occult uterine *leiomyosarcoma*, making its incidence in myomectomy 0.12% (95% CI 0.02–0.073%). When all the patients are considered, occult uterine *leiomyosarcoma* was identified in 6 of the 6,944 patients, and the general incidence of occult uterine *leiomyosarcoma* was calculated as 0.08% (95% CI 0.03–0.018%), which is similar to its incidence in patients undergoing hysterectomy. Among the patients included in the study, 4,572 (65.8%) underwent abdominal hysterectomy, 1,022 (14.7%) underwent total laparoscopic hysterectomy, 579 (8.3%) underwent vaginal hysterectomy and 771 (11.1%) underwent myomectomy.

The most common indication of the patients who underwent abdominal and laparoscopic hysterectomy was symptomatic leiomyoma (39%), whereas their second most common indication for hysterectomy was treatment-resistant menometrorrhagia (23%). The most common indication of patients who underwent vaginal hysterectomy was pelvic organ prolapse (64%).

Among the patients included in our study, the primary surgical indication of those identified with occult uterine *leiomyosarcoma* was for symptomatic leiomyoma in all of them. Moreover, 2 patients also had an indication for treatment-resistant menometrorrhagia in addition to symptomatic leiomyoma.

The mean age of the patients included into the analysis was 48.63 years, whereas our subgroup analysis revealed that the patients who underwent abdominal hysterectomy, total laparoscopic hysterectomy, vaginal hysterectomy and myomectomy had a mean age of 48.91, 49.20, 61.20 and 37.28 years, respectively. The mean age of patients identified with occult uterine *leiomyosarcoma* was 46.5 years, which was lower than that of other patients. The patients' body mass indices varied between 22 and 28. None of the patients identified with occult uterine *leiomyosarcoma* had any tamoxifen use prior to surgery. One patient used an oral contraceptive, whereas none of the other patients had any oral contraceptive use or received hormone replacement treatment. The uterus weight of the patients who underwent hysterectomy varied between 146 and 2500 g. The patient whose uterus weighed 2500 g was found to be obese compared with the other patients, and it was understood that this patient did not attend her routine gynaecological examinations regularly.

The findings of the patients are summarised in Table 1. Six patients identified with occult uterine *leiomyosarcoma* had no pathological findings in their preoperative cervical smear and endometrial samples. Preoperative ultrasonography examination was performed on only 5 patients, whereas patient number 4 also had a magnetic resonance imaging performed in addition to ultrasonography, although their findings were not interpreted to be indicative of malignancy.

All of the patients were operated by gynaecology specialists under suitable conditions. Five patients had oophorectomies performed in addition to hysterectomy, and 1 patient only had a myomectomy surgery performed. Morcellation was not applied in any patient. In all patients, the operated piece was removed as a single whole piece, and we observed that, except for patient number 4, a frozen sample examination was not performed on the collected pieces, as there was no suspicion of malignancy. A frozen sample examination was performed on only 1 patient. The results of this examination were checked only according to the mitosis count, and the final pathological diagnosis of *leiomyosarcoma* was established in the final pathological examination.

Three patients identified with occult uterine *leiomyosarcoma* had stage 1c *leiomyosarcoma*, two had stage 1b *leiomyosarcoma* and one had stage 2 *leiomyosarcoma*. Combined radiotherapy plus chemotherapy was used in the secondary treatment of 4 patients, whereas 1 patient received only radiotherapy and 1 received conservative treatment. None of the patients showed recurrence during their monitoring period, and all patients were still alive at the time this article was penned. The mean disease-free survival was determined as 60 (40–86) months.

DISCUSSION

A total of 6,944 patients who underwent hysterectomy and myomectomy surgeries at our clinic for benign reasons within a seven-year period were included in the study. Occult uterine *leiomyosarcoma* was identified in 6 of the 6,944 patients, and the general incidence of occult uterine *leiomyosarcoma* was calculated as 0.08% (95% CI 0.03–0.018%). Following the FDA's notable 2014 report, which presented a prevalence of 1/498 (0.2%) for occult uterine *leiomyosarcoma*, there has been a visible increase in the literature in the frequency of studies conducted on this subject [17]. Many studies have reported the rates of occult uterine *leiomyosarcoma* at their own clinics, with incidences varying between 0% and 0.89%. A summary of these studies is provided in Table 2.

In their 2008 study that focused solely on patients who underwent myomectomy, Sinha et al. [18] determined the incidence of occult uterine *leiomyosarcoma* to be 0.40%, whereas Brohl et al. [19] identified this incidence to be 0.24%. In our analysis, the rate of occult uterine *leiomyosarcoma* following myomectomy surgery was calculated

Table 1. Information of patients with occult uterine leiomyosarcoma

Patient	Age [years]	BMI	Primary diagnosis	Primary surgery	Uterine weight [g]	Sarcoma type	Stage	Treatment	Status	Follow-up [months]
1	52	28	ULM	TAH	241	LMS	1c	RT + CT	Live	60
2	47	29	ULM + TRM	TAH	146	LMS	1b	RT + CT	Live	48
3	54	31	ULM	TAH	610	LMS	2	RT + CT	Live	40
4	47	38	ULM	TAH	2500	LMS	1c	RT	Live	60
5	47	27	ULM + TRM	TAH	469	LMS	1c	RT + CT	Live	86
6	32	22	ULM	Myomectomy	128	LMS	1b	None	Live	72

ULM — uterine *leiomyoma*; TRM — treatment-resistent menorrhagia; TAH — total abdominal hysterectomy; LMS — *leiomyosarcoma*; RT — radiotherapy; CT — chemotherapy

Table 2. Comparison of occult uterine leiomyosarcoma studies

Author	Year	Centers that include study	Operation type	Study duration	Number of patients	Rate of Occult LMS, n (per 100)
Parker et al. [26]	1994	Two	Hysterectomy, Myomectomy	1988–1992	1332	3 (0.23)
DiNapoli et al. [21]	2018	Single	Hysterectomy, Myomectomy	2010–2014	1959	4 (0.20)
Kundu et al. [20]	2017	Single	Hysterectomy, Myomectomy	2004–2014	2825	10 (0.35)
Seidman et al. [27]	2012	Single	Hysterectomy, Myomectomy	2005–2010	1091	2 (0.18)
Brohl et al. [19]	2015	Multiple	Myomectomy	2005–2014	2075	5 (0.24)
Sinha et al. [18]	2008	Single	Myomectomy	1998–2005	505	2 (0.40)
Multinu et al. [28]	2019	Multi	Hysterectomy	1999–2013	3759	4 (0.11)
Leung et al. [29]	2008	Single	Hysterectomy	1996–2005	1297	3 (0.23)
Ramm et al. [30]	2012	Multiple	Hysterectomy	2004–2009	708	1 (0.14)
Kho et al. [15]	2016	Single	Hysterectomy	2000–2014	10109	9 (0.89)
Yuk et al. [2]	2016	Multiple	Hysterectomy	2010–2012	12850	8 (0.06)
Theben et al. [31]	2013	Single	Hysterectomy	2005–2010	1584	2 (0.13)
Wright et al. [32]	2014	Multiple	Hysterectomy	2006–2012	36470	none
Wan et al. [33]	2013	Single	Hysterectomy	2003–2011	640	1 (0.16)
Current Study		Single	Hysterectomy, Myomectomy	2010–2017	6944	6 (0.08)

LMS — *leiomyosarcoma*

to be 0.12%. In addition to the specific geographical region where analyses are performed, racial and genetic differences are possibly the causes of these different results.

A review of the literature shows that while the incidence of occult uterine *leiomyosarcoma* in patients who undergo only hysterectomies can be 0.89% at the highest [15], the incidence of occult uterine *leiomyosarcoma* varies between 0.20% and 0.38% when all patients who underwent hysterectomy and myomectomy are included in the analysis [20, 21]. In our study, the incidence of *leiomyosarcoma* was calculated to be 0.08%, which is relatively lower than that reported in other studies. There are only a limited number of studies in Turkey regarding the incidence of occult *leiomyosarcoma*; however, a previous study in Turkey has reported an annual *leiomyosarcoma* incidence of 0.26% [22].

Currently, no tests that might be used to diagnose *leiomyosarcoma* preoperatively during the evaluation of patients for uterine leiomyoma are available. Unexplained pain and atypical vaginal bleeding in the presence of uterine leiomyoma along with a rapid increase in the leiomyoma's size can serve as warnings with regards to *leiomyosarcoma* [7, 23]. As vaginal bleeding independently can be observed in submucosal myomas of any additional pathology and pain can also occur following a possible degeneration in the myomas, these two symptoms — vaginal bleeding and pain — have rather low value in preoperative differential diagnosis [24, 25]. Parker et al have also reported that a rapid increase in the size of the uterus cannot be used in distinguishing *leiomyosarcomas* from leiomyomas [26].

As uterine *leiomyosarcomas* that have not been identified during preoperative differential diagnosis can possibly spread into the abdominal cavity, it is suggested that it is not suitable to perform power morcellation following minimally invasive procedures in the absence of adequate protective equipment for the intra-abdominal area [18, 20]. The major limitation of this study was its retrospective nature. The fact that the hospital's information underwent a major overhaul in the 2000s and that we could not include patients admitted prior to this period considerably restricted our ability to increase our study sample size. Nevertheless, compared with the data obtained from single-centre studies performed in Turkey and worldwide, we believe that our study makes a marked contribution to the literature with its number of patients and the rates it determined. Simultaneously, we also believe that our study serves as an important source because it illustrates the situation in Turkey based on comparisons with other studies.

CONCLUSIONS

In our study, the incidence of occult uterine *sarcoma* following myomectomy and hysterectomy was found to be lower than that reported in the literature. We believe that the underlying reason for this lower incidence includes not only genetic causes and racial differences but also preoperative imaging and preoperative endometrial and cervical sampling that is performed on every patient. Although it might not seem cost-effective when viewed solely form a cost-effectiveness standpoint, we believe that detailed

preoperative examination is useful given the possibility of medico-legal complications, additional treatment needs of patients and pain and anxiety the patients might experience. Conducting international multi-centre prospective studies on such patients will likely play a guiding role in determining the appropriate incidence of *leiomyosarcoma* and in identifying the proper measures against it.

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Analyzing the clinical significance of postoperative methotrexate in the management of early abdominal pregnancy: analysis of 10 cases

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ABSTRACT

Objectives: To assess the clinical value and treatment outcomes of postoperative methotrexate (MTX) therapy in the management of early abdominal pregnancy.

Material and methods: We retrospectively analyzed ten (10) cases of early abdominal pregnancy at our hospital between 7th August, 2006 and 20th April, 2017.

Results: Out of the ten (10) cases identified, six (6) patients and four (4) patients underwent surgery (laparotomy or laparoscopy) only and surgery (laparotomy or laparoscopy) plus IM 50 mg/m^2 methotrexate (MTX) within 24 hours of surgery respectively. The gestation age and serum β-HcG levels were significantly lower ($p < 0.05$, 6.0 ± 1.82 and 8073.2 ± 9561.0) in the surgery plus MTX group in comparison to (7.33 ± 3.61 and 15625 ± 21275.2) for the surgery only group. Ultrasound imaging findings reported extra uterine pregnancy in all cases and diagnostic surgery was necessary to locate precise site of implantation to plan further treatment. Days of hospitalization were shorter in the surgery + MTX group than in the surgery only group (3.00 ± 0.816 versus 5.66 ± 2.80).

Conclusions: Earliness in diagnosis coupled with the appropriate (methotrexate) MTX regime could help prevent unwanted complications that could arise from delayed or misdiagnosis.

Key words: abdominal ectopic pregnancy; early abdominal pregnancy; serum β-HcG; methotrexate; diagnostic laparoscopy

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INTRODUCTION

Abdominal ectopic pregnancies (AEP) are the rarest form ectopic pregnancies. With an estimated incidence of 1/6000 to 1/9000 births and 1/2200 to 1/10200 pregnancies, their mortality rate is reported to be 7.7 times and 89.8 times higher in tubal pregnancy and intrauterine pregnancy respectively [1, 2]. They can be referred to as; early when gestation is at or before 20 weeks and late when gestation is after 20 weeks [3]. Although rarely used clinically, signs and symptoms, levels of serum beta human chorionic gonadotrophin (ß-hCG), ultrasound and magnetic resonance imaging can be diagnostically productive in certain instances [4, 5]. Diagnostic laparoscopy has become the cornerstone treatment for AEP, but they can also be managed medically with systemic or local methotrexate (MTX), ultrasound guided potassium chloride (KCL), danazol and mifepristone [6, 7]. While few cases of early abdominal cases have been managed with surgery plus methotrexate, no studies, according to our knowledge have investigated the importance of methotrexate in these scenarios [8, 9]. We retrospectively studied the records of ten (10) who were diagnosed with early abdominal pregnancy in our hospital and were managed with surgery alone or surgery plus MTX. This study was necessary because, an in-depth understanding of the presentation, diagnosis and management of this rare form of ectopic pregnancy would help to minimize cases of late or misdiagnosis which could result in loss of fertility or even maternal mortality [10].

MATERIAL AND METHODS

A single institution retrospective study was carried out between 7th August, 2006 and 20th April, 2017 at the First Affiliated Hospital of Wenzhou Medical University, Zhejiang Province, China where ten (10) cases of early abdominal pregnancies were identified. Information on patient's biodata, pregnancy history, presenting features and reproductive outcomes were retrieved from our computerized medical chart as documented by three different surgeons who oversaw their

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management. Although high titers of serum ß-HCG prompted the suspicion of ectopic pregnancy, the definitive diagnosis of early abdominal pregnancy (before 20 weeks gestation) was made based on perioperative findings at varying implantation sites and was later confirmed by pathological examination. Cases of tubal pregnancies and pregnancies at locations that do not fit the criteria of early abdominal pregnancy and pregnancy beyond 20 weeks gestation were all excluded. Permission to carry on with this study was granted after careful evaluation by the Ethics Committee of The First Affiliated Hospital of Wenzhou Medical University (wydw2017–0115) and after patients gave their verbal consent through telephone calls. We subsequently divided the 10 cases into two main categories depending on the treatment modalities each patient received as surgery only and surgery plus IM 50 mg/m^2 methotrexate (MTX). Details on maternal age, pregnancy history, gestational age, presenting symptoms, pre and post-operative blood levels of beta human chorionic gonadotropin (ß-hCG), implantation sites, first and second lines of treatment, blood loss, days of hospitalization and reproductive outcomes were all documented. Amount of blood loss during laparoscopy was evaluated from the suction-irrigation tube and from direct suction combined with the weight of soaked pads during laparotomy. Presenting symptoms among the patients included abdominal pain and vaginal bleeding. Statistical calculations were done using independent sample t-test, where significant differences between the two groups were deemed at $p < 0.05$.

RESULTS

Clinical characteristics of the participants

The comprehensive information on all the ten (10) cases of primary abdominal pregnancies is shown in Table 1. The mean ± SD for age was 29.9 ± 5.93 years while the gestational age as estimation by last menstrual period (LMP) was 6.8 ± 2.973 weeks. The median gravidity and parity was 2 (range 1–3) and 1 (range 1–3) respectively. Risk factors recorded include previous pelvic inflammatory disease (2 of 10, 20%), history of In Vitro Fertilization (3 of 10, 30%), previous tubal surgery (3 of 10, 30%) and two (2 of 10, 20%) patients with no existing factors. In all the 10 cases, 4 patients presented with complaints of vaginal bleeding and abdominal pain, 5 with only abdominal pain and only one with vaginal bleeding. Case 8 reported with the highest level of serum ß-hCG of 58121 Iu/L. Details of the report on preoperative ultrasonographic findings are summarized in Table 2. Only three cases were managed with laparotomy, the remaining seven cases (2010–2017) were all managed laparoscopically. Varied sites of implantation reported include pouch of Douglas (3 of 10, 30%), mesosalpinx (3 of 10, 30%), vesicouterine pouch (2 of 10, 20%), intestinal wall (1 of 10, 10 %) and omentum (1 of 10, 10 %). Only 4 patients (Case 5, 6, 7, 9) received a second line treatment of IM 50 mg/m^2 methotrexate (MTX) within 24-hours of surgery. The overall mean ± SD for days of hospitalization was 4.6 ± 2.547 days with Case 1 staying the longest (11 days). Four patients were lost to follow up, but two (case 5 and 6) out of the six patients we contacted in 2017 had achieved spontaneous delivery at 4 and 2 years respectively following their treatment.

Pre and post-operative serial measurement of serum ß-hCG

Graphical representation of serum ß-hCG levels on the first day of admission (Day 0) and throughout the course

Table 1. Patient characteristics

Case	Year	Age	Pregnancy history	Risk factors	Weeks of GA	Symptoms	Serum β-HCG level (Iu/L)	Implantation site	Treatment		Days In hospital	Reproductive outcome
									1st TX.	2nd TX.		
1	2006	33	G2P0	Previous TS	13	AP	6,414	Mesosalpinx	LAP	_	11	No delivery
2	2006	32	G3P2	Previous TS	7	VB+AP	11,705	POD	LAP	_	5	Post TL
3	2008	27	G1P1	PID	5	VB+AP	12,048	Mesosalpinx	LAP	_	3	–
4	2010	32	G2P1	None	6	VB	307	Intestinal wall	LSC	_	4	–
5	2011	25	G1P1	PID	7	AP	20,731	POD	LSC	MTX	3	1 SD, after 4 years
6	2013	27	G2P1	None	8	VB+AP	512	VUP	LSC	MTX	4	1 SD, after 2 years
7	2014	18	G1P0	IVF	5	VB+AP	842	Mesosalpinx	LSC	MTX	3	–
8	2015	37	G2P1	Previous TS	10	AP	58,121	POD	LSC	_	6	–
9	2017	30	G0P0	IVF	4	AP	10,208	Omentum	LSC	MTX	2	Infertility History
10	2017	38	G0P0	IVF	3	AP	5,155	VUP	LSC	_	5	Infertility History

AP — abdominal pain; G — gravidity; GA — gestational age; IVF — in vitro fertilization; LAP — laparotomy; LSC — laparoscopy; MTX — methotrexate; P — parity; PID — pelvic inflammatory disease; POD — pouch of Douglas; SD — spontaneous delivery; TL — tubal ligation; TS — tubal surgery; TX — treatment; VB — vaginal bleeding; VUP — vesico-uterine pouch

Table 2. Transvaginal ultrasound imaging characteristics

Case	Radiologic comments
1	A cystic mass shadow measuring 16 × 10 × 13 mm in the posterior wall of uterus + pelvic fluid
2	Gestation sac consistent with 6 weeks in the pouch of Douglas + free peritoneal fluid
3	A heterogenous mass 29 × 19 × 18 mm near the left ovary + suspected bleeding in the pouch of Douglas
4	A 21 × 29 × 42 mm cystic area + pelvic fluid with internal echoes
5	Free fluid in the lower abdomen + pelvic solid mass in the pouch of Douglas
6	A 22 × 17 mm vital embryo + cardiac activity in the pouch of Douglas
7	A possible extra-uterine (right side of the uterus) with an empty uterus and normal adnexa
8	A hyperechogenic mass (20 × 27 × 23 mm) behind the uterus on the left side + pelvic fluid
9	No intrauterine gestational sac + possible hemantoma (43 × 28 × 31 mm) close to the left ovary
10	Mass-like area measuring 27 × 36 × 34 mm + fluid in the anterior and posterior cul-de-sacs

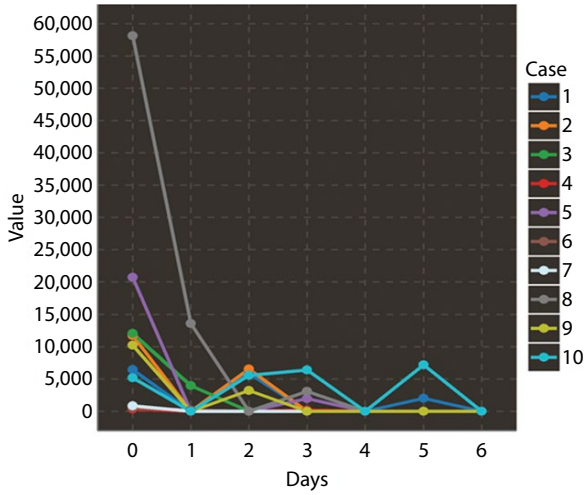

Figure 1. Serial measurement of serum ß-hCG. Day 0 represents the first day of admission and days 1, 2, 3, 4, 5 and 6 represent post-operative days

of treatment (Post-operative Day 1–6) is shown in Figure 1. Case 8 and Case 4 recorded the highest (58121 Iu/L) and the lowest (307 Iu/L) levels of serum ß-hCG respectively. Levels of serum ß-hCG were also assessed on 1st, 2nd, 3rd, 4th, 5th and 6th post-operative days. All patients displayed a sharp decline in their levels on the first day after surgery. However cases 2, 9, 10 showed a slight upsurge in their levels on post-operative day 2 but not as high as the levels on the day of admission (Day 0). Serum ß-hCG levels continued to plummet from post-operative day 3 through to 6th operative day except for case 10 that showed an obvious fluctuating trend throughout the course of treatment.

Correlation between treatment modalities and clinical parameters

The surgery plus methotrexate group presented with a mean gestational age of 6.0 ± 1.82 vs the 7.33 ± 3.61 among the surgery only group with a significant difference

Table 3: Management of primary abdominal pregnancy: surgery only vs surgery plus methotrexate (MTX)

Variables	Group 1: SURGERY ONLY (mean ± SD)	Group 2: SURGERY + MTX (mean ± SD)
Number of Cases	6	4
Gestational Age (weeks)	7.33 ± 3.61	6.0 ± 1.82
Day 0: Serum β-HcG Level (Iu/L)	15625 ± 21275.2	8073.2 ± 9561.0
Day1-6: Serum β-HcG Level (Iu/L) Intra-operative blood loss (mL)	5935.66 ± 4378.6 1370 ± 1909.9	1071.4 ± 1269.11 625 ± 330.4
Number of abortions	1.666 ± 1.63	0.50 ± 0.57
Days of hospitalization	5.66 ± 2.80	3.00 ± 0.816

(p = 0.000049). The surgery only group recorded more number of abortions than the surgery plus methotrexate group. Levels of serum ß-hCG on the day of admission were significantly correlated and higher in the surgery only group that (15625 ± 21275.2 *vs* 8073.2 ± 9561.00, p = 0.046065. Further successive measurements of serum ß-hCG throughout the course of therapy and on the day of discharge demonstrated that the group that was managed with surgery and methotrexate had lower levels of serum ß-hCG in comparison to the group that had undergone surgery only (1071.4 ± 1269.11 *vs* 5935.66 ± 4378.6, p = 0.01824). The two groups were significantly correlated in terms of length of hospital stay (p < 0.05). The surgery plus methotrexate group were discharged from hospital much earlier than the group who received surgery only (3.00 ± 0.816 *vs* 5.66 ± 2.80) Table 3.

DISCUSSION

From a select population of 8,547 ectopic pregnancies diagnosed in our institution between 7th August, 2006 and 20th April, 2017, only 10 (0.11%) cases were diagnosed and treated as early abdominal pregnancy representing the least form of ectopic pregnancy in our institution. Endo-

metriosis, the current usage of an intrauterine device and a history of tubal surgery or ectopic pregnancy are some of the documented risk factors for abdominal pregnancy and also implicated in other forms of ectopic pregnancies [11]. The sites of implantation from the commonest to the least reported include the pouch of Douglas (pouches surrounding the uterus), uterine serosa and adnexa, abdominal organs, omentum, bowel/appendix, liver (common site is the right lobe), spleen, retroperitoneal and the wall of the abdomen. Similar implantation locations were discovered in this present study. All cases indexed in this study met the established criteria for primary abdominal pregnancy: (1) normal ovaries and tubes with no evidence of injury, (2) no evidence of uteroplacental fistula, and (3) the pregnancy is adhered exclusively to the peritoneal surface early enough in gestation to eliminate the possibility of secondary implantation after primary nidation in the fallopian tube [12].

The diagnosis of early abdominal pregnancy is a huge clinical hurdle as most of the investigative tools are sometimes unreliable. Presenting symptoms are not strong diagnostic tools due to the absence of typical pathognomonic symptoms to properly define early abdominal pregnancy. Additionally, due to the upsurge of serum ß-hCG levels in other forms ectopic pregnancies and the difficulty associated with singling out early abdominal pregnancy based on ultrasonographic features, these investigations are not very instrumental in diagnosis as well [4, 5, 13]. In this present study, diagnostic surgery was the first line option due to the worsening nature of their symptoms and our high suspicion of ectopic rupture. We proceeded quickly with either diagnostic laparotomy or laparoscopy to avert any mortalities or complications and to also aid in the formulation of a better post-operative treatment regime. Until recently, laparotomy was the conventional surgical approach but several reports have exhibited the novelty of diagnostic laparoscopic approach in early abdominal pregnancy management [9, 14]. In one study to compare the treatment outcomes of these two modalities in abdominal pregnancies, it was observed that, with advancement in technology and improved surgical skills more cases can be confidently managed laparoscopically. The authors also reported varying advantages of management with laparoscopy ranging from reduced blood loss to short hospital stay [15].

Diagnostic laparoscopy was carried out uneventfully and peri-operative findings included normal uterus and adnexa in all cases, hemoperitoneum of about 250cc and 320cc for cases 3 and 9 respectively and were transfused with 2 units of whole blood and 3 units of packed red blood cells respectively during surgery. Further examination of the abdomen revealed bloody lesions that were loosely or tenaciously adhered to varying locations in the abdomen. These lesions were removed with the help of non-traumatic laparoscopic forceps and bipolar scissors. In all laparoscopic cases, we achieved hemostasis with the help of bipolar coagulation ruling out the need for suturing. Laparotomy was successfully carried out on three patients (Case 1, 2, 3) but factors that necessitated this choice of management were not recorded. Clinically, the decision to opt for laparotomy can be decided on factors like the anatomical position of the pregnancy or the laparoscopic skills and confidence of the surgeon [16]. Because of the likelihood of implantation on vascularized surfaces which may have high propensity to separate at any time to cause heavy bleeding, the decision between these two management modalities should be precise and prompt [17].

Methotrexate (MTX) has proven to be an effective agent in managing ectopic pregnancy medically since its introduction in 1982 [18]. Its effectiveness has been likened to surgery in terms of treatment results and preservation of future fertility [19, 20]. Successful treatment which meant avoidance of surgery was recorded to be 94.4% in women with initial β-hCG levels of 1000 to 1999 mIU/mL and 81.8% in their counterparts with levels from 10,000 to 150,000 mIU/mL. In early abdominal pregnancy, however, there is a high probability of reverting to surgical management among patients who receive systemic or local injections of MTX as first line therapy [6, 13, 21]. The decision for the use of post-operative MTX in ectopic pregnancy include cases were, potential life-threatening torrential bleeding can be foreseen or when there is an upswing or a less than 20% drop in the levels of serum ß-hCG measured consecutively on 3 days apart or prophylactically when incomplete resection or persistent ectopic pregnancy is likely [22, 23]. By virtue of the position of their lesions on highly vascularized organs and presence of hemoperitoneum which was suggestive of rupture, the surgeons advised the use of methotrexate (MTX) in Case 5, 6 and 7. On the other hand, Case 9 received methotrexate (MTX) because the clinicians suspected persistence of her pregnancy which was evidenced by upsurge in her serum HCG levels on post-operative day 2. Although, cases 2, 8 and 10 witnessed fluctuations in their serum HCG levels post-operatively to also permit the use of MTX, contra-indicatory factors like existing peptic ulcer (Case 2), hemodynamic instability (Case 8) and non-compliance (Case 10) did not make them good candidates [24]. Regarding treatment outcomes, we cannot confidently draw any valid inference from post-operative serum levels among the two groups. The gestational ages and the pre-operative HCG levels were lower in the surgery + MTX group in comparison to the surgery only group and therefore it is likely the reason why their serum ß-HCG levels on hospital discharge were lower. Additionally, the reduced blood loss among the surgery + MTX group could also account for their shorter days of hospitalization. Data from this present study regarding future fertility is inconclusive, although the use of MTX is

reported to enhance future fertility in other forms of tubal ectopic pregnancy [25].

CONCLUSIONS

The rarity, complex history and atypical clinical characteristics of abdominal ectopic pregnancy make its diagnosis and management extremely puzzling. Conservative surgery and medical therapy can be regarded as appropriate treatment modalities but diagnostic laparoscopy has become the optimal choice because it ensures earliness in diagnosis and offers a better view of the location to determine the size and relative vascularity. A thorough inspection of the abdominal viscera should be carried out to rule out implantation at uncommon sites. Adjuvant MTX therapy can help reduce complications especially when torrential bleeding from vascularized sites can be anticipated but the selection of good candidates still remains crucial. The paucity of information on abdominal pregnancy retrieved from only case reports and series limits this study to a larger extent. Non-compliance from patients in this indexed study makes the data on serial post-operative serum ß-HCG levels statistically insufficient to draw any strong conclusions from in terms of treatment outcomes. Further studies are therefore needed to adequately examine the usefulness of post-operative MTX clinically.

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Statement of ethics

Permission to carry on with this study was granted after careful evaluation by the Ethics Committee of The First Affiliated Hospital of Wenzhou Medical University (wydw2017-0115) and after patients gave their verbal consent through telephone calls.

Authors' contributions

EA conceived, designed the study and drafted the manuscript, GI and LS helped data collection, analyzed the data and help draft the manuscript. XW revised the manuscript, providing intellectual content. All authors commented on and approved the final manuscript.

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Safety and success rate of vaginal birth after two cesarean sections: retrospective cohort study

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ABSTRACT

Objectives: Cesarean section is a lifesaving procedure with short and long-term consequences. Growing rates of cesarean sections worldwide arise problems for subsequent birth. The aim of this study was to compare safety of vaginal birth after two cesarean sections with repeat third cesarean section to help healthcare providers and patients make well informed decisions about mode of subsequent delivery.

Material and methods: This was a retrospective cohort study conducted in a tertiary reference hospital. Database of all deliveries (2010–2017) after two previous cesarean sections was created from electronic and paper medical records. Preterm deliveries, abnormal karyotype and neonates with congenital anomalies were excluded from the study. The final analysis included 412 cases for maternal outcome analysis and 406 cases for neonatal outcome analysis.

Results: Trial of labor after two cesareans in comparison to repeat cesarean section increases the risk of hemorrhage (OR: 10.84) and unfavorable composite maternal outcome (OR: 2.58). Failed trial of labor increases this risk of hemorrhage (OR: 15.27) and unfavorable composite maternal outcome (OR: 4.59) even further. There were no significant differences in neonatal outcomes. 22 out of 35 trials of labor ended in successful delivery giving a success rate of 62.85%. 5 of 7 labor inductions ended in repeat cesarean section giving 28.6% success rate. There were no maternal deaths and emergency hysterectomies.

Conclusions: Trial of labor, especially failed trial of labor, is associated with an increased risk of perinatal complications.

Key words: vaginal birth after two cesareans; cesarean section; trial of labor; uterine rupture; obstetric labor complications

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INTRODUCTION

Cesarean section is a well-established surgical technique when vaginal delivery carries a substantial risk for the mother or baby or is otherwise contraindicated. Despite obvious benefits it may pose serious short and long-term consequences [1, 2]

Cesarean section rates are increasing worldwide, being as high as 55% in some regions. The current rate of cesarean delivery in Poland is 36.1% [3–6]. Women with a previous cesarean section decide on having another child regardless of the documented higher risks of such pregnancy [7, 8]. Choosing the right mode of delivery is a challenge for the mother and healthcare provider. Both vaginal delivery after cesarean and repeat cesarean delivery (RCS) are associated with maternal complications [9–13]. Risk of most maternal complications increases proportionally to the number of cesarean sections [14, 15]. Whether or not trail of labor after two cesarean sections (TOLAC-2) increases neonatal mortality is still to be established. [16–18].

Obstetric colleges worldwide, including Polish, recommend trial of labor after one cesarean and state that trial after two cesareans is not contraindicated [19–21].

Objectives

The aim of this study was to make a pragmatic comparison of TOLAC-2 and RCS. These results may help clinicians and women make informed decisions about delivery route. The main thesis of this study was that TOLAC-2 carries no greater risk than RCS.

MATERIAL AND METHODS

Anonymous electronic records of all 47,011 singleton deliveries between 2010–2017 were extracted from the hospital patient management system. 432 records of women with pre-

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vious two cesarean deliveries were identified, and individual paper records were analyzed to extract data unavailable in electronic records. Predefined exclusion criteria for maternal outcome were: preterm deliveries (17 cases), placenta previa (3 cases). 412 cases were included in the maternal analysis. Predefined exclusion criteria for neonatal outcome were: abnormal karyotype, major congenital anomalies (definition: EUROCAT Guide 1.4) [22]. 406 cases were included in the neonatal analysis. Data extraction process is shown on Figure 1.

The cohort was divided into two groups depending on intended mode of delivery: TOLAC-2 and RCS. Each group was additionally divided into two subgroups. TOLAC-2 was divided into successful vaginal delivery after two cesareans (VBAC-2) and failed TOLAC-2. RCS was divided depending on timing of procedure — as scheduled and unscheduled (i.e. preformed before planned operation date, exclusively because of onset labor).

Safety and success rate of VBAC-2 was the main focus of the analysis. Analyzed maternal outcomes were maternal death, postpartum hemorrhage, hysterectomy, uterine rupture, need for blood products transfusion, bladder or bowel injury. The outcomes were analyzed separately, given their relative scarcity, and in combination as composite maternal outcome. There is no CROWN core outcome set for trial of labor.

Uterine rupture was defined as any detected cesarean scar dehiscence, independently of size or clinical symptoms. A retrospective study did not allow for reliable discrimination between symptomatic uterine rupture and asymptomatic uterine scar dehiscence. Postpartum hemorrhage was defined as estimated blood loss of 500 mL after vaginal or 1000 mL after cesarean delivery, as defined by World Health Organisation (WHO) [23].

The medical records were searched for information on use of the Bakri balloon, curettage or additional operative procedures after VBAC-2. Additionally, cesarean section protocols were searched for information on use of additional sutures or other surgical intervention to stop bleeding. Each of the described were categorized as need of additional hemostatic procedures even if blood loss did not meet criteria for hemorrhage. Patient documentation did not specify if use of additional uterotonic, was prophylactic or treatment, making this analysis impossible.

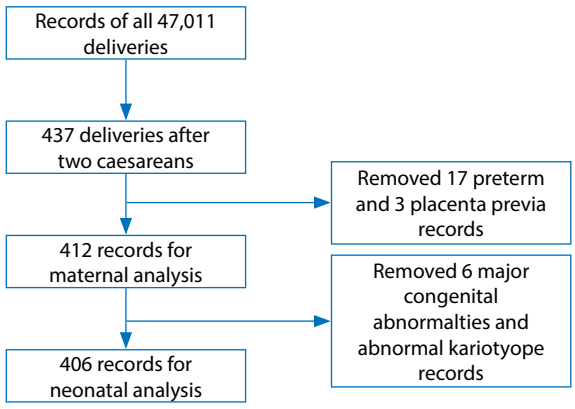

Figure 1. Data extraction process

Surgical complications were defined as intraoperative damage of bladder or intestine, postoperative hematoma, impaired wound healing or need for relaparotomy.

Composite maternal outcome was defined as occurrence of any mentioned above but uterine rupture. Uterine rupture was not included in the composite maternal outcome due to high risk of detection bias. If a woman had multiple outcomes, she was counted only once.

Length of hospital stay was calculated in full days using admission and discharge date and compared for subgroups.

Neonatal outcome was defined as 5-minute Apgar score < 7, intraventricular hemorrhage, periventricular leukomalacia, hypothermia, seizures, neonatal sepsis, diagnosed birth asphyxia and neonatal death. They were analyzed separately and combined into composite neonatal outcome. Cord blood pH was not routinely tested making any comparisons likely to be biased.

Effort has been made to check consistency and completeness of database. If electronic and paper records data extraction yielded different results, then the records were double-checked and corrected. Database was checked for duplicate records. There was no missing outcome data.

Statistical analysis

Statistical calculations were performed using Microsoft Office Excel (Microsoft Corp., Redmond, USA) and R [R Development Core Team (2012). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. ISBN 3-900051-07-0, URL http://www.R-project.org/]. The statistical analysis of odds ratio (OR) of the maternal and neonatal outcomes was performed on a basis of χ^2 test and normal test (used as a basis for p-value estimation and assessment of statistical significance). Both normal and χ^2 models resulted in consistent estimates. Confidence intervals (CI) for OR were derived on a basis of a normal model, assuming 95% level of confidence. For outcomes of uterine rupture in unscheduled RCS and need of transfusion in VBAC-2 subgroups, p-value calculated using χ^2 model were equal to 0.048 and 0.047 respectively. In these two cases, the table presents p-values derived using normal model. The analysis of the statistical significance of the differences in blood loss between selected groups was performed on a basis of two sample t statistic, assuming 95% level of confidence. All significance tests were two sided and conducted at the 5% significance level.

Bioethics Committee of the Centre of Postgraduate Medical Education approval (reference number 47/PB/2018) for this project was obtained on 11th of April 2018. According to Polish law creation of an anonymous database does not need individual participants' agreement.

RESULTS

Comparison of baseline characteristics of the studied population is presented in Table 1. We did not find significant differences in any of the analyzed variables including pregnancy complications (cholestasis of pregnancy, diabetes in pregnancy, pre-pregnancy hypertension and pregnancy hypertension — data not shown).

Success rates of VBAC-2 were calculated among 35 women who underwent TOLAC-2. In this group 22 had a VBAC-2, there was no operative vaginal deliveries and 12 required an emergency cesarean section.

The number and percentage of women willing to undergo TOLAC-2 was similar in the years 2010–2016, with substantial rise in 2017. In 2017 there were 19 TOLAC-2 including 12 VBAC-2 (12,5% of all deliveries after two cesareans) — see Figure 2.

In the analyzed period there were 7 labor inductions after two cesareans, 4 with *i.v.* Oxytocin infusion, 1 with intracervical Foley catheter insertion and 2 with both methods used. Of those, 2 ended in vaginal birth, 3 in emergency cesarean section because of threating birth asphyxia, and 2 in cesarean section because of arrested first stage of labor. Remaining 28 TOLAC-2 patients where admitted to the hospital in the first stage of labor, there were no admissions during second stage of labor.

Maternal outcomes are presented in Table 2 († p-values delivered from normal model). Uterine rupture (11 cases)

Table 1. Baseline demographic characteristic of studied population

	Repeat caesarean section			Trial of labour		
	Scheduled repeat caesarean section	Unscheduled repeat caesarean section	Repeat caesarean section — total	VBAC-2	Failed TOLAC-2	Trial of labour — total
Maternal age [years]	35.35 (± 3.86)	34.35 (± 4.77)	35.25 (± 3.96)	32.45 (± 4.27)	33.85 (± 3.26)	32.97 (± 3.97)
Parity	3.04 (± 0.21)	3.08 (± 0,43)	3.07 (± 0.41)	3.3 (± 0.95)	3.5 (± 0.83)	3.38(± 0.89)
BMI at booking	24.13 ± 4.52	22.38 ± 3,99	23,97 (± 4.5)	22.55 ± 2.73	22.79 ± 1.75	21.94 (± 2.48)
BMI at delivery	28.92 ± 4.41	27.45 ± 4.20	28.79 (± 4.41)	26.34 ± 3.11	28.12 ± 2.91	26.98 (± 3,12)
Weeks of pregnancy (completed)	38.5 (± 0.71)	38.06 (± 0.94)	38.39 (± 0.74)	39.91 (± 0.92)	40.00 (± 1.08)	39.88 (± 1.09)
Birthweight [g]	3,464.59 (± 407)	3,302.83 (± 411.40)	3,449 (± 409)	3,760.68 (± 392.50)	3,886.15 (± 448.75)	3,807 (± 412)

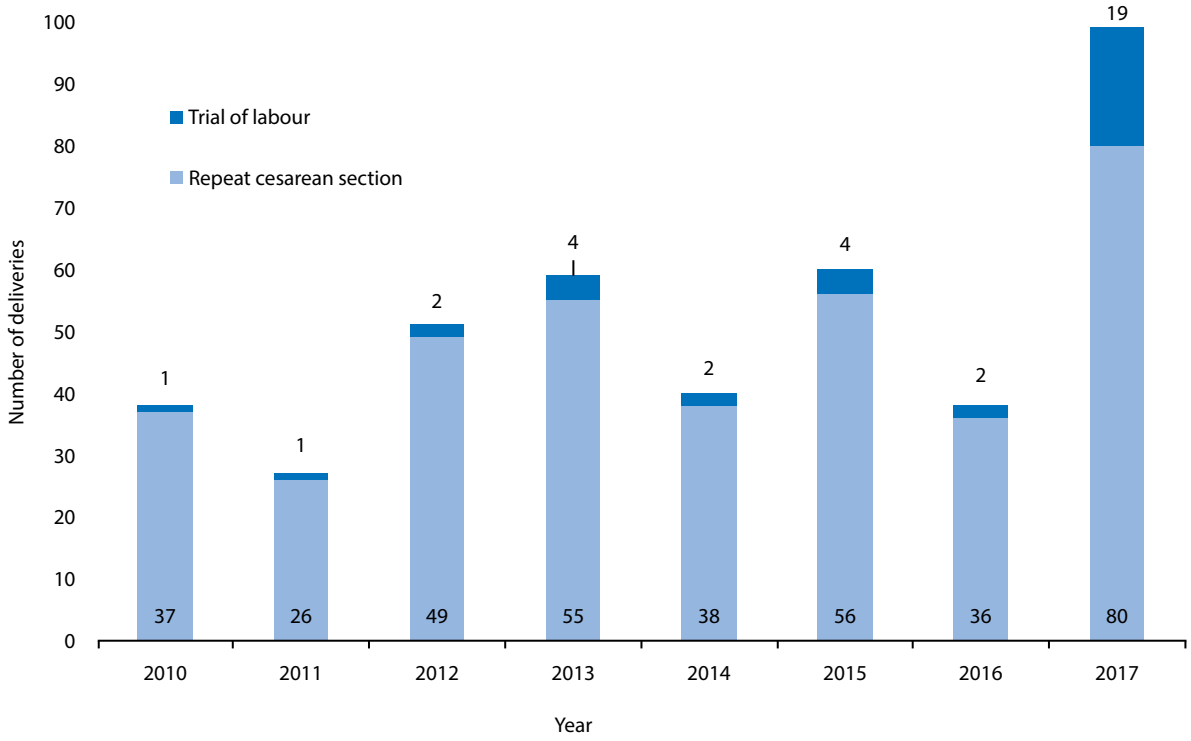

Figure 2. Frequency of trial of labor after two cesareans

Table 2. Maternal outcomes. † p–values delivered from normal model

			Total number of deliveries	Maternal death	Hysterectomy	Uterine rupture	Haemorrhage	Surgical complications	Need of additional haemostatic procedures	Need of transfusion	Composite maternal outcome
Repeat caesarean section	Scheduled repeat caesarean section (reference)	Number of cases	340	0	0	8 (2.4%)	4 (1.2%)	9 (2.6%)	20 (5.9%)	2 (0,6%)	30 (8.8%)
		OR (95% CI)	–	–	–	1.0	1	1	1	1	1
		p-value	–	–	–	–	–	–	–	–	–
	Unscheduled repeat caesarean section	Number of cases	37	0	0	3 (8.1%)	1 (2.7%)	2 (5.4%)	6 (16.2%)	1 (2.7%)	10 (27%)
		OR (95% CI)	–	–	–	3.66 (0.93–14.45)	2.33 (0.25–92.44)	2.10 (0.44–10.11)	3.10 (1.16–8.28)	4.69 (0.42–53.06)	3.83 (1.69–8.66)
		p-value (χ^2)	–	–	–	0.063†	0.44	0.34	0.019	0.17	0.0006
	Repeat caesarean section — total	Number of cases	377	0	0	11 (2.9%)	5 (1.3%)	11 (2.9%)	26 (6.9%)	3 (0.8%)	40 (10.6%)
		OR (95% CI)	–	–	–	1.25 (0.5–3.14)	1.13 (0.30–4.24)	1.11 (0.45–2.7)	1.19 (0.65–8.8)	1.36 (0.23–56.25)	1.23 (0.75–6.41)
		p-value	–	–	–	0.63	0.85	0.82	0.58	0.73	0.42
Trial of labour	VBAC–2	Number of cases	22	0	0	0	2 (9.1%)	0	2 (9.1%)	1 (4.5%)	3 (13.6%)
		OR (95% CI)	–	–	–	–	8.40 (1.45–8.65)	–	1.60 (0.35–7.33)	8.05 (0.7–92.39)	1.63 (0.46–5.83)
		p-value (χ^2)	–	–	–	–	0.0048	–	0.54	0.094†	0.45
	Failed TOLAC–2	Number of cases	13	0	0	0	2 (15.4%)	1 (7.7%)	2 (15.4%)	0	4 (30.8%)
		OR (95% CI)	–	–	–	–	15.27 (2.52–92.44)	3.06 (0.36–26.17)	2.91 (0.60–14.02)	–	4.59 (1.33–15.81)
		p-value (χ^2)	–	–	–	0.57	0.0001	0.28	0.16	–	0.0085
	Trial of labour — total	Number of cases	35	0	0	0	4 (11.4%)	1 (2.9%)	4 (11.4%)	1 (2.9%)	7 (20.0%)
		OR (95% CI)	–	–	–	–	10.84 (2.58–45.47)	1.08 (0.13–8.80)	2.06 (0.66–6.42)	4.97 (0.44–56.25)	2.58 (1.04–6.41)
		p-value (χ^2)	–	–	–	0.36	0.0001	0.94	0.2	0.15	0.035

was exclusively detected during cesarean section. Each VBAC-2 individual had digital examination of cesarean scar after delivery and no dehiscence was found. None of 12 cesarean sections in the failed TOLAC-2 group was conducted because of presumed scar dehiscence, also no scar dehiscence was found in this group during surgery.

VBAC-2 subgroup had lowest mean estimated blood loss, followed by scheduled RCS, failed TOLAC-2 and unscheduled RCS. In comparison to scheduled RCS subgroup, the risk of hemorrhage was highest in failed TOLAC-2, followed by VBAC-2 and unscheduled RCS. Need for additional hemostatic procedures, compared to scheduled RCS was highest in unscheduled RCS, followed by failed TOLAC-2 and VBAC-2 subgroup. We have found two cases of incomplete placenta in VBAC-2 group, one of them was the reason for maternal hemorrhage. Second case of bleeding occurred because uterine subatony.

Risk of transfusion after TOLAC-2 was higher than after RCS but the result was statistically insignificant. The identified surgical complications were exclusively related to cesarean section. Of 377 women in RCS group 11 had surgical complications. In failed TOALC-2 group one woman had surgical complications during cesarean section. Relaparotomy had to be performed in two cases, one because of intrabdominal hemorrhage (scheduled RCS subgroup), second because of bladder injury (unscheduled RCS subgroup).

Composite maternal outcome showed higher risk of complications in TOLAC-2 group. However, VBAC-2 subgroup comparison with scheduled RCS showed no statistically significant difference in VBAC-2 safety. Failed TOLAC-2 and unscheduled RCS composite maternal outcome where both higher than reference scheduled RCS. Maternal outcomes were compared in an intention-to-treat analysis, showing much higher risk of hemorrhage in TOLAC-2 group. Mean hospitalization time in RCS was 4.45 days and 3.80 days in TOLAC-2. Odds ratios for each outcome are shown on Figure 3.

Neonatal outcomes (Tab. 3) were analyzed separately and combined into composite neonatal outcome. Neither of the individual neonatal outcomes nor composite neonatal outcome reached statistical significance. We did not observe 5-minute Apgar score < 7, intraventricular hemorrhage, periventricular leukomalacia, hypothermia, neonatal sepsis and neonatal death in our cohort (data not shown).

Maternal outcomes from intention-to-treat, planned TOLAC-2 or RCS, are presented in Table 4. ITT analysis showed greater risk of hemorrhage in TOLAC-2 patients but did not show difference for other analyzed outcomes.

No maternal death or hysterectomy took place in our cohort; thus, we were not able to analyze those outcomes.

DISCUSSION

Our findings suggest that vaginal birth after two cesareans carries a higher risk to mother and has no effect on the neonate. We did not find increased risk of uterine rupture

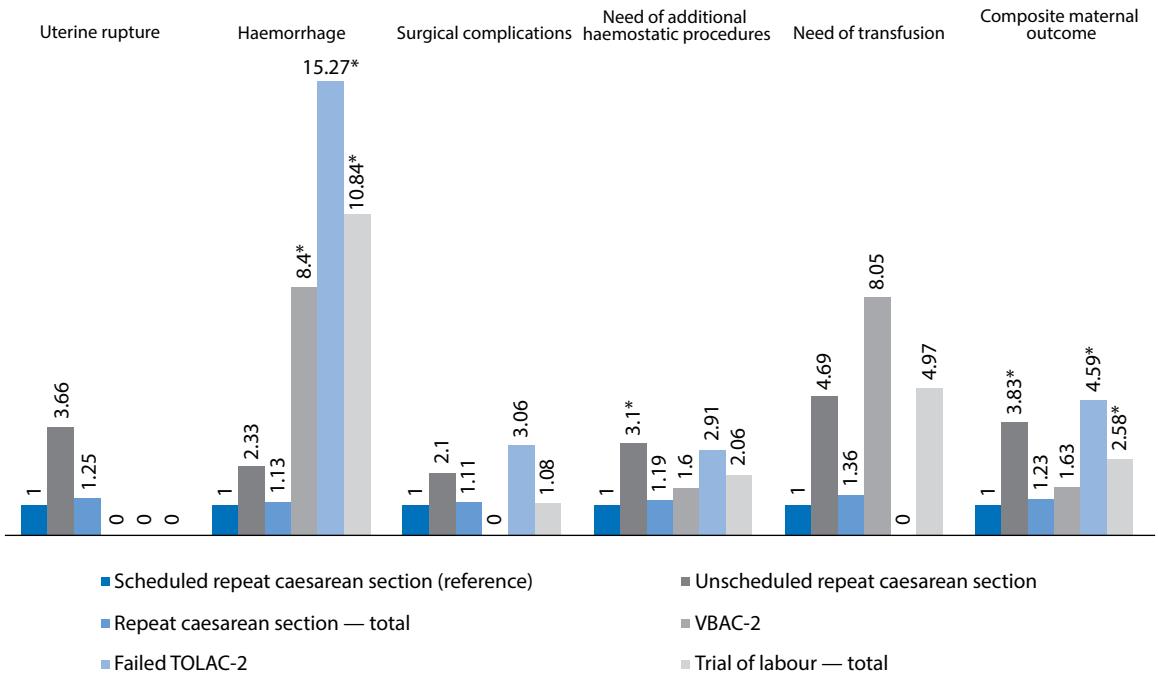

Figure 3. Odds ratio for maternal complications. Scheduled repeat caesarean section as reference; VBAC-2 — vaginal birth after two cesareans, TOLAC-2 — trial of labor after two cesareans; * Statistically significant

Table 3. Neonatal Outcomes — all results delivered from χ^2 model

Neonatal outcomes in groups and subgroups																
	Repeat caesarean section						Trial of labour									
	Scheduled repeat caesarean section (reference)			Unscheduled repeat caesarean section			Repeat caesarean section — total			VBAC-2			Failed TOLAC-2			Trial of labour — total		
	Number of cases	OR (95% CI)	p-value	Number of cases	OR (95% CI)	p-value	Number of cases	OR (95% CI)	p-value	Number of cases	OR (95% CI)	p-value	Number of cases	OR (95% CI)	p-value	Number of cases	OR (95% CI)	p-value
Total number of deliveries	334	–	–	37	–	–	371	–	–	22	–	–	13	–	–	35	–	–
Respiratory difficulties	10 (3.0%)	–	–	0	–	–	10 (2.7%)	0.9 (0.37–2.18)	0.81	0	–	–	1 (7.7%)	2.7 (0.32–22.83)	0.34	1	0.95 (0.12–2.18)	0.96
Birth aspyxia	1 (0.3%)	–	–	0	–	–	1 (0.3%)	0.9 (0.06–14.45)	0.94	0	–	–	0	–	–	0	–	–
Neonatal seizures	1 (0.03)	–	–	0	–	–	0	–	–	0	–	–	0	–	–	0	–	–
Composite neonatal outcome	12 (3.6%)	–	–	0	–	–	12 (3.2%)	0.9 (0.42–1.91)	0.79	0	–	–	1 (7.7%)	2.24 (0.27–18.83)	0.45	1 (2.9%)	0.67 (0.09–5.27)	0.82

during trial of labor, but risk of hemorrhage was very high. Composite maternal outcome risk was also higher in TOLAC-2 group, especially in failed TOLAC-2. Therefore, good qualification for vaginal birth is essential for decreasing trial of labor complications. Trial of labor has a high enough success rate to justify recommending it to the patient.

We tried to select all clinically relevant outcomes. Need of use of uterotonic drugs to treat hemorrhage was one of the selected outcomes, but paper and electronic records did not contain enough data to reliably allow such analysis. All other selected outcomes data is provided, even if the analysis yielded insignificant results.

Electronic and paper records where cross-checked, minimalizing risk of error.

Limitation of this study is its retrospective character. Differentiation between uterine scar dehiscence and rupture or if use of uterotonics was prophylactic or for treatment purposes was impossible.

During study time there were total 47011 births and only 35 TOLAC-2. This is probably an effect of low patient awareness of VBAC-2 availability, healthcare provider reluctance to propose trial of labor after two cesarean sections because of fear of complications and medico-legal issues. To our knowledge there are no Polish trials trying to establish to what extent each cause is responsible for this situation. International studies emphasize healthcare provider view on complications, medico-legal problems, better "predictability" of RCS, patient anxiety [24, 25]. Rise of number of TOLAC-2 in 2017 was probably an effect of widespread information of Hospital policy in social media.

The risk of uterine rupture in this study was 2.67% and is similar to uterine rupture rate in work of Caughey et al. [26], Macones et al. [9] and by Landon et al. [27]. Metanalysis by Tahseen and Griffiths show risk of uterine rupture of 1.36% [10]. In the studied cohort all uterine ruptures were detected during cesarean section. Detection of scar dehiscence is rare with transcervical digital scar revision [28, 29]. Gamer et al. also reported a high risk of detection bias in a trial scoped for detecting uterine rupture by transcervical manual control [29]. Results obtained by Spaans et al. [30] with uterine scar dehiscence detected mostly during cesarean section show similar pattern to this study.

Risk of postpartum hemorrhage was the most prominent difference between mode of delivery groups. Risk of substantial blood loss is much higher in trial for labor group. Current literature review shows there is no study describing the rate of postpartum hemorrhage in TOLAC-2. Small numbers make drawing conclusions difficult but we think that changed uterine architecture and altered contraction mechanics could be responsible for increased blood loss, especially in failed TOLAC-2 where changes are probably the greatest.

Study by Macones et al. [9] and metanalysis of Tahseen and Griffiths [10] show VBAC-2 to have a lower risk of transfu-

Table 4. Maternal outcome regarding intended mode of delivery

Maternal outcome – intention to treat analysis						
	RCS (reference)			TOLAC-2		
	Number of cases	OR (95% CI)	p	Number of cases	OR (95% CI)	p
Haemorrhage	5 (1.3%)	–	–	4 (11.4%)	9.6 (2.45–37.59)	0.0001
Surgical complications	11 (2.9%)	–	–	1 (2.9%)	0.98 (0.12–7.81)	0.98
Need of additional haemostatic procedures	26 (6.9%)	–	–	4 (11.4%)	1.74 (0.57–5.31)	0.32
Need of transfusion	3 (0.8%)	–	–	1 (2.9%)	3.67 (0.37–36.22)	0.23
Composite maternal outcome	40 (10.6%)	–	–	7 (20%)	2.11 (0.86–5.13)	0.095

sion. The presented study found a contradictory result but did not reach statistical significance.

In this cohort the risk of surgical complications was two times higher for unscheduled RCS and three times higher in cesarean section because of failed TOLAC-2. Although the results were not statistically significant, they are consistent with results presented by Silver et al. [31] and Phipps et al. [32].

Composite maternal outcome analysis showed that vaginal birth after two cesareans is associated with a 2.58 higher risk of complications, similar to that reported by Macones et al. [9] Although a 2.58 increase in risk is considered high it has to be kept in mind that patients who underwent TOLAC-2 were very motivated. However, a higher risk of complications is mainly related to failed trial of labor while complications of successful VBAC-2 are much less frequent. Intention to treat of intended mode of delivery complications showed increased risk of hemorrhage in TOLAC-2, without increased risk of other complications. This result needs emphasizing, as women and healthcare provider could decide about intended mode of delivery, not about actual mode of delivery.

A paper of Tahseen and Griffiths [10] quoted an overall success rate of 71.7%, with individual studies varying from 45 to 83%. In our cohort 62.85% of patients achieved vaginal birth.

No evidence was found to support the idea of increased neonatal morbidity or mortality after TOLAC-2. Such risk for delivery after one cesarean section is described in a paper of O'Neil et al. [16] but authors found substantial cohort effect, with risk decreasing over time, with no risk increase in the most recent period. Older work of Smith et al. [17] also describe much higher risk for perinatal death after trial of labor after cesarean comparing to RCS, but this data comes from years 1992–1997. The results of the presented study are similar to those reported by Menacker et al. in 1998–2002 cohort [33].

Current recommendations of obstetric colleges worldwide state that planned VBAC may be supported in women with two or more previous lower segment caesarean deliveries" — Royal College of Obstetrics and Gynaecology, "Given the overall data, it is reasonable to consider women with two previous low-transverse cesarean deliveries to be candidates for TOLAC" — American College of Obstetrics and Gynecology, "trial of labor in women with more than 1 previous Cesarean is likely to be successful but is associated with a higher risk of uterine rupture" — Polish Society of Obstetrics and Gynecology, "TOLAC (after two cesareans) is possible" — French National College of Obstetricians and Gynecologists [19–21, 34]. Encouragement from professional organizations could have an impact on graduate increase of TOLAC-2.

CONCLUSIONS

This study shows TOLAC-2 to be reasonable in terms of safety and has a good success rate. It is associated, especially failed TOLAC-2, with increased risks and women should be openly informed about them. In light of this study both VBAC-2 and RCS are high-risk procedures and should be performed only if highly trained personnel and resources are available.

From a practical point of view TOLAC-2 is not of greater risk to the patient if it ends in vaginal delivery. Of course, healthcare provider could not foresee exactly if trial will be successful, but careful qualification for trial of labor could prevent at least some of the delivery complications.

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Assessment of selected parameters of placental microstructure in patients with intrahepatic cholestasis of pregnancy

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ABSTRACT

Objectives: Intrahepatic cholestasis of pregnancy (ICP) is the most common liver disorder during pregnancy. Cholestasis is associated with increased risk of fetal complications: prematurity, perinatal hypoxia and meconium stained amniotic fluid, and sudden intrauterine fetal death. The exact mechanisms associated with cholestasis fetal sequelae are not fully understood. The aim of the study was the histopathological evaluation of placentas from patients with cholestasis and healthy pregnant women to establish whether cholestasis is accompanied by changes in placental microstructure.

Material and methods: The effect of cholestasis on placental microstructure was investigated using placental tissue from patients with cholestatsis treated with ursodeoxycholic acid (UDCA) and from uncomplicated pregnancies. Five placental histopathological features were analyzed: number of syncytial knots, number of capillaries per villous, structure of stroma, presence of Hofbauer cells, and villitis of unknown etiology.

Results: There were no statistically significant differences in any of the studied parameters between cholestasis-affected and healthy control groups.

Conclusions: There are no diffrences in placental microstructure in cholestasis patients treated with UDCA and in patients with uncomplicated pregnancy.

Key words: intrahepatic cholestasis of pregnancy; ursodeoxycholic acid; placenta; histology

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INTRODUCTION

Intrahepatic cholestasis of pregnancy is the most common liver disorder during pregnancy, occurring in 1% of pregnancies. Very frequently ICP develops during the late second and third trimesters. Pregnant women with cholestasis present characteristic symptoms: pruritus, especially during the night, associated with abnormal liver function. These signs usually resolve after delivery. Among others, the most important biochemical feature of ICP is elevated serum bile acid levels (> 10 mmol/L) [1]. Cholestasis is associated with increased risk of fetal complications: prematurity, perinatal hypoxia and meconium stained amniotic fluid, and sudden intrauterine fetal death [2]. The increased risk of detrimental perinatal results correlates with high bile acid concentration (> 40 mmol/L) [3]. The exact mechanisms associated with cholestasis fetal sequelaes are not fully understood. In the normal course of pregnancy, the total concentration of bile acids in fetal serum is only sligthly higher than in maternal serum. Because the fetal hepatobiliary and renal systems are not fully developed and cannot eliminate bile acids, the latter must be transferred across the placenta to be eliminated by the maternal liver. In patients with cholestasis, as a result of high levels of bile acids in the serum, the transplacental bile acid gradient is reversed, causing impairment placental transport [1, 4].

Bile acids induce vasoconstriction of the chorionic vessels in the placenta that causes impaired fetal-maternal transport across the placenta, damage of the placental structure and reduced transport of nutrients and oxygen to the fetus.

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Little is known about the effect of intrahepatic cholestasis of pregnancy on the placental structure. Most reports involving sudden intrauterine fetal death are not connected with prominent morphological changes in the placenta or the features of its chronic insufficiently [5, 6].

The aim of the study was to evaluate the histopathological changes of placentas from patients with cholestasis and healthy pregnant women to establish whether cholestasis affects placental microstructure.

MATERIAL AND METHODS

Twenty patients with intrahepatic cholestasis and 40 women as controls with physiological pregnancy who delivered in 2018 in the Gynecologic and Obstetrical University Hospital, Poznan, Poland were qualified to this prospective case-control study. Recognision of cholestasis was determined after excluding other liver diseases (viral hepatitis, acute fatty liver of pregnancy, pre-eclampsia, primary biliary cirrhosis and HELLP syndrome), on the basis of unexplained itching associated with increased bile acid (> 10 mmol/L) and liver dysfunctions. We also excluded patients with complications of pregnancy other than ICP. We included patients with physiological pregnancy in the control group. Patients in the control group did not have cholestasis in their previous pregnancy or pruritus in the previous or current pregnancy. Inclusion criteria for pregnant women with cholestasis and controls demanded that all patients have single, live-born newborn.

All participants gave written informed consent. The obtained data included concentration of transaminases and bile acid at the time of diagnosis and delivery, gestational week at diagnosis and delivery, the highest concentration of bile acid and transaminases, neonatal birth weight, umbilical pH value, Apgar score, placental weight, and placental/neonatal birth weight ratio (Tab. 1). All women with ICP were treated with ursodeoxycholic acid (UDCA). All the participants were nonsmokers.

The study was approved by the Ethical Committee of Poznan University of Medical Sciences.

Collection of samples and slide preparation

After delivery placentas were weighed and fixed in 4% buffered formalin for 10 days. After fixation, the samples were dehydrated using in sequence: 70–100% series of ethyl alcohol dilutions, xylene, and embedded in 58°C paraffin. Samples were cut at 5 mm using a microtome (Leica SM 2010R) and mounted on slides. The slides were incubated for 2 h at 58°C to remove excess paraffin and ensure laminar adhesion. Deparaffinization was performed in three changes of xylene for 10 min each. Next, the slides were rehydrated through a 100–70% series of ethyl alcohol dilutions and washed in distilled water. Finally, deparaffinized samples were stained with hematoxylin and eosin (HE) and examined with a light microscope with camera attachment (Axioskop 40 ZEISS) with 100x and 400x magnification.

Histology

Histological analysis of the preparations (n = 20 ICP patients, n = 40 control patients) was performed by pathologist unaware of gestational age and disease status.

Evaluation of syncytial knots

The definition of syncytial knots was described by Geenes et al. [7] as the presence of at least 10 aggregated syncytiotrophoblast nuclei that were not in direct contact with communicating villi surfaces. They illustrate areas of intensified apoptosis. In pregnancies with a pathological course complicated by intrauterine growth restriction and pre-eclampsia the amount of syncytial knots enhances.This phenomenon is a result of increased placental apoptosis. Exposure placental explant patches to influence of hyperoxia, hypoxia or reactive oxygen species in vitro causes creation of syncytial knots [7].

Table 1. Characteristics of maternal and delivery outcomes: values expressed as median (range) or mean (± SD)

	ICP (n = 20)	Control (n = 40)	P value
Maternal characteristics			
Age [years]	30 (± 5)	30 (± 5)	0.869
Gravity	1 (1–6)	(1–4)	0.402
Parity	0–5	0–3	0.415
Fetal characteristics			
Gestation age at delivery [weeks]	37 (± 2)	38 (± 2)	0.698
Birth weight [g]	2892 (± 683)	3623 (± 2763)	**0.043**
Apgar score 5 minutes	10 (5–10)	10 (8–10)	0.058
Umbilical artery pH	7.3 (7.2–7.5)	7.3 (7.1–7.5)	0.516
Placental weight [g]	529 (± 42)	544 (± 68)	0.164
Placenta/naonatal birth weight ratios	0.16 (0.02–0.038)	0.18 (0.13–0.62)	**0.001**

In each placental sample, in three fields of view, the number of syncytial knots was counted manually. A count of syncytial knot density per mm^2 of villous tissue was allowed by the determination the surface area of villous tissue in the frames.

Evaluation of Hofbauer cells (HBCs)

Hofbauer cells are fetal origin [8]. They are placental villous macrophages, which emerge in placental tissue from 18 days after conception and persist to the end of pregnancy. By the fourth to fifth month of pregnancy, their identification becomes difficult as villous stroma becomes compressed [9]. Functions of tissue macrophages are phagocytosis of cellular debris and antigen presentation in response to infectious agents and inflammation [10]. Due to villitis of unknown etiology (VUE) and varial infection HBCs proliferation or hyperplasia is observed [11, 12]. In placentas from complicated pregnancies (gestational diabetes mellitus, intrauterine growth restriction, pre-eclampsia), the number of HBCs seems to increase while in placentas from uncomplicated pregnancies, HBCs either disappear or become less in number after the fourth month of pregnancy [13].

HBCs were identified as round or ovoid cells with eccentric nuclei and granular cytoplasm. The HBCs were counted in two high-power fields per slide at 400× magnification from three different fields in each section. The mean value per villous was calculated (Tab. 2).

Villitis

Villitis arises due to hematogenous infection of the placenta by TORCH infection. In contrast, majority of cases are immune mediated and are not an effect of infection [14]. There are two types of villitis: acute and chronic.In the first type of villitis, which is often a result of infection, polymorphonuclear leukocytes infiltrate the villi with or without associated necrosis. Whereas in the second type of villitis the tissue is infiltrated by macrophages and lymphocytes usually with concomitant fibrosis and cellular proliferation of the villi [15, 16].

Statistical Analysis

For statistical analysis, SigmaStat version 3.5 software (Systat Software, Inc., Point Richmond, CA, USA) was used. The analysis of the results was based on the Student's t-test for variables with parametric distributions. For variables with non-parametric distributions, the Mann–Whitney rank sum test was used. The Fisher exact test was used for assessment of the villitis distribution. $P < 0.05$ was considered statistically significant.

RESULTS

Biochemical characteristics of the ICP patient's population is shown in the Table 3. There were no differences in neonatal,maternal and obstetrical outcomes. Nevertheless, there was a statistically significant difference in birth weights (2892 ± 683 g vs 3623 ± 2763 g, $p = 0.043$) and placenta/neonatal birth weight ratios (0.16 vs 0.18, $p = 0.001$) in neonates born to women with and without cholestasis, respectively (Tab. 1).

The histological slides of 20 patients with ICP and 40 healthy controls were examined. Placentas from both groups were found to be appropriate for their gestational age. Five placental histopathological features were analyzed: number of syncytial knots, number of capillaries per villous, structure of stroma, presence of HBCs, and VUE. The placentas from both groups exhibit normal microstructure: compact stroma and appropriate number of capillaries per villous (< 10).

There were no statistically significant differences in any of the remaining three parameters between the cholestasis and healthy control groups (Tab. 3). Representative images are shown in Figure 1.

Table 2. Placental histology of the study population

	ICP (n = 20)	Control (n = 40)	P value
Hofbauer cells/villous [median (range)]	2 (0–5)	1 (0–3)	0.397
Syncytial knots [median (range)]	21 (12–34)	15 (9–29)	0.143
Structure of stroma	compact	compact	–
Villitis of unknown etiology	1 (5%)	3 (7.5%)	0.999
Number of capillaries per villous	< 10	< 10	–

Table 3. Biochemical characteristic of ICP patient population, median (range)

Sample	Week of delivery [week]	Bile acid (highest value) [mmol/L]	Alat [U/L]	Aspat [U/L]	Bile acid at delivery [mmol/L]
N = 40	37 (± 2)	37.5 (11–171.3)	188.1 (13.5–1228.9)	101.2 (16.7–695.2)	22.4 (10.8–102)

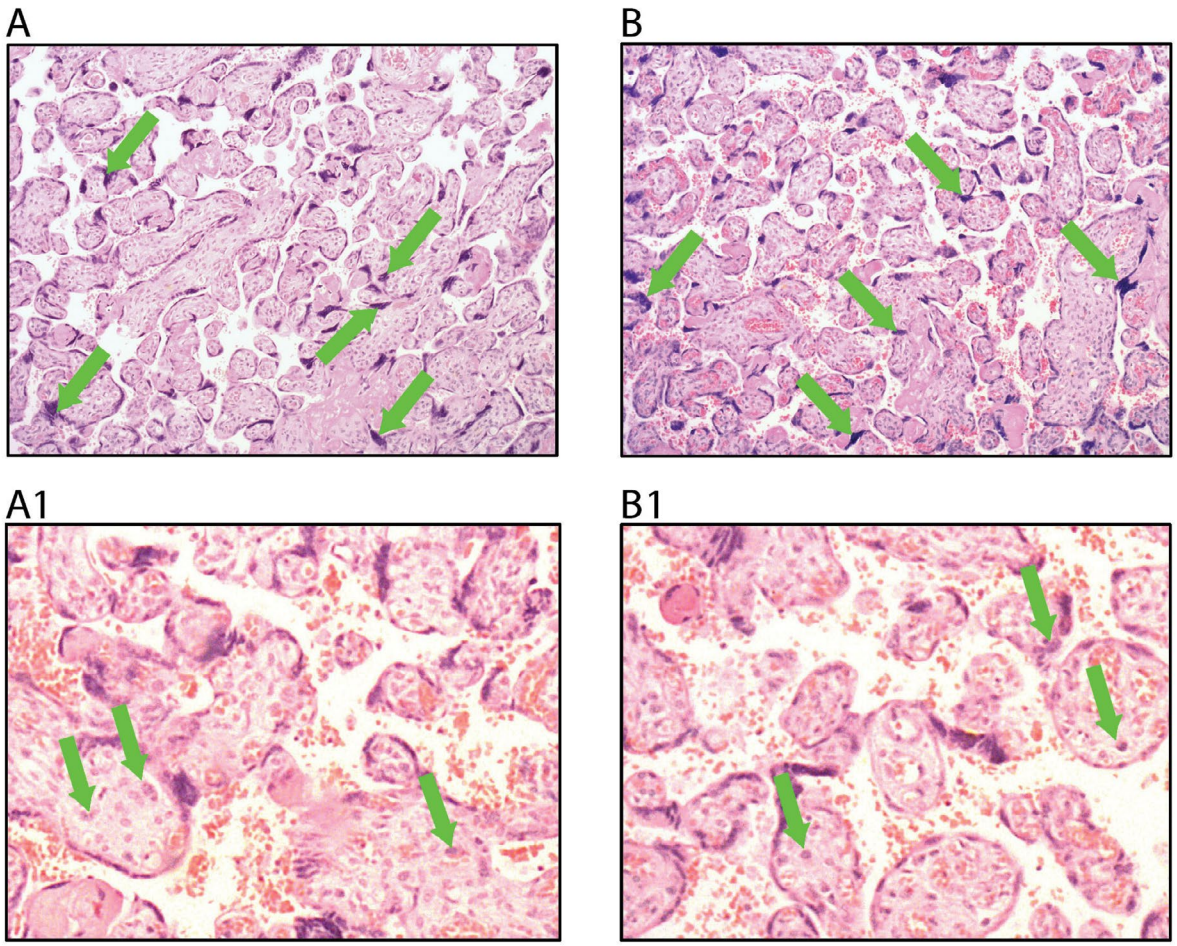

Figure 1. Representative images villi of trophoblast in a 20× (**A**, **B**) and 40× (**A1**, **B1**) lens magnification microscope stained by H + E obtained from women with normal pregnancy (**A**, **A1**) and with pregnancy complicated by cholestasis (**B**, **B1**) treated with ursodeoxycholic acid. The green arrows indicate the syncytial knots (**A**, **B**) and Hofbauer cells (**A1**, **B1**).

DISCUSSION

In this paper, we analyzed the histopathological images of placentas of patients with pregnancy complicated with cholestasis, and non-complicated, phisiological pregnancy. All pregnant women with cholestasis were treated with UDCA which is considered the first-line treatment for ICP, because it normalizes the transplacental bile acid gradient, significantly reducing fetal and maternal bile acid levels [17]. Five placental histopathological features were analyzed: number of syncytial knots, number of capillaries per villous, structure of stroma, presence of HBCs and VUE. In our study, we did not find any differences in the microstructure of the placenta of patients with cholestasis relative to patients with normal pregnancy.

Our results are in accordance with Patel et al. [18] who compared the placentas of 24 pregnant women with ICP and 30 healthy women. They found no differences in maternal, neonatal, and obstetrical outcomes. They found a significant difference between the groups only in the gestation age at delivery. Patients with cholestasis delivered two weeks earlier than the controls. The authors analyzed 17 placental histopathological parameters and didn't find statistically significant differences in any of these features between patients with cholestasis and healthy pregnant women. Comparison of the placentas from women, treated and not treated with UDCA, demonstrated a statistically significant reduction in VUE (9% vs 53%, $p = 0.03$), which implies that UDCA has an anti-inflammatory impact on the placenta. However, the exact mechanism by which UDCA decreases placental inflammation is not known.

Guven et al. [19] investigated the alterations in the architecture of the umbilical cord and the placenta in selected pregnancy complications. They stated a significant enhancement in the amount of syncytial knots in placentas from women with pre-eclampsia, oligohydramnions, polyhydramnions, and repeated cesarean sections, but not in ICP

and control groups. Furthermore, they found a significant reduction in the diameter and volume of the arterial lumen of an umbilical artery in the ICP group compared to the control group. The arterial tunica intima and tunica media were thicker in ICP than in the control group.

The available data of the histopathological analysis of placenta in patients with cholestasis and its comparison with that of the group of healthy pregnant women indicates morphological differences. These changes include higher amount of syncytial knots and enhancement surface of terminal villi, and were observed in pregnant women with cholestasis untreated with UDCA.

In the article of Geenes et al. [20] slides prepared from 28 ICP patients and 12 healthy controls were subjected to histological examination. In the placentas achieved from pregnant women with cholestasis a couple of morphological abnormalities were found to be more frequent as compared to the placentas from physiological pregnancies. These contained chorionic villi that had dense fibrotic stroma and were small for the gestational age, focally-thickened amniotic basement membranes, increased in number of syncytial knots and stricture of intervillous space. The number of syncytial knots was significantly higher in placentas from untreated women with ICP compared to those from uncomplicated pregnancies ($p = 0.02$). However, there was no significant difference in the amount of syncytial knots in the placentas achieved from women with cholestasis treated with UDCA compared to healthy pregnant women.

Wikström Shemer et al. [21] in a prospective case-control study using the computerized stereology method, examined placentas from 10 untreated and 10 UDCA-treated patients with cholestasis, and eight healthy pregnant women for morphological differences. They analyzed five histopathological features of placentas (volume fraction of collagen, surface area of terminal villi and capillaries, chorangiosis,anumber of syncytial knots and volume of placenta).

The results of their research demonstrated that cholestasis influences the microarchitecture of placenta by enhancement the number of syncytial knots and terminal villous and capillary surface area. The UDCA treatment had protective effect on placental micro architecture. The analyses of placentas of UDCA-treated cholestasis, compared to untreated ICP, showed statistically significant differences in amount of syncytial knots, capillary surface area and terminal villous. The statistical differences were not detected in any analyzed parameters in placentas between UDCA-treated cholestasis patients and healthy pregnant women.

Increased capillary growth in terminal villi and syncytial knots were both described as a sign of hypoxia which is commonly evident in placentas coexisting with diseases with reduced blood perfusion (diabetes mellitus and pre-eclampsia).

Conclusions from the two abovementioned cited studies indicate that ICP is associated with a couple of anomalies of the placenta microstructure, including an enhancement in the amount of syncytial knots. However, in placentas of women treated with UDCA, the number of syncytial knots was comparable to those in placentas from uncomplicated pregnancies [20, 21].

The studies of Geenes et al. [20], Wikström Shemer et al. [21], and Patel et al. [18] were published in 2011, 2012, and 2014 respectively and, probably for that reason, some patients did not receive treatment with UDCA which is currently the first-line treatment for cholestasis.

The final answer to the question, whether treatment with UDCA in women with cholestasis improves obstetric outcomes, will be obtained after the completion of the triple-masked, placebo-controlled, randomised trial — PITCHES (Phase III trial in IntrahepaTic CHolestasis of pregnancy to Evaluate urSodeoxycholic acid in improving perinatal outcomes) which is currently randomized [22].

Our study has a number of limitations. Our work was carried out on a relatively small group of patients, but the real cholestasis, confirmed with biochemical data is rather rare in our population. To reduce statistical error, the histological examination of placentas should be carried out on a larger and an independent cohort. All patients with cholestasis included in this study, as well as all patients with cholestasis who delivered in 2018 in Gynecologic and Obstetrical University Hospital in Poznan, were treated with UDCA before delivery. UDCA treatment of pregnant women with cholestasis is standard in our hospital; therefore it was not possible to compare placental microstructure between patients with pregnancy complicated by cholestasis treated and not treated with UDCA.

CONCLUSIONS

Based on obtained results, we can conclude that the histopathological structure of the placenta of patients with cholestasis treated with UDCA does not differ from women with normal pregnancy.

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Association between intrahepatic cholestasis in pregnancy and gestational diabetes mellitus. A retrospective analysis

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ABSTRACT

Objectives: Intrahepatic cholestasis of pregnancy (ICP) is a liver specific disorder affecting 0.08%–27.6% pregnant women. It is characterized by reduced expression of the primary bile acid farnesoid receptor (FXR). In recent studies, it has been showed that FXR has an impact on normal glucose homeostasis. Based on that it was suggested that the level of bile acids correlates with glucose level. The aim of the study was to evaluate the association between ICP and gestational diabetes mellitus (GDM).

Material and methods: 102 singleton patients complicated by ICP were included to the study and divided into two groups: non-GDM group (74 patients) and GDM group (28 patients). ICP was diagnosed based on the serum bile acids level > 10 µmol/L and GDM with the 75 g oral glucose tolerance test and FIGO guidelines. Demographic and clinical outcome data (including maternal age, BMI and infant weight) and ICP and GDM biochemical markers were collected.

Results: The incidence of GDM in ICP patients was 27.45%. 73% of women included to the study developed mild cholestasis. Lower levels of serum bile acids were correlated with GDM group. When compared mean total bilirubin level was significantly higher in non-GDM group. Transaminases (ALT, AST) and neonate condition including mean birth weight revealed no significant difference between the groups. On the other hand, prevalence of large for gestational age was significantly higher in non-GDM group ($p < 0.00001$).

Conclusions: The incidence of ICP is higher in women with GDM.

Key words: gestational diabetes mellitus; intrahepatic cholestasis of pregnancy; bile acids; preterm delivery

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INTRODUCTION

Intrahepatic cholestasis of pregnancy (ICP), also known as obstetric cholestasis, is a liver specific disorder associated with elevated serum bile acids, liver function tests, pruritus and increased rates of adverse fetal outcomes. The incidence of ICP depends on demographic variation affecting 0.08–27.6% pregnant women. The highest rate is seen in South America in Chile (11.8–27.6%) [1]. In Poland, estimated rate of ICP is 1.5% but is based on few studies on small population.

Gestational diabetes mellitus (GDM) is a disorder diagnosed based on hyperglycemia that is recognized for the first time during pregnancy. The rate of pregnant women developing the condition varies between 1–14% and is higher in Asian than in Caucasian ethnicity [2, 3]. There are few risk factors of the development of GDM, for example obesity, age above 35 years old and family history of T2DM [2]. It has been showed that GDM has an impact on the outcome in both mother and fetus. It predisposes the neonate to macrosomia, hypoglycemia, hyperbilirubinemia, polycythemia, respiratory disorders, shoulder dystocia and in the future to obesity and ultimately diabetes. The prevalence of the disorder is increasing and it correlates with progressive rising of obesity and T2DM cases in population [4].

The direct cause of correlation between ICP and GDM is unknown. There is increasing amount of studies that show the role for the primary bile acid receptor Farnesoid X receptor (FXR) in glucose and lipid levels apart from its known impact on bile acids metabolism [5]. It is suggested that during gestation if the homeostasis of one mentioned substances is dysregulated it might correlate with higher risk of abnormal levels of another. One of the prospective study of 31 patients with ICP reported a significantly higher

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blood glucose level while oral glucose tolerance testing (OGTT) [6].

Based on that it was suggested that the level of bile acids correlates with cholesterol and glucose level. Consequently, there is increasing amount of studies that ICP is associated with a higher risk of developing GDM. We decided to investigate further the correlation between these both conditions.

Objectives

The aim of this study was to investigate the association between ICP and GDM in a group of pregnant women diagnosed with ICP who undergone routing screening for GDM.

MATERIALS AND METHODS

A total group of 5676 singleton patients who gave birth at the Department of Obstetrics and Gynecology between January 2015 and December 2017 were included in the retrospective study. Intrahepatic cholestasis of pregnancy was diagnosed according to PTGiP (Polish Gynecological and Obstetrics Society) recommendations and it was based on the serum bile acids level above > 10 μmol/L, elevated liver function tests and pruritus. After 24 weeks, universal screening for GDM was performed using the World Health Organization (WHO) 75 g oral glucose tolerance test (OGTT) and diagnostic criteria were based on the FIGO (The International Federation of Gynecology and Obstetrics) guidelines including: fasting blood glucose level above 92 mg/dL; 75 g OGTT 1-hour blood glucose level of ≥ 180 mg/dL; 75 g OGTT 2-hour blood glucose level above 153 mg/dL [7].

Based on the upon diagnostic criteria 102 out of 5676 patients registered in the clinic during the period were diagnosed with ICP. They were divided into 2 groups: non-GDM group of 74 patients diagnosed with ICP and OGTT results within the reference range and GDM group of 28 patients diagnosed with ICP and GDM.

Both groups were compared in terms of maternal age, pre-gestational BMI, pregnancy weight gain, delivery week, the method of delivery, the percentage of preterm birth and biochemical results. The groups were also compared in terms of neonatal status assessed using the Apgar score 1 minute and 5 minutes after birth and other neonatal outcomes such as birth weight.

One-factor analysis was performed with the global significance level of 0.05. Variables were compared by means of Student's t-test, Mann-Whitney's U-test, and chi-squared test.

Table 1. The main maternal results of the study group

Variable	Study group
Vaginal delivery	26.4%
Cesarean section	73.6%
Pre-pregnancy BMI ≥ 25 kg/m^2 [%]	33%
Gestational weight gain [kg]	11.84 ± 5.33
FGL	84.35 ± 21.94
0 h OGTT	83.15 ± 21.97
1 h OGTT	133.78 ± 50.32
2 h OGTT	117.44 ± 44.23

RESULTS

5676 patients delivered in our hospital between 2015–2017. Out of these, 485 (8.54%) developed gestational diabetes mellitus. 102 (1.80%) patients were included to our study with diagnosis of intrahepatic cholestasis of pregnancy.

The main maternal results of the study group are presented in the Table 1. The mean age of the patients was 31.89 ± 4.84 (range 23–44) with 54% nulliparous and 46% multiparous. The mean gestational age at delivery was 255.53 ± 15.53 (range 236–286). 73 patients (71.6%) delivered between 34–36 week and 6 (5.9%) before 34 week of gestation. Most of patients (73.6%) gave birth by cesarean section.

Figure 1 represents the prevalence of ICP in the population and in pregnancies complicated by GDM. The results showed that the incidence of ICP was 3 times higher in patients with GDM diagnosis ($p < 0.0001$). Figure 2 describes the prevalence of GDM in the population and in pregnancies

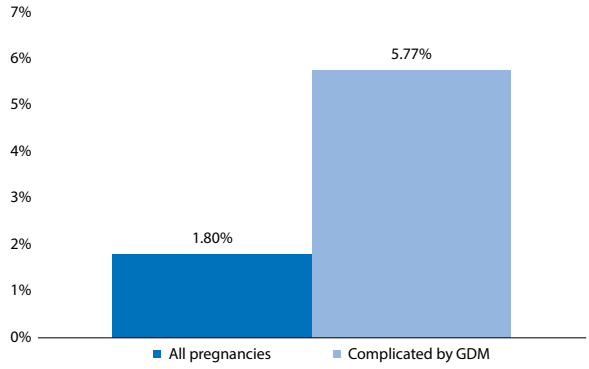

Figure 1. Prevalence of ICP in pregnancy

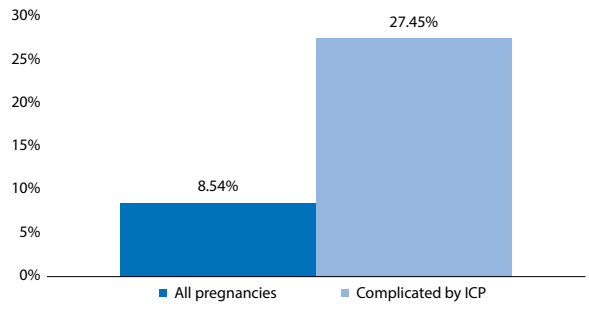

Figure 2. Prevalence of GDM in pregnancy

complicated by ICP. The analysis revealed the prevalence of GDM tripled in a group of patients who developed ICP in comparison to all pregnancies ($p < 0.0001$).

Patients were divided into two groups based on the prevalence of GDM. In non-GDM group (74 patients) were diagnosed with ICP and had glucose level results between the reference range and in GDM group (28 patients) were diagnosed with ICP and GDM. The demographics and maternal results of the groups are presented in Table 2.

When compared, there was no significant difference in maternal age between the groups ($p = 0.38$). Patients were analyzed by gravidity and parity. The results revealed higher incidence of multigravidity and multiparity in non-GDM group than in GDM group but the difference was not statistically significant ($p > 0.05$). Maternal results showed that pre-pregnancy BMI ≥ 25 kg/m^2 was significantly more often seen in patients in GDM group ($p = 0.039$). On the other hand, weight gain was observed as not significantly higher in non-GDM group than GDM group (12.19 kg vs 10.82 kg).

The diagnosis of GDM was performed between 24–28 gestational age. The 75 g OGTT results revealed significant difference between non-GDM group and GDM group. Furthermore, the groups differed in fasting glucose level results ($p = 0.002$).

Most of our patients had preterm delivery. We divided them into 3 groups: delivery below 34 Hbd, delivery between 34–36 Hbd and delivery above 36 Hbd. Most of patients from both groups had delivery between 34–36 Hbd. When compared, non-GDM and GDM group did not differ significantly in amount of given births in each from above described 3 groups ($p = 0.33$).

The study group was also analyzed based on the route of delivery. In the non-GDM group rate of cesarean section was 71.2% and in the GDM group 76.9%. The route of delivery did not differ significantly between the two groups ($p = 0.396$). Based on our results gestational diabetes mellitus had no significant impact on the route of delivery in patients diagnosed with ICP.

Laboratory liver function tests results of the study group are presented in the Table 3. The study revealed that bile acids were not statistically higher in non-GDM group than in GDM group (34.27 vs 25.86;

Table 2. Maternal results and delivery data analysis

Variable	Non-GDM group (74 patients)	GDM group (28 patients)	p value
Age [years]	31.51 ± 4.5	32.42 ± 4.56	0.38
Multigravida [%]	60%	46.15%	0.22
Multiparous [%]	50%	39.29%	0.34
Pre-pregnancy BMI ≥ 25kg/m^2 [%]	24,32%	50%	0.039
Gestational weight gain [kg]	12.19 ± 4.91	10.82 ± 6.34	0.26
FGL	81.91 ± 8.04	90.84 ± 18.53	0.002
0h OGTT	79.72 ± 6.72	91.96 ± 19.6	0.005
1h OGTT	118.57 ± 25.37	175.28 ± 45.77	0.00002
2h OGTT	103.55 ± 22.98	154.28 ± 37.97	0.00001
Gestational age	252.6 ± 15.6	251.0 ± 17.2	0.74
Delivery < 34 Hbd	8.1%	0%	0.33
Delivery 34–36 Hbd	68.9%	78.6%	0.33
Delivery > 36 Hbd	23%	21.4%	0.33
Vaginal delivery	28.8%	23.1%	0.396
Cesarean section	71.2%	76.9%	0.396
Birth weight [g]	2899.9 ± 617.2	2885.8 ± 736.93	0.08

Table 3. Laboratory liver function tests

Variable	Non-GDM group (74 patients)	GDM group (28 patients)	p value
Total bilirubin level	1.04 ± 2.13	0.78 ± 1.36	0.013
ALT [range]	6–1031	13–475	0.27
AST [range]	14–469	29–201	0.12
Bile acids < 40umol/L	71.2%	79.2%	0.73

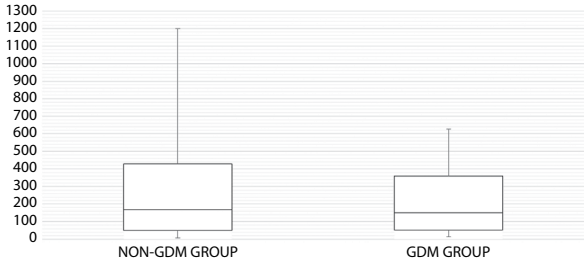

Figure 3. Alanine aminotransferase results, mean ± SEM

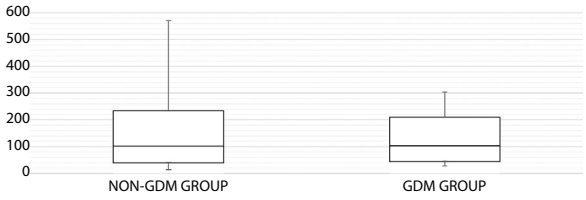

Figure 4. Asparagine aminotransferase results, mean ± SEM

p = 0.33). Similarly, the transaminases mean results (ALT and AST) showed no significant difference between non-GDM and GDM group (ALT: 194.35 vs 147.77, p = 0.27; AST: 110.2 vs 78.07, p = 0.12). Figure 3 and 4 represent the results of ALT and AST describing mean and SEM in both groups. When the aminotransferases results were compared, it was observed wide range between the lowest and the highest rate of both ALT and AST in both groups included to the study.

As shown on Figure 5 most of patients included to the study (73%) developed mild cholestasis with bile acids below 40 umol/L. When the severity of cholestasis was compared, the rate of mild cholestasis was 71.2% in non-GDM group an 79.2% in GDM group (p > 0.05). It was analyzed whether the levels of the serum bile acids have an impact on the prevalence and severity of GDM. The Figure 6 reveals the higher prevalence of GDM correlated with lower levels of serum bile acids. GDM grade 2 developed in patients only in the group with bile acids below 40 umol/L (4.55% of patients diagnosed with mild ICP developed GDMG2). On the other hand, analysis showed that the difference was not statistically significant (p = 0.73). When compared mean total bilirubin level was significantly higher in non-GDM group compared to GDM group.

The neonate's results showed no significant difference in birth weight between the groups (p = 0.08). The prevalence of SGA was observed in 13.48% and LGA in 34.83% of neonates analyzed in the study. When compared it was statistically higher prevalence of small for gestational age in GDM group (p < 0.00001). Large for gestational age was statistically higher in non-GDM group than GDM group, 36.92% and 29.17% respectively (p < 0.00001).

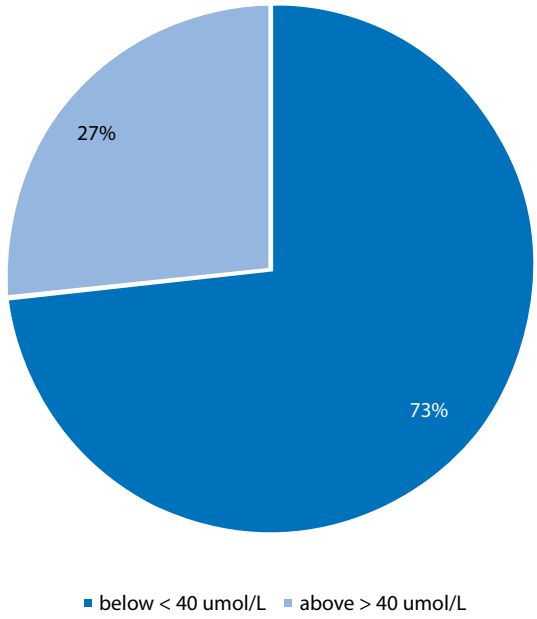

Figure 5. Prevalence of mild and severe intrahepatic cholestasis in pregnancy

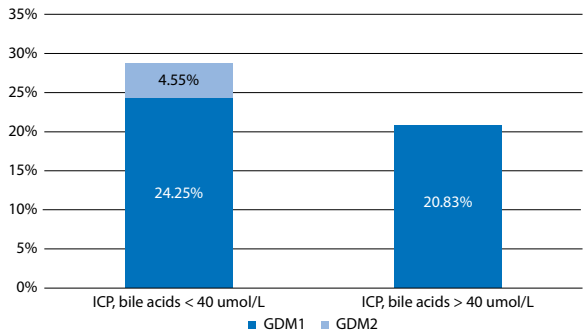

Figure 6. Prevalence of GDM in mild and severe cholestasis

DISCUSSION

Nowadays Pathology of Pregnancy is an increasing problem worldwide. It is connected to sedentary lifestyle that has an impact on higher rate of obesity, diabetes and hypertension.

There are many studies that confirm that weight before pregnancy has an impact on both fetus and pregnant woman. [8–11]. In our study, almost one quarter of patients with ICP and half of patients with ICP and GDM had BMI before pregnancy ≥ 25kg/m^2. The difference between the groups was statistically different. Thus, it might be taken to account weight loss before pregnancy prevents complications of pregnancy in some patients from the risk group [12, 13].

Most of our patients had preterm delivery. Our study revealed that most of our patients gave birth between 34 and 36 week of gestation. According to the literature, it seems

that GDM increases risk of preterm delivery [14]. Interestingly, in our study there was no statistical difference in number of preterm deliveries between GDM and non-GDM group. It might be correlated with the effective treatment of GDM in the hospital as other studies suggest [15].

Preterm delivery increases rate of cesarean sections. As other studies show GDM increases risk of CC instead of vaginal delivery in comparison to general population of pregnant women [16–18]. In our study the incidence of CC was over 70% percent in both studied groups. Interestingly, we found that having more than one pathology of pregnancy did not have significant impact on the route of delivery.

Another problem that shows our study is age of women deciding for pregnancy. As our results revealed mean age of our study group was above 30 years old. It has an impact on both fetus and pregnant patients leading to increased risk of pathology of pregnancy. It has been proven that age above 35 years old is a risk factor of gestational diabetes [19]. Changing habits of population may lead in the nearest future to increased rate of this condition. Based on our results and other studies it may also have an impact on rate of intrahepatic cholestasis of pregnancy [6, 20].

Few studies revealed that bile acids metabolism correlates with insulin resistance. It is thought, that bile acids are involved in the regulation of hepatic glucose metabolism by FXR-mediated pathways [21, 22]. Based on that some studies searched whether ICP might increase risk of GDM [20]. Martineau et al. evaluated the incidence of GDM in ICP patients is higher than in general population and the rate by then is 13.6% [23]. Our study confirmed the thesis. We received higher proportion of the patients in our study (29.94%). It might relate to smaller study group included in our research work than in the mentioned article (57 724 vs 5676 patients). Furthermore 1st Department of Obstetrics and Gynecology, Medical University of Warsaw is Grade III referral Hospital and consequently it admits a higher rate of patients with pathology of pregnancy than is seen in general population.

In our results ALT are higher than AST values in patients with ICP. ALT is thought to be more sensitive marker of ICP [1]. In one of the studies it was analyzed that the increase of ALT is 2–10-fold in serum levels than the rise of ALT [24].

The biggest advantage of this research was the uniform inclusion criteria of patients to the study. The other advantage is small amount of missing data. There are also few limitations of the study. First, it was conducted in Clinic with Pathology Ward, that might have an impact on rate and severity of both GDM and ICP. The glycaemia and bile acids level might be slightly higher than in general in patients with upon mentioned diagnoses as it is III Range of Reference Hospital admitting also the most severe cases. Secondly, as it was conducted in Warsaw it does not impress general population in Poland. It should be compared with the studies from smaller cities to have the point of view how both conditions correlate in general in Poland. Lastly, the study group was a small population and that might had an impact on not statistically different results in the study between the groups and based on that to not make definitive conclusions.

CONCLUSIONS

We found that ICP correlates with impaired glucose tolerance. These findings might have an impact on healthcare of the fetus and pregnant women with diagnosis of one of the mentioned conditions. The results of the earlier studies are the evidence supporting the thesis about association between ICP and GDM. It might be taken into an account a consideration of screening for glucose intolerance in patients with diagnosis of new-onset cholestasis. To make clarify the steps regarding mentioned test more studies are required. It will help to find out the direct reason responsible for higher rate of coincidence of the upon two conditions. Consequently, it may have role in better care of the pregnant woman and fetal well-being.

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Evaluation of asthma course in pregnancy

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ABSTRACT

The prevalence of asthma has been rising in recent decades. It is the most common disease among pregnant women and affects ca. 12% of this population. The course of asthma in pregnancy may change. In 1/3 of patients, it worsens; in 1/3 of patients, the symptoms are milder; in 1/3 of patients, it remains unchanged. Well-controlled asthma decreases the risk of pregnancy complications. Uncontrolled and severe asthma increases the risk of congenital malformations and obstetrical complications for both mother and baby. Exacerbations may also contribute to poor pregnancy outcomes. These occur mostly either in the first or in the second trimester. The most common triggers are viral infections and treatment non-compliance. The key to maintaining and gaining control of asthma is active treatment of asthma and its exacerbations.

Key words: asthma; pregnancy; asthma exacerbations; asthma treatment; asthma diagnosis

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INTRODUCTION

The prevalence of allergic diseases and asthma has been rising in recent decades, reaching 5% of the adult, and 10% of the child and teenage population in Poland. Asthma is the most common disease complicating pregnancy, which affects 12% of pregnant women [1], and may lead to poor maternal and neonatal outcomes, especially in severe, uncontrolled, or inappropriately managed cases [2]. Likewise, pregnancy, by leading to multiple changes in the organism, influences the course of asthma. It is believed that the course of asthma during pregnancy improves in approximately one third of patients, in one third the course of the disease remains stable, and in one third it worsens. Worsening usually affects patients with uncontrolled and severe asthma, however it can also occur in patients with well-controlled symptoms [3]. Pregnant women with asthma need multidisciplinary and careful management.

The aim of this study is to summarize current knowledge on the bilateral relationship between asthma and pregnancy, and to sum up any recommendations concerning the management of asthma in pregnancy, as this remains a challenge in many aspects.

The possible influence of physiological pregnancy changes on the course of asthma

Developing pregnancy triggers many adaptive changes in the organism. Changes in the anatomical, hormonal, and immune system are particularly important for the control of asthma.

Anatomical changes in physiological pregnancy include: edema, increased vascularity in the upper respiratory tract, mucosa, and bronchodilation. The diaphragm is displaced, leading to changes in breathing, from a respiratory to abdominal pattern. Tidal volume (TV) and inspiratory capacity (IC) increase, while functional residual capacity (FCR), total lung capacity (TLC) and vital capacity (VC) decrease during the course of pregnancy. Forced expiratory volume in one second (FEV1), peak expiratory flow (PEF) and airway resistance remain unchanged [4, 5].

Other changes in the respiratory tract include an increase in the respiratory rate and oxygen consumption (for approximately 20%). Eventually, PaO_2 (partial pressure of oxygen) increases to the values 100–105 mm Hg, PCO_2 (partial pressure of carbon dioxide) decreases to the values 27–32 mm Hg. The resulting alkalosis leads to renal loss of bicarbonates and to a decrease of bicarbonates blood concentrations to the values between 18–21mEq/L (Tab. 1). Even a small rise in pCO_2 concentrations (above 35 mm Hg) may indicate respiratory failure and may lead to fetal acidosis. A decrease in PaO_2 concentration below 70 mm Hg, indicates maternal hypoxemia and may also lead to fetal hypoxemia [4, 5].

Pregnancy leads to intensive hormonal changes. The blood concentration of many hormones rises. A two-fold change is observed in cortisol, a nine-fold change in pro-

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Table 1. Reference ranges for arterial blood gases in pregnancy [5]

Investigations	Pregnant
pH	7.40–7.45
pCO_2[2] mmHg	27–32
pO_2[1] mmHg	100–105
Base excess	No change
Bicarbonate (mmol/l)	18–21
Saturation	95–98%

[1] Pa O_2 partial pressure of oxygen; [2] $PaCO_2$ partial pressure of carbon dioxide

gesterone, and a 100–1,000 fold in estrogenes serum concentration. The increase in cortisol and progesterone should potentially lead to bronchodilatation; however, due to the competitive affinity of the above-mentioned hormones to the glucocorticoids receptor, the effect may be limited [5, 6].

Immunological changes in lymphocyte proportions during pregnancy, described as Th_2 domination, may predispose to asthma exacerbations [5, 7]. Moreover, to prevent a maternal response to fetal antigens, the concentration of Th regulatory cells increases. This state results in decreased activation of effector lymphocytes T and natural killers (NK), which, in turn, leads to immunosuppression [7]. This increases susceptibility to viral infections and elevates the risk of possible complications if infection occurs [6]. One of the studies confirmed that the co-existence of asthma and pregnancy may predispose respiratory and urinary tract infections [8].

The influence of asthma on the course of pregnancy

Correspondingly, asthma may influence the course of pregnancy in numerous ways.

An association between asthma and gestational diabetes, perinatal hemorrhage, placental defects [2], pre-eclampsia [9], and congenital defects including cleft palate and gastroschisis [10], have been confirmed in several meta-analyses. Some studies indicated a risk of cesarean section [2], preterm birth [11], low birth weight, longer hospitalization of the newborn and even newborn death [12]. Possible mechanism of mentioned complications include hypoxia, maternal inflammation, changed uterine smooth muscle relaxation, reduction of placental 11 beta hydroxysteroid dehydrogenase enzyme and drug (mainly betamimetics) influence [10, 11], and is mostly linked with exacerbations [11]. Many authors and guidelines suggest that the complications may be prevented if appropriate effective treatment is used [11, 13]. The latter was confirmed in research from recent years, in which women with diagnosed asthma were enrolled in the programme before 18 week of gestation and obtained active management. This consisted of monthly visits with objective assessment, including spirometry, fractional exhaled nitric oxide (FENO) and the adjustment of medication. A reduction in the prevalence of uncontrolled asthma of 80% was observed. Achieving good asthma control prevented most of the previously mentioned complications. However, the study confirmed that a small, but significantly higher, risk of pre-eclampsia and small for gestational age (SGA) is associated with asthma, despite good control [3]. The risk of SGA increases with increased asthma severity.

Diagnostic tests in pregnancy

Proper diagnosis and evaluation of asthma control is crucial, particularly during pregnancy. General approach to asthma diagnose in pregnancy is the same as in non-pregnant patients. Tests generating a risk of pregnancy complications (provocation tests and skin prick tests) are contraindicated during the whole course of pregnancy [4]. Acceptable tests are shown in a Table 2. Lung function tests are considered to be safe during pregnancy. Interpretation may be difficult, especially during the third trimester of pregnancy [14], due to associated physiological changes. One recent study demonstrated moderate changes in the pulmonary function. FEV1 declined significantly in second semester (mean 139 mL), then improved significantly in the last weeks of gestation (mean 51 mL higher to baseline). FVC and FEV6 changed insignificantly. Authors suggest that FEV6 may be used in asthma monitoring during pregnancy as it correlated positively with FVC. Nevertheless, changes in pulmonary function were not significantly associated with changes in asthma control [15]. PEF remains a valuable test during pregnancy. It should range between 380–550 L/min, but each asthmatic individual needs to establish his or her best effort. Maintaining levels > 90% of personal best value is considered optimal control [4]. Contraindications

Table 2. Diagnostic tools in pregnancy

Diagnostic tools in pregnancy	Remarks	Contradictions
PEF	useful/no changes, normal values described in the text	pre-eclampsia, cervix insufficiency
Spirometry	useful, problematic evaluation in advanced pregnancy,	pre-eclampsia, cervix insufficiency
FENO	useful	no contraindications
Blood gases	changes in normal values	no contraindications
Oximetry	changes in normal values	no contraindications
Provocation tests	–	generally contraindicated
SPT, ICT	–	generally contraindicated

Table 3. Main points for good asthma management in pregnancy on the basis of a GINA report [13]

• Active asthma treatment outweighs the potential risk of medication use **(evidence A)**
• Use of available medication to achieve good symptom control and prevent exacerbation is justified, even if the safety is not completely proven **(evidence A)**
• Cessation of ICS is a risk factor for exacerbations **(evidence A)**
• Reduction of treatment is not recommended **(evidence D)**
• Educational resources for patients
• Monthly monitoring is recommended
• Monitoring and proper management of respiratory infections
• Early treatment of exacerbations with SABA, oxygen and systemic GCS is recommended

ICS — inhaled glucocorticosteroids; GCS — glucocorticoseroids; SABA — short acting betamimetics

Table 4. Treatment of asthma in pregnancy [1, 13]

Step 1	**ICS (small dose)*** or none
Step 2	**ICS (small dose)*** **or LTRA*** or theophylline
Step 3	**ICS (small dose) + LABA*** **or ICS (medium dose)*** **or ICS (high dose)*** **or ICS small dose + LTRA*** or ICS small dose + teophylline
Step 4	**ICS (medium or high dose) + LABA*** **ICS high dose + LTRA*** ICS high dose + theophylline add tiotropium
Step 5	**Higher lever care*** **oral glucocorticost eroids*** add tiotropium

*Emboldened text suggests more suitable therapeutic option in pregnancy

for lung function testing include cervix insufficiency and pre-eclampsia [14].

Furthermore, the FENO test was found to be a useful diagnostic tool, and was proven to help in gaining asthma control, if used with monthly control [16]. Moreover, multidisciplinary management [14] and asthma control test were also proven to be useful during pregnancy. The latter test correlates well with actual asthma control.

Asthma treatment in pregnancy, peripartum and lactation

Pregnancy

Despite constant concern about medication safety in pregnancy, asthma treatment is generally considered safe. Principals are adequate to those concerning non-pregnant patients (Tab. 3, Tab. 4). The authors agree that the treatment must be intensified if asthma control is insufficient, as complications of undertreated asthma markedly exceed the possible, but not fully proven, side effects of the treatment (Tab. 5). The basis of treatment are inhaled glucocorticoids (ICS). Other drugs including ipratropium, leukotriene receptor antagonists (LTRA), short and long acting betamimetics (SABA, LABA), systemic glucocorticosteroids and omalizumab are also accepted in treatment, particularly in partly and uncontrolled asthma. Theophylline is not recommended to be used in pregnancy due to possible side effects. There is no

Table 5. Treatment in pregnancy

Treatment in pregnancy	Former FDA class	Possible side effects	Studies confirming occurrence of malformations	Remarks	Studies confirming safety of drugs
Betamimetics	C	Cleft lip and palate, omphalocele	Garne [10]	Meta-analysis of Eltonsy indicates defects both in studies concluding on safety and those asserting side effects of the treatment [17]	Eltonsy [18]
Inhaled Glucocorticosteroids	B/C	Musculoskeletal and heart defect for large doses	Blais [19]	Defects confirmed only for large doses of inhaled GCS	Garne [10]
Systemic glucocorticosteroids	C	Preterm birth, low birth weight, pre-eclampsia	Gregersen [20]	Mentioned findings should be balanced against severe asthma control	–
Antileukotriens	B	No connection	–	Short observation period	Bakhireva [21]
Antimuscarinic agents	B (ipratropium)	–	–	–	–
Omalizumab	B	No connection	–	Short observation perriod	Namazy [22]
Mepolizumab	–	–	–	–	–

ISC — inhaled glucocorticosteroids; LABA — long acting betamimetics; LTRA — acting betamimetics

sufficient data concerning tiotropium and mepolizumab in pregnancy.

Although guidelines on asthma treatment are easily accessible, most studies confirm a tendency to reduce treatment in pregnant women.

Up to 40% of patients declared to give up treatment after getting pregnant without consultation with a doctor [6]. The declarations mentioned may be partly confirmed by a Dutch study using a large database, comprising of detailed data on prescriptions. It shows a clear tendency for a reduction in the number of prescriptions issued after a diagnosis of pregnancy, which may indicate a decline in treatment after getting pregnant. This phenomenon may partly be the result of a milder course of asthma during pregnancy [23]. In addition, the problem of under-treatment is related to medical personnel, as pregnant asthmatics were significantly less likely to be given oral steroids, either in the emergency department or on discharge from hospital, than non-pregnant women [9], regardless of recommendations and results of studies that concluded on the relative safety of systemic GCS use for asthma exacerbations [12]. In the study cited, the use of systemic GCS was not related to poor perinatal outcomes, except for an increases rate of caesarean delivery.

Proper education on the treatment and safety of both patients and physicians may play an essential role in the improvement of asthma treatment during pregnancy.

Peripartum

Although exacerbations of asthma in peripartum period are rare, regular treatment should be maintained to avoid exacerbations. Hyperventilation [13] and drugs indicated due to obstetric and anesthetic management of labour may influence asthma and cause bronchospasm [24]. Short acting betamimetics are drugs of choice for peripartum bronchospasm [4, 13]. Neonates require blood glucose control for the subsequent 48 hours after exposure to excessive doses of mentioned drugs, to detect possible hypoglycemia [13]. Specification and safety of the most frequently used drugs in peripartum period is enclosed in Table 6.

Breastfeeding

Although studies concerning safety of anti-asthmatic drugs are limited, most of the drug groups are considered safe in lactation. For inhaled glucocorticosteroids (budesonide, fluticasone) infant exposure is far below the therapeutic level for an infant. Available in vitro studies for ciclesonide predict undetectable exposure of infant [25]. Inhaled betamimetics are accepted during breastfeeding as their concentrations in mothers' blood remain low. [25, 26]. Antileukotrienes, anticholinergic agents and omalizumab are accepted if necessary for asthma control and the excretion into milk or bioavailability (omalizumab) is suggested to be minimal [27]. Among oral glucocorticosteroids prednisolone is preferred to avoid double peak of parent medicine and

Table 6. Drugs used in peripartum period [24]

Group of drugs	Drugs safe in asthma	Drugs contraindicated in asthma
Induction of labour	In some cases drugs may be administered with caution eg. oxytocin	generally contraindicated
Analgesia	opioids administered with caution (risk of bronchoconstriction)	contraindicated in actively wheezing patient and in respiratory distress
Anestesia		
Epidural anesthesia	opioids	
	local anestetics	avoid high and dense level of anesthesia due to possible impairment of accessory respiratory muscles
General anastesia	only if regional anesthesia is contraindicated	
Intravenous	ketamine	
	propofol	
Volatile halogenated agents	isoflurane	
	sevoflurane	
Miorelaxants	pancuronium	atracurium
	cis-atracurium	
	rocuronium	
Other treatment		betablockers
		ergot alkaloids

metabolite. The amount of drug excreted in milk remains low up to dose 80 mg [25].

Patophysiological factors influencing the course of asthma during pregnancy

Exacerbations

Exacerbations of asthma during pregnancy represent a significant problem that may lead to unfavourable pregnancy outcomes. About 5 to 20% of asthmatic pregnant women require medical intervention due to the occurrence of exacerbations of asthma during pregnancy [9]. It has been suggested that well-controlled asthma, together with no history of previous exacerbations and no prescribed controller medication, is associated with a lower risk of exacerbations during pregnancy [28]; however, these may occur in up to 37% of pregnancies complicated by well-controlled asthma, and 40% of these exacerbations may be severe [3].

In most of the studies, exacerbations occurred in the second trimester of pregnancy [9]. However, in one recent study, exacerbations were detected most frequently during the first trimester of pregnancy [3]. Moreover, Blais et al. [29] confirmed the risk of congenital malformation and its association with exacerbations in 19% in of pregnancies during the first trimester. These findings may indicate a need for the intensification of treatment and management of asthma preconceptionally.

The most important trigger of exacerbations are infections, to which pregnant women are more susceptible due to adaptive changes in the immune system. Respiratory tract infections are the most frequent of these [8]. It was also confirmed that both pregnancy and asthma raise the risk of AH1N1 influenza [30]. Furthermore, influenza vaccination in pregnant asthmatics increased the improvement of the condition by 50%, in comparison with 15% in the patients who had not been vaccinated [31].

Another important factor for exacerbations is lack of treatment compliance [9]. Further factors include inadequate prenatal care, lack of or inappropriate GCS treatment, and smoking [6].

Some authors consider obesity and excessive weight gain in pregnancy a risk factor for the exacerbation of asthma in pregnancy. Furthermore, an increased risk of gestational diabetes has been noticed in the group of patients with the co-morbidities of asthma and obesity [6].

The occurrence of severe exacerbations creates a risk of pre-term birth, small for gestational age [6] and pre-eclampsia [3, 6].

Toxins and allergens exposure

Smoking, both active and passive, is an underestimated factor influencing the course of asthma during pregnancy. About 15% of pregnant women are active smokers [32]; another 30% are passively exposed to cigarette smoke [33]. Data from the United States shows that from 6 to 30% of pregnancies complicated with asthma are also complicated by active smoking [12]. Another study found more smokers among the group of pregnant women with asthma than among pregnant women without asthma [6].

Table 7. Side effect of smoking in pregnancy

• placenta previa
• abruptio placentae
• premature rupture of the membranes,
• pre-term birth
• intrauterine growth restriction
• sudden infant death syndrome

Smoking causes many well recognised pregnancy complications [32] (Tab. 7); moreover, in pregnant women with asthma, it increases the risk of severe exacerbation and risk of urinary tract infection and pre-term birth [34].

A few studies examined the influence of atopy on the course of asthma in pregnancy. The research of Stenius-Aarniala, from 1988, found a more frequent occurrence of exacerbations in non-atopic asthma.

Other factors

Some minor factors may also contribute to a worsening of asthma control during pregnancy or may additionally burden pregnancy.

The influence of psychological stress on the occurrence of exacerbations during pregnancies with asthma has been investigated in many studies. Some of them indicate that anxiety, and a perception by the patient of the asthma as being uncontrolled, may influence exacerbations and be a risk factor for a cesarean section. A more frequent occurrence of depression in pregnancies complicated by asthma exacerbations was confirmed by the Tata research, citated by Murphy [6].

However, some factors are found to be questionable.

No association was found between GERD and asthma severity during pregnancy. A possible reason for this phenomenon may be related to an equal frequency in the presentation of GERD in pregnant and non-pregnant populations [35].

A few studies have suggested that fetal sex influences the course of asthma during pregnancy, with the course of asthma worsening with a female fetus. However, the data is inconsistent.

Education

Many guidelines point out the importance of education in asthma management and control [13]. This may be even more

important during pregnancy, as up to 80% of female patients attempting to conceive are concerned about the influence of therapy on the fetus, and up to 40% cease treatment without consultation with a doctor. Pre-conceptional education, with an emphasis on treatment and symptoms of uncontrolled asthma, may play an important role in asthma management [6].

Summary

Management of asthma during pregnancy remains a challenge in everyday practice. The essentials of good asthma management include proper education and active treatment of patients. Frequent and accurate monitoring is vital to prevent, detect and treat exacerbations, and other conditions influencing the course of asthma. Gaining and maintaining good asthma control may prevent adverse perinatal outcomes for both mother and baby.

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Pregnant surgeon — assessment of potential harm to the woman and her unborn child

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ABSTRACT

Although most countries developed regulations concerning pregnant women at work, they are not strictly adjusted for every profession. In the European countries directives prevent pregnant women from working during night shifts, but apart from a vague paragraph about avoiding hazardous agents, there are no guidelines specific for pregnant surgeons. The aim of the study was to analyse the risks and consequences of working in the operating theatre during pregnancy. An in-depth analysis of available literature, laws and regulations concerning health and safety of pregnant surgeons was performed. Not only they are surgeons exposed to radiation and infectious agents like any other physicians, but they also face the risk of strenuous physical activity affecting their pregnancy. The unpredictability of this occupation, prolonged hours and stress associated with work can all affect the future mother and her child. The available research on potential risks for pregnant women performing surgical activities named such consequences as premature birth, miscarriage, foetal growth retardation, hypertensive disorders and infertility. There are no unanimous guidelines for pregnant surgeons on how long and to which extent they should work. The key is to maintain a balance between limiting the likelihood of pregnancy complications and respecting women's voluntary wish to continue professional development.

Key words: fetal development; pregnancy; reproductive behaviour; surgeons; surgery

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INTRODUCTION

In the light of a growing number of female doctors performing surgeries, there is a need to study the risks and consequences of working in the operating theatre during pregnancy. Although most countries have legal regulations concerning pregnant women at work, they are not strictly adjusted for every profession. In the European countries the directives prevent pregnant women from working during night shifts, but apart from a vague paragraph about avoiding hazardous agents, there are no guidelines specific for pregnant surgeons [1].

Not only are surgeons exposed to radiation and infectious agents like any other physicians, but they also face the risk of strenuous physical activity. The unpredictability of this occupation, prolonged hours and stress can all affect foetal development. Most of listed risk factors have been analysed in various studies in order to examine whether there is any association between performing surgeries and unfavourable pregnancy outcomes such as miscarriage, intrauterine growth restriction (IUGR) or preterm delivery. A questionnaire conducted in Germany did not reveal any increase in the risk of complications among pregnant surgeons in comparison to the general population [2]. Another study proved a correlation between preterm delivery and long working hours, shift work, lifting, standing and heavy physical workload, all of which are included in surgeon's activities [3].

Considering the increasing proportion of women in healthcare, there is a growing number of female doctors who work in operating theatres. Not only does this apply to surgeons, but also to gynaecologists, interventional radiologists and other specialties. There are medical fields in which

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significantly less female doctors decide to practice than male doctors, as observed distinctly among orthopaedic surgical trainees. This even led to discussion whether sex determined selection results in annual residency applications [4]. The issue was assessed by Baerlocher [5], who concluded no occurrence of such discrimination. He highlighted that the underlying reason for such sex distribution is explicitly connected with conscious choice of career path. "Work-life balance" stands as a main deterrent to pursuing surgery professional career among junior female doctors [6]. Female surgeons with children stated that "children and family" tended to hinder their careers [7]. For the fear of falling behind their male colleagues or extension of training and even exclusion from surgery, women postpone their decision of pregnancy. But notwithstanding those drawbacks, percentage of women enrolled in medical career path outnumbered men in some countries like the UK. According to the Universities and Colleges Admissions Service (UCAS) almost 60% of accepted applicants for medical studies were female [8]. Such sociologic transformation entails enforcement of law towards childbearing-friendly surgical training programs. Statistically, most of female surgeons have at least one child during their career and do not cease their surgical activities until 21st gestational week [2]. It is not clearly restricted, at which stage of gestation women are advised to stop operating. Moreover, it is shown that there is a predilection among consultants to cease operating significantly later in comparison to assistant doctors [2]. Also, more experienced surgeons holding higher positions show a tendency to inform their supervisors about their pregnancy later than their younger colleagues [2]. In a Germany-wide survey 80% of female gynaecologists and surgeons expressed a desire for a change of the law that strains from work and/or traineeship [2]. Therefore, there is a strong need to study potential risk factors and consequences of performing surgeries for pregnant doctors.

Laws and regulations

In countries associated under the European Union flag, European Commission law is in force. Council Directive 92/85/EEC "Protecting pregnant workers and new mothers" with its amendments states the main restrictions in the field of pregnant female work [9]. The main regulations apply to risks posed by hazardous substances and industrial processes, working condition in still posture, exposure to biological, chemical or physical agents, and night shifts. Allowance of undergoing antenatal examinations during working hours, the constant position at work and reassurance that pregnancy cannot cause dismissal are also regulated in the above directive. The employer should not only inform the pregnant woman about the contact with hazardous substances or other risk factors, but also is entailed to assure the safety from damage to her health in workplace.

In Poland the law obliges the employer to shift the pregnant/breastfeeding women from hazardous work to workplace within safe conditions, pare down working hours, or even grant the woman health and safety leave for the time of pregnancy. However, such actions should not affect her salary [10]. All the restrictions are discussed in greater detail in the Journal of Laws of the European Union and they aim to reduce strain from labour or exposure to hazardous agents [11]. Although the law is precisely addressing the risk factors, it does not implement to healthcare professionals and to the subject of pregnant surgeons. Evaluation in this area is to be considered as it was expressed explicitly in the survey among female surgeons and gynaecologists [2].

An attempt to implement the law protecting pregnant doctors was embodied in Heidelberger Schwangerschafts & Elternzeitprogramm (HeiSEP) [12]. This program fosters the decision of childbearing among young doctors, giving them a chance to plan their future career via precise and long-range plan, which consists of sections as follows: integration in the clinic, continuation of academic development, status of trainee program, continuation of professional development, and reintegration after the maternity leave. Due to such mutual exchange of possibilities and preferences between the pregnant and her employer it is possible to adjust activities in the clinic, ranging from operating to scientific work. Such flexibility does not exclude pregnant or breastfeeding women from attending surgeries and offers continuous development of practical skills.

Risk factors

Gravid or lactating women in the surgical ward are exposed to hazardous substances, which might affect pregnancy outcomes. These hazards may be divided into physical, biological, and chemical [13]. Biological hazards include mostly blood-borne pathogens. However, some infections, e.g. human papilloma virus, are known to be carried in the smoke plumes generated by laser and electrosurgical devices. Solid chemical hazards are found primarily in the form of chemical disinfectants. While liquid chemicals are used primarily in disinfection, sterilization, medication, and tissue preservation, gas chemicals are primarily associated with anaesthesia, disinfection, sterilization, and surgical equipment. Physical hazards can also occur, as a thermal hazard of an autoclave or high-pressure gases used in the operating theatre. A rapidly developing foetus is much more susceptible to low dose exposure to hazardous materials than an adult [14].

Pregnant women working in healthcare institutions are exposed to infectious diseases. Pregnancy, however, does not seem to be an independent risk factor for occupationally acquired infectious diseases, but it seems imperative to make use of primary prevention and obedience to infec-

tion control precautions. Prevention extends from obligatory staff immunization to regular up-to-date vaccination against influenza and pertussis. Pregnant healthcare workers (HCWs) with occupational exposure to communicable diseases should be directed immediately for appropriate post-exposure prophylaxis and observed for development of active infection [15]. Annual mean rates of needle stick injuries and blood contact cases per 1,000 employees by different risk groups show that in surgery — 12.0 needle stick injuries (NSIs) and 0.6 blood contact cases (BCCs) — there is a smaller risk of contracting a blood-borne disease than in hospital overall (29.9 NSIs and 2.8 BCCs per 1000) [16]. This implies that pregnant surgeons who want to continue their work in the operating theatre are not more exposed to viral infections than other HCWs. The most frequently mentioned risk associated with harm to foetal development is associated with biological agents, such as viral infections: HCV, HIV, Rubella Virus, CMV, Human Parvovirus B19, VZV as well as bacterial: *L .monocytogenes*, or parasitic infections: *T. gondii* [17, 18]. Other biological agents qualified as detrimental to employees' health which cause harm to pregnant female or impair foetal development are Ebola virus, *S. typhi* or *S. dysenteriae* [17, 18].

When discussing a pregnant female conducting surgery, other risk factors of adverse pregnancy outcomes should be also mentioned. Among these are using puncturing instruments, surgery duration over 4 hours, night shifts and responsibility during emergencies [19]. In an nation-wide survey conducted among Hungarian women, reproductive health was compared between physicians and controls [20]. In this study the burn-out syndrome was classified as the firm predictor of stress characteristic for medical profession. Female doctors continue working while pregnant, which may affect the outcome of pregnancy, as work stress is an explicit risk factor for various complications [20, 21]. Female physicians were bearing more high-risk pregnancies (26.3% vs. 16.3%) compared with the general female population [21]. Moreover, female physicians are documented to have longer time-to-pregnancy interval and more frequent infertility treatment during the reproductive age than the control group.

Waters and Dick compared studies evaluating the effect of long standing hours on pregnancy outcomes such as low birth weight (LBW), preterm birth, stillbirths, and late spontaneous abortions [22]. There is an explicit association between the strained still erect body position of duration over 8 hours per day, classified as prolonged standing and pathological pregnancy events. Although regular physical activity during pregnancy is in fact recommended by the American College of Obstetricians and Gynecologists (ACOG) with differentiation between safe sports such as low-impact aerobics, jogging or swimming and risky sports which can cause mechanical harm to foetus, such as contact sports [23]. Overall, the benefits of exercise exceed potential risks, with some exceptions, when women bear a complicated pregnancy. Nonetheless, extrapolation of such benefit according to occupational physical activity may present problems, as the border separating beneficial exercise from potentially hazardous level of activities is vague.

Consequences

Prolonged and exhausting line of work during pregnancy can result in premature birth. This was the complication which was detected most often in German studies among pregnant surgeons, with 7.1% of them reporting to have experienced premature birth and 2% perceiving this complication as a result of surgical activities [2]. Other complications mentioned in the survey included miscarriage (2.9%), IUGR (2.9%) and premature rupture of membranes (PROM) (0.6%). However, none of these consequences correlated either with the number of hours spent during surgery, or with the time of stepping down from surgical obligations. The incidence of those complications was not higher than in the general population, in which the risk of IUGR is 8.9%, of miscarriage 12–31%, of premature birth 5–7%, and of the occurrence of PROM 2.9–3.5% [24–26]. Other complications including pelvic pain and vaginal bleeding were neither associated with the number of hours spent at work.

According to the systematic review by Bonzini et al. [3] physical challenges at work can result in an increased number of complications during pregnancy. Authors analysed the relationship between three adverse outcomes of pregnancy (preterm delivery, LBW and gestational hypertension) and five occupational exposures (long working hours, shift work, lifting, standing, and heavy physical workload). The main message was that preterm delivery was related to each of these exposures. Fewer links were found between other outcomes. At the surgical ward a pregnant doctor faces combination of prolonged standing position with heavy lifting and bending, which may lead to lowering the uterine blood flow and intra-abdominal pressure increase [27]. Although the evidence is not strong enough to support mandatory restrictions for professions with the risk of strenuous activities, there is a clear recommendation towards the limitations of demanding activities.

Also, timing of reproduction during the medical career has an impact on its outcome. Undertaking pregnancy during residency training increases the risk of adverse events [28]. Certain complications have a higher likelihood of occurrence among residents than specialists due to different character of their work [28]. Longer operating hours and more than six night shifts per month predispose residents to more obstetric complications. In addition, pregnant residents are more likely to develop hypertensive disorders, IUGR, placental

abruption, and miscarriage than pregnant women of similar age in the general population [28].

As Zhang et al. [29] investigated in their study that occupational exposure to radiation, chemicals and noise is associated with increased risk of antepartum foetal death, birth defects, small-for-gestational-age, and spontaneous abortion. Moreover, working in healthcare or research sector shows concomitance with numerous reproduction pathologic outcomes such as fertility problems, late spontaneous abortions, prematurity, chromosomal anomalies, mental retardation, and childhood cancer events among offspring [29]. In 1997 Zadeh and Briggs attempted to evaluate the risk of X-ray radiation on reproduction, weighting up two groups: surgeons and obstetricians. The conclusion, however, indicated that working in healthcare sector is the occupational hazard itself. Data obtained from questionnaires sent to orthopaedic surgeons, gynaecologists and obstetricians revealed a significantly higher prevalence of congenital anomalies in offspring than in the general population [30].

Prevention

The European Agency for Safety and Health at Work imposed on EU countries limits maximum value of occupational exposure to chemical, physical and biological agents. The European Framework Directive on Safety and Health at Work (Directive 89/391 EEC) adopted in 1989 serves as an obligation for employers to create a safe working conditions. This issue is regulated in the Directive 92/85/EEC with emphasis on pregnant and breastfeeding women [1]. The consequences of the mentioned law are reflected in prophylactic actions undertaken by employer such as measurement of exposure to risk factors, notifying the gravid or lactating staff about the jeopardy, evaluation of potentially hazardous activities, submission to safety procedures, regulations restricting night shifts and additional workload as well as adjustment of the workplace to childbearing personnel. When considering HCWs, the national healthcare organization is obliged to obey current guidelines minimizing occupational hazard of biological, physical, chemical agents, with special care for female staff in the reproductive age.

According to guidelines established in 1998 by Hospital Infection Control Practices Advisory Committee of Centers for Disease Control and Prevention (CDC) detailed strategies of preventing infectious diseases among HCWs are recommended [31]. Among those are vaccination, isolation precautions, management of exposure to infectious agents, work restrictions for exposed or infected worker. The health service for personnel is responsible for educating the employees about the principles of infection control, collaborating with infectious control department to observe the epidemiology of diseases, providing care for employees bearing work-related illnesses, identifying and measuring occupational risk, containing costs by preventing diseases resulting in absence or disabilities.

As the risk of occupational infectious diseases contracted at hospital is high, proper hand hygiene, vaccination and protective equipment like gloves or safety devices are important in minimizing the risk [17]. Specific recommendations according to doses and type of vaccines are to be found in the review by Lynch and Spivak [15]. Women in the childbearing age are encouraged to receive immunization for vaccine-preventable diseases. Adherence to precautions and safety procedures when taking care of infected patients is an imperative. According to the CDC Guidelines, there is no study stating whether transferring seronegative staff to areas with less contact with patients who are reservoir of CMV decreases the risk of infection during pregnancy, for CMV can survive on surfaces and objects for short period of time [31]. Additionally, HCWs who provide help to high-risk contagious patients present similar prevalence of primary CMV infection as the other workers without such contact [31]. Using standard precautions and proper hand hygiene is recommended as sufficient to reduce the risk of transmission.

Strain and following harm to pregnancy outcome associated with imposed body position during pregnancy when reaching the task on the table can be decreased with using a proper interventions. These are as follows: using compression stockings or support hosiery, flooring condition, floor mats, shoe inserts, sit-stand workstations and ergonomics pre-trainings [22].

Improvement of working conditions and prevention of burnout syndrome appear to be important factors in prevention of unfavourable pregnancy outcomes. Holistic approach involves work-process efficacy, well-balanced workload, cooperative hospital management and organization, colleagues' support, work-home balance, feeling of control, and personal situation such as parenthood [32]. As it was studied by Roberts et al. having children is crucial for mental and physical health of HCWs [33]. The parenthood seems to be essential as in one survey stated, burnout syndrome is rather a consequence than a cause of reproductive morbidity among female doctors. Organization of work during pregnancy allowing constant development of one's personal professional skills is of a special concern for care of mental health.

CONCLUSIONS

The need for risks assessments of harm to pregnant doctors working in surgery is increasing in the light of a growing number of female doctors. There are no unanimous guidelines for pregnant surgeons on how long and to which extent they should work. The key is to maintain balance between limiting the likelihood of pregnancy complications and respecting women's voluntary wish to continue profes-

sional development. Most important risk factors include occupational stress, long and unpredictable working hours, exhausting line of work and exposure to infections. They can be related to consequences such as premature birth, miscarriage, foetal growth retardation, hypertensive disorders and infertility. Nonetheless, due to a small scale of various studies and limited number of enrolled subjects, further research is needed.

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Saliva, hair, tears, and other biological materials obtained non-invasively for diagnosis in pregnancy: a literature review

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ABSTRACT

As medical technology evolves, clinicians are increasingly choosing relatively painless non-invasive methods of patient diagnosis and treatment. There are two principles behind this: greater patient comfort and lower cost. Tears, hair, saliva, urine, and faeces can replace blood for diagnosis. The varied constituents in these biological materials can serve as biomarkers for the detection of both local and systemic diseases. In this paper, we review a range of diagnostic techniques — all using biological material obtained via non-invasive procedure — for detecting medical conditions in pregnant women.

PubMed, Medline, Embase, and the Cochrane Library were searched from January 1996 until December 2018. Forty seven studies were included: thirty-five original articles, nine reviews and three meta-analysis.

Analysis showed that saliva, hair, tears, and other biological material — obtained via non-invasive methods — may serve as clinically informative biomarkers. These biomarkers may be used for: toxicology, psychological studies, disease detection, biomonitoring, and drug abuse. The analysis of tears, hair, saliva, urine, and faeces is a safe, noninvasive and useful diagnostic tool within groups of pregnant women, but further investigation is necessary to fully realize the promise of these novel diagnostic tools.

Key words: tears; saliva; faeces; urine; hair; noninvasive

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INTRODUCTION

As medical technology evolves, clinicians are increasingly choosing relatively painless non-invasive methods of patient diagnosis and treatment. There are two principles behind this: greater patient comfort and lower cost.

A milestone was achieved recently in fetal medicine: the debut of non-invasive testing via cell-free fetal DNA (cffDNA). Although still considered to be a method for screening rather than diagnosis, in certain cases cffDNA tests may be a useful option, replacing invasive techniques such as amniocentesis or chorionic villous sampling (CVS).

Tears, hair, saliva, urine, and faeces can replace blood for diagnosis. The varied constituents in these biological materials can serve as biomarkers for the detection of both local and systemic diseases. In this paper, we review a range of diagnostic techniques — all using biological material obtained via non-invasive procedure — for detecting medical conditions in pregnant women.

Urine

Urine is a readily extractable biological fluid. Urine testing is an increasingly common non-invasive means of obtaining clinical data [1]. Such tests have an established part in maternal-fetal medical practice *e.g.* for detecting and monitoring proteinuria.

Due to its particular physiological function, urine is often characterized by irregular variation between individual persons, or at successive stages for a single individual. Large variations reflect urinary sensitivity to both normal physiological change as well as abnormal pathological change *in vivo* [1]. In the absence of homeostatic mechanisms — and unlike blood — urinary variation may indicate more change, especially in the early stages of disease. Urine samples can be collected long-term and painlessly. Moreover, urine collection is safer and cheaper than blood collection. Membrane technology [a new technique that absorbs urine proteins found on PVDF (polyvinylidene fluoride membrane), which can then be dried and stored] and other modern techniques,

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have made collecting and storing urine samples even easier. Biomarkers found in urine may indicate the following:

ZIKV infection

Saliva and urine have been recognized for their value in diagnosing viruses such as Zika [2], which has seen a violent outbreak on a global scale. Zika may present in a milder form — lasting approximately one week — with symptoms such as rash, fever, myalgia, arthralgia, conjunctivitis, headache, and malaise. However, vertical transmission of the Zika virus may present fetal growth restriction, placental insufficiency, microcephaly, CNS, or even fetal death [3]. A recent study described the lower efficiency of experimental transmission for Zika's main assumed vector: *Aedes Aegypti*, together with signs of probable sexual transmission. This led to consideration of other possible sources for Zika. Bonaldo et al. tested 5 saliva and 9 urine samples of patients from Rio de Janeiro. The results showed infectious Zika virions in the saliva and urine of patients in the acute stage, which may be a key factor in the dissemination of the virus. Bringhal et al. also tested saliva and urine, finding that: 95% (52/55) of urine samples taken from patients within 5 days of symptom appearance tested positive by RT-PCR; merely 56% (31/55) of serum samples taken on the same day tested positive by RT-PCR; 82% (9/11) of urine samples taken > 5 days after symptoms began tested positive by RT-PCR; zero RT-PCR tests for serum samples were positive. Such findings indicate that urine may be the best type of sample to detect the acute stage of Zika. Considering the importance of other non-vectorial transmission routes, the epidemiological relevance of this calls for additional study.

Podocytes: a potential new biomarker for preeclampsia

There is no straightforward, cheap, dependable, test to predict with high accuracy whether preeclampsia will occur during pregnancy. The priority is to identify biomarkers — which should be non-invasively obtained and easily determined — to improve the efficient detection of this condition.

There is growing evidence that the urinary excretion of viable podocytes may be a useful indicator of preeclampsia. Garovic et al. extracted podocyte cells from urine in preeclamptic women. The study demonstrated a significant relationship between podocyturia and proteinuria. Furthermore, it was shown that the quantity of podocyte cells excreted in urine is a sensitive indicator of renal damage as well as protein excretion among patients with preeclampsia.

Another discovery was that urinary podocyte cells were absent in healthy pregnant women, as well as those presenting hypertension but no other preeclamptic symptoms [4]. Aita et al. [5] noted a strong link between podocyte quantity lost in urine and blood pressure, although not in the case of proteinuria. In 2012, Zhao et al. noticed a reduced expression of podocyte-slit diaphragm proteins — including polarity proteins, podocin, and nephrin — in preeclampsia. Tracing the relationship between urine podocyte cells and preeclampsia may show great promise, nonetheless, additional research is required [6].

SLOS

Non-invasive urine collection can identify the rarest of genetic fetal diseases. For example, the steroid metabolome, once extracted from maternal urine, can be used to confirm a diagnosis of Smith-Lemli-Opitz Syndrome (SLOS) [7]. The optimum standard for prenatal diagnosis is an increased level of 7-dehydrocholesterol (7-DHC), tested via either gas chromatography or mass spectrometry, and measured from the amniotic fluid after 14 weeks or from chorionic villous samples (CVS) between 10 and 12 weeks. Both amniocentesis and CVS are invasive procedures and risk miscarriage [8]. Consequently, testing specific steroid compounds (dehydroestriol, 7-dehydropregnanetriol, 8-dehydropregnanetriol) in the maternal urine has been suggested as a non-invasive method for diagnosing SLOS [9]. Guo et al. have described how particular concentrations of these steroid compounds present in urine, with each SLOS analyte expressed as a ratio of its natural counterpart, can indicate SLOS between 14 and 22 weeks. This has been confirmed by other research such as Jezela-Stanek et al. [10] who successfully diagnosed prenatal SLOS employing maternal urine steroid ratios.

Faeces

Inflammatory bowel disease (IBD) is very common among adults of reproductive age [11]. When active, the condition increases risks associated with pregnancy, including preterm birth (PTB) and intrauterine growth restriction [12]. Possessing a recognized clinical tool to monitor IBD during pregnancy is an important, albeit challenging, care factor. In patients who are not pregnant, endoscopy is the optimum technique for assessing IBD severity. According to international guidelines, when an endoscopy is required, a sigmoidoscopy is usually the preferred method, ideally in the second trimester [13]. Employing other methods could be preferential when an endoscopy is unnecessary. Sedatives and extended procedures could harm maternal circulation. Consequently, non-invasive methods are of great value to monitor IBD.

One such method employs faecal calprotectin (FC) [14]. This is an accurate biomarker for mucosal inflammation, which correlates with histological inflammation as well as endoscopic activity [15]. Julsugaard et al. studied 46 pregnant women and found that FC is not affected by physiological changes

occurring during pregnancy. Furthermore, the combination of the physician's global assessment (PGA) and FC may be the best alternative to endoscopy for measuring disease activity. PGA and FC are also superior to other biomarkers such as the plasma concentration of C-reactive protein (CRP). The study also described how — instead of colonoscopy — FC could be employed to differentiate non-specific IBDs and distinguish them from irritable bowel syndrome [16]. However, no similar study has been carried out during pregnancy and thus additional research is required.

Tears

Tears are a mixture of proteins, mucins, lipids, salts, and water. A recent proteomic study discovered 1526 proteins in tears [17], meaning that this biological fluid is less complex than either serum or plasma. Because of variations in the lacrimal functional unit (LFU), studying the composition of tears has been suggested as an ideal method for identifying biomarkers linked to different systemic disease ingredients [18]. Recent efforts have sought to identify new tear biomarkers for ocular diseases — *e.g.* dry eye disease (DED) symptomatic of diabetes — as well as systemic disease. Kan's study was intended to assess tear function in pregnant women with gestational diabetes mellitus (GDM) [19]. The result was surprising: GDM appears to have no negative affect on tear function testing. This could be because of the absence of long-term hyperglycaemia, the presence of which may have affected tear function in pregnant women. As a readily obtainable biological fluid, tears could be employed in future medical testing, although this requires additional study.

Hair

Different methods of hair analysis are used for: toxicology, anthropological studies, disease detection, biomonitoring, and drug abuse. Human hair is often a useful source of tissue sample as it is readily obtainable as well as stable. Furthermore, sample storage and preparation is straightforward: no specialised preservation method is needed. Hair — depending on its length — may signify a time period of days, months, or even years. Hair analysis is also extensively used in pregnancy.

FASD

An example of this would be testing maternal hair for ethyl glucuronide. Hair ethyl glucuronide (hEtG) is a biomarker for prenatal alcohol exposure. Alcohol consumption may cause fetal abnormalities such as Fetal Alcohol Spectrum Disorder (FASD) or Intrauterine Growth Restriction (IUGR) [20]. Reducing the number of children harmed by prenatal alcohol exposure (PAE) can be achieved by early, accurate diagnosis of prenatal alcohol consumption, together with targeted harm reduction strategies [21]. One associated challenge concerns the high level of maternal underreporting because of the social stigma around drinking alcohol during pregnancy. Consequently, further screening of biochemical alcohol biomarkers is called for. Because of its high sensitivity and specificity as an indicator of heavy chronic alcohol consumption, hEtG is a promising biomarker. Notwithstanding that, direct ethanol metabolites such as ethyl glucuronide (EtG) serve a key role in confirming PAE, although their utility may be reduced by their shorter half-life in blood and urine. Maternal hair analysis permits retrospective PAE analysis for several months. Screening blood or urine for alcohol biomarkers during the first prenatal visit gives negative results in many pregnant women who cease alcohol consumption upon realizing they are pregnant. Furthermore, hair analysis can indicate dangerous alcohol consumption in the periconceptional period — the critical stage of organogenesis. A meta-analysis of chronic alcohol users by Boscolo-Berto et al. (2014) [22] described an overall sensitivity of 96% and specificity of 99% for hEtG. Furthermore, hEtG — as a direct ethanol metabolite — has a higher specificity than other alcohol biomarkers tested in urine or blood. Such biomarkers are known to be affected by various maternal conditions and pregnancy related physiological changes, including liver conditions, hypertension, gestational age, and iron deficiency. In light of these advantages, hEtG would appear to be a reliable biomarker for prenatal alcohol consumption.

Postpartum depression

Estimates suggest that rates of postpartum depression (PPD) in women range from 10–15%. Studies have long established how PPD can negatively affect the maternal-infant bond, as well as exacerbate outcomes in the child's development — both physically and psychologically [23]. To prevent PPD onset and its negative effects, the early detection of PPD associated factors is necessary. The psychological or behavioural predictors for PPD include: age < 25, low-earnings, a history of miscarriages or terminations, PMS, antenatal depression, and antenatal anxiety. Although the above predictors are well known, there is a scarcity of biological forecasters. One promising PPD biomarker is hair cortisol. Measuring the levels of this hormone can detect chronic stress occurring in the prior three months. Unlike more typical samples — *e.g.* blood — situational variables or circadian rhythms do not affect this value [24]. Caparros-Gonzalez et al. studied 44 pregnant women over three pregnancy trimesters and the postpartum period; they employed psychological questionnaires and tested for hair cortisol levels. The study found significant variations in the hair cortisol levels between the groups with and the groups without symptoms of PPD in the first and

third trimesters [25]. Hair cortisol levels predicted 21.7% of PPD symptom variation. The research provided evidence that antenatal stress, psychopathological symptoms, and hair cortisol levels at various stages of pregnancy can predict PPD. These results encourage further research aimed at improving maternal care in clinical settings. To summarize, effective prenatal stress screening is both possible and measurable. Consequently, it could be employed on a wider scale to reduce the harm caused by postnatal depression [26].

IVF success rate

Massey et al. [27] have studied women undergoing IVF treatment, examining the relationship between hair cortisol, salivary cortisol, and pregnancy. Results indicated that there was a significant negative association between concentrations of hair cortisol and clinical pregnancy outcomes ($p = 0.017$). The study offered preliminary evidence that longer-term systemic cortisol could have an effect upon pregnancy outcomes. Consequently, psychological intervention to lower cortisol levels prior to IVF treatment, such as CBT or mindfulness, could improve patient outcomes.

Fetal defects

Hair sample analysis is more reliable than blood analysis when measuring the concentration and chronic exposure of different metals in individual pregnant women [28]. Hair samples are more stable and easier to collect than blood. Studies on the concentration of metal in hair samples have given valuable insight on the potential origins of congenital defects. For example, a higher titanium level in a woman's hair during periconception was linked with a greater risk of neural tube defects (NTD) in children. This could be partially mitigated by the mother's diet [29]. Furthermore, exposure by the mother to cadmium and arsenic could significantly increase the risk of congenital heart defects (CHDs) in children [30]. An increased aluminum concentration in maternal hair may significantly increase the likelihood of a child being born with a CHD. Such conditions include conotruncal heart defect, septal defect, and right-sided obstructive heart defect [31]. Because of the wide dissemination of the above metals in our 21st century lives, and their potential risk to a developing fetus, women should be strongly encouraged to adjust their diets during periconception and pregnancy. Testing hair samples can indicate when dietary and lifestyle changes should be introduced by pregnant women; the implementation of such changes could lead to a fall in the number of fetal abnormalities.

Predictors of viral suppression in women infected with HIV

It is recognized that sufficient antiretroviral drugs (ARV) can protect HIV infected pregnant women and decrease the risk of viral transmission to children. Unfortunately, drug compliance can be compromised by psychological changes occurring during pregnancy. This — combined with altered drug barriers — can affect ARV pharmacokinetics, potentially limiting drug exposure. There is therefore an urgent need for an objective means of measuring ARV compliance in pregnant women. The most commonly tested biological sample for repetitive drug use during pregnancy is maternal hair. Hair grows at a rate of 1 cm per month; it is thereby possible to assess the pattern of drug compliance over three trimesters [32].

PROMOTE was a Ugandan study on HIV-infected pregnant women at 12–28 weeks, who were randomly assigned either lopinavir or efavirenz-based antiretroviral therapy (ART) [33]. The study concluded that measuring ARV concentrations in subjects' hair was a promising method for accurately predicting viral suppression among them. The technique could lower the risk of perinatal HIV transmission during the critical stages of delivery and breastfeeding.

Saliva

Clinicians first used saliva for medical diagnosis after WW2 [34]. Known as the "mirror of body health", saliva indicates both the local and general health of a patient. It is used to detect key biomarkers of both oral and systemic diseases, as well as indicating an individual's exposure to varied substances. Recently, saliva testing has become a recommended means for detecting body fluid biomarkers, since it is cheap, non-invasive and painless [35]. Furthermore, saliva does not clot, is less prone to potential infection, and can be easily collected, carried, and kept.

Preterm birth

One tenth of deliveries are preterm; this is the second main cause of neonatal morbidity and mortality. It has proved difficult to identify an optimum biomarker to accurately predict those women who will deliver preterm. Although various current biochemical and biophysical markers have been investigated, a reliably accurate biomarker has yet to be found [36]. Priya et al. [37] tested levels of progesterone in the saliva of asymptomatic high-risk women to predict PTB, comparing this with transvaginal sonographic (TVS) cervix length. The study examined asymptomatic women ($n = 90$) with singleton pregnancies at 24–28 weeks. Subjects had a history of PTB, preterm pre-labour membrane rupture, or late spontaneous miscarriage (at 20–28 weeks). Results showed a positive linear correlation between TVS cervix length and progesterone levels in the saliva. This suggests that the change in TVS cervix length may be indicated by the concentration of progesterone in the saliva. The two tests were compared; salivary progesterone was found to be a better predictor of PTB than cervix length at < 34 weeks,

but not at < 37 weeks. This may suggest that the cervix becomes shorter followed by a decrease in progesterone. It is desirable to isolate the subset of women who could gain maximum benefit from progesterone supplements from a larger set of high-risk asymptomatic women; this can be achieved by measuring progesterone levels in the saliva. The study underlined that a low level of progesterone in the saliva (< 2575 pg/mL) at 24–32 weeks can identify women at risk of PTB.

Monitoring of prenatal smokers

Smoking is the No.1 cause of avoidable mortality in women and a main preventable cause of negative pregnancy outcomes in high-income economies. The most serious health conditions linked to maternal smoking include: preeclampsia [38], placental abruption, uteroplacental insufficiency, premature membrane rupture, decreased blood flow to the fetus, as well as intrauterine growth retardation [39]. Due to the quantity of severe health conditions linked to smoking, it is essential to both monitor exposure and encourage quitting. Initial smoking assessment in pregnant women is often based on self-reporting via a questionnaire. However, with the increase in stigma around smoking during pregnancy, there is a higher probability that women will not self-report their smoking.

Biochemical verification — by means of non-invasive techniques such as saliva or urine tests — can assess smoking prevalence with greater reliability. Being a matrix, saliva can be destroyed easier than urine; it is therefore used for fast screening of smoking status. Studies performed in high-income economies have shown that pregnant women's self-reporting of smoking can underestimate prevalence by 24–28% [40, 41]. The difference may be explained by the raised awareness of the risks of smoking while pregnant, combined with increased stigma towards pregnant smokers.

To conclude, self-reporting is an unreliable measure of smoking in pregnancy. Since it underestimates the number of smokers, additional screening for biomarkers of nicotine intake is required. The concentration of salivary cotinine appears to be an accurate biomarker, which permits active smokers to be separated from passive [42]. An important benefit of cotinine over nicotine as a biomarker for smoking is that approximately 72% of nicotine is converted into cotinine. The half-life of cotinine averages around 17 h compared to 2–3 h for nicotine. The saliva cotinine cut-off level for active smokers was 10 ng/mL (sensitivity 96%, specificity 95%) while for passive smokers it was 1.5 ng/mL (sensitivity 63%, specificity 71%) [43].

GDM and oxidative stress

Oxidative stress (OS) is thought to be the key factor in the development and progress of gestational diabetes mellitus (GDM). It also plays a role in complications related to GDM, including pregnancy-induced hypertension and intrauterine growth retardation [44]. A useful biomarker for testing oxidative stress levels in GDM populations is saliva [45]. Zygula et al. studied 89 pregnant women (n = 89; GDM = 59; control = 30). The saliva of each subject was analyzed for malondialdehyde (MDA), total antioxidant capacity (ORAC), and inactivation of aldehyde dehydrogenase (IALDH). Oxidative stress was not found in GDMG1 but was found to be moderate in GDMG2. In GDMG2, higher concentrations of salivary MDA and IALDH were found. Salivary OS was correlated with — and found to be most significant for — ORAC. Salivary ORAC could be a systemic biomarker for oxidative stress [45]. Salivary MDA and the inactivation of ALDH could be biomarkers for OS in the oral cavity. Screening the saliva of pregnant women for OS biomarkers could prove beneficial for oral health problems, gestational diabetes, or even premature delivery [46]. One study found that MT2A present in saliva could be a potential biomarker for the risk of premature delivery. Notwithstanding this, additional research is necessary to confirm these results [46].

Glucose nano-biosensor

The finger-prick test is part of standard diabetes management, which is painful and inconvenient for self-monitoring patients. Non-invasive glucose testing could improve compliance and glucose control, as well as decreasing both the complexity and costs of disease management. A new disposable on-chip salivary nano-biosensor has been suggested as a non-invasive technique. The working electrode is functionalized with single-walled carbon nanotubes, chitosan multilayers, gold nanoparticles, and glucose oxidase, with layer-by-layer assembly. The biosensor can detect glucose to 0.1 mg/dL and gives results in 30 seconds. Studies have shown that these salivary biosensors are a reliable, reproducible and efficient technology, which enables continuous salivary glucose monitoring [47].

SUMMARY

Saliva, hair, tears, and other biological material — obtained via non-invasive methods — can serve as clinically informative biomarkers. Multiple studies have described how these biomarkers can be used in new techniques for prognosis, laboratory or clinical diagnosis, observation, and management of patients with varied medical conditions. Biological samples — which contain soluble biological markers — have the advantage of being easily collected and stored. These biomarkers can also be used within groups of pregnant women to detect various diseases or medical conditions. However, further research is necessary to fully realise the benefits of these novel approach to diagnostic.

Conflict of interests

The authors declare no conflict of interests.

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VIA MEDICA

RECOMMENDATIONS

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Polish Society of Gynecologists and Obstetricians Guidelines for the application of hysteroscopy in gynecology

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This guideline presents current management recommendations which may be modified and altered in justifiable cases, after careful analysis of a given clinical case, which in the future might constitute grounds for modification and updating.

OBJECTIVES

The objective of this guideline is to present up-to-date knowledge about the application of hysteroscopy in gynecology, based on the experience of the authors and reliable sources from the literature.

INTRODUCTION

Hysteroscopy is a minimally invasive procedure which is performed to diagnose and treat diseases of the uterine cavity and the cervical canal. The two types of the procedure include diagnostic and operative hysteroscopy. Diagnostic hysteroscopy allows for a direct visualization of the cervical canal, uterine cavity and tubal ostia and, if necessary, a targeted biopsy. Operative hysteroscopy facilitates intrauterine and/or intracervical lesion excision using mechanical or electrosurgical resection methods as well as laser techniques. Due to technological advances and miniaturization of the hysteroscopic tools, the number of diagnostic hysteroscopies with simultaneous excision of the lesions (the so-called 'see-and-treat' hysteroscopy) is steadily increasing [1, 2].

Hysteroscopy is a safe procedure and is well-tolerated by the patients [3].

INDICATIONS FOR HYSTEROSCOPY

Due to the wide range of possible applications of uterine cavity and cervical canal imaging, the list of indications for hysteroscopy continues to expand. Also, hysteroscopy allows to collect tissue samples, when necessary.

The indications for hysteroscopy include [3–7]:

- Abnormal uterine bleeding in reproductive age women;
- Post-menopausal bleeding;
- Suspicion of endometrial hyperplasia and other endometrial pathologies (endometrial polyps, diagnostic process for endometrial hyperplasia and endometrial cancer);
- Corroboration of histopathology results;
- Suspicion of submucosal or intramural fibroids;
- Suspicion of congenital uterine anomaly;
- Suspicion of intrauterine adhesions;
- Corroboration of ultrasound diagnosis of uterine abnormalities;
- Repositioning and/or removal of an intrauterine device or other foreign bodies from the uterine cavity;
- Suspicion of retained products of conception;
- Suspicion of lesions within the cervical canal;
- Part of the diagnostic process for infertility and/or recurrent miscarriage;

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— Endometrial ablation/resection;
— Vaginoscopy (*e.g.* removal of a foreign body from the vagina in young girls – *virgo*).

Indications for hysteroscopy may also include clinical situations in which uterine cavity, cervical canal and tubal ostia imaging is vital for the diagnostic and therapeutic management of the affected patients, *e.g.* treatment of symptomatic niche in the cesarean section scar, injection of methotrexate or other pharmacological agents into the gestational sac located in the cesarean section scar, diagnostic and/or operative hysteroscopy, with or without biopsy, before operative procedures in gynecology [8, 9].

In case of suspicion of intrauterine lesions, hysteroscopy is used during the diagnostic process for infertility, recurrent miscarriage or before assisted reproductive techniques (ART). At present, hysteroscopy is not routinely recommended in the diagnosis of infertility or before IVF procedures if ultrasonographic appearance of the uterus is normal [10–13].

CONTRAINDICATIONS TO HYSTEROSCOPY

Absolute contraindications to hysteroscopy include [3, 14]:
— suspected or diagnosed normal viable intrauterine pregnancy;
— active infection of the genital organs, including herpes simplex of the genital area;
— cervical cancer.

Relative contraindications to hysteroscopy include:
— excessive uterine bleeding;
— severe systemic disease.

Bleeding from the genital tract is not an absolute contraindication to hysteroscopy but obstructed visualization of the intrauterine structures may be expected. In such cases, it is necessary to select adequate instruments (flow hysteroscope with proper diameter and isoosmotic medium) [15].

INSTRUMENTS

Types of hysteroscopes

Both, for the operative and diagnostic hysteroscopy, the type of the hysteroscope should be adjusted to the type of the procedure and operator's experience, as well as modified to the intraoperative conditions [4, 16, 17]. It is advisable to use a hysteroscope with the smallest possible diameter of the sheath, individually tailored to the needs of the patient, and allowing for optimal visualization and least traumatic procedure [3, 4, 18].

Media types

Visualization of the intrauterine structures requires distension of the uterine cavity using medium agents. The choice of the distending medium for hysteroscopy is at the discretion of the operator. At present, the 0.9% sodium chloride (NaCl) is the liquid medium of choice for diagnostic hysteroscopy [3, 18, 19]. Other than in exceptional situations, a gaseous medium — carbon dioxide (CO_2) — is not advisable in order to avoid the presence of gas embolism [3]. Also, the use of 0.9% NaCl is associated with lower frequency of vasovagal syncope as compared to CO_2 [4]. A liquid medium, as opposed to gaseous one, allows to wash out the mucus and the blood from the uterine cavity, thus improving visualization and shortening the duration of the procedure [20, 21]. For operative hysteroscopy, only liquid media are used. Their advantage consists in washing out the tissue fragments and blood which occur during intrauterine lesion excision, thus obtaining adequate view of the uterine cavity during the procedure [18–20].

Liquid media are subcategorized into:
— non-electrolyte dissension media (5% mannitol, 3% sorbitol, and 1.5% glycine) and
— isotonic electrolyte-containing media (0.9% sodium chloride, Ringer's solution).

As for electric conductivity, non-electrolyte dissension media are nonconductive, so they are used during procedures with monopolar electrodes [3, 18]. On the downside, they are hypotonic. In the event of excessive absorption into the circulatory system, they may lead to fluid overload, hyponatremia, and lowered plasma osmolarity, which might result in cerebral edema or even death [3, 18, 22]. Electrolyte-containing media are electrically conductive and cannot be used for procedures with monopolar electrodes [3, 18–20]. They are, however, the medium of choice for operative hysteroscopy with bipolar electrodes [3, 18]. Their isotonicity is their primary advantage, as they reduce the risk for hyponatremia and lowered plasma osmolarity.

BEST PRACTICE IN HYSTEROSCOPY

Eligibility criteria

Patients are deemed eligible for the procedure on the basis of the pelvic exam and medical history. Additionally, an ultrasonographic examination should be performed, using transvaginal probe, if possible. In justified cases, additional imaging methods (*i.e.* sonohysterography and nuclear magnetic resonance) may also be applied during patient eligibility check. The abovementioned methods, unlike hysteroscopy, allow for the assessment of the myometrium and the external uterine contour. Additional imaging methods, especially transabdominal or transrectal ultrasound, and sometimes laparoscopy, can be used intraoperatively and may increase both, safety and effectiveness of some advanced hysteroscopic procedures [23–25].

Informed consent

Written informed consent must always be obtained before every hysteroscopic procedure. It is necessary to

discuss the following with the patient: hysteroscopy type, benefits and risk related to the procedure, and alternative methods of management.

Timing of the procedure

For menstruating women, the first phase of the cycle, immediately after the bleeding ceases, is the optimal time to carry out the procedure, as the endometrium in the early proliferative phase is thin and allows for a better visualization of the intrauterine structures and possible pathologies [3]. In the secretory phase, thickened endometrium may impede imaging and visualization, thus increasing the risk for misdiagnosis (underdiagnosis of small lesions and overdiagnosis of endometrial polyps).

In post-menopausal women, hysteroscopy may be performed at any given time.

Cervical preparation

Difficulty in inserting the hysteroscope through the cervical canal into the uterine cavity is among the main causes for unsuccessful hysteroscopy and is responsible for approximately 50% of the related complications [4, 26]. Therefore, in selected cases of operative hysteroscopy, pharmacological preparation of the cervix using misoprostol (vaginally, 200–400 μg) is allowed [3, 4, 27–30]. Randomized studies found no proof of increased number of successful procedures or lowered risk for complications or pain reduction for diagnostic hysteroscopy [27–29, 31]. Thus, routine use of misoprostol for cervical preparation before diagnostic hysteroscopy is not recommended [4].

Notably, the use of misoprostol for cervical preparation is an off-label approach.

In cases of cervical stenosis, osmotic distending media, intraoperative ultrasound, vaginoscopic approach, manual dilation and hysteroscopic dissection of the stenotic cervical canal may be also applied [26, 32].

Endometrial preparation

Pre-operative administration of the endometrial thinning agents may be considered in women undergoing elective operative hysteroscopy (*e.g.* uterine septum resection, submucosal fibroid resection, endometrial ablation) to ensure a better view during the procedure [33]. Such management is not recommended for diagnostic hysteroscopy as it might affect the histopathology results.

Vaginal preparation

After excluding the contraindications to hysteroscopy (like active inflammation of the genital organs), vaginal discharge ought to be examined before the procedure. If no signs of inflammation are present, hysteroscopy may be conducted. Culture of the cervix is not routinely required. It is advisable to visualize the vaginal portion of the cervix using the speculum and wash the vagina and the vaginal portion with an antiseptic solution suitable for mucous membranes. Vaginoscopic approach (*i.e.* the so-called 'no touch' technique) is also allowed [4, 34, 35]. It consists in insertion of the hysteroscope into the vagina, through the cervical canal and into the uterine cavity without the use of a speculum or cervical instrumentation. Vaginoscopic approach is recommended in situations when it is difficult or impossible to insert a speculum. The procedure may be conducted without the need to disinfect the vagina if vaginal discharge is normal.

Settings

Advances in technology and increasing miniaturization of the hysteroscopes allow to conduct diagnostic and simple operative hysteroscopies in outpatient settings [4, 36, 37]. The decision between outpatient and hospital setting should be made with caution.

Hospital settings should be recommended to patients with: [3, 38]:

- intrauterine lesions which require advanced operative procedures;
- cervical stenosis or atresia;
- concomitant diseases which elevate the risk for complications;
- limited uterine maneuverability;
- no tolerance of local anesthesia.

In the remaining cases, ambulatory settings may be recommended to patients.

Elimination of perioperative pain

Hysteroscopy-related pain remains to be one of the main limitations for a successful procedure in ambulatory settings, so it is vital to be familiar with techniques of pain reduction [38, 39]. Friendly atmosphere and engaging the patient in a conversation play a significant role in reducing pain and anxiety associated with the procedure [40]. Depending on the emotional condition of the patient and her attitude, anesthesia in not necessary during a diagnostic hysteroscopy in most women [41, 42]. The benefits of avoiding anesthesia include shortened time of the procedure and no adverse effects, especially no pain associated with paracervical block [41].

Also, small-diameter sheath hysteroscopes are key elements in pain reduction. Randomized studies revealed that the use of hysteroscopes with sheath diameter less than 4 mm correlates with significantly less pain as compared to the use of higher diameter hysteroscopes with simultaneous paracervical block [43].

Opioids reduce pain during and after the procedure, but caution is advised due to possible adverse effects [4, 44].

Non-steroidal anti-inflammatory agents (NSAIDs) do not relieve the pain during hysteroscopy but significantly reduce it after the procedure [4, 45]. Local anesthetics, *e.g.* lidocaine spray on the vaginal portion of the cervix, is not an effective means of pain relief during hysteroscopy [46]. Likewise, lidocaine and mepivacaine administration into the cervical canal proved ineffective [46].

Paracervical block using lidocaine or mepivacaine reduces pain associated with cervical dilation and endometrial biopsy, and lowers the risk for severe pain during hysteroscopy [47], so it should be considered in cases when cervical dilation is necessary or when intrauterine lesions are to be removed [4, 47].

Sedation, regional or general anesthesia should not be used in ambulatory settings as they require strict monitoring of the vital signs and are connected with possible complications [48]. They should only be administered in setting where adequate anesthesiologic standards are maintained.

HYSTEROSCOPIC BIOPSY

Hysteroscopic endometrial biopsy should replace diagnostic curettage of the uterine cavity [49]. Sensitivity of the hysteroscopic endometrial biopsy is significantly higher, especially in case of focal lesions. Diagnostic curettage of the uterine cavity, if conducted as a sole diagnostic procedure, is not sufficient for full diagnostics of the endometrium in case of focal lesions [50, 51]. Therefore, hysteroscopy and targeted biopsy should be considered in women with indications for histopathological examination of the endometrium (*e.g.* in the diagnosis of endometrial cancer) [51, 52]. It makes it possible to collect focal lesions, which might otherwise be omitted during blind biopsy or curettage, for evaluation [51, 52]. In case of extensive suspicious changes in the uterine cavity, subsequent curettage is allowed.

It is not always possible to obtain enough endometrial tissue for histopathologic evaluation, especially in post-menopausal women with endometrial atrophy [53–55]. In a meta-analysis of studies on endometrial biopsy, non-diagnostic histopathology results were found in as many as 54% of the women with post-menopausal bleeding [54]. According to reliable reports in the literature, results of imaging studies are sufficient to plan further management in case of patients with non-diagnostic histopathology results [53–55]. If hysteroscopy confirmed atrophic endometrium and histopathology results are non-diagnostic, repeat biopsy is not necessary, unless new indications are present [53–55].

Risk for tumor cell dissemination in the peritoneal cavity

Hysteroscopy is associated with a certain risk for tumor cell dissemination into the peritoneal cavity due to the passage of the medium through the fallopian tubes. The available data are not conclusive with regard to a possible increase in the incidence of positive peritoneal cytology after the use of hysteroscopy in the diagnosis of endometrial cancer. So far, various meta-analyses have found a link between the use of liquid media and higher incidence of positive peritoneal cytology, but no relationship between potential tumor cell dissemination and disease progression was detected [56–61].

In order to reduce the risk for cell dissemination in cases of suspected endometrial cancer, it is advisable to use the lowest possible pressure of the distending medium, preferably not exceeding 50 mmHg. In a study using saline solution and intrauterine pressure of 25–50 mmHg, the authors found that hysteroscopy did not increase the risk for microscopic intraperitoneal tumor cell dissemination as compared to curettage [62]. More prospective studies in that area are necessary.

COMPLICATIONS OF HYSTEROSCOPY AND THEIR PREVENTION

Early complications:

- uterine perforation;
- heavy bleeding;
- absorption of the distending medium;
- gas embolism;
- fluid overload.

Late complications:

- iatrogenic adhesions after hysteroscopy;
- pelvic inflammatory disease.

Uterine perforation

The incidence of uterine perforation during diagnostic and operative hysteroscopy has been estimated at 0.13% and 0.5–3%, respectively [62, 63]. Perforation may occur either during the attempt to enter the uterine cavity or intraoperatively, during lesion excision. Risk factors for perforation during hysteroscope insertion include [4, 63]:

- cervical stenosis and the need for cervical dilation (as a result of atrophy, previous surgery, or no previous vaginal delivery);
- torsion of the cervical canal and uterine cavity (frequently occurs in case of fibroids and pelvic adhesions).

The highest risk for uterine perforation is associated with the excision of massive intrauterine adhesions [63]. Should perforation occur, it is possible to either monitor the patient or consider performing laparoscopy or laparotomy to stop the bleeding and assess for possible intestine or bladder trauma [3]. Assessment of the bowel and the bladder is necessary in the event of uterine perforation using an electrosurgical tool or laser due to the risk for thermal injury [64]. Suturing of the uterine perforation is advised in reproductive age women to prevent a possible uterine scar rupture during subsequent pregnancy [65]. It is important

to bear in mind that if the perforation is localized within the cervix or the lateral uterine wall, it may cause bleeding into the retroperitoneal space [3].

If fundal perforation occurs while using a thin hysteroscope, a thin Hegar device, or an uterine probe in a post-menopausal woman without signs of bleeding into the abdominal cavity, it is possible to simply monitor the patient. Detailed imaging to exclude bleeding into the abdominal cavity and a 24-hour monitoring at a postoperative care unit are necessary. Should patient clinical and laboratory (complete blood count, C-reactive protein) parameters remain stable after 24 hours, the perforation may be diagnosed as non-symptomatic and not requiring surgical intervention.

In cases when hysteroscopic entry is difficult, it is advisable to establish the path of the cervical canal and its relation to the uterine axis before 'blind' cervical dilation [3, 26]. For that purpose, a small-diameter flexible or rigid hysteroscope may be used, which allows for visual control during dilation of the cervical canal with the tip of the hysteroscope or microtools inserted through the operative channel [26]. Uterine probe, bimanual examination, transvaginal, transrectal or transabdominal ultrasound are also useful while attempting to establish the path of the cervical canal and its relation to the uterine cavity. Difficulty with hysteroscopic entry into the uterine cavity may be reduced by cervical preparation with misoprostol [29].

Hemorrhage

Clinically significant bleeding during diagnostic hysteroscopy is rare and is usually associated with uterine perforation. The incidence of clinically significant bleeding related to operative hysteroscopy has been estimated at 0.61% [63]. Apart from uterine perforation, other causes for bleeding include cervical trauma, bleeding at the operation site or bleeding diathesis.

In the event of intraoperative bleeding, coagulation using mono- and bipolar electrodes may be applied (the choice of the electrodes depends on the medium used during the procedure).

Postoperative bleeding from the uterine cavity may be stopped by using uterotonics, antifibrinolytics, or balloon tamponade (*e.g.* using a Foley's catheter).

If none of the above methods proved sufficient, it may be necessary to perform uterine artery embolization or hysterectomy. The patient should be made aware of that risk and information about a possible hysterectomy should be included in the informed consent for all hysteroscopic procedures [3, 63].

Embolism

Air embolism may occur during hysteroscopy using either gaseous medium — CO_2 or liquid medium, as air bubbles are present in the liquid medium as well [18, 66]. The symptoms include dyspnea, chest pain, tachycardia, anxiety, sudden hypotension and hypoxemia [18]. Vascular access and a pressure gradient are necessary for CO_2 or air to get into the cardiovascular system, and then to the right ventricle and to the pulmonary arteries [3]. Therefore, to avoid this complication, it is vital to keep the rate of the CO_2 flow below 100 mL/min., and the uterine cavity pressure below 100 mmHg [3]. Importantly, laparoscopic insufflators should not be used for hysteroscopic procedures as they have very high CO_2 flow rate [3]. Carbon dioxide should not be used during operative hysteroscopy due to the risk for CO_2 passage into the open vessels [18]. To avoid air passage into the uterine cavity during hysteroscopy with liquid medium, tubing and hysteroscopy channel ought to be flushed until all air bubbles are removed. Caution is also advised when bags containing liquid media are changed to avoid air entering tubing [3].

FLUID OVERLOAD

Operative hysteroscopy intravascular absorption syndrome (OHIA) occurs when a significant amount of the liquid medium is absorbed into the circulation [63, 67]. At present, the incidence of OHIA has been estimated at < 1% [18, 63, 68, 69]. The absorption occurs by the opened uterine veins as a result of pressure gradient (venous pressure: 10–15 mmHg, distending media pressure in the intrauterine cavity: 40–60 mmHg) [63]. Absorption of the distention media may also occur by peritoneal surface due to the retrograde passage of the fluid through the Fallopian tubes [18].

Risk factors for fluid overload include high (excessing the mean blood pressure) pressure in the uterine cavity, prolonged duration of the procedure, and contact between the medium and the opened myometrial venous sinuses (mainly during electrosurgical fibroid resection or the resection of the endometrium) [70–72].

Massive absorption of a hypotonic medium (glycine, mannitol, sorbitol) leads to hyponatremia, which is manifested with headache, nausea, vomiting and fatigue. In case when sodium levels drop below < 120 mmol/L, lowered plasma osmolarity will lead to cerebral edema, including the risk for brain herniation [3, 28, 73].

Massive absorption of an isotonic medium (0.9% sodium chloride, Ringer's solution) will not cause electrolyte imbalance but may lead to hypervolemia with pulmonary edema and heart failure [3, 18].

In accordance with the international consensus, a fluid deficit (difference between the volume of fluid infused into the uterus and the volume of fluid evacuated from the uterus) should not exceed 1000 mL for hypotonic (glycine, mannitol, sorbitol) and 2500 mL for isotonic solutions. These thresholds apply to healthy reproductive age women [18].

In case of elderly women with renal and cardiovascular problems, the upper fluid deficit levels should be 750 mL and 1500 mL, respectively [19]. Therefore, careful monitoring of the fluid deficit during hysteroscopy is necessary. The procedure should be stopped when the fluid deficit is reaching the abovementioned limits or when the clinical symptoms of fluid overload occur. In order to lower the risk for hyponatremia and the related complications, iso-osmotic media such as 0.9% sodium chloride or Ringer's solution should be the preferred choice for operative hysteroscopy [18]. The information about fluid deficit should be included in the operation report.

Iatrogenic adhesions after hysteroscopy

Hysteroscopic resection of the intrauterine lesions is associated with significantly lower risk for *de novo* adhesion formation as compared to curettage [74]. Therefore, uterine curettage in order to obtain endometrial samples in women undergoing diagnosis for infertility should be avoided. The incidence of adhesion formation after operative hysteroscopy depends on the type of the procedure. Polypectomy is associated with the lowest and multiple submucosal fibroid resection with the highest risk for adhesion formation, respectively [74]. The following procedures may decrease the risk for intrauterine adhesion formation after hysteroscopy: avoidance of electrosurgical tools, early second-look hysteroscopy, estrogen therapy, intrauterine systems (IUD, balloon), stem cells, hyaluronic acid gels or carboxymethyl cellulose gels [74–76]. At present, we lack reliable data advocating routine use of any of the abovementioned methods of preventing adhesions after hysteroscopy [75].

Pelvic inflammatory disease

The incidence of inflammatory diseases after hysteroscopic procedures has been estimated at < 1%, so routine antibiotic prophylaxis is not required [77–79]. Guidelines on patient eligibility and preparation for the procedure, which constitute preventive measures for post-hysteroscopic inflammation, have been presented earlier in the text.

SUMMARY

The benefits of diagnostic hysteroscopy include direct visualization of the intrauterine structures and, when necessary, performing a minimally invasive targeted biopsy for histopathology evaluation.

Operative hysteroscopy allows for a minimally invasive excision of intrauterine lesions.

Hysteroscopy is well-tolerated and safe for the patients.

Hysteroscopy is the basis of the modern diagnostic process and the treatment of uterine diseases, and every effort should be made to increase its availability in Poland.

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Laparoscopic treatment of an intrauterine device mislocated in the abdominal region

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A 41-year-old patient (gravida 2, para 2) after two cesarean sections (2007, 2010) due to ophthalmologic indications was admitted for a diagnostic laparoscopy to search for an intrauterine device (IUD) that had relocated to the abdominal cavity. The woman was asymptomatic; inflammation markers were normal. Previous hysteroscopy had not found any defect of the cesarean section scar but confirmed adhesions in the uterine cavity. The IUD with a levonorgestrel (Mirena) was implemented in November 2018. After 3 months, the IUD was not visible in the uterine cavity on ultrasound. An abdominal X-ray showed a perforated IUD in the right iliac fossa (Fig. 1A). On laparoscopy, the IUD was found to be ingrown in the greater omentum next to the intestinal wall (Fig. 1B–C). The insert was separated from the adhesions with the omentum without damaging the intestine and removed through the lateral trocar. No perforation within the uterus nor damage to abdominal organs were found. The postoperative course was uneventful. The patient was discharged home on the second day post-procedure.

Uterine perforation is a complication of IUD implementation with a frequency of 0–1.3 per 1000 applications. It is associated with the risk of damaging intestines and other abdominal organs by the perforated insert [1]. This case is unique because the IUD was inserted 6 months earlier and the patient did not feel any discomfort during this period. The UID relocation was found accidentally during the follow-up visit.

The relocated UID must be removed due to the risk of damaging abdominal organs [2]. The overall rate of successful laparoscopic procedures for UID removal in cases of uterine perforation reaches 64% of UIDs [3]. Removal of a lost insert may require conversion to a laparotomy, especially when no perforation is visible within the uterus or adhesions and intestinal damage occur. In this case, the IUD removal was performed laparoscopically.

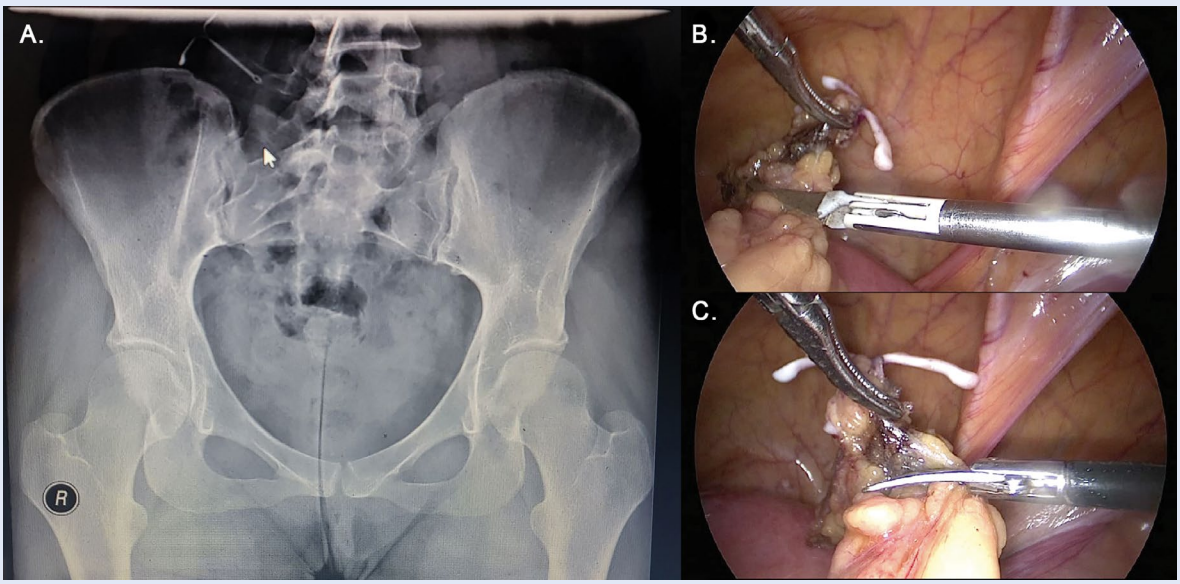

Figure 1. Perforated intrauterine device: A — the device marked with an arrow in the right iliac fossa; an abdominal X-ray; B — laparoscopic image of a perforated intrauterine device ingrown in the greater omentum next to the intestinal wall, C — laparoscopic removal of the intrauterine device

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