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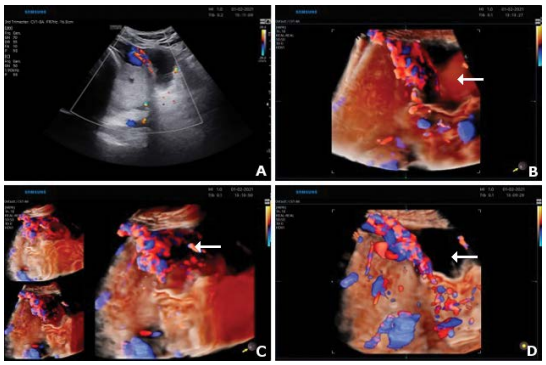

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Anterior abdominal fixation — a new option in the surgical treatment of pelvic organ prolapse

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ABSTRACT

Objectives: To present anterior abdominal fixation — a new surgical technique for the treatment of pelvic organ prolaps (POP) and to evaluate the results of the treatment of patients with stage III and IV POP operated using this technique.

Material and methods: Anterior abdominal fixation for treating stage III and IV POP was carried out in 42 women, who were qualified according to the Pelvic Organ Prolapse Quantification System (POP-Q) scale at baseline and after 12 months. The Pelvic Floor Disability Index-20 (PFDI-20), along with its symptom scales, were evaluated.

Results: The mean age 42 operated women was 64.5 years, and the average BMI was 27.3 (83% women were overweight). At baseline, 29 (69%) women had POP stage IV, and 13 (31%) women had POP stage III. Overall, 14 (33%) underwent laparoscopy, 28 (67%) underwent laparotomy. At 12 months, 14 (33.3%) women had POP stage I; 21 (50%) women had POP stage II. Seven patients (16.6%) experienced a recurrence of disease with advancement at the degree of III/IV; 4 (9.5%) women required adjuvant surgery in the form of anterior and posterior vaginal wall surgery. No early complications after surgery were observed. The comparison of the results before and after surgery showed statistically significant improvement in terms of the P-QoL score as well as PFDI-20 along with its 3 symptom scales.

Conclusions: Anterior abdominal fixation of the uterus to the anterior abdominal wall is effective, safe, and technically easy to perform in the treatment of POP of advanced stage.

Key words: pelvic organ prolapse; quality of life; women's health

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INTRODUCTION

Pelvic organ prolapse (POP) in women is defined as the lowering of the pelvic organs, leading to the protrusion of the vagina, cervix or the entire uterus. It mainly affects postmenopausal women and is accompanied by symptoms related to the lowering of the urethra, bladder, small intestine and/or rectum [1]. Risk factors of POP can be divided into congenital factors, which include disorders of the connective tissue structure, abnormal innervation of the pelvic organs, and defects in the build of the pelvis or the spine, as well as acquired factors, which include multiple vaginal births, heavy physical work, a chronic cough, constipation, age, obesity, and the removal of the uterus [2, 3]. The most common symptoms of POP include: a feeling of heaviness in the vagina, noticeable protrusion of the uterus or vaginal walls through the labia, abnormal urination and/or defecation, sexual dysfunction [4].

In the treatment of pelvic organ prolapse, conservative treatment methods are used first. They include: weight reduction, training of the pelvic diaphragm muscles (Kegel exercises), and also pharmacological improvement of the quality of the vaginal mucosa and vaginal pessaries. In the case of ineffective conservative treatment, surgical treatment of POP, which is performed by transvaginal or transabdominal access, is used. It is conducted using laparotomy or laparoscopy and involves the suspension of the uterus or vagina to the uterosacral ligaments or sacrospinous ligaments, or is performed using Mayo culdoplasty or the McCall method [5].

Despite the use of many surgical techniques in the treatment of POP in women, there is still no single method that is safe, effective and that has a short learning curve. In the past, for the so-called "gold standard" of surgery, some operators recognized sacrocolpopexy and/or sacrouteropexy. This is due to the fact that this operation suspends the vagina and

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uterus posteriorly in the vaginal axis and has a high degree of effectiveness. On the other hand, because of the possibility of the occurrence of serious complications (damage to the organs and vessels of the smaller pelvis, pre-sacral haemorrhage, defecation disorders, adhesions, urinary incontinence), and also the high degree of difficulty of the procedure — this type of surgery nowadays does not meet the gold standard criterion [6]. When choosing the optimal technique for a given patient, it is important to take into account the current type of defect, the patient's age, physical activity, obstetric interview, procreation plans, operations in this area and, above all, the patient's preferences. A similarly important element in the selection of the optimal surgical technique is the degree of difficulty of the procedure and the operator's experience [5].

In recent years, there has been increased attention paid towards patient's preferences and concerns about the impact on the quality of sexual intercourse, and also the psychological feelings associated with removing or saving the uterus. As a result, there is a tendency to decrease the number of hysterectomies in favour of sparing surgical procedures that preserve the uterus [7–9]. The surgical techniques of POP with the saving of the uterus include, among others, suspension of the uterus to the uterosacral ligaments, sacrouteropexy, pectopexy, and the Manchester technique [6]. Effective surgical treatment of pelvic organ or vaginal stump prolapse requires apical suspension, either with the option of removing the uterus, or saving it. Most of the results of surgical treatment of POP come from retrospective data analyses — the preferred surgical access is undoubtedly vaginal and laparoscopic access as it is minimally invasive and does not require the cutting of the peritoneal cavity [5]. Regarding the above assumptions, in the 2nd Department of Obstetrics and Gynecology of Wroclaw Medical University, Wrocław, Poland, a new surgical technique for the treatment of POP in women in stages III and IV, according to the Pelvic Organ Prolapse Quantification System (POP-Q) scale, was developed. It involves the laparoscopic suspension of the uterus to the anterior abdominal wall — that is, in the anterior direction by means of transfascial insoluble sutures and with the use of a polypropylene mesh applied retroperitoneally and supra-fascially — anterior abdominal fixation.

The aim of the study was to present a new surgical technique for the treatment of POP and to initially evaluate the results of the treatment of patients with stage III and IV POP assessed on the POP-Q scale who were operated on in the 2nd Department of Gynecology and Obstetrics using the technique described below.

MATERIAL AND METHODS

In this study, the effect of surgical treatment of 42 women operated on due to pelvic organ prolapse, who were in stages III and IV according to the POP-Q scale, was assessed. The patients underwent surgery that involved the suspension of a pelvic organ (uterus, cervix or vaginal stump) to the fascia of the straight abdominal muscles with the use of insoluble monofilament threads, and also the protection of insoluble sutures with a polypropylene mesh that was fixed to the anterior abdominal wall. The effect of the treatment was assessed using the POP-Q scale during a gynecological examination 12 months after the surgery.

Until now, surgical procedures using the surgical method presented in this study have been performed for 42 patients with stage III or IV POP according to the POP-Q scale. The method involved the laparoscopic or laparotomy suspension of the uterus in the anterior direction, *i.e.* to the anterior abdominal wall, with the use of two insoluble monofilament sutures and a polypropylene mesh applied supra-fascially. The mesh was used to strengthen the flaccid fascia of the rectus abdominis, and also to reinforce non-dissolving sutures. Being an artificial material, the mesh was implanted retroperitoneally over the fascia of the rectus abdominis, which makes the procedure easy and effective, and at the same time, excludes the risk of adhesions and erosion of the mesh into the peritoneal cavity. The operation enables the uterus to be saved, which reduces the invasiveness of the method, as well as shortens the procedure time. The use of the described surgical technique was approved by the Bioethics Committee of Wroclaw Medical University, Wrocław, Poland.

The technique of the procedure

The following steps show how to perform the operation:

1. Placement of the manipulator into the uterine cavity through the cervical canal in order to obtain uterine mobility.
2. Introduction of standard laparoscopic equipment to gain access to the abdominal cavity. One optical trocar and two side trocars are used.
3. Approximately 3 cm above the pubic symphysis, a 3 cm long transverse skin incision is made and the subcutaneous tissue is bluntly separated to the level of the rectus abdominus fascia; the fascia is not incised.
4. The first retroperitoneal suture for the uterus — the first suture is made with a straight needle and involves the puncturing of the fascia, rectus abdominis, and peritoneum into the peritoneal cavity. The needle is then punctured through the uterus at a specific point, *i.e.* at the level of the isthmus, above the entrance of the uterine arteries — from the front of the uterus to the back — and then in the opposite direction — from the posterior wall of the uterus to the front at the same level — and again through the muscles and fascia to the outside (U-shaped suture). The determination and

precise puncture in the marked place, *i.e.* at the level of the isthmus and above the entrance of the uterine arteries, is critical as it provides a safe distance from the uterine artery and a low risk of complications.

5. The second transperitoneal suture — a straight needle is also used, and the steps are the same as for the first suture — the uterus is punctured slightly above the first suture.
6. Fixing the mesh directly over the fascia — the mesh used in the procedure has dimensions of 4 × 2 cm. The mesh is placed under the subcutaneous tissue, exactly in the place of the previously prepared fascia. The sutures that were conducted through the uterus and mesh to the abdominal wall, when the mobile uterus is pulled up to the abdominal wall, they are tied together over the mesh.
7. When the sutures are tied, the uterus is pulled up and forward towards the abdominal wall in such a way that its anterior wall meets the peritoneum of the anterior boundaries of the abdominal cavity.

Data concerning demographic information, disease advancement on the POP-Q scale and the type and course of surgery in 42 operated women were evaluated at baseline. Additionally, the subjective severity of pelvic floor complaints was assessed on the basis of the Pelvic Organ Prolapse Quality of Life (P-QoL) questionnaire and the Pelvic Floor Disability Index-20 (PFDI-20) questionnaire. The data from the PFDI-20 questionnaire were divided into groups of questions concerning symptoms associated with POP using the Pelvic Organ Prolapse Distress Inventory 6 (POPDI-6), symptoms associated with distal gastrointestinal disorders using the Colorectal-Anal Distress Inventory 8 (CRAD-8), and symptoms associated with the dysfunction of the urinary system using the Urinary Distress Inventory 6 (UDI-6). After 12 months, the results of the procedures were assessed by re-examining the advancement of the disease and perceived symptoms.

The collected data were statistically analysed. The data were presented as means and standard deviations as well as numbers and percentages. The Kolmogorov-Smirnov test was used to test for normal distribution. The Wilcoxon signed-rank test both for paired comparisons was used. Data were considered to be statistically significant at a value of $p < 0.05$. Statistical analysis was carried out with Statistica software (StatSoft, Tulsa, OK, USA).

RESULTS

The average age of the operated women was 64.5 years, the average weight was 71 kg, the average height was 1.62 m, and the average BMI was 27.3 (83% were overweight patients). As many as 69% of the patients reported being involved in physical work in the past or now, and the remaining 31% performed white-collar work, which confirms the influence of physical work on the degree of the defect.

The operated patients reported on average 2 vaginal childbirth deliveries. The average weight of a newborn was 3651 g, with a minimum of 2650 grams and a maximum of 4500 g. Such a high weight had at least 25% of the newborns. In the preoperative examination, the disease was assessed as stage IV according to POP-Q in 29 women (69%), and as stage III in 13 women (31%).

Overall, 14 (33%) operations were performed using laparoscopy, and the remaining 28 (67%) using laparotomy. In 14 (33%) patients, conservative uterine-sparing surgery was performed. The average time of the procedure, including the preparation of the patient, was 115 minutes in the case of laparotomy, and 85 minutes in the case of laparoscopy. The mean blood loss during the procedure, assessed on the basis of the decrease in the haemoglobin level in the venous blood count, was 1.66 mg/dL, with no significant differences in both groups.

In 35 out of 42 patients (83.3%), clinical improvement was observed. A gynecological postoperative examination 12 months after the surgery revealed that the degree of organ prolapse on the POP-Q scale was on average I/II. In details, 14 (33.3%) women had POP stage I, and 21 (50%) patients had POP stage II. Seven (16.6%) patients had a recurrence of disease with an advancement at stage III/IV on the POP-Q scale 12 months after the surgery. Four (9.5%) patients required adjuvant surgery in the form of anterior and posterior vaginal wall surgery.

No early complications after surgery were observed in any of the patients.

At baseline and 12 months after surgery, the subjective feelings related to pelvic floor problems in the operated patients were assessed on the basis of self-completed P-QoL and PFDI-20 questionnaires and both showed significant improvement. Based on these scales, 35 (83.3%) women had a significant subjective improvement in perceived ailments related to POP, as well as an improvement in the quality of life. The postoperative results of 7 (16.6%) women were comparable to those before the operation.

The comparison of the results before and after surgery showed statistically significant differences between the studied P-QoL domains. Also the change in the score from baseline to at 12 months showed significant improvement for all questionnaires (PFDI-20, POPDI-6, CRAD-8, UDI-6) which scores are presented in Table 1. The average level of PFDI-20 before the surgery is more than twice as high as after the surgery, which means a significant improvement in the perception of pelvic floor problems. The frequency of experiencing the examined symptoms and their impact on life after the surgery is statistically significantly different from the frequency before the surgery.

Table 1. Results of the assessment of pelvic organ prolapse before and after the surgery

	mean ± SD	mean ± SD	Wilcoxon signed-rank test
	before the surgery	after the surgery	
PFDI-20	191.74 ± 27.11	97.20 ± 53.67	0.000000
POPDI-6	80.49 ± 12.04	33.74 ± 25.54	0.000000
CRAD-8	49.14 ± 10.31	29.89 ± 13.79	0.000000
UDI-6	62.11 ± 11.73	33.57 ± 18.22	0.000000

CRAD-8 — Colorectal-Anal Distress Inventory 8; PFDI-20 — Pelvic Floor Disability Index-20; POPDI-6 — Pelvic Organ Prolapse Distress Inventory 6; SD — standard deviation; UDI-6 — Urinary Distress Inventory 6

After the surgery, subjective and objective improvement was observed in most of the operated patients with regards to vagina and uterine prolapse, as well as to the urinary system. This was especially the case for those with advanced POP and urine retention before the surgery. It should be emphasized at this point that the discomfort of patients with POP stage III/IV is so great that some imperfections of the method, such as pulling the pelvic organ in the anterior direction in the non-physiological vaginal axis, or the need to execute additional vaginal wall plastic surgery, are fully acceptable for the patients.

CONCLUSIONS

The anterior abdominal fixation of the uterus to the anterior abdominal wall is effective, safe, and technically easy to perform in the treatment of POP of advanced stage. It is associated with a lower rate of intraoperative complications than other methods used in POP, *e.g.* sarcocolpopexy, and a lower risk of damage to large blood vessels. Moreover, the results are satisfying for patients. The technique of uterine suspension using laparoscopy is particularly preferred. In some patients with a mixed type of POP, it may be necessary to perform additional plastic surgeries of the posterior vaginal wall. The use of a supra-fascial mesh strengthens the flaccid fascia and prevents against the risk of mesh erosion and the development of intraperitoneal adhesions.

Conflict of interest

The authors declare no conflict of interest.

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Cytogenetic analysis of early pregnancy loss after assisted reproduction treatment using intracytoplasmic sperm injection

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ABSTRACT

Objectives: To evaluate the incidence of numerical chromosomal abnormalities in the patients with early pregnancy loss (EPL) following in vitro fertilization, and evaluate the role of different confounders of the risk of chromosomal abnormality-related pregnancy loss.

Material and methods: A retrospective chart review of all patients from our in vitro fertilization (IVF) center who conceived using assisted reproduction techniques between April 2017 and 2019, who experienced a subsequent early pregnancy loss, and whose abortus materials were successfully karyotyped were included.

Results: Of the 243 patients experienced an early loss, the overall rate of chromosomal abnormality was 46.75%. The overall rate of aneuploidy in our patient group was 88.8% (64/72), whereas 6.94% (5/72) of the abnormal karyotypes were polyploid. The most common type of trisomy was Trisomy 16 (20.0%; 11/55) followed by Trisomy 15 (14.5%; 8/55). Univariate and multivariate analyses showed that maternal age (< 35 years) and the total number of retrieved oocytes per cycle (≥ 5) were risk factors for a chromosomal abnormality (< 0.001; < 0.05, respectively). The adjusted OR of karyotypic abnormalities was 0.45 for the antagonist cycle type ($p < 0.05$), and 0.58 for frozen embryo transfer ($p < 0.05$).

Conclusions: Karyotypic abnormality is one of the main reasons for pregnancy loss following an IVF procedure. Although the pregnancy rates increased as a result of novel technologies, the ratio of EPL is still high. The implementation of preimplantation genetic screening techniques might lower the incidence of EPL due to chromosomal abnormalities, thus decreasing the burden on the physicians and the patients.

Key words: abortus; early pregnancy loss; assisted reproduction; ICSI; cytogenetic analysis

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INTRODUCTION

Early pregnancy loss (EPL) is the most frequent pregnancy-related complication and accounts for 10–20% of clinically confirmed pregnancies. Most of the cases occur before the 20 weeks of gestational age, and up to 50% of them are related to chromosomal abnormalities [1].

Although the wide use of assisted reproductive technology (ART) improved the pregnancy ratio especially in cases with higher maternal age, EPL is still common following ART due to numerous causes including medication administered during the process, the technique used, and various patient-related factors [2]. The etiologies underlying the pathogenesis of EPL in the cases that underwent ART procedures are different from the ones that conceived naturally [3]. Applying for an ART procedure increases the expectation of pregnancy for the patients despite the increased rate of EPL in this group, and the analysis of possible causes and taking measures for prevention are of concern in order to minimize the psychological and economic burden for the patients. Being the most common cause of EPL in ART cases, chromosomal abnormalities include mostly numerical abnormalities, mosaicisms, and structural chromosomal defects involving autosomal and/or gonosomal chromosomes [4].

The present retrospective study aims to explore the effect of different patient- and procedure-related variables on the risk of chromosomal abnormalities in cases that underwent ART and experienced an EPL.

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MATERIAL AND METHODS

We performed a cohort of 243 spontaneous miscarriages of a specific institution specialized in ART and in vitro fertilization (IVF) techniques between April 2017 and 2019. Ethical approval was obtained from the institutional board. Pregnancies occurred using intracytoplasmic sperm injection (ICSI) and experienced an early pregnancy loss were scanned retrospectively, and among these, 235 were karyotyped successfully. Exclusion criteria included: abnormal karyotype of one parent, spontaneous pregnancy with the induction, intrauterine insemination (IUI), multiple pregnancies, inadequate fetal tissue for analysis, and lack of the consent for karyotyping.

Of the resulting 154 nonviable embryos, 72 with abnormal karyotype acted as the outcome group and compared to the nonviable embryo group (n = 82) with normal karyotyping results in terms of variables including basic demographic information, procedure-related factors such as a previous history of frozen embryo transfer (FET) cancellation, type of the protocol administered for ovarian stimulation, total oocytes retrieved implanted embryo type, sperm abnormality, the gestational week at the time of EPL, endometrial thickness and serum hormone levels. The oocyte output rate was calculated using the number of oocytes retrieved/AFCx100% formula. Informed consent was obtained from each patient, and they were informed that their clinical data could be used for research purposes.

IVF treatment

Of the 154 women, 37 women were diagnosed with unilateral or bilateral tubal obstruction. The male partners of 73 women were diagnosed with azoospermia or oligoasthenoteratozoospermia. Sixteen couples had infertility-causing sperm and hysterosalpingography (HSG) abnormalities in both females and males. The remaining 60 cases were diagnosed with idiopathic infertility.

Natural, antagonist, and semi-antagonist protocols were performed for ovarian stimulation. Controlled ovarian stimulation was performed using recombinant FSH (rec-FSH) and GnRH antagonist agents as previously described [5]. The dose of the stimulating agent was determined based on the woman's serum hormone levels, age, BMI, and other patient-related characteristics according to the performing gynecologist's personal experience. 10.000 IU of human chorionic gonadotropin (hCG) was administered when more than two follicles reached a diameter of 18–20 mm. After 32–35 hours of induction, oocyte collection was performed through transvaginal ultrasound-guided aspiration.

All the participants in the study group received intracytoplasmic sperm injection (ICSI). After the transfer of Day-3, Day-4, or Day-5 embryos, serum beta-hCG levels were measured on the 12–14th day of the embryo transfer and were accepted as a positive result for the values ≥ 10 IU. Clinical pregnancy was confirmed when the intrauterine gestational sac was detected, and the fetal heartbeat was present on the transvaginal USG at 21 days after the transfer. The diagnosis of EPL was confirmed with transvaginal ultrasonography, and curettage of the uterine cavity was performed afterward. Collected samples were routinely sent to the genetic diagnosis center for karyotype analysis. Chorionic villi samples were obtained cautiously in order to avoid maternal contamination. Samples were subjected to karyotype analysis after culture, harvesting, and G-banding. More than 20 cells in metaphase were examined and reported.

Statistical analysis

All data were stored in a computerized database. Statistical calculations of the data were performed using the SPSS software package program, version 12.0 for Windows. The comparison of the variables between two subgroups was done using 2-tail Student's t-test for independent samples. A Chi-square test was performed when appropriate. Univariate and multivariate analysis were used to determine potential risk factors and calculate the adjusted ORs for chromosomal abnormalities. Quantitative data were presented as mean ± standard deviation (SD), and risk factors were reported as odds ratio (OR) and 95% confidence interval (CI). A p-value < 0.05 was considered statistically significant.

RESULTS

The mean age of patients was 37.66 ± 4.86 in the abnormal karyotype group and 33.50 ± 5.98 in the normal karyotype group. The mean gestational age was 8.55 ± 1.69 weeks (median: 8.0 weeks) in the chromosomal abnormality group versus 9.07 ± 3.37 weeks (median: 8.0 weeks) in the normal karyotype group. In 94.63% of cases, the pregnancy terminated before the 12th week of gestation. Overall cytogenetic results revealed that 46.75% (72/154) of the miscarriages showed an abnormal karyotype.

The male to female ratio of the embryos was 1:1.8 (55/99), and the ratio of karyotypic abnormalities in male and female embryos was 56.3% and 41.4%, respectively. The overall rate of aneuploidy in our patient group was 88.8% (64/72), whereas 6.94% (5/72) of the abnormal karyotypes were polyploid. The most common type of trisomy was Trisomy 16 (20.0%; 11/55) followed by Trisomy 15 (14.5%; 8/55). Three patients had monosomy X. Double aneuploidy was present in five cases.

The baseline characteristics of the groups with normal and abnormal karyotype were summarized in Table 1. The frequency of abortus was 70.12% (108/154), and abnormal karyotype was 61.11% (44/72) in the cases who received frozen embryo transfer. Microdeletions or microduplications were identified in six cases (8.33% of the identified

Table 1. Comparison of the characteristics of early pregnancy loss cases with or without a fetal chromosome abnormality

	Chromosomal Abnormality (n = 72)	Controls (n = 82)	p value
Maternal age [years]	37.66 ± 4.86	33.55 ± 5.98	< 0.0001
BMI	26.42 ± 5.09	26.21 ± 4.93	0.78
Total number of previous pregnancy loss	0.56 ± 0.94	0.41 ± 0.83	0.27
Endometrial Thickness	10.66 ± 2.05	10.32 ± 1.98	0.92
Oocyte output rate	111.81 ± 66.70	125.27 ± 74.20	0.24
Total number of oocytes retrieved	11.19 ± 10.52	17.32 ± 12.74	< 0.001
AMH level (ng/mL)	1.91 ± 3.24	2.97 ± 2.42	< 0.05
Estradiol level at the time of HCG administration (pg/mL)	2417 ± 2300	3981 ± 3634	< 0.001
Progesterone level at the time of oocyte collection (ng/mL)	0.82 ± 0.86	1.25 ± 1.20	< 0.01
Gestational week at the time of loss	8.55 ± 1.69	9.07 ± 3.37	0.52

BMI — body mass index; AMH — anti-Mullerian hormone

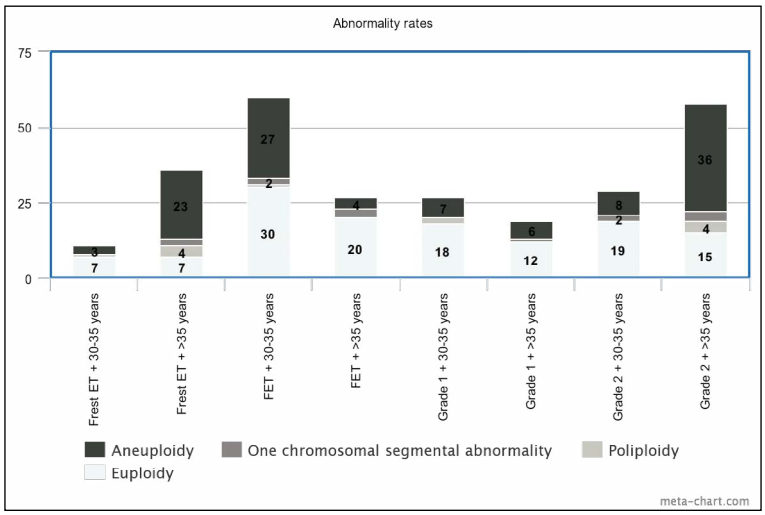

Figure 1. Distribution of the chromosomal abnormalities among different patient characteristics

abnormalities), including three duplications, one deletion, and two complex abnormalities. The distribution of the chromosomal abnormalities among different patient characteristics was shown in Figure 1.

The frequency of abnormal karyotypes in abortus cases was significantly higher, while the maternal age was >35 years. There was a statistically significant difference in the maternal age, baseline anti-Mullerian hormone (AMH) value, estradiol, and progesterone levels at the time of oocyte collection, total oocytes retrieved between the two groups. The BMI values, the total number of pregnancy loss, the number of FET cancellation, endometrium thickness, number of women with previous pregnancy loss, oocyte output rates were similar between the groups. The results from the univariate and multivariate regression analyses were summarized in Table 2. Univariate and multivariate analyses showed that maternal age (< 35 years) and the total number of retrieved oocytes per cycle (≥ 5) were risk factors for a chromosomal abnormality (< 0.001; < 0.05). The adjusted OR of karyotypic abnormalities was 0.45 for the antagonist cycle type ($p < 0.05$), and 0.58 for frozen embryo transfer ($p < 0.05$).

DISCUSSION

EPL is the most common pregnancy-related complication and up to 20% of clinically confirmed pregnancies end within the first trimester. Although the etiology underlying SA is highly complex and including various genetic, organic, and systemic factors, the presence of a chromosomal abnormality is the most frequently observed aspect in the pathogenesis. Among them, numerical abnormalities, mainly trisomies are the most widely observed pathologies [6].

The success of an ART procedure depends on the ratio of live birth, and identification of factors and evaluation of possible reasons causing an undesirable outcome is crucial. In the present study, data from multiple linear regression analysis showed that maternal age and oocyte numbers were independent predictors of chromosomal abnormality in the patients who underwent IVF treatment and experi-

Table 2. Univariate and multivariate analysis of factors related to abortus with chromosomal abnormality

	Chromosomal Abnormality (n = 72)	Controls (n = 82)	Crude OR (95% CI)	p value	Adjusted OR (95% CI)	p value
Age [years]						
< 30	4	18	Baseline variable			
30–35	17	37	1.73 (0.60–7.04)	NS	1.69 (0.48–4.32)	NS
> 35	51	27	2.15 (2.61–27.65)	< 0.0001	1.84 (2.02–19.54)	< 0.001
DET cancellation						
No	54	65	Baseline variable			
Yes	18	17	1.20 (0.59–2.71)	NS	0.98 (0.36–1.86)	NS
Sperm Abnormality						
No	37	34	Baseline variable			
Yes	35	38	0.92 (0.44–1.62)	NS	0.78 (0.27–1.14)	NS
Endometrial Thickness						
8 mm	54	71	Baseline variable			
≤ 8.0 mm	17	11	1.78 (0.87–4.69)	NS	0.93 (0.46–2.44)	NS
Cycle type						
Natural	27	14	Baseline variable			
Antagonist	40	62	0.59 (0.15–0.71)	< 0.001	0.45 (0.13–0.58)	< 0.05
Semi-natural	5	6	0.97 (0.11–1.66)	NS	0.88 (0.07–1.12)	NS
Total oocytes retrieved						
≤ 5	26	15	1.56 (0.88–4.25)	< 0.05	1.27 (0.76–3.57)	< 0.05
6–20	34	38	Baseline variable			
≥ 21	11	28	0.53 (0.19–1.01)	< 0.01	0.51 (0.17–0.89)	< 0.05
Transferred embryo type						
Fresh	28	18	Baseline variable			
Frozen	44	64	0.66 (0.21–0.89)	< 0.05	0.58 (0.17–0.74)	< 0.05

enced an EPL. Additional confounders DET cancellation, presence of a sperm abnormality, endometrial thickness had no impact on the chromosomal abnormality risk. We also found that there was a significant difference between the two groups in terms of AMH levels, E2 and P4 levels at the time of oocyte collection, the total number of collected oocytes whereas, the total number of previous pregnancy loss, *body mass index* (BMI), endometrial thickness, number of patients with a previous pregnancy loss did not differ.

In their large case series of 676 spontaneous miscarriages following ART protocols, Martinez et al. reported that the 51.88% of the miscarriages after ART and 51.82% conceived by ICSI had an abnormal karyotype with mostly autosomal trisomies, among which, trisomy of the chromosome 16 was the most observed genotype, which is consistent with our findings [6]. It has been suggested that trisomies develop during oogenesis, and acrocentric' chromosomes 13–15, 21, and 22 were the most affected ones as a result of failures during the meiosis, especially for the oocytes stayed in meiosis I phase for up to 40 years [7]. The frequency of triploidy was 6.94% in our group, which was relatively higher than the previous reports [8, 9]. Polyploidy was observed in the abortus material obtained from women with a mean age of 38.4 (ranging between 32–44 years) possibly due to increased chromosomal nondisjunction and improper spindle formation during meiosis as a result of advanced maternal age. The probability of dispermy might be excluded since the records of the IVF procedure under the microscope did not reveal any sign of the incident.

It has been shown that AMH levels are associated with the implantation rates following ART procedures [10, 11]. In our series, we observed that the AMH levels and the total number of collected oocytes in the cycle were significantly lower in the chromosomal abnormality group. This might be a result of age-related decline in the levels of the hormone and ovarian reserve, and age-related increase in chromosomal abnormality rates. Thus, AMH levels could not be suggested as an indicator of possible chromosomal abnormality-related EPL. Similarly, the levels of E2 and P4 were also lower in the chromosomal abnormality group, possibly due to age-dependent factors. It has been shown that aneuploidy ratio was significantly higher in women older than 35 years old and with lower AMH levels, even after age stratification, suggesting that age-related changes in the oocytes rather than diminished ovarian reserve might be causing the embryonal aneuploidy [12].

Endometrial thickness was suggested to be an indicator of pregnancy outcome, and birth rates were shown to be higher when the endometrial thickness was above a limit of 8 mm [13]. In our study group, we did not observe a significant difference between the two groups in terms of endometrial thickness. Additionally, when we sub-grouped patients in terms of endometrial thickness and chromosomal abnormality, the multivariate analysis did not yield a significantly increased risk for this measure.

The implantation rates were shown to be higher after frozen single blastocyst transfer, whereas the ratio of pregnancy loss after frozen and fresh single blastocyst transfer was similar [14]. In our cases, we found that the relative risk of chromosomal abnormality was significantly lower in the frozen embryo group. Consistent with our findings, Wu et al. found a higher ratio of chromosomal aberration in the cases who underwent fresh ET procedure in their study of EPL cases conceived using different ART [15]. Freezing and elective transfer of embryos might be a factor in relatively lower risk, eliminating the endocrinological endometrium related perturbations.

The ratio of female fetuses among the abortus cases was significantly higher in our series in accordance with the previous data. Although the presence of a gender-related mechanism underlying these results has not been revealed yet, there are several possible suggestions including discrepancies during the intrauterine inactivation of X-chromosome and presence of X-chromosomal recessive lethal mutations [16, 17]. However, it has been reported that maternal cell contamination can be the result of a higher female ratio in abortus materials, and the ratio of maternal contamination was shown to be up to 22% by a recent single-nucleotide polymorphism chromosomal array analysis study [18, 19].

When compared to the comprehensive worldwide data collected from the abortus cases conceived by ICSI, the ratio of fetuses with abnormal karyotyping results is slightly lower in our study group, suggesting that might be a cause of our extended exclusion criteria [9, 20]. However, the karyotyping method used for the screening of aborted embryos might be underestimating a proportion of the cases. Although the karyotyping technique used in the context of this study is a conventional golden standard method, it still bears several limitations including lower resolution limited to larger chromosome segments, therefore missing microdeletions, microduplications and subtle rearrangements, and insufficiency in detecting mosaic cases, especially when low-level mosaicism is present [21]. Although novel technologies as array-based comparative genomic hybridization (aCGH), and next-generation sequencing technologies are recommended for the detection of chromosomal abnormalities in the SA cases in order to provide better accuracy, the cost of the methods is relatively high [22].

Revealing the presence of a chromosomal aberration underlying the SA is of utmost importance to provide a better pregnancy outcome for the patient and future cases, yet, the etiology for almost half of the cases remains unclear. A recent meta-analysis by Robbins et al. reported that pathogenic variants of the genes clustered in the pathways related to gene expression, embryonic development, mitosis, and cell cycle progression, and inflammation and immunity might be causing non-aneuploid early pregnancy loss [23]. However, these genes can not be scanned through conventional methods and preimplantation genetic detection (PGD) techniques, and meanwhile, the routine implementation of the investigation is impractical. Implementation of a PGD procedure during the ART process is related to a lower rate of miscarriage among women between 35–37 years old, and a higher rate of a live-birth among women > 37 years old [24]. Although PGD is an alternative method that might be introduced to reduce the EPL rates and prevent implantation of chromosomal abnormality carrying embryos, hence improving the clinical prognosis, it is not demanded by most of the couples due to its higher cost. Furthermore, current PGD methods can only detect copy number gain or losses, and if present, some triploidy, and tetraploidy cases will still remain undetected [25].

The strengths of this study present the data derived from elective single embryo transfer cases that allow to rule out the embryo related factors. As parental confounders might be a risk factor for fetal chromosomal abnormality-related abortus, we excluded the individuals with any maternal or paternal abnormal karyotype that can contribute to chromosomal abnormalities. Additionally, we meticulously embraced the included cases among the pregnancy loss data of our center. The ratios of chromosomal abnormalities, abnormality types, and the chromosomes involved in trisomy cases were well in agreement with existing literature and might be a reflection of the clinical practice. Laboratory and

technical equipment, conditions, staff, and applied protocols were the same in all cases. However, there are limitations to this study. We did not subgroup the cases according to the day of embryo transfer due to a small number of patients per group, making the statistical evaluation difficult; thus the possible effects of culture medium related factors and incubation duration might be undervalued.

CONCLUSIONS

The present study shows that karyotypic abnormality is one of the main culprits for EPL, with an increasing rate as a result of maternal age and other defined confounders. Of the chromosomal alterations, aneuploidy was the most detected abnormality type in our series. Although recent advances in ART improved the pregnancy rates in patients with different infertility etiologies, the ratio of EPL following ART protocols still did not deteriorate to desirable levels. Increasing the ratio of live birth after ART treatment is the expected outcome, and further studies and reports of different series are needed in order to understand the underlying etiology of EPL and prevent chromosomal abnormality-related losses, and possible birth defects. Herein, we suggest that PGD using sensitive methods is necessary notably for women older than the age of 35 years in order to prevent EPL incidents of ART pregnancy, thus prevent and lower the physiological, psychological, and economic burden.

Conflict of interest

The authors declare no conflict of interest.

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Different modes of delivery and hormonal stress response

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ABSTRACT

Objectives: The aim of the study was to determine how the type of delivery affects the stress response cycle and the level of cortisol, progesterone and corticoliberin.

Material and methods: The study was conducted among 26 pregnant women admitted to the Gynecology and Obstetrics Ward due to an approaching delivery date or the onset of labor. The participants were aged between 20 and 41 years, with a mean age of approximately 30 years. After delivery, blood was drawn in parallel from the maternal antecubital vein, the umbilical cord vein and the umbilical cord artery. The levels of stress hormones were assessed by ELISA. The results were subjected to statistical analyses, and correlation coefficients were calculated for individual variable pairs. The analysis also examined the participation of pregnant woman in antenatal education.

Results: A high correlation was observed between cortisol and progesterone levels in venous and arterial cord blood and physiological delivery. The mean cortisol level was 247.37 ng/mL in venous cord blood and 233.59 ng/mL in arterial blood and the respective mean progesterone levels were 331.81 ng/mL and 342.36 ng/mL. The highest cortisol concentration was determined in the primiparas umbilical cord blood (236.182 ng/mL in the vein, 230.541 ng/mL in the artery). Correlation between cortisol level in venous and arterial cord blood and prenatal education was also noted (venous cord blood: r = –0.5477; F = 10.2833; p = 0.0038; cord arterial blood: r = –0, 4436; F = 5.8789; p = 0.0232).

Conclusions: The results obtained emphasize the importance of the hypothalamic-pituitary-adrenal (HPA) axis as one of the potential mechanisms actively involved in childbirth. The determined levels of cortisol and progesterone in the maternal and umbilical cord blood varied significantly depending on the type of delivery, with higher concentrations being observed in the case of natural delivery. In addition, the highest levels of cortisol were determined in primiparas; however, lowered umbilical cord blood cortisol levels were observed in pregnant women who had participated in antenatal education, regardless of the number of deliveries.

Key words: physiological delivery; cesarean section; stress hormones; cortisol; progesterone; corticoliberin

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INTRODUCTION

Stress is now an integral part of human life. During pregnancy, both the mother and the developing fetus are exposed to various environmental stimuli. A number of stress-related hormonal reactions occur during labor, and these affect the presence of stress markers in the maternal and fetal blood. Perinatal care has improved significantly in developed countries over the past 100 years, but psychological support is probably the most neglected aspect of obstetric medicine, despite being acknowledged as key for the well-being of the pregnant woman and her future child [1, 2].

Stress is defined as a state of disharmony present in the body or as a state of destabilization of homeostasis [3]. An important role in stressful situations is played by the hypothalamic-pituitary system, which includes corticoliberin (CRH), vasopressin (AVP), glucocorticosteroids and catecholamines (adrenaline, noradrenaline). Stressful situations are also associated with an increase in the secretion of cortisol, prolactin and proopiomelanocortin metabolites, which include adrenocorticotropic hormone (ACTH) and beta-endorphin (BE). Exposure to stress in the early prenatal period or exposure to stress during childbirth may affect the individual stages of neonatal development [4].

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During pregnancy, the CRH produced by the placenta increases gradually in the maternal and fetal circulation, mainly during the third trimester and during labor, reaching maximum values of 1000–10000 pg/mL. This causes an increase in cortisol concentration, which inhibits hypothalamic CRH secretion [3, 4].

During pregnancy, the amount of progesterone produced by the secretory tissue increases with the growth of the placenta. However, the correlation between placental weight and maternal progesterone concentration is negligible, indicating that other important factors regulate its synthesis. The mechanism involved in the spontaneous onset of labor in women remains indefinite, but it is thought that high levels of progesterone are necessary for active labor [3].

Objectives

The aim of this study was to assess the effect of the type of delivery on the concentration of cortisol, progesterone and corticoliberin present in maternal and umbilical cord blood serum. Other perinatal factors, such as antenatal education, were also included in the analysis. The obtained results were compared with available medical literature.

MATERIAL AND METHODS

Study group

The study was conducted among 26 pregnant women from the Obstetrics and Perinatology Clinic, Department of Obstetrics and Perinatology, Medical Univeristy of Lodz, and the Gynecology and Obstetrics Ward, Maria Skłodowska-Curie Memorial Provincial Specialist Hospital in Zgierz. Pregnant women were admitted to the ward in response to an approaching delivery date or the onset of labor. The participants were aged between 20 and 41 years old, with an mean age of about 30 years. Of the 26 participants, 13 cesarean sections and 13 physiological deliveries were performed during the period April 15, 2019 to May 15, 2019. All pregnancies were single ones and delivery took place between 34 and 40 weeks of gestation (mean value about 37 weeks). In addition, 21 pregnant women received anesthesia, and 18 underwent antenatal education.

Pregnancy was accompanied by a number of conditions. Among the study group, hypothyroidism was experienced by two participants, hypertension by two, and gestational diabetes by two. In addition, individual patients suffered from systemic lupus erythematosus, endometriosis, bronchial asthma and multiple sclerosis.

Blood samples were obtained in parallel from both mother and fetus. Briefly, 5–8 mL of blood was collected from the maternal antecubital vein and 5–8 mL from the venous and arterial cord blood. The samples were then centrifuged at 4000 rpm for 10 minutes. The obtained serum was frozen and sent in dry ice to the Department of Biopharmacy, Faculty of Pharmacy, Medical Univeristy of Lodz, Poland. Samples were stored at –70°C until analysis. The study was conducted with the consent of the Bioethical Committee of the Medical University of Lodz — resolution No. RNN/43/19/KE of March 12, 2019.

Assay

The levels of cortisol, progesterone and corticoliberin in the maternal blood serum and umbilical cord blood serum were determined by ELISA, based on a competitive test. The following kits were used: CORTISOL ELISA DiaMetra, PROGESTERONE ELISA DiaMetra, ELISA For Corticotropin Releasing Hormone (CRH) Cloud-Clone Corp.

Statistical methods

The results were subjected to statistical analysis using STATISTICA 13.1 software. The arithmetic mean and standard deviation were calculated, the minimum and maximum values and the median were determined. The obtained results were analyzed. Correlation coefficients were determined at the significance level $p < 0.05$.

RESULTS

The mean postnatal condition of the newborn assessed on the Apgar scale was 9.4. In the group of pregnant women for whom pregnancy was completed by physiological delivery (mean age 31.5 years). The mean advancement of pregnancy in which the delivery took place was 37.7 weeks. In the study group, 53.85% underwent antenatal education. The mean body weight of the newborn was 3068 g, with five male and eight female newborns. The mean postnatal condition of the newborn was 9.4, assessed on the Apgar scale.

Among the group who underwent caesarean section (mean age 30.2 years) and 84.62% participated in antenatal education. The mean stage of gestation at delivery was 37.9 weeks. There were five male newborns delivered in the study group, and eight females. The mean newborn body weight was 3120 g. The mean postnatal state of the newborn expressed was 9.5 on the Apgar scale. The characteristics of the participants are presented in Table 1.

Higher cortisol levels were observed in the umbilical cord blood of the women who underwent natural labor (Fig. 1): 247.3734 ng/mL for venous cord blood and 233.5890 ng/mL for arterial blood. The minimum and maximum values were 133.2070 ng/mL and 404.7190 ng/mL in venous cord blood, and 90.7540 ng/mL and 370.7240 ng/mL in arterial cord blood. The median value was 245.6940 ng/mL in venous cord blood and 238.9290 ng/mL in the arterial blood; the standard deviations were 79.0383 ng/mL in venous cord blood and 79.0020 ng/mL in arterial blood.

Table 1. Characteristics of pregnant women

Mother/fetus details	Physiological delivery (n = 13)	Delivery by caesarean section (n = 13)
Mother's age	31.5 ± 5.77	30.2 ± 4.93
Week of pregnancy	37.7 ± 1.93	37.9 ± 1.72
Antenatal education [%]	53.85	84.62
Birth weight [g]	3068 ± 493	3120 ± 543
Newborn gender (male/female)	5/8	5/8
Apgar score	9.4 ± 1.04	9.5 ± 0.88

Figure 1. The mean cortisol concentration in umbilical vessels according to the type of delivery

In the case of natural labor, higher levels of progesterone were observed in umbilical cord blood (Fig. 2), with progesterone concentrations of 331.8078 ng/mL in venous cord blood and 342.3588 ng/mL in arterial blood. The minimum and maximum values were 275.1470 ng/mL and 389.6970 ng/mL in venous umbilical cord blood, and 312.8570 ng/mL and 383.3860 ng/mL in arterial blood. The median values were 328.8580 ng/mL in venous cord blood and 335.2240 ng/mL in arterial blood; the standard deviations were 28.25252 ng/mL in venous cord blood and 22.3280 ng/mL in arterial blood.

The CRH concentrations in maternal blood and in venous and arterial cord blood did not significantly correlate with the type of delivery : maternal blood ($r = 0.2090$; $F = 1.0966$; $p = 0.3054$), venous cord blood ($r = 0.3687$; $F = 3.776$; $p = 0.0638$), arterial cord blood ($r = 0.0466$; $F = 0.0523$; $p = 0.8211$) (Fig. 3.)

The highest cortisol concentration was determined in the primiparas umbilical cord blood (236.182 ng/mL in the vein, 230.541 ng/mL in the artery) (Fig. 4).

Participation in antenatal education women significantly correlated with the cortisol concentrations of both venous and arterial cord blood during delivery: venous cord blood ($r = –0.5477$; $F = 10.2833$; $p = 0.0038$), arterial cord blood ($r = –0.4436$; $F = 5.8789$; $p = 0.0232$) (Fig. 5.).

DISCUSSION

Literature data concerning cortisol show clearly that its concentration is closely related to the method of termination of pregnancy. A study conducted in 1976 showed that vaginal delivery increases cortisol levels as opposed to caesarean section. Farquharson et al. [3] showed an increase in cortisol concentration in children born by sudden caesarean section compared to planned surgery or vaginal delivery. A significant correlation was observed between umbilical cord cortisol concentration and the type of delivery (Fig. 1). Cortisol concentration also correlated with the number of deliveries, with a significantly higher level observed in the first child than in the following ones (Fig. 4). The mechanism of this difference is not fully understood, however, these results are consistent with earlier studies on the cortisol concentration in primiparas and multiparas [3]. A correlation was also observed between umbilical cord blood cortisol concentration and the antenatal education of pregnant women (Fig. 5). Lower venous and arterial cord blood cortisol concentrations were observed in pregnant

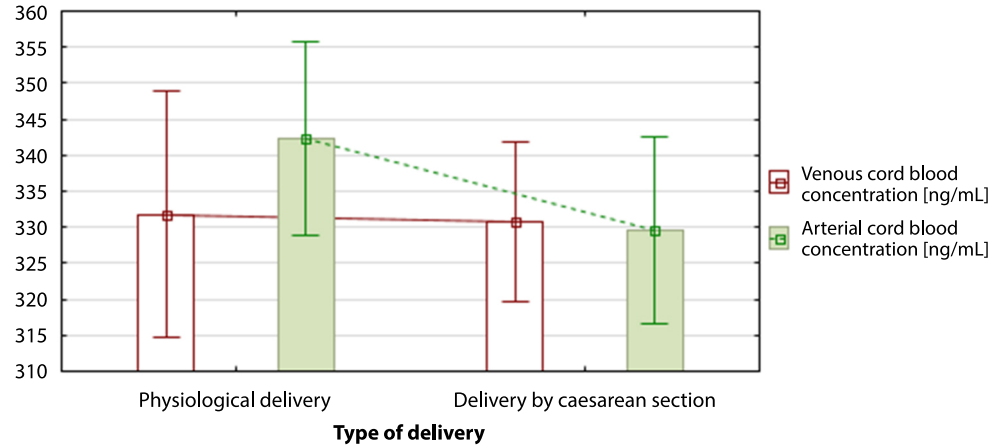

Figure 2. The mean progesterone concentration in umbilical cord blood according to the type of delivery

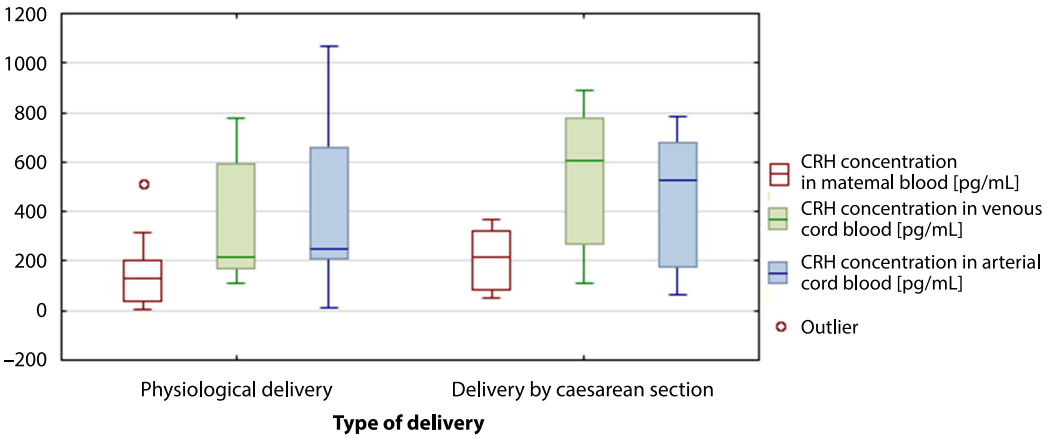

Figure 3. Corticoliberin concentration in maternal blood, as well as in venous and arterial cord blood according to the type of delivery; CRH — corticoliberin

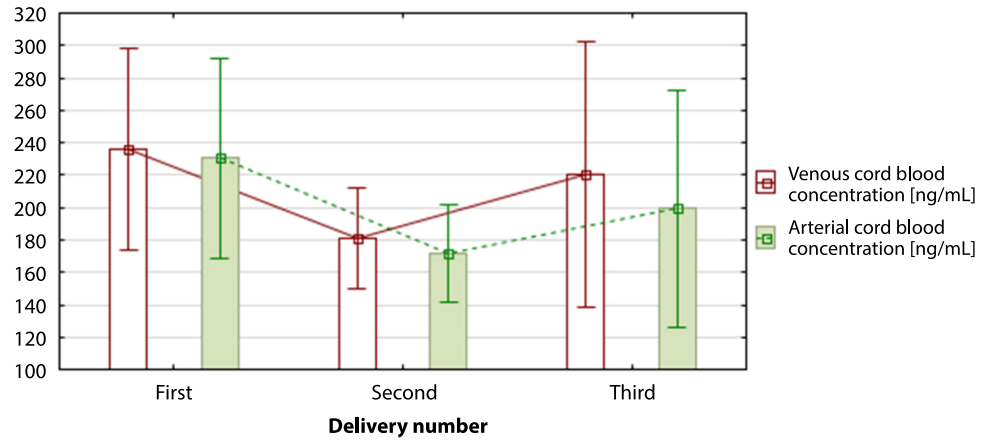

Figure 4. The mean umbilical cord blood cortisol concentration according to the order of delivery

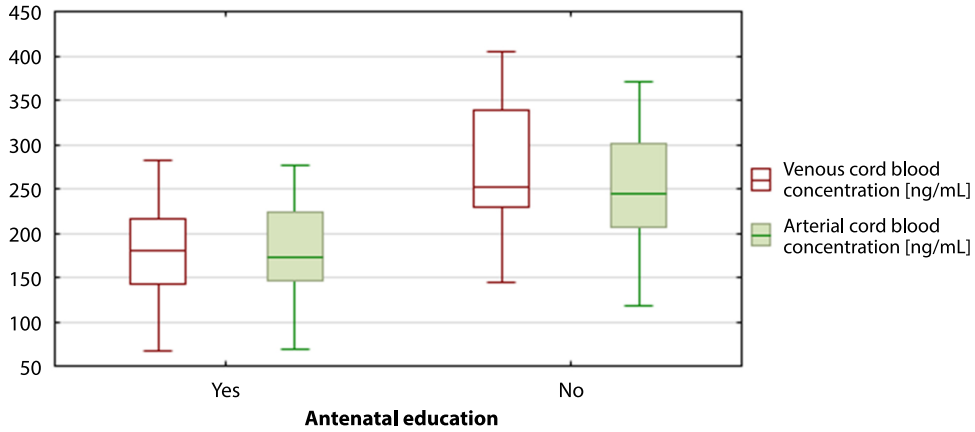

Figure 5. Correlation between cortisol concentration in venous and arterial cord blood and participation in antenatal education

women who participated in antenatal education compared to those who did not.

Data on the role of progesterone as a stress biomarker during termination of pregnancy are disputable. Löfgren et al. [3] report significantly higher serum concentrations of progesterone in mother and child as a result of natural delivery than during planned caesarean section. Aisien et al. [4] also found elevated progesterone levels in the blood of a fetus exposed to stress during delivery. This may be one way to protect the fetus against stress factors and the consequence of hypoxia. The results of this study show that higher levels of progesterone in umbilical cord blood were determined in the group of pregnant women giving birth naturally than in the case of cesarean section.

Our findings regarding the relationship between corticoliberin concentration and the method of completion of pregnancy are not in line with those of previous studies. Earlier studies have reported the presence of higher levels of CRH, a similar hormone to cortisol, in blood following vaginal delivery [3]. The CRH neuropeptide is released from hippocampal neurons using environmental signals, including stress. During pregnancy, it is produced by the placenta, which also stimulates the release of cytokines. Consequently, it is difficult to distinguish the source of CRH production during labor.

Births, both natural one and those occurring as a result of cesarean section, took place around the 37th of pregnancy. No significant correlation was observed between the increase in individual hormones and the week of completion of pregnancy.

CONCLUSIONS

The obtained results emphasize the importance of the hypothalamic–pituitary–adrenal axis (HPA) as one of the potential mechanisms actively participating in labor.

The concentration of cortisol and progesterone in the blood of mother and fetus correlates with the type of delivery. Physiological delivery increases the release of most of the tested hormones, in contrast to the caesarean section. In addition, participation in antenatal education reduces the cortisol level in umbilical cord blood.

The first delivery is associated with greater stress and higher cortisol level compared to subsequent deliveries.

The age of the pregnant woman does not affect the concentration of stress hormones during childbirth.

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Conflict of interest

None.

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Physical activity improves sleep quality in women

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ABSTRACT

Objectives: The aim of the study was to check whether women with a higher level of physical activity are less likely to experience sleep problems.

Material and methods: 80 women aged 45–65 from Silesia took part in the pilot study.

The research tool was a self-survey, the International Physical Activity Questionnaire (IPAQ), the Athens Insomnia Scale (AIS), and the Menopause Rating Scale (MRS). The data was prepared in the STATISTICA 10 program.

Results: The mean age of the respondents was 51.75 ± 5.57. The most common symptoms were psychological problems (mean MRS: 4.29 ± 3.25).

A sedentary lifestyle was reported in 57.14% of the respondents. There was a significant difference between women suffering from insomnia and women with normal sleep in terms of the level of physical activity ($p = 0.025$).

Conclusions: Physical activity significantly affects the quality of sleep among middle-aged women.

Key words: IPAQ; MRS, AIS; menopause

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INTRODUCTION

Physical activity (PA) is defined as any form of body movement caused by muscle contractions, where energy expenditure exceeds resting energy levels and physical fitness is improved [1]. Regular physical activity has many health benefits, so it is very important to do regular exercises every day. Nevertheless, despite the well-known benefits of regular exercise, most middle-aged women are not physically active enough [2, 3]. What is more, the results of the research show that the decline in physical activity begins in middle-aged women (45–65 years old) [2, 4]. According to the guidelines of the World Health Organization (WHO), adults should engage in at least 150 minutes of moderate physical intensity (3–6 METs, where the metabolic equivalent of 1MET is defined as the amount of oxygen consumed while sitting at rest and is 3.5 mL O2 per kg. body weight/min) per week, or at least 75 minutes of intense intensity (6 METs) per week, or a combination of moderate and high intensity PA. Moreover, all adults should perform moderate to vigorous strength exercise two or more days a week that covers all major muscle groups. The guidelines also encourage adults to avoid a sedentary lifestyle, as any, even the smallest dose of physical activity is better than total lack of PA [5]. The results of the most recent studies show that approximately 27% of middle-aged women meet the guidelines for physical activity [6, 7]. Middle-aged women may experience many mental and somatic disorders that reduce their quality of life. Sleep problems are very common among menopausal women [8, 9]. The results of studies on 12,603 menopausal women showed that 38% of respondents had sleep problems [10]. The results of another study, carried out on a group of 6,079 menopausal women showed that 43% suffered from insomnia [11].

Sleep problems in menopausal women are associated with numerous factors including age-related physiological changes, menopausal symptoms, stress, mood disorders, and chronic health problems [12]. Although sleep problems are common in middle-aged women, there is a lack of research into the prevalence of this problem related to women's levels of physical activity.

The aim of the research was to verify, whether women with higher levels of physical activity are less likely to experience sleep problems.

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MATERIAL AND METHODS

80 women aged 45–65 from Silesia took part in the pilot studies. Participation in the study was voluntary and anonymous. The inclusion criteria for the research were: age 45–65 years, consent to participate in the research. The exclusion criteria were depression in the history, contraindications to physical activity, incomplete completed questionnaire. 17 people were excluded from the analysis. The study protocol was reviewed and approved by the Bioethical Committee of the Medical University of Silesia in Katowice (KNW/0022/KB/103/18).

The Athenian Insomnia Scale (AIS)

The Athenian Insomnia Scale (AIS) was used to assess insomnia, which is one of the most commonly used scales both for diagnostic purposes and in research into the effectiveness of treating insomnia [13]. The AIS is a short, eight-point scale that measures the symptoms of insomnia [14]. The validation studies showed high reliability and validity of this tool [15]. A score on the AIS scale of 6 or more points means a value that allows to conclude the occurrence of insomnia (scale sensitivity — 93%, scale specificity — 85%) [14].

The International Physical Activity Questionnaire (IPAQ)

The International Physical Activity Questionnaire (IPAQ) was used to assess the level of physical activity — short form (IPAQ-SF). The International Physical Activity Questionnaire-Short Form (IPAQ-SF) is a self-report questionnaire evaluating the physical activity level among adults ranging from 15 to 69 years . The questionnaire consists of questions about the frequency and duration of low, moderate and high intensity physical activity for at least 10 minutes continuously in the last 7 days [16, 17]. Physical activity level was expressed as MET-min (where the metabolic equivalent of 1 MET is defined as the amount of oxygen consumed when sitting at rest and is 3.5 mL O2 per kg body weight/min) per week and calculated by multiplying the MET assigned to it (vigorous — 8 MET, moderate — 4MET and walking — 3.3 MET), by the number of days it was performed during the previous 7 days. According to the IPAQ guidelines, women were classified to group with low, moderate or high levels of physical activity.

Menopause Rating Scale (MRS)

The validated and standardized MRS scale was used to assess the severity of menopausal symptoms. MRS contains 11 descriptions of climacteric symptoms, including: hot flashes, sweating, heart problems, sleep problems, depressed mood, irritability, anxiety, physical and mental exhaustion, sexual problems, bladder problems, vaginal dryness, discomfort associated with joints and muscles.

The intensity of each symptom is rated on a scale of 0 (no symptoms) to 4 (very severe). The symptoms are presented in 3 groups:

1. psychological symptoms described in questions 4 to 7,
2. somatic and vegetative symptoms — questions 1, 2, 3 and 11,
3. urogenital symptoms — questions 8, 9 and 10.

The total sum of points obtained on the MRS scale ranged from 0, which meant no menopausal symptoms, to 44, which was characterized by the highest intensity of symptoms [18, 19].

Statistical analysis was performed using the Statistica 10 (Statistica v10, StatSoft, Krakow, Poland). Arithmetic means, median, standard deviations, and range of variability (extreme values) were calculated for measurable variables. Frequency of occurrence (percent) was calculated for qualitative variables. All quantitative type variables were checked by Shapiro-Wilk test to determine the type of distribution. The chi-square test was used to perform the relationship between IPAQ and AIS value. The level of $\alpha = 0.05$ was used for all comparisons.

RESULTS

The mean age of the respondents was 51.75 ± 5.57. Women declared menopausal symptoms, with the least degree of urogenital problems (mean 2.3 ± 2.5) and the highest degree of psychological symptoms (4.29 ± 3.25). Most of respondents had higher education (69.84%), lived in the city (79.37%), led a sedentary lifestyle (57.14%). The problem of insomnia concerned 44.44% of women (Tab. 1).

The results showed that there was a difference between women suffering from insomnia and women with proper sleep in terms of the level of physical activity ($p = 0.025$). The greatest problem of insomnia concerned physically inactive women (64.29%). Women with high physical activity did not declare insomnia problem (Tab. 2).

DISCUSSION

Middle-aged women experience a wide range of symptoms associated with this period of life. The results of many studies showed that women most often complained of urogenital and somatic symptoms [7, 20–23]. The results of our study showed that women most often declared the occurrence of psychological and somatic symptoms, which is confirmed by the results of other studies conducted on a group of women during perimenopause [24, 25]. Low level of physical activity affects more than half of middle-aged women, which is confirmed by the results of our study [26]. In middle-aged women there is a decline in physical activity [2, 4, 27]. Many authors have proven the effect of physical activity on the alleviation of menopausal symptoms [7, 26, 28]. Although many studies concern the issue of physical activity

Table 1. Characteristics of the study group

	Mean	Median	Min	Max	SD
Age	51.75	52.00	45.00	65.00	5.57
BMI	24.53	24.13	17.69	35.76	2.87
MRS psychological symptoms	4.29	4.00	0.00	12.00	3.25
MRS somatic symptoms	3.71	3.00	0.00	12.00	2.85
MRS urogenital symptoms	2.30	2.00	0.00	10.00	2.50
Variable	**N**	**%**			
Educational level					
University High school Elementary school	44 8 11	69.84 12.70 17.46			
Place of living					
Country Village	50 13	79.37 20.63			
A permanent partner					
Yes No	56 7	88.89 11.11			
PA level (IPAQ)					
Low Moderate High	36 19 8	57.14 30.16 12.70			
Insomnia					
Yes No	28 35	44.44 55.56			
Insomnia					
Yes No	28 35	44.44 55.56			

BMI — body mass index; SD — standard deviation; MRS — menopause rating scale; IPAQ — International Physical Activity Questionnaire

Table 2. The level of physical activity and insomnia

Insomnia (AIS)	Physical activity level (IPAQ)			
	Low	Moderate	High	p
Yes	64.29%	35.71%	0.00%	p = 0.025
No	51.43%	25.71%	22.86%	

IPAQ — International Physical Activity Questionnaire; AIS — Athens Insomnia Scale

in perimenopausal women and its impact on menopausal symptoms, there are no reports on the relationship between AF in the context of sleep quality in this group of women. The fact, that sleep worsens during the menopause is widespread among women and clinicians [29–32]. The results of our study showed that insomnia affected a significant part of middle-aged women (64.29%). This is confirmed by the fact that this problem affects a significant percentage of middle-aged women around the world, as about 44% of Spanish women, 41% of respondents from Ecuador, 51% of Japanese women, and 54% of respondents from Turkey suffer from insomnia [11, 33–35].The above data from different regions of the world seem to be consistent and emphasize the fact that about half of middle-aged women experience sleep problems.

The aim of this study was to assess the relationship between the level of physical activity and insomnia in middle-aged women. The results showed that women with a high level of physical activity did not complain about the problem of insomnia at all, while women with a sedentary lifestyle were much more likely to suffer from insomnia. The lack of reports in the literature makes it impossible to compare this issue with the results of other authors, therefore the research will be continued on a larger population of women.

CONCLUSIONS

Physical activity significantly affects the sleep quality of middle-aged women.

The health benefits of physical activity are well known. However, there is a need to educate women in this area to present this non-pharmacological method of sleep improvement. The research will be continued on a larger group, taking into account other factors that may correlate with sleep.

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Conflict of interest

The authors declare no conflict of interest.

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Knowledge and opinions of patients and medical staff about patients' rights

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ABSTRACT

Objectives: The awareness of patients' rights among medical personnel and patients themselves, together with their opinions concerning these rights, is a challenging issue for health professionals. Patients' rights are very specific legal regulations that have been drafted to protect patients' dignity and autonomy. The main objective of this research was to assess the knowledge of patients' rights among medical personnel of health care institutions and among patients themselves. Specific objectives were also adopted, such as: assessment of the impact of the mode of hospital admissions on the knowledge of patients' rights, analysis of factors influencing the knowledge of patients' rights and the analysis of sources of knowledge concerning patients' rights.

Material and methods: The study was conducted among two groups: patients and medical personnel. A group of 618 patients (including 411 women and 207 men) and 901 medical professionals (doctors, nurses, midwives) was examined via a questionnaire designed to verify their knowledge of patients' rights and to collect their opinions on the applicable laws. An integral part of the questionnaire for patients was The Hospital Anxiety and Depression Scale (HADS).

Results: The research showed a high knowledge of patient's rights demonstrated by the surveyed doctors, nurses and midwives. Good knowledge of patients' rights among healthcare professionals was reflected in good level of informing patients about their rights, which correlates with their high level of awareness.

Conclusions: The following conclusions were drawn based on the research: education, seniority and profession determine the knowledge and respecting patients' rights, the mode of admission to hospital is a factor determining the knowledge of applicable patients' rights, medical staff's lack of knowledge about existing patients' rights has a significant impact on exercising these rights or their violation.

Key words: right; patient; patients' rights

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INTRODUCTION

Patients' rights are a specific type and integral part of human rights. They were created with the dignity and autonomy of patients in mind and are essential in today's medicine. Patients' rights are the realization of human rights in specific situations related to the use of medical services.

First discussions around patients' rights started in the 20th century and they have been closely linked to the history of wars and human race (both soldiers and civilians). Human rights are reflected in international documents such as the Universal Declaration of Human Rights (1948), the European Convention on Human Rights and Fundamental Freedoms (1950), the European Social Charter (1961) and the International Covenant on Civil and Political Rights (1966). The need to define patients' rights was forced by the processes taking place in medicine, the development of medical sciences and technologies and the sense of threat to human rights and dignity in the process of medical treatment. These rights are supposed to protect patients from abuses in diagnostics and medical treatment as well as improper application of biological and medical achievements (medical experiments). The public debate on patients' rights was caused by two events in medicine of the 60s: the disclosure of research for scientific purposes carried out on patients without their consent (often on minors, the disabled and terminally ill), which took place in the US in 1966,

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and the first heart transplantation carried out by Professor Christian Barnard in Cape Town in 1967. These events have caused many disputes, questions and doubts of an ethical, philosophical and legal nature. That is how the process of creating new deontological standards by the World Medical Associations has begun [1].

Due to the development of new communication technologies and the internet in particular, it is important that patients' knowledge is reliable and fully understood by them. Only verification can show whether they are known and observed by both parties.

The main objective of this research was to assess the knowledge of patients' rights among medical personnel of health care institutions and among patients themselves. Specific objectives were also adopted, such as the assessment of the impact of the mode of hospital admissions on the knowledge of patients' rights, analysis of factors influencing the knowledge of patients' rights and the analysis of sources of knowledge concerning patients' rights.

MATERIAL AND METHODS

Study population

The prospective study covered a group of medical workers — 901 persons, including 200 doctors, 493 nurses and 208 midwives (Tab. 1, Fig. 1 and 2) and a group of 618 patients, including 411 women and 207 men (Tab. 2). The following inclusion criteria were adopted for the medical staff: medical profession regardless of the basis of employ-

Table 1. Medical staff's job seniority in years

Statistical parameter	Doctors	Nurses	Midwives	Kruskal-Wallis test
Number	175	406	162	p = 0.0001
Mean	13.4	24.7	14.1	
Standard deviation	9.5	9.3	9.8	
Lower quartile	5.0	20.0	6.0	
Median	12.0	26.0	12.0	
Upper quartile	20.0	31.0	21.8	
Test of normality	p < 0.000001	p < 0.000001	p < 0.000001	

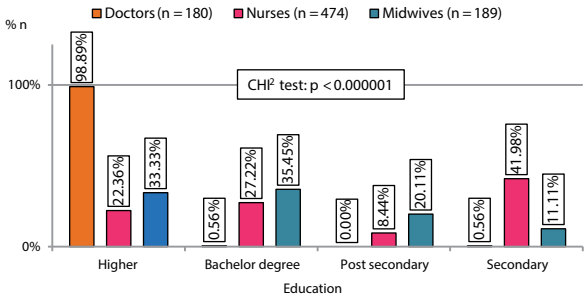

Figure 1. Education of the study group (medical personnel)

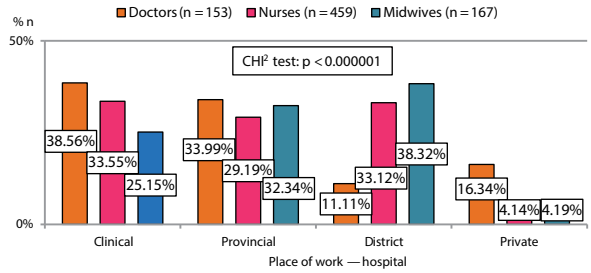

Figure 2. Workplace of the study group (medical personnel)

Table 2. Age in the study group — patients (women and men)

Statistical parameter	Women	Men	Mann-Whitney's U TEST
Number	406	206	p = 0.009
Mean	50.3	53.9	
Standard deviation	16.9	14.2	
Lower quartile	35.3	44.0	
Median	51.0	57.0	
Upper quartile	64.0	65.0	
Test of normality	p < 0.000001	p = 0.001	

ment; consent to participate in the survey and fully completed questionnaire. For the group of the surveyed patients the criteria for inclusion in the survey were: admission to the hospital for treatment or diagnosis; informed consent of the patient to conduct the survey and fully completed questionnaire.

The research was carried out in the period from 2 January 2017 to 30 December 2017 in hospitals of the Silesian Province. It was conducted after obtaining the consent of the directors of the units concerned.

Research methods

The research tool was a questionnaire developed by the authors of this study, which included open and closed questions concerning patients and medical staff's knowledge and opinions about patients' rights as in the Act of 6 November 2008 on Patients' Rights and Ombudsman of Patients' rights (Journal of Laws, 2009 no. 52 poz. 417).

The anonymous research questionnaire for medical personnel consisted of the following parts: a general interview (containing twenty-five questions, including three multiple-choice questions), and a sociometric interview containing questions about occupation, seniority, education, specialization, the hospital where the subject currently works, the ward and attitude towards religion.

The anonymous research questionnaire for patients included a general interview containing twenty-four closed questions, including three multiple-choice questions. The questions aimed to collect respondents' subjective evaluation of their level of knowledge about patients' rights and their opinions concerning these. It also collected sociometric data such as age, gender, place of residence, education, professional status, hospital where the patient was currently staying, total number of stays in the hospital, mode of admission to the hospital (emergency, referral) and attitude towards religion.

An integral part of the questionnaire for patients was The Hospital Anxiety and Depression Scale (HADS) by A. S. Zigmond and R. Snaith. The HADS scale is the most used tool developed for the study of non-psychiatric patients between the age of 16-65 years, with HADS measuring the condition rather than the trait. The scale consists of two independent subscales measuring anxiety and depression levels. Each of them contains seven statements concerning the current condition of the tested subject, which can be assessed in a range of 0 to 3 points.

The points obtained were counted separately for anxiety and depression. Scores of up to 7 points in each of the subscale indicate the norm, scores between 8 and 10 points are a borderline score for moderate anxiety/depression symptoms, while scores 11 and above indicate the pathological level of anxiety/depression.

For statistical analysis of the surveys Excel 2001 and STATISTICA 10 were used. $P < 0.05$ was assumed as the level of statistical significance. The following tests were used in statistical research: Shapiro-Wilk normality test, Mann-Whitney's U test, Kruskal-Wallis test, Yates's chi-squared test and the exact Fisher test.

Ethical statement

All subjects gave their informed consent for inclusion before they participated in the study. The study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the Ethics Committee of the Medical University of Silesia (KNW/0022/KB/212/15).

RESULTS

The research showed a high knowledge of patient's rights demonstrated by the surveyed doctors, nurses and midwives (Fig. 3). The question concerning knowledge of particular regulations was answered by all respondents. Statistical significance has been obtained for four domains: patients' right to health services ($p < 0.000001$), patients' right to respect for dignity and intimacy ($p < 0.000001$), patients' right to store valuables in deposit ($p < 0.000001$) and patients' right to pastoral care ($p < 0.000001$) (Tab. 3).

Participants of the study (medical personnel in the vast majority of cases) indicated medical publications, participation in conferences and symposiums as the main source of knowledge on patients' rights. They also emphasized the fact that they gained knowledge in medical schools. Good knowledge of patients' rights among healthcare professionals was reflected in good level of informing patients about their rights (Fig. 4), which correlates with their high level of awareness (Fig. 5).

Despite knowing and respecting patients' rights, respondents indicated that they witnessed situations where patients' rights were violated. These were mainly the cases of the lack of respect for dignity, lack of reliable information about the health condition/surgical procedures performed and discussing patients' health condition/carrying out inter-

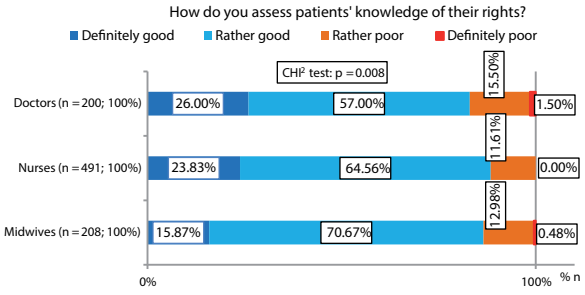

Figure 3. State of knowledge on the applicable patient rights (medical personnel)

Table 3. Knowledge of elements of patient rights by medical personnel

Element of law	Doctors (n = 200)	Nurses (n = 493)	Midwives (n = 208)	CHI² test
The patient's right to health services	85.00%	94.52%	80.77%	p < 0.000001
The patient's right to information	95.00%	97.57%	96.15%	NS (p = 0.19)
The patient's right to confidentiality	94.00%	95.13%	91.83%	NS (p = 0.22)
The patient's right to consent to health services	91.50%	95.13%	92.31%	NS (p = 0.12)
The right of the patient to respect his or her intimacy and dignity	92.50%	99.80%	96.15%	p < 0.000001
The patient's right to access their medical records	93.50%	95.54%	94.23%	NS (p = 0.47)
The patient's right to respect for his or her private and family life	83.00%	87.83%	88.46%	NS (p = 0.17)
Patient's right to store his or her valuables in deposit	83.50%	94.52%	64.90%	p < 0.000001
The patient's right to pastoral care	71.00%	96.15%	91.83%	p < 0.000001

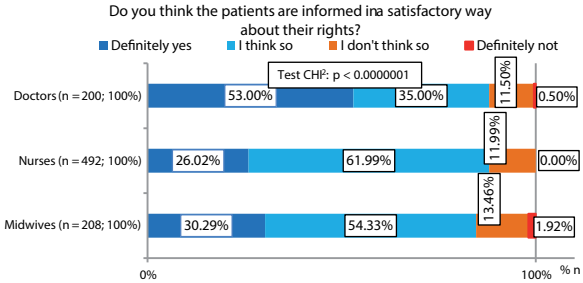

Figure 4. The level of informing patients about their rights (medical personnel)

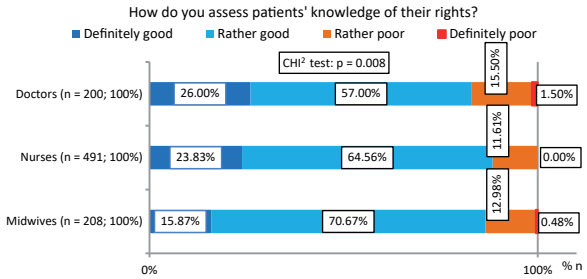

Figure 5. Patients' knowledge of their rights

Table 4. Non-compliance with patient rights according to medical personnel

Violated patients' right	Doctors (n = 36)	Nurses (n = 26)	Midwives (n = 83)	CHI² test
No respect for patient intimacy	33.33%	100.00%	19.28%	p < 0.000001
Lack of reliable information on health condition/surgery	5.56%	26.92%	6.02%	p = 0.005
Lack of respect for the dignity of the patient / insulting him or her	22.22%	26.92%	12.05%	NS (p = 0.13)
No protection of personal data/leaving documentation in a public place	13.89%	15.38%	4.82%	NS (p = 0.11)
Refusal to allow a person to accompany the patient when providing information	0.00%	7.69%	1.20%	NS (p = 0.11)
Information given via telephone to third parties about the patient's condition	0.00%	7.69%	4.82%	NS (p = 0.36)
Discussing the patient's health/carrying out an interview in the presence of third parties	2.78%	42.31%	10.84%	p = 0.0004
Refusal of access to medical records/restriction of access to medical records	2.78%	3.85%	3.61%	NS (p = 0.95)

view in the presence of third parties (Fig. 4, Tab. 4). They also indicated situations in which it is possible to limit the rights of patients such as safety/health/life threat (p = 0.0003), epidemic threat (p = 0.001), incapacitated patient (p = 0.03), in order to save life (p = 0.02), direct coercion (p = 0.03) with the individual right to refuse certain health services resulting from one's religious beliefs.

A similar analysis was carried out among patients in order to verify the respect of patients' rights by health care professionals and the knowledge of these rights by patients themselves.

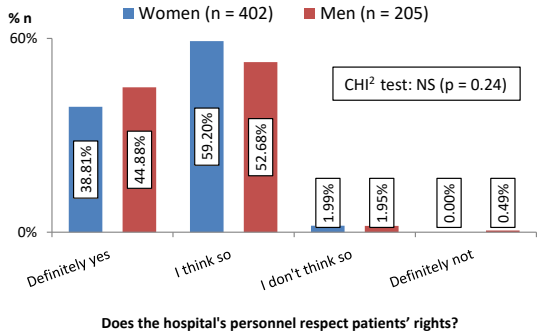

Figure 6. Respect for patient rights during current hospitalization

More than half of the respondents (84.92% of women and 80.93% of men) were admitted to hospital on a scheduled referral basis, the remaining patients on an emergency basis due to their current clinical state.

The group of the surveyed patients, both women and men, had satisfactory knowledge of the existing patients' rights in Poland. 97.09% of women and 94.69% of men claimed to have a good knowledge of these. When asked about the sources of their knowledge, 50% of women and 58.21% of men claimed it was the knowledge collected during previous hospitalizations.

It has been shown that during the current treatment/diagnostic process, about 30% of respondents, both men and women, were not informed about their rights. The remaining patients claimed they were informed about their patients' rights in full detail according to the Act in force.

The participating patients, both men and women, claimed that the hospital where they were currently staying was almost 100% compliant with the patients' rights (Fig. 6).

Despite knowing and respecting patients' rights the surveyed patients also witnessed the situations in which these rights were violated (*e.g.*, right to respect for intimacy and dignity, about 50%), however the violation of the law did not concern the respondents themselves. The same domain was indicated by healthcare professionals.

An integral part of the questionnaire for patients was The Hospital Anxiety and Depression Scale (HADS). In this study, 61.44% of female subjects and 49.20% of male subjects (out of 376 women and 187 men) did not show any depressive disorders. The borderline was observed in 24.47% of women and 28.88% of men. Depressive disorders were diagnosed in 14.10% of women and 21.93% of men. The diagnosis of occurring anxiety disorders significantly correlates with the analytical assessment of both the knowledge of the patient's existing rights and the subjective evaluation of medical situations in which the patient's rights are not respected.

DISCUSSION

The medical staff and patients' knowledge and opinions on the patient's rights in force in Poland are inseparably connected with the quality of provided health services and thus patient safety. Health care services, due to their specific nature, are not just about guaranteeing the patient a specific health result or a complete cure. Professional medical personnel need to ensure that health services are provided with due care and in accordance with current medical knowledge, with respect and knowledge of the law to ensure patient safety.

The research showed a significant increase in patients' knowledge of their rights. The research carried out on a group of 618 patients showed unequivocally that the knowledge of patients' rights in force has significantly improved. The data also suggest that those taking part in the research are familiar with particular provisions of the Act on Patient's Rights, and this knowledge was obtained from medical staff (doctor, nurse, midwife). Similar trends were observed in the research conducted in Poland by the Public Opinion Research Centre (CBOS) and Wł. Derczyński, K. Wroński and many other researchers [2–5].

There has been a significant increase in patients' awareness of their rights. The direct impact on the increase in the knowledge of patients' rights by those concerned may also result from the provisions of the Act of 27 August 2004 on health services financed from public funds (Journal of Laws of 2018, item 1510, as amended) stating that under Article 64 the therapeutic entity is obliged to display information on patients' rights in a visible place for patients (*i.e.*, in hospital wards, emergency rooms) and it is subject to control by the National Health Fund. The factors that differentiated the level of knowledge on patients' rights in previous studies were the level of patients' education and the place of their residence.

As the main source of knowledge, medical personnel named scientific publications, and to a small extent provisions of the Act on Patient's Rights and the Ombudsman of Patients' rights and the medical school. Similar results were obtained in the studies by Olejniczak et al. and L. Wdowiak [6–8], which showed that the knowledge of patients' rights is highly unsatisfactory [8, 9]. Foreign researchers have also shown a lack of knowledge of legal regulations concerning patients' rights among newly employed healthcare workers in Barbados. This is due to a lack of medical law, including patient rights in education programs. Insufficient education in this respect will translate into insufficient knowledge of doctors, nurses and midwives taking up employment in their professions [9, 10].

Different results concerning the sources of knowledge on patient`s rights were obtained by the team headed by J. Gotlib. The respondents, 86% of physicians and 70% of nurses, indicated the Act on Patients' Rights and the Ombudsman of Patients' Rights as the main source of knowledge; however, their knowledge was either average or poor [9].

The study by G. Iwanowicz-Palus et al. showed that physicians' knowledge was largely dependent on their age, position and level of specialization. In the survey conducted by Iwanowicz-Palus, more than half of the nurses indicated the Charter of Patients' Rights as a source of knowledge about patient's rights (studies conducted before 2008) [9, 10]. Similar results were obtained by E. Grochans, who conducted a survey among nurses. These with higher vocational education proved to have greater knowledge about patients' rights [11].

It was found as a result of the conducted research that knowledge and informing patients about their rights does not correlate with patients' own evaluation. Based on the analysis of this research, it was noted that the staff highly assessed the degree of information provided to patients about their rights, which was also highly appreciated by the patients themselves. As to the essence of the violation of patients' rights by medical personnel, the research showed that the right indicated by patients was the right to respect for intimacy and dignity. Out of all patients' rights, the right to respect for dignity appears to be the most fundamental and, together with the right to life and freedom, belongs to fundamental human rights [8, 12–14]. Nursing and Midwifery Code of Ethics of the Republic of Poland, the Code of Medical Ethics and all medical acts clearly oblige medical personnel to respect the personal dignity of each patient. Respect for the right to dignity obliges medical personnel to treat patients with dignity regardless of their age, gender or education. This treatment allows the patients to make conscious decisions. The research showed that it was medical staff who witnessed the violation of this law most often. Complaints against medical personnel also concerned failure to respect the right to intimacy and dignity.

As other researchers point out, the patient's right to medical records is most often violated by medical personnel. It is manifested by the refusal to allow the patients to access their own medical documentation [15–17]. However, the analysis of this research showed that this law was not blatantly violated in case of our respondents. For the patient, access to his or her medical records is the exercise of his or her rights to information [15–20].

The right to information about one's medical condition is one of the crucial rights contained in the Act on Patients' Rights and the Ombudsman of Patients' Rights, as it is inextricably linked with the expression of informed consent to the proposed treatment, diagnostic, surgical and nursing procedures [21, 22].

In a significant percentage of patients in hospital, mental disorders such as anxiety or depression are observed. There is a discussion around the co-occurrence of depression and chronic diseases, while less research has been done into anxiety, even though it is one of the most common emotional responses to the disease [21–26]. This research showed that the level of anxiety was statistically significantly higher than that of depression, but it should be noted that the level of both anxiety and depression was significantly higher in men, independent of the age of the respondents.

The presented results of this research indicate the need provide ethical education including the knowledge about the patient's rights, in particular the right to dignity and intimacy as well as the right to information, health services and medical records.

CONCLUSIONS

Education, occupation and employee's seniority are important determinants of knowledge and respect for patient's rights. Patients' mode of admission to the hospital is a modifier that determines the knowledge of their current rights. Lack of knowledge of the applicable patient's rights by the staff has a significant impact on the exercise or non-observance of patients' rights.

Conflicts of interest

No competing financial interests exist. The authors report no financial, personal, political, intellectual or religious conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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Early planned labor induction vs expectant management in late preterm pre-labor rupture of membranes: maternal and neonatal outcomes

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ABSTRACT

Objectives: To compare expectant management with early planned labor induction in pregnancies complicated by late preterm pre-labor rupture of membranes (PPROM).

Material and methods: A retrospective file review was conducted in a single tertiary center from January 2015 to September 2019. Singleton pregnancies complicated by late PPROM at 34–36 completed weeks of gestation were enrolled. We compared maternal and neonatal complications between expectant management and early planned labor induction.

Results: We retrospectively assigned 41 women to the expectant management group and 39 to the early planned labor induction group. No difference was found in the mode of delivery between the groups. Women in the expectant management group had a longer antepartum hospital stay compared with the induction group (median of three versus one day, $p < 0.01$). Neonates were delivered at a more advanced gestational age in the expectant management group compared with that in the induction group (35 5/7 versus 35 2/7 weeks, $p < 0.01$). In the induction group, 74.4% of the neonates were admitted to the intensive care unit (ICU), and 66.7% received antibiotics compared with 51.2% of neonates admitted to ICU and 29.3% receiving antibiotics in the expectant management group ($p = 0.04$ and $p < 0.01$, respectively).

Conclusions: In pregnancies complicated by late PPROM, early labor induction was associated with a shorter antepartum maternal hospital stay but a higher neonatal ICU admission rate and more frequent antibiotic administration than expectant management. We consider expectant management to be an acceptable alternative to early labor induction in PPROM.

Key words: cesarean section; chorioamnionitis; labor induction; neonatal respiratory distress syndrome; premature rupture of membrane (pregnancy)

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INTRODUCTION

Late preterm pre-labor rupture of membranes (PPROM) complicates one percent of pregnancies between the 34 0/6 and 36 6/7 weeks of gestation [1]. A non-reassuring fetal status, cord prolapse, placental abruption, and chorioamnionitis are all indications for prompt delivery. However, the optimal approach to manage women with late PPROM but without an indication for prompt delivery is still discussed. The American College of Obstetricians and Gynecologists endorse both expectant management and immediate delivery [2]. The Royal College of Obstetricians and Gynecologists considers expectant management to be the best practice management [3].

A recent meta-analysis [4] of 2,563 mothers showed that neonates who were delivered immediately were more frequently diagnosed with respiratory distress syndrome, admitted to the neonatal intensive care unit (NICU), and kept in hospital for prolonged periods of time. In the immediate delivery group, maternal outcomes exhibited a reduced risk of antepartum hemorrhage and chorioamnionitis but an increased rate of cesarean sections (CS).

A multicenter randomized trial demonstrated a significant decrease in neonatal respiratory morbidity in mothers at risk for late preterm delivery who were treated with one course of corticosteroids [5]. Still, to date, there is insufficient evidence regarding the long-term neurodevelopmental

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implications and metabolic risks of such treatment in infants [6, 7].

At our institution, we induced labor in all women with late PPROM who then received antibiotic prophylaxis during labor without antenatal corticosteroids administration until 2016. Since 2016, we adopted a different protocol and started offering expectant management that included corticosteroids to women with uncomplicated PPROM until 37 0/7 weeks of gestation.

The aim of this study was to compare the maternal and neonatal outcomes between expectant management and delivery at 34 weeks of gestation in women with PPROM at our institution.

MATERIAL AND METHODS

The protocol of this retrospective study was approved by the local Institutional Review Board (Helsinki Committee) of the Galilee Medical Center, Nahariya, Israel (date of approval April 28, 2019, number 0041-19-NHR).

We reviewed the records of 186 women with late PPROM at 34–36 completed weeks of gestation who were admitted to our hospital between January 2015 and September 2019. The diagnosis of PPROM was based on the following criteria in either the history or during physical examination: a history of leaking fluid and pooling of amniotic fluid observed on sterile speculum examination. If there was no clear pooling, the AmniSure ROM test (AmniSure International LLC, Boston, MA, US) was used, an immune-chromatography method to detect traces of placental alpha microglobulin-1 protein in the vaginal fluid to confirm the diagnosis.

The exclusion criteria consisted of multiple pregnancy, fetal malformations, meconium-stained amniotic fluid, anhydramnios, non-reassuring fetal status, placental abruption, suspected chorioamnionitis, and active labor or urgent CS upon admission. Furthermore, our indications for immediate delivery before the completion of 37 weeks in the expectant management group were a non-reassuring fetal status, cord prolapse, anhydramnios, placental abruption, and chorioamnionitis. In addition, labor was induced if patients refused to continue the conservative follow-up. Based on these criteria, we excluded 58 women with active labor, three with fetal malformations, 57 who underwent immediate cesarean section, and eight in whom labor was induced immediately.

Eventually, 80 cases were enrolled in the study. The patient selection process is described in Figure 1. We divided these patients into two groups: The planned labor induction group consisted of 39 women who underwent planned labor induction with oxytocin (if they did not experience spontaneous labor within 12 hours after PPROM). The expectant management group consisted of 41 women who were monitored and managed expectantly until either spontaneous delivery or 37 0/7 weeks, whatever occurred earlier.

All women were hospitalized from the time of diagnosis until delivery.

The expectant management included:

1. Maternal monitoring for signs of infection including clinical parameters (maternal temperature, presence of uterine tenderness, frequency of contractions, and maternal and fetal heart rate) and laboratory parameters (monitoring white blood cell counts and C-reactive protein every 48 hours).
2. Fetal monitoring included fetal movement count and performing six nonstress tests daily and a biophysical profile twice a week. Oligohydramnios was not considered to be an indication to induce labor.
3. Patients were treated with prophylactic antibiotics for one week, and, from 2017, they additionally received

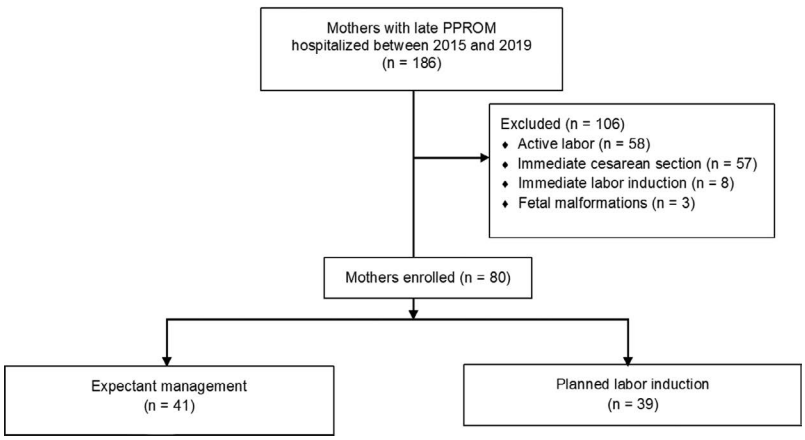

Figure 1. Selection of participants for this comparison of outcomes between early induced labor with expectant management in women with late preterm pre-labor rupture of membranes (n = 80); PPROM — preterm pre-labor rupture of membrane

one course of antenatal corticosteroids at admission if they had not received it previously.

4. Screening for infection included a recto-vaginal swab for a group B strep test and a urine culture that were both obtained on admission.

We recorded information on maternal demographics, the obstetric history, including previous pre-term delivery or PPROM, and the current pregnancy follow-up, including cervical shortening and antenatal corticosteroid administration. Furthermore, we recorded the length of the latency period (time from PPROM until delivery), maternal and fetal monitoring data, whether labor progressed spontaneously or had been induced for medical indications, mode of delivery, rates of antepartum and postpartum hemorrhage (APH and PPH), antepartum fever, intrapartum chorioamnionitis, placental and membrane culture results, antepartum and postpartum hospitalization duration, total hospital stay, postpartum antibiotic administration, and placental histopathological findings. The neonatal outcomes included the Apgar score, birth weight, cord pH, neonatal respiratory support, hospitalization length, data concerning infectious disease evaluation at the NICU, and any complications related to prematurity, such as respiratory distress syndrome, transient tachypnea of newborn, hypoglycemia, intraventricular hemorrhage, necrotizing enterocolitis, hyperbilirubinemia, and stillbirth.

Statistics

Continuous variables are presented as the mean ± standard deviation or as median and range. Qualitative variables are presented as frequencies and percentages. Comparisons of continuous variables between the two groups were performed with either the independent sample t-test or Mann-Whitney test based on the sample size of the groups and the variables' distribution shape. Categorical variables were analyzed using Pearson's chi-square or Fisher's exact test. A two-tailed p-value < 0.05 was considered statistically significant.

All statistical analysis was conducted by the statistical department at Galilee Medical Center using IBM SPSS Statistics for Windows, version 25.0 (IBM Corp., Armonk, NY, USA).

RESULTS

The baseline characteristics of the two groups are represented in Table 1. There were no differences in maternal age, gravity, parity, and the gestational age at admission was similar for the two groups (median of 35 1/7 weeks). A non-significant trend towards having a history of PPROM or preterm delivery was noted in the induction group compared with the expectant management group (23.1% versus 7.3%, respectively, p = 0.06). In the expectant management group, 78% of women received antenatal steroids compared with only 7.7% in the labor induction group (p < 0.01).

Table 1. Baseline characteristics of 80 women with late preterm pre-labor rupture of membranes

	Expectant management group (n = 41)	Labor induction group (n = 39)	p value
Maternal age, years (mean ± SD)	30.20 ± 6.56	30.59 ± 5.48	0.77
Gravity (median, range)	2 (1–7)	3 (1–8)	0.21
Parity (median, range)	1 (1–5)	2 (1–4)	0.19
ART-conceived, n (%)	4/41 (9.8)	1/39 (2.6)	0.36
History of PPROM or preterm delivery, n (%)	3/41 (7.3)	9/39 (23.1)	0.06
Cervical shortening, n (%)	2/40 (4.9)	3/39 (7.7)	0.67
Previous cesarean delivery, n (%)	4/41 (9.8)	5/39 (12.8)	0.73
Thrombophilia, n (%)	2/41 (4.9)	2/39 (5.1)	1.0
Hypertensive disorders, n (%)	1/41 (2.4)	0/39 (0)	1.0
Diabetes, n (%)	7/41(17.1)	2/39 (5.1)	0.15
Positive group B streptococcus vaginal swab at admission, n (%)	5/23 (21.7)	0/11 (0)	0.15
Gestational age at admission, weeks (mean ± SD)	35.13 ± 0.61	35.10 ± 0.69	0.87
White blood cell count, median (range)	11.25 (6.01–34.0)	11.08 (7.59–15.85)	0.87
C-reactive protein, median (range)	8 (0.90–46.10)	10 (0.40–52.0)	
Steroids given during pregnancy, n (%)	9/41 (22)	5/39 (12.8)	0.38
Steroids given at admission, n (%)	32/41 (78)	3/39 (7.7)	< 0.01
Duration of PPROM, hours (median, range)	80.80 (25.67–302.60)	20.18 (12.38–75.30)	< 0.01

ART — assisted reproductive technology; PPROM — preterm pre-labor rupture of membrane; SD — standard deviation

Table 2. Maternal outcomes in 80 pregnancies with late preterm pre-labor rupture of membranes

	Expectant management group (n = 41)	Labor induction group (n = 39)	p value
Antepartum LOS in hospital, days, median (range)	3 (1–13)	1 (0–3)	< 0.01
Postpartum LOS in hospital, days, median (range)	3 (1–12)	3 (2–7)	0.85
Total LOS in hospital, days, median (range)	7 (3–23)	4 (3–7)	< 0.01
Antepartum hemorrhage, n (%)	1 (2.4)	2 (5.1)	0.61
Antepartum fever, n (%)	4 (9.8)	2 (5.1)	0.67
Intrapartum chorioamnionitis, n (%)	/ (7.3)	1 (2.6)	0.61
Mode of delivery			
Vaginal delivery, n (%)	31 (75.6)	32 (82.1)	0.78
Vacuum extraction, n (%)	1 (2.4)	0	
Cesarean section, n (%)	9 (22.0)	7 (17.9)	
Postpartum hemorrhage, n (%)	0 (0)	3 (7.7)	0.11
Urinary tract infection, n (%)	1/20 (4.8)	0	1.00
Postpartum antibiotic administration, n (%)	4 (9.8)	4 (10.3)	1.0
Any positive culture*, n (%)	38/40 (95.0)	34 (87.2)	0.26
Histological chorioamnionitis, n (%)	9/24 (37.5)	6/27 (22.2)	0.35

LOS — length of stay; *At least one positive culture of one of the following: uterus, placenta, membranes, or umbilical cord

The median duration of PPROM in the expectant management group was significantly longer compared with the induction group (80.80 versus 20.18 hours, respectively, $p < 0.01$).

The maternal outcomes are detailed in Table 2. Women in the expectant management group had a longer antepartum hospital stay than the induction group (median of three versus one day, $p < 0.01$), with no significant difference in the postpartum hospital stay. Women in the induction group had a shorter total hospital stay than the expectant management group (median of four versus seven days, respectively, $p < 0.01$).

In the expectant management group, 24 (58%) of the women had spontaneous labor prior to 37 weeks, two (4.8%) underwent induction when they had completed 37 0/7 weeks, and 17 (36 %) underwent labor induction prior to 37 weeks for the following reasons: eight (19.5%) for suspected fetal distress, four (9.7%) on maternal request, two (4.8%) because of severe oligohydramnios, and one (2.4%) because of suspected chorioamnionitis.

No significant difference was found between the groups in the rates of positive cultures, histological chorioamnionitis, and the different pathogens. *Escherichia coli* (*E. coli*) was the most frequently isolated organism in both groups, followed by *Enterobacter faecalis*. In addition, *Klebsiella pneumoniae, Bacteroides vulgaris*, *Enterobacter cloacae complex, Bacteroides fragilis* and *Proteus mirabilis* were also isolated.

The neonatal outcomes are shown in Table 3. Neonates were delivered at a more advanced gestational age in the expectant management group compared with the induction group (35 5/7 versus 35 2/7 weeks, respectively, $p < 0.01$). None of the neonates had a 5-minute Apgar score of less than 7 or pH < 7.1 in either group. In the induction group, 74.4% of the neonates were admitted to the NICU compared with 51.2% in the expectant management group ($p = 0.04$). In the induction group, 66.7% of the neonates received antibiotics compared with 29.3% in the expectant management group ($p < 0.01$).

No case of stillbirth or neonatal death was reported in our study population.

DISCUSSION

In our population of women with PPROM, planned labor induction was related to higher neonatal ICU admission and antibiotic administration rates than expectant management, while the latter resulted in a longer maternal hospital stay.

These results are in accordance with the findings of previous studies. The PPROMT study [8] was a randomized controlled trial comparing immediate delivery versus expectant management in 1839 women with late PPROM and reported that, compared to labor induction, expectant management resulted in a longer maternal hospital stay since 75% of these mothers were managed in the hospital until delivery. In our study, all women undergoing expectant management were hospitalized upon admission and, consequently, had longer antepartum and total hospital stays but no difference in the postpartum stay.

Table 3. Neonatal outcome in 80 pregnancies with late preterm pre-labor rupture of membranes

	Expectant management group (n = 41)	Labor induction group (n = 39)	p value
Gestational age on delivery, weeks (median ± SD)	35.72 (± 0.76)	35.25 (± 0.69)	< 0.01
Birth weight, g (median ± SD)	2576.95 (± 311.21)	2475.18 (± 263.22)	0.11
Intrauterine growth restriction, n (%)	0 (0)	2 (5.1)	0.23
Apgar score at 5 min, median (range)	9 (7–10)	9 (8–10)	0.84
Umbilical cord pH, median (range)	7.30 (7.26–7.40)	7.31 (7.26–7.37)	0.58
Need for resuscitation at birth, n (%)	2 (4.9)	1 (2.6)	1.00
Admission to NICU, n (%)	21 (51.2)	29 (74.4)	0.04
LOS in NICU, days, median (range)	8 (2–23)	8 (2–17)	0.49
Fever at birth	1 (2.4)	2 (5.1)	0.61
Antibiotics administration, n (%)	12 (29.3)	26 (66.7)	< 0.01
Neonatal sepsis, n (%)	0	0	–
Pneumonia, n (%)	0	1 (2.6)	0.48
Respiratory distress syndrome, n (%)	0	0	–
Transient tachypnea of newborn, n (%)	3 (7.3)	1 (2.6)	0.61
Invasive ventilation, n (%)	2 (4.9)	1 (2.6)	1.00
Non-invasive ventilation, n (%)	2 (4.9)	2 (5.1)	1.00
Surfactant administration, n (%)	0	1 (2.6)	0.48
Hypoglycemia, n (%)	2 (4.9)	2 (5.1)	1.00
Intraventricular hemorrhage, n (%)	0	2 (5.1)	0.23
Necrotizing enterocolitis, n (%)	0	0	–
Hyperbilirubinemia, n (%)	20 (48.8)	25 (64.1)	0.18

SD — standard deviation; LOS — length of stay; NICU — neonatal intensive care unit

However, in contrast to the PPROMT study [8] and a recent meta-analysis [4] that showed a higher risk of APH and PPH with expectant management, in our study, there was no difference in the frequency of APH or PPH in this group compared to labor induction. These studies included multiple pregnancies, and women who presented with ruptured membranes earlier in pregnancy became eligible upon reaching 34 weeks of gestation and were then followed beyond 34 0/7 weeks. The different inclusion criteria and study design could explain the differences in the results since multiple pregnancies are considered at risk for PPH.

Previous studies reported a higher risk of clinical and histological chorioamnionitis [9, 10] in women who underwent expectant management. In contrast, we did not find any difference in maternal infections between the groups. All patients in our study received antepartum antibiotics, either intravenously, orally, or both. In the PPROMT study [8], a similar proportion (86 %) of patients in both groups received antepartum antibiotics, but women in the expectant management group showed higher rates of intrapartum fever and postpartum antibiotic use. A recent meta-analysis [11] showed that the use of prophylactic antibiotics is effective in reducing maternal infections in women undergoing expectant management. This discordance between the findings could be related to our small sample size.

PPROMEXIL [9] and PPROMEXIL-2 [10] were randomized controlled trials conducted in the Netherlands and compared labor induction versus expectant management in non-laboring women with PPROM between 34 and 37 weeks. Like our findings, no difference in the CS rate was found between the two approaches. Other studies [4, 8] found higher CS rates in women with immediate delivery induction. The fact that the Dutch trials involved multiple centers in one country [9, 10], while the other trial [8] involved 65 centers in 11 countries. could have affected the CS rate. Both were multicenter studies, but the difference most probably results from different national approaches. For instance, in the PPROMEXIL-2 trial [10], only 13% of the patients in the induction group underwent CS compared with a twice as high rate of 26% in the PPROMT study [8]. However, the indications for CS were not reported in these studies, making it difficult to draw definite conclusions concerning the differences in CS rates.

Similarly, to previous studies [9, 10], pregnancy was prolonged by three days in our mothers with expectant management, and their newborns were less likely to be admitted to the NICU. Still, the length of stay of neonates admitted to the NICU was similar in both groups. These findings are in line with previous studies [4, 9]. Neonatal admission to the NICU results in higher costs and might increase the risk of nosocomial infections [12], but also interrupts the bonding process and increases parental stress [13].

We did not find any difference in neonatal infectious complications (*e.g.*, fever at birth, positive blood cultures, or sepsis) between the groups, but more neonates in the planned induction group received antibiotics than in the expectant management group. Previous studies did not find any difference in neonatal sepsis, positive blood cultures, or antibiotic administration [4, 8, 9]. Furthermore, although in our study neonates in the expectant management group were born at an advanced gestational age, expectant management neither reduced neonatal respiratory morbidity nor affected the need for ventilation. On the opposite, previous studies [4, 8, 11] showed benefits for expectant management, whereas immediate delivery increased the risk of respiratory distress and mechanical ventilation.

Our data is underpowered to identify differences in neonatal mortality and morbidity between the two approaches, but a recent meta-analysis reported that planned early birth increased the risk of neonatal death (RR 2.55, 95% CI 1.17–5.56) without reducing the risk of neonatal sepsis (RR 0.93, 95 % CI 0.66–1.30) [11].

In our study, 78% of the women in the expectant management group received one course of steroids at admission compared with only 7.7% of women in the induction group. This disparity resulted from the new approach introduced in 2017 when we started administering one course of steroids in women with late PPROM [5, 14–16]. Despite this, steroid administration in gestation periods of ≥ 34 0/7 weeks is still controversial, mainly because of concerns about the long-term neurodevelopmental outcomes in newborns [17].

One of the strengths of this study is that we examined a clearly defined population of women with late PPROM between 34 0/7 and 36 6/7 weeks. Previous studies [8, 9, 12] included women with lower gestational ages at PPROM (< 34 0/7) and were followed from 34 weeks onward. Furthermore, detailed maternal and fetal data were recorded over a period of five years. Unlike previous studies, our data were collected from a single center with defined standards of clinical practice, treatment, and care. Despite the relatively small sample size, we could demonstrate a distinct difference in neonatal outcomes, such as higher NICU admission rates and more frequent neonatal antibiotic treatment in the induction group.

Our study has several limitations. As a retrospective cohort study, risk of confounding bias remains even with the use of multivariable statistical techniques. Furthermore, it was underpowered to detect significant differences in certain maternal and fetal complications, such as neonatal sepsis and mortality, because of the small sample size.

CONCLUSIONS

We found that early planned labor induction in pregnancies complicated by late PPROM was associated with a shorter antepartum maternal hospital stay, but longer neonatal ICU stay and higher rates of antibiotic treatment than expectant management. Thus, we consider expectant management to be a safe and acceptable alternative to early labor induction in PPROM.

Conflict of interest

None.

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The effect of various pressure of pneumatic uterine bracket by using saccule sterine external stent on incidence of supine hypotensive syndrome

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ABSTRACT

Objectives: The saccule uterine external stent with a pneumatic uterine bracket reportedly prevents the incidence of supine hypotension syndrome (SHS) during cesarean section under combined spinal — epidural anesthesia (CSEA). However, the preventive effect is affected by the pressure within pneumatic uterine bracket. This study aims to explore the optimal pressure.

Material and methods: One hundred forty-eight pregnant women were selected and randomly divided into three groups: Group A (the control group, n = 49), Group B (n = 49), and Group C (n = 50). The pressure within pneumatic uterine bracket was set at 240 mmHg, 260mmHg, and 280mmHg, respectively, during cesarean section under CSEA for participants in groups A, B and C. The intraoperative comfort rate and incidence of SHS were recorded.

Results: No significant difference in the anesthetic efficacy was observed among the three groups ($p > 0.05$). However, there was a significant difference in the occurrence of SHS, with a reduction of 30 mmHg in blood pressure. The incidence of SHS belong the three groups showed significant differences (36.73% in Group A, 18.37% in Group B and 18.00% in Group C, $p < 0.05$). In addition, significant differences ($p < 0.05$) in the intraoperative comfort rate were also found among the three groups, with the comfort rate of 69.39% in group A, 91.84% in group B and 90.00% in Group C.

Conclusions: The optimal pressure within pneumatic uterine bracket for preventing SHS hypotension is about 260 mmHg. These findings might contribute to the prevention of SHS.

Key words: pneumatic uterine bracket; gasbag pressure; cesarean section; supine hypotension syndrome

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INTRODUCTION

Supine hypotensive syndrome (SHS) is characterized by severe supine hypotension in late pregnancy. The clinical presentations of SHS include dyspnea, dizziness, nausea and vomiting. The intrinsic hypotension in parturients further decreases the fetoplacental blood flow, thus resulting in fetal intrauterine hypoxia, acidosis and even post-neonatal cerebral palsy [1]. These symptoms were reportedly relieved by turning to the lateral position [2]. In addition, the occurrence of SHS is associated with anesthesia methods and anesthetic drugs, which account for the significant differences in incidence of SHS reported by different studies [3, 4]. Combined spinal-epidural anesthesia (CSEA) is a common anesthesia method that widely used in obstetrics. Because CSEA avoids the adverse effects of anesthetic drugs on the fetus under the general anesthesia and facilitates postoperative analgesia efficiently [3]. However, CSEA has been reported to increase the incidence of SHS after the anesthesia [4]. The incidence of SHS in pregnant women was significantly increased after the anesthesia, with the incidence of 80% [5].

A self-made pneumatic uterine bracket has been found to perform excellent clinical efficacy in reducing the incidence of SHS during the cesarean section (Chinese National Patent for Utility Modes.: ZL 201320122209.6). However, the air sac pressure of the equipment enhances requirement for materials of final product. The joint stress points and

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air-adding pathways on both sides of pneumatic uterine bracket are integrated plate structure. After installation, the plate structure is located between the waist of parturients and surgical beds. The gasbags on both sides of pneumatic uterine bracket are fixed at the soft part between costal margins (the left and right costal margins) and the ilium via the middle plate structure. Therefore, the improved pressure within the gasbags demands increased load-bearing ability and increased thickness of the plate structure. While the increased thickness of the plate structure is associated with severe lumbar hyperextension of parturients after installation.

Objectives

This study aims to investigate the influence of different air sac pressure on the incidence of SHS and comfort level of the puerperas and determine the optimal pressure.

MATERIAL AND METHODS

Subjects

One hundred forty-eight puerperas, aged from 28 to 42 years old, of American Society of Anesthesiologists (ASA) grading I to II were recruited for cesarean section under CSEA between May 2018 and April 2019 in The Second Affiliated Hospital of Chengdu Medical College. Exclusion: (1) Puerperas with gestational hypertension (the diagnostic criteria was according to the 2018 International Society for the Study of Hypertension in Pregnancy Classification, Diagnosis and Management Guidelines); (2) The anesthesia block plane was T4-T6; (3) The epidural injection of local anesthetic drugs before the operation due to poor anesthetic effect; (4) The neonatal weight is less than 2 Kg. All participants signed the informed consent document, and the research was approved by the Ethics Committee of The Second Affiliated Hospital of Chengdu Medical College.

Participants were randomly divided into three groups: Group A (control group, n = 49), Group B (n = 49), and Group C (n = 50). Pressure of pneumatic uterine bracket was set at 240 mmHg, 260mmHg, and 280mmHg, respectively, during cesarean section under CSEA for participants in groups A, B and C. The age, height, weight, gestational age, uterine height, abdominal perimeter and newborn weight were collected. Whether puerperas had SHS before anesthesia was also identified.

Anesthesia methods

CSEA was used for all parturients. After the parturient entering the operation room, oxygen was inhaled at 4 L/min via the face mask. Electrocardiogram (ECG), blood pressure (BP), heart rate (HR) and oxygen saturation of the parturient were monitored. Meanwhile, 500 mL of colloid solution was rapidly infused. Fifteen milligrams of ropivacaine hydrochloride were injected into subarachnoid cavity rapidly. The epidural

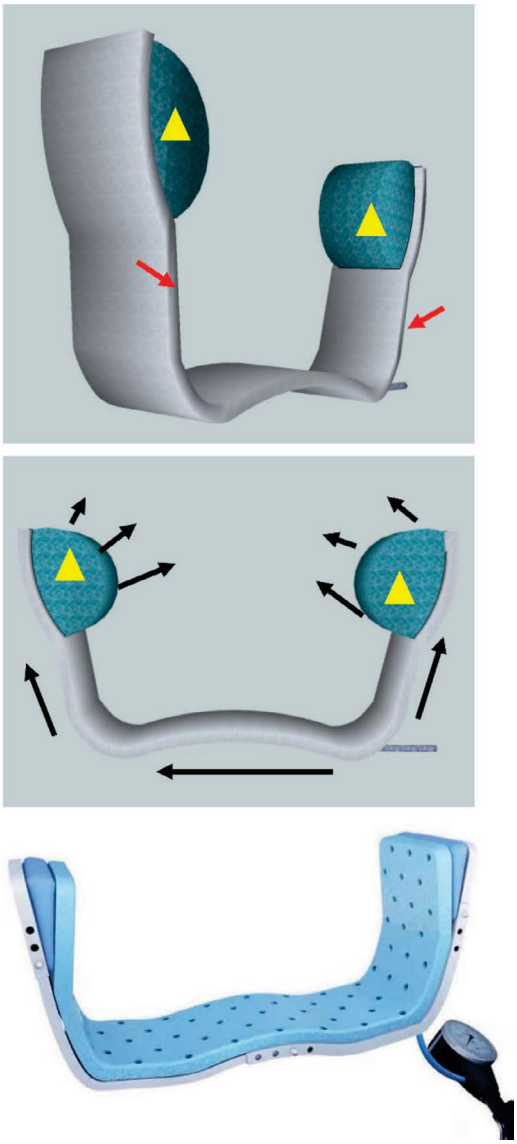

Figure 1. The structure of pneumatic uterine bracket. Yellow triangles indicate the gasbags. Red arrows indicate the air-adding pathways. Black arrows indicate the direction of air flow and pressure

catheterization was standby. After fixing the epidural pipe, pneumatic uterine bracket (the structure of the pneumatic uterine bracket was shown in Fig. 1) was installed immediately. The installation position was at back waist, and gasbags on both sides of pneumatic uterine bracket were fixed at the soft part between costal margins (left and right costal margins) and ilium via the middle plate structure (installation method was illustrated in Fig. 2). Subsequently, parturients were turned to a prostrate position. Gasbags in groups A, B, and C was pressurized to 240 mmHg, 260 mmHg, and 280 mmHg, respectively. Pressurization time of the air bags was five to seven minutes. Air pressure within gasbags was decompressed rapidly after the incision of lower segment of the uterus and suction of the amniotic fluid. The lateral decu-

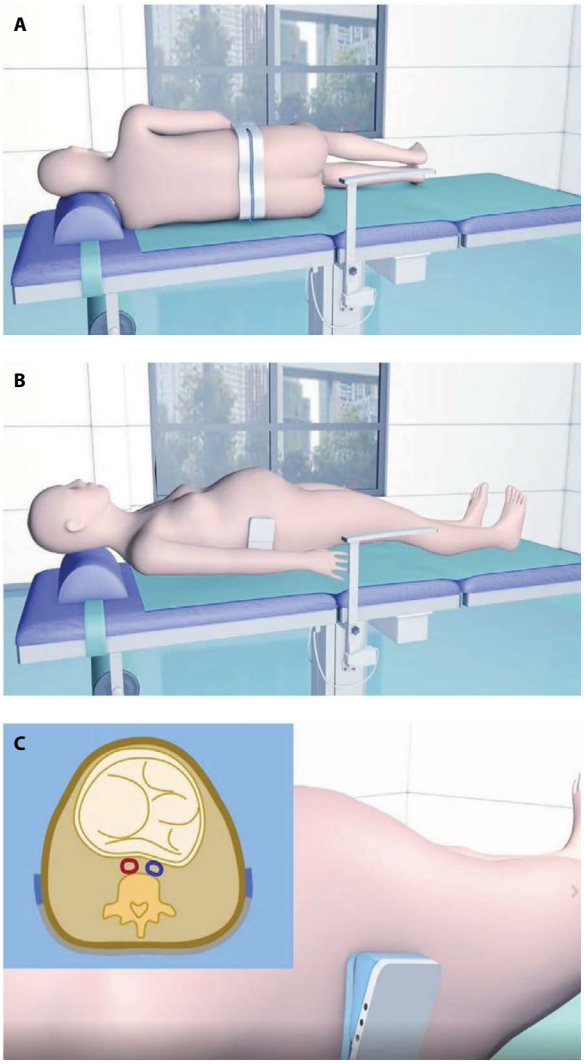

Figure 2. The installation method of pneumatic uterine bracket; **A.** After the installation, the plate structure was installed at the back of the maternal waist to make sure that the gasbags were fixed at the soft part between costal margins and the ilium; **B.** Parturient lying on the operating table after the installation; **C.** Pressurized gasbags separated the enlarged uterus from the compressed inferior vena cava

bitus time of parturients in all groups was within two minutes after subarachnoid injection. Data were then recorded.

Observation indicators

Evaluation of the anesthetic effect

The degree of pain was judged by a visual analogue scale (VAS). Pain scores ranged from 0 to 10 points, where 0 represents No pain and 10 represents Maximum pain imaginable. Scores were recorded at skin incision, fetal removal and closure suture.

The degree of muscle relaxation was evaluated by the surgeon. An evaluation was conducted at the end of the operation according to the commonly used evaluation criteria. The degree of muscle relaxation included three subscales: "very satisfied", "satisfied", and "dissatisfied". The "very satisfied" subscale reflects high plane of anesthesia, good muscle relaxation and good anesthetic effect, which do not affect the surgical procedures. The "satisfied" subscale corresponds to acceptable interference by relative muscle relaxation. While the "dissatisfied" subscale reflects low plane of anesthesia and poor muscle relaxation, which severely affects surgical procedures.

Main indicators of SHS

Because SHS are mainly occurred three to seven minutes after subarachnoid injection of local anesthetics (*i.e.*, the period ranging from anesthesia complete to lower uterine segment incision) [6]. Maternal hemodynamics during this period were evaluated. The number of subjects whose heart rate (HR) was increased by 20 beats/min, the number of subjects whose systolic blood pressure was decreased by 4 kPa (30 mmHg), the number of subjects whose systolic blood pressure dropped below 10.6 kPa (80 mmHg), and the number of subjects with severe SHS were recorded. Participants with HR above 120 beats/min and systolic blood pressure below 70 mmHg should be treated in time to avoid compression of the inferior vena cava through the change of body position and injection of ephedrine (10 mg).

Evaluation of maternal adverse reactions

The number of parturients feeling dizziness, dyspnea, nausea and vomiting during the operation was recorded. The adverse reactions were assessed by the comfort level of the puerperas during the operation and included three subscales: "very satisfied (no discomfort)", "satisfied (slight and tolerable discomfort)" and "dissatisfied (serious discomfort)".

Statistical methods

The measurement data were presented as mean ± standard deviation ($\bar{\chi} \pm s$). The differences in groups were tested by analysis of variance. An LSD test was used for the post-hoc test. Enumeration data were tested by chi-square test. All d statistical analyses were performed using the SPSS23.0 software. $P < 0.05$ was considered as statistically significant.

RESULTS

Basic data of all puerperas

The basic information of puerperas was presented in Table 1. As shown in Table 1, there was no significant difference in the age, height, weight, pregnant period, uterine height, abdominal perimeter, neonatal weight and the percentage of parturients with SHS before anesthesia among the three groups ($p > 0.05$).

Anesthetic effect under different pressure

The degree of pain and muscle relaxation was presented in Table 2. As shown in Table 2, there was no significant dif-

Table 1. The basic information of puerperas

	Age	Hight [cm]	Weight [kg]	Pregnant period [d]	Uterine height [cm]	Abdominal perimeter [cm]	Neonatal weight [g]	Whether parturients had SHS before anesthesia	
								Yes	No
Group A	30.69 ± 2.66	159.04 ± 4.82	69.00 ± 9.43	272.20 ± 7.39	33.82 ± 2.12	102.71 ± 6.97	3350.00 ± 348.14	13 (26.53%)	36 (73.47%)
Group B	31.59 ± 2.78	158.14 ± 4.91	68.37 ± 8.73	272.43 ± 7.05	33.33 ± 2.15	102.20 ± 6.40	3243.06 ± 321.93	11 (22.45%)	38 (77.55%)
Group C	30.68 ± 3.52	158.18 ± 3.73	67.73 ± 9.03	272.20 ± 8.13	34.00 ± 2.52	101.68 ± 6.00	3331.20 ± 458.19	14 (28.00%)	36 (72.00%)
F/χ^2	1.613	0.622	0.245	0.015	1.156	0.317	1.101	0.428	
p	0.203	0.538	0.783	0.985	0.318	0.719	0.335	0.842	

Note: There was no significant difference among the three groups and no further pairwise comparison was required

Table 2. The effect of anesthesia

Groups	VAS scores			Evaluation of abdominal muscle relaxation	
	During incision (M1)	Fetus extraction (M2)	During stitching (M3)	Very satisfied	Dissatisfied
Group A (n = 49)	1.49 ± 0.68	2.31 ± 1.21	1.49 ± 0.65	44 (89.80%)	5 (10.20%)
Group B (n = 49)	1.51 ± 0.62	2.47 ± 1.23	1.47 ± 0.62	42 (85.71%)	7 (14.29%)
Group C (n = 50)	1.58 ± 0.73	2.68 ± 1.48	1.56 ± 0.67	43 (86.00%)	7 (14.00%)
F/χ^2	0.242	1.011	0.268	0.796	
p	0.786	0.366	0.766	0.863	

VAS — visual analogue scale

ference in VAS scores among three groups at skin incision (M1), fetal removal (M2) and closure suture (M3) ($p > 0.05$). The evaluation of abdominal muscle relaxation by surgeons demonstrated that 5 patients in group A (10.20%), 7 patients in group B (14.29%) and 7 patients in group C (14.00%) were dissatisfied. There was no significant difference in anesthetic effect among the three groups ($p > 0.05$).

The incidence of SHS under different pressure

During the period from subarachnoid injection to the incision of the lower uterine segment, the incidence of the SHS among the three groups were shown in Table 3. As shown in Table 3, in Group A, there were 26 (53.06%) cases showing increased heart rate of more than 20 beats/min, 18 cases (36.73%) showing a decrease in systolic blood pressure of 4 kPa (30 mmHg), and 12 cases (24.49%) showing a decrease in systolic blood pressure to 10.6 kPa (80 mmHg). There were 13 cases (26.3%) showing severe SHS that must be timely treated in group A. In Group B, there were 17 cases (34.69%) showing increased heart rate of more than 20 beats/min, 9 cases (18.37%) showing a decrease in systolic blood pressure of 4 kPa (30 mmHg), and cases (8.16%) showing a decrease in systolic blood pressure to 10.6 kPa (80 mmHg). There were 5 cases (10.20%) showing severe SHS that must be timely treated in group B. In Group C, there were 15 cases (30%) showing increased heart rate of more than 20 beats/min, 9 (18.00%) cases showing a decrease in systolic blood pressure of 4 kPa (30 mmHg), and 4 cases (8.00%) showing a decrease in systolic blood pressure to 10.6 kPa (80 mmHg). There were 5 cases (10.00%) showing severe SHS that must be timely treated in group C. The results from chi-square tests reflecting SHS incidence were shown in Table 3. As shown in Table 3, the difference in SHS incidence between groups A and B was significant ($p < 0.05$). SHS incidence also showed significant difference between groups A and C ($p < 0.05$). However, no significant difference in the incidence of SHS between groups B and C ($p > 0.05$) was observed. It was also found that the incidence of SHS in Group A was significantly higher than that in other two groups (Tab. 3).

Comfort level and intraoperative adverse reactions in parturients

As shown in Table 4, intraoperative dizziness occurred in 14 cases (28.57%), 5 cases (10.20%) and 4 cases (8.00%) in groups A, B and C, respectively. Obviously, the incidence of intraoperative dizziness in parturients from group A was significantly higher than that in parturients from groups B and C ($p < 0.05$), while there was no significant difference in the incidence of intraoperative dizziness in parturients from groups B and C ($p > 0.05$). During the operation, the incidences of nausea and vomiting in group A, group B, and group C were 26.53%, 8.16% and 10.00%, respectively. The incidence of nausea and vomiting in group A was significantly higher than that in groups B and C ($p < 0.05$), with

Table 3. The incidence of supine hypotension syndrome pregnant women

Groups	Period from subarachnoid injection to the incision			
	Heart rate increased by more than 20 beats/min	Systolic blood pressure decreased by 4 kPa (30 mmHg)	Systolic blood pressure decreased to 10.6 kPa (80 mmHg)	Cases with severe SHS that must be timely treated
Group A (n = 49)	26 (53.06%)	18 (36.73%)	12 (24.49%)	13 (26.53%)
Group B (n = 49)	17 (34.69%)[a]	9 (18.37%)[a]	4 (8.16%)[a]	5 (10.20%)
Group C (n = 50)	15 (30.00%)[a]	9 (18.00%)[a]	4 (8.00%)[a]	5 (10.00%)
χ^2	6.144	6.131	7.552	3.950
p	0.046*	0.047*	0.023*	0.139

*p < 0.05; aCompared with group A, there were significant differences; SHS — supine hypotension syndrome

Table 4. The degree of adverse reactions of the puerperas

Groups	After anesthesia			
	Dizziness	Nausea and vomiting	Dyspnea	Comfort evaluation (very satisfied and satisfied)
Group A (n = 49)	14 (28.57%)	13 (26.53%)	9 (18.37%)	34 (69.39%)
Group B (n = 49)	5 (10.20%)[a]	4 (8.16%)[a]	4 (8.16%)	45 (91.84%)[a]
Group C (n = 50)	4 (8.00%)[a]	5 (10.00%)[a]	4 (8.00%)	45 (90.00%)[a]
χ^2	9.568	7.943	3.326	11.235
p	0.014*	0.019*	0.230	0.004*

*p < 0.05; [a]Compared with group A, there were significant differences

no significant difference observed between group B and C (p > 0.05). In addition, the incidence of dyspnea in group A, group B, and group C were 18.37%, 8.16% and 8.00%, respectively. The incidence of dyspnea was significantly higher in group A than that in groups B (8.16%) and C (8.00%), with no significant difference found in the incidence between groups B and group C (p < 0.05).

After the operation, 34 cases (69.39%) in group A, 45 cases (91.84%) in group B and 45 cases (90.00%) in group C were highly satisfied and satisfied. The comfort rate in group A was significantly lower than that in group B and C (p < 0.05), and there was no significant difference in the comfort rate between group B and C (p > 0.05). Compared with group A, there were significant adverse reactions caused by blood pressure reduction during the operation between group B and group C (p < 0.05), while there were no significant differences in the adverse reactions caused by blood pressure reduction during the operation between groups B and group C (p > 0.05). There were significant differences among the three groups in the comfort level during the obstetrics (p < 0.05), with parturient in the group B having highest comfort rate.

DISCUSSION

The occurrence of SHS in parturients under CSEA is related to many factors, including maternal age, fetal weight and the presence or absence of SHS in late pregnancy [7, 8].

The newborns in China in 2018 and 2019 was 15.23 million and 14.65 million, respectively. In 2018, the cesarean section rate was 36.7%, which indicates that more than five million puerperas receive cesarean sections every year. How to reduce the incidence of SHS, improve the maternal satisfaction and ensure the safety of newborns has been a critical topic for both anesthesiologists and obstetricians.

The commonly used methods for the prevention and treatment of SHS include expansion before spinal anesthesia [9, 10], administration of pressure-boosting drugs [11–14], administration of the isobaric local anesthetic drugs and reduction of the dosage of local anesthetic drugs, and pre-evaluation of SHS before operation [10, 15]. However, these methods suffer from drawbacks.

The pathophysiology of SHS indicates the postural intervention as the best way to prevent the incidence of SHS. Clinically, the commonly used methods are to tilt the surgical bed to the left, move the uterus to the left, and place wedges under the lumbar spine of the puerpera [16]. Because the uterus mostly is in the right position, the enlarged uterus after left inclination avoids the serious compression on inferior vena cava and abdominal aorta and increases the volume of blood regurgitation, thus decreasing the occurrence of hypotension fundamentally and reducing the degree of hypotension even if SHS occurs. However, in clinical practice, postural intervention is usually unable to be implemented

due to the influence of surgery and the non-ideal environment. Kundra et al. [17], reported that the left shift of the uterus as far as possible by manipulation in the supine position of parturients after spinal anesthesia can effectively avoid the oppression of the uterus on the abdominal aorta and the inferior vena cava. However, the manipulation, which seriously affects the disinfection and surgical operations, is difficult to conduct. The excessive left-leaning surgical beds also greatly increase the fear of the puerperas, thus further influencing the maternal satisfaction.

The pneumatic uterine bracket used in the present study is another form of postural intervention, and its structure diagram is shown in Figure 1. Our previous study [18] confirmed that this method is superior to traditional methods, which ensures the advantages of postural intervention (*i.e.*, to effectively prevent the occurrence of SHS), without affecting the operations of surgeons and anesthesiologists or increasing maternal discomfort.

However, we found problems in the selection of the proper materials for the subsequent mass production. In the previous research, a metal skeleton has been selected to produce pneumatic uterine brackets. The metal plate used in the previous study was very hard and had a small deformation arc after compression, so even the metal plate with the thickness of 0.5 cm can meet the balloon pressure above 280 mmHg [18]. The installation method of the pneumatic uterine bracket was shown in Figure 2. The reaction force support points of the pressure depend completely on double side gasbags between the board structure. After the installation, the plate structure with hidden inflation tubes is located between the physiological curvature of the back waist of the parturients and the operation bed. In our previous research, the metal structure, which was extremely hard and had small deformation curves after compression was utilized. Therefore, the sheet metal even with a thickness of 0.5 cm can support the pressure above 280 mmHg within the gasbags [18]. The mass production and large area promotion of pneumatic uterine bracket demand the usage of medical polyvinyl chloride (PVC). Medical PVC materials are also required in order to ensure the low cost and easy operation. High pressure requires the increased thickness of the PVC link plate in the middle. The enhanced thickness will cause the obvious the overextension of the back waist of the parturients, thus reducing the maternal comfort. The purpose of this study was to investigate the minimum pressure that can effectively prevent the incidence of SHS after balloon pressurization and to reduce the thickness of disposable medical PVC products of pneumatic uterine brackets.

In this study, during the period from anesthesia to the incision of the lower uterine segment, the proportions of parturients with systolic blood pressure decreased by 4 kPa (30 mmHg) and systolic blood pressure decreased to below 10.6 kPa (80 mmHg) and parturients receiving prompt treatment were significantly higher in Group A than that in groups B and C, with no significant difference observed between groups B and C. The results indicated that the pressure of 240 mmHg did not contribute to prevent the incidence of SHS. For the proportion of parturients with heart rate increased more than > 20 beats/min was the highest in Group A, there was no significant difference between groups A and B. Therefore, a larger sample size is needed to confirm the difference between groups A and B in further studies. The comparison results of maternal adverse reactions (including dizziness, nausea, vomiting and comfort) among the three groups demonstrated that, such as and comfort evaluation, both of Group B and Group C were better than Group A. The maternal comfort level of Group A was significantly lower, which was also related to the imperfect role of Group A in preventing SHS hypotension. There was no significant difference in the rate of dyspnea within the three groups, indicating that the compressed bilateral gasbags raised the uterus efficiently to avoid dyspnea derived from the compression. In the study, we also observed that two cases in Group C were dissatisfied with the comfort level because of the tight feelings around the waist. Although there was no significant statistical difference between Group C and Group B, further observation was still needed with the increasing of the sample size.

It can be judged from this study that the pressure of 260 mmHg can effectively maintain the effect of pneumatic uterine bracket to prevent SHS hypotension, and meanwhile avoid the discomfort caused by the high blood pressure of the puerpera. It is the minimum blood pressure requirement of pneumatic uterine bracket to prevent SHS hypotension.

CONCLUSIONS

The minimum pressure of Pneumatic uterine bracket for preventing SHS hypotension is about 260 mmHg. Under such a pressure, the desired prevention effect of SHS hypotension can be achieved. In addition, the maternal discomfort of puerperas will not be caused by too high pressure.

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Conflict of interest

None.

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Comparison of the effects of TENS stimulation and water immersion on relieving labour pain suffered byprimiparas

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ABSTRACT

Objectives: The aim of this study was to compare pain suffered by primiparas when delivering a child in a traditional way with deliveries where either TENS stimulation or water immersion was used.

Material and methods: Primiparas were divided into 3 groups. In group 1 there were 45 women for whom TENS stimulation was applied during delivery. Group 2 consisted of 38 women who remained in the water during the actual birth of the baby. Group 3 served as the control group and was composed of 32 women. The intensity of pain during delivery was assessed by means of a numerical scale. During the first delivery period, pain was assessed three times at cervical dilation of 2, 3 and 4 fingers.

Results: The analysis of pain suffered by primiparas at 2-finger widening showed no statistically significant differences between the groups. However, the analysis of pain experienced at 3-finger opening showed significant differences between the group of women using TENS stimulation in comparison with the control group. When comparing pain at 4-finger opening, statistically significant differences were found between the group of women who delivered in water in comparison to both the control group and the group using TENS stimulation.

Conclusions: TENS stimulation and water immersion are good methods to relieve labour pain; particularly helpful in the first period of labour. They are also safe, alternative, non-pharmacological methods of reducing labour pain.

Key words: TENS; water immersion; delivery pain; physiological delivery

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INTRODUCTION

Hydrotherapy has been used since the times of the ancient Greeks and ancient Romans as a natural means of relieving birth pain. In more recenttimes, in Europe in the 1970s, Michael Odent was a great proponentof water immersion. During childbirth, women can enjoy full immersion in a bath, pool or shower [1]. The warming effect during bathing reduces the pain of childbirth by increasing the production of oxytocin, which in turn contributes to the reduction of pain receptors. In addition, warm water calms the woman down, reducing her pain [2].

Transcutaneous Electrical Nerve Stimulation (TENS) is one of the most commonly used neuromodulation techniques used in physiotherapy for reducing pain. It is applied for the treatment ofboth acute and chronic pain syndromes [3]. The analgesic effect of TENS is based on the theory of pain inhibition, derived from the control gate theory according to Melzack and Wall 1965 and on central pain inhibition. Animal studies indicate that all three types of opioids (endorphins, enkephalins and dynorphins) are triggered during TENS stimulation regardless of the type of frequency. However, the frequency of the current affects the advantage of producing certain opioids. BURST electrostimulation increases blood endorphin levels up to 3.5 times [6]. High-frequency TENS, on the other hand, triggers greater production of enkephalins and dynorphins [4]. Application

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of electrical current during labour does not burden the body, nor does itexpose either mother or foetus to any threat [4–6].

Objectives

The aim of the study is to compare pain experienced by primiparas during a physiological delivery taking place in a traditional way withdeliveries where TENS stimulation or water immersion was used.

MATERIAL AND METHODS

The research was conducted from March 2010 to October 2012 in the Maternity Clinic of the Medical University of Gdańsk Clinical Hospital in Gdańsk and in the Francis Żaczek Independent Public Health Care Center in Puck, both in northern Poland. The research was approved by the bioethics commission of Gdansk on 12th January 2010. Beforebeing subject tothe tests, every patient was informed about the purpose of the tests and about the way they were to be carried out. They then read and signed the Patient Information and the Conscious Consent to Participate in the Clinical Study.

After meeting the study participation criteria, the patients were divided into three groups. The patients were assignedarbitrarily to groups 1 and 3 in a non-random way and both groups were divided between Gdansk and Puck (afterthe homogeneity of both groups was confirmed).

Group 2 consisted of arbitrary, non-randomly selected patients allocated to the Puck hospital, because only that hospital had the facilities to deliver in water.

Criteria for joining the tests:

- healthy, full-term pregnancy — at least the 38th week of pregnancy
- correct positioning of the foetus
- cervical dilation at the start of the study of up to 4 cm
- spontaneous delivery
- no contraindications to the use of TENS stimulation in group 1 or water immersion in group 2
- patient's consentto testparticipation

Exclusion criteria:

- lack of patient's consent
- application of pharmacological methods of reducing labour pain in the form of epidural, spinal, Dolargan or nitrous oxide
- delivery by Caesarean section

Patients giving birth for the first time were divided into three groups:

Group 1–45 women who were subject to TENS during delivery.

Group 2–38 women who were subject towater immersion during delivery.

Group 3–32 women who were not subject to either TENS or water immersion, as a control group.

During delivery, the intensity of pain was assessed using a numerical scale combined with a descriptive scale where 0 indicatedno pain and 10 indicated unbearable pain. During the first delivery period, pain was recordedthree times when the cervix wasopen at 2, 3 and 4 fingers (*i.e.*, 4, 6 and 8 cm). Pain in the second delivery periodwas assessed immediately after delivery.

Water immersion during childbirth wasonly available in Puck. Women were introduced into the deliverybathtub at the time they had cervical dilation from 3 to 9 cm (average 6 cm). A single stay in the bathtub lasted approx. 60 minutes. A 30-minute CTG test was performed before water immersion. During water immersion, foetal heart rate was tested after each contractionby means of a portable heart rate detector. The water level was up to the primipara's umbilicus and the water temperature was 37°C.

The TENS delivery procedure was carried out by means of a two-channel Neuro Track Obstetric TMTENS electrostimulator by Verity Medical LTD (Fig. 1). The Axelgaard ValuTrode LITEby Axelgaard manufacturing Co. self-adhesive disposable electrodes measuring 4.5 x 9.5 cm were used. The electrodes were covered with gel in the MultiStick® Gel technique.

In the first period of delivery, two electrodes were glued to the patient's back at the height of Th10–L2 (Fig. 2). In the event of sacral pains, a second pair of electrodes was glued onto the segment S2–S4 of the spine. At the end of the first delivery period, the electrodes were transferred to the S2–S4 segment of the spine (Fig. 3).

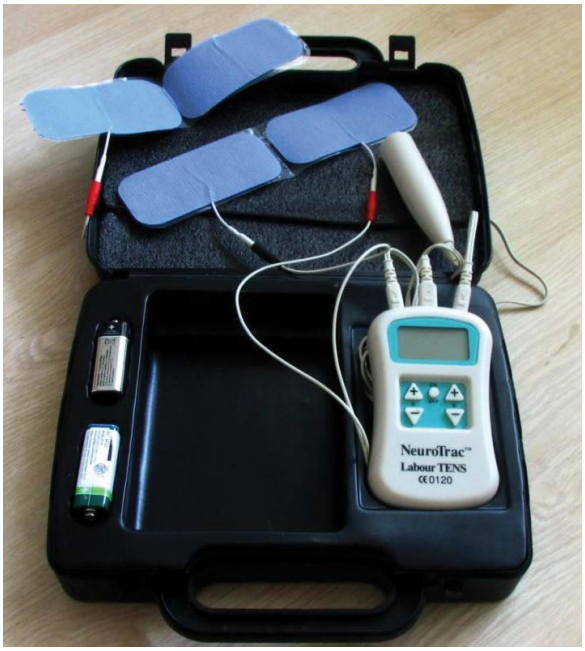

Figure 1. Neuro Track Labour TENS Electrostimulator together with electrodes (own source)

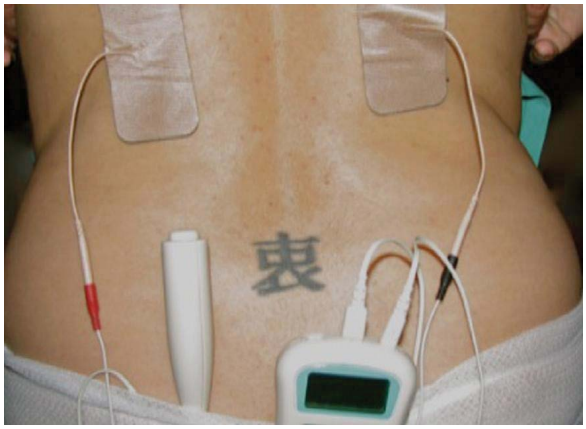

Figure 2. Positioning of electrodes during the first period of labour (own source)

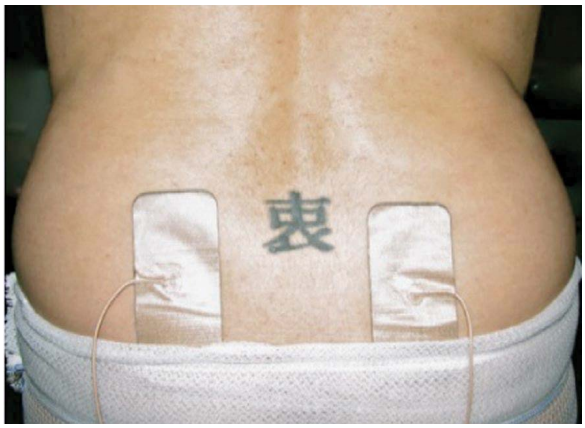

Figure 3. Positioning of electrodes during the second period of labour (own source)

Table 1. Characteristics of studied patients

	∑ observationn	Age (range)	Age $\bar{x}$	Week of pregnancy (range)	Week of pregnancy $\bar{x}$
Group 1 (TENS)	45	18-39	29	38–42	40.31
Group 2 (immersion)	38	20-34	25	38–42	40.61
Group 3 (control)	32	19-38	28	38–42	40.16

TENS — Transcutaneous Electrical Nerve Stimulation

At the beginning of the stimulation, the electrostimulator was operated by a physiotherapist. The accompanying person in the delivery room and/or the primipara was then instructed how to operate the electrostimulator.

The electrostimulator generated a current with rectangular, asymmetrical, biphasic pulses. Two current programs were used for the stimulation. During labour contractions, 90 Hz current with apulse width of 220 μs was used.

During the break between contractions, BURST current was applied. This stimulation is characterised by the appearance of a high frequency (150 Hz) pulse wave twice a second with a pulse width of 200 μs. The intensity of the current was adjusted by the primipara.Stimulation was supposed to cause a strong sensation of tingling or hitting, but without feeling pain or discomfort.

The electrical stimulation started atthe cervix opening of 4 cm or less and continued until the end of delivery. During the session, the patient could move around the room, jump on a ball or lie down. When using the toilet or shower, the electrostimulator was disconnected, but these breaks were not longer than 30 minutes. During gynaecological examination and cardiotocographic (CTG) recording of the patient, the electrostimulator was turned on.

One-way analysis of variance (ANOVA) was used to comparethe test results. If significant, a post-hoc test Scheffe test was performed. The STATISTICA packagewas used for all analyses.

RESULTS

The characteristics of the studied groups are presented in Table 1.

The mean, standard deviation, and theminimum and maximum of the intensity of painsuffered by primaparas in TENS, water immersion, and control groups, depending on the degree of dilation and during the second stage of labour are shown in Table 2.

In primiparas with 2-finger dilation,the analysis ofpain results indicatedthat there were no statistically significant differences between the group means (Tab. 3). However, the analysis of pain results for 3-finger opening showed significant differences between the means forthe group of women using TENS and for the control group; women using TENS rated their mean pain 1 unit lower than women from the control group (Tab. 4). When comparing pain at 4-finger opening, statistically significant differences were found between the group subject to immersion and both the control and TENS groups (Tab. 5). The mean rate indicated by thepatients from the control group was 8.72, that for TENS was 7.76 while the mean for patients giving birth in water was 6.71 (Tab. 6).

Table 2. Characteristics of the pain intensity in primiparas at particular stages of delivery

Pain during:	Opening at 2 fingers	Opening at 3 fingers	Opening at 4 fingers	In the second stage of labour
$\tilde{\chi}$ TENS	4.16	5.62	7.76	8.13
$\tilde{\chi}$ immersion	3.92	6.03	6.71	7.11
$\tilde{\chi}$ control	4.78	6.72	8.72	7.34
Min TENS	0	1	2	2
Min immersion	0	4	4	2
Min control	2	3	4	2
Max TENS	10	10	10	10
Max immersion	9	10	10	10
Max control	9	10	10	10
SD TENS	2.13	1.85	1.88	2.22
SD immersion	1.98	1.68	1.54	2.13
SD	1.74	1.82	1.61	2.44

TENS — Transcutaneous Electrical Nerve Stimulation; SD — standard deviation

Pain assessment for the second stage of labour showed no statistically significant differences between the groups (Tab. 2).

DISCUSSION

One of the basic purposesof the current study was to determine the degree of pain reduction as a result of applying TENS stimulation or water immersion relative to the patients in the control group, and with each other.

Birth pain, as previously shown, depends on many factors, both physical and mental [2]. Bączyk et al. [7], basedon their own research, stated that women were most afraid of their health, the health of their babies, and well-being after delivery. However, the main source of fear was severe birth pain (93.8% of respondents).

Pain assessment is also very difficult. It depends on the patient's mental characteristics and tends to be very subjective. It is not possible to objectify the pain assessment. Furthermore, pain relief, despite standardised methods, often does not give the same results to all patients. Various differences between sufferers and theirmental attitudes significantly affect the level of perception of pain [8]. Due to the nature of the currentstudy, a simple and quick method of assessing pain, namely the numerical scale in combination with a descriptive scale was used. Some other researchers also used a similar pain assessment [9–12].

The effectiveness of non-pharmacological methods of reducing pain during labour is less than for pharmacological methods. However, the fact that non-pharmacological methods of decreasing labour pain do not have negative consequences for both the baby and the mother during and after delivery, should be considered. They offer an alternative forpeople who do not want, or cannot take advantage of, pharma-

Table 3. Scheffe Test. Pain when opening at 2 fingers in the primiparas

	Group	{1}	{2}	{3}
1	TENS		0.865352	0.395329
2	Immersion	0.865352		0.198050
3	Control	0.395329	0.198050	

Table 4. Scheffe Test. Pain when opening at 3 fingers in the primiparas

	Group	{1}	{2}	{3}
1	TENS		0.592291	0.033004*
2	Immersion	0.592291		0.275860
3	Control	0.033004*	0.275860	

Table 5. Scheffe Test. Pain when opening at 4 fingers in the primiparas

	Group	{1}	{2}	{3}
1	TENS		0.023446*	0.054149
2	Immersion	0.023446*		0.000018*
3	Control	0.054149	0.000018*	

Table 6. Scheffe Test. Assessment of pain in the second stage of labor in primiparas

	Group	{1}	{2}	{3}
1	TENS		0.122520	0.321773
2	Immersion	0.122520		0.907570
3	Control	0.321773	0.907570	

cological agents. It is also important to educate woman about non-pharmacological pain relief methods in labour to help them to decide howtheir delivery should proceed [13].

Research on the effect of TENS stimulation applied during labour has been going on since 1977 [14, 15]. Since then, researchers have proposed several different methods for arranging electrodes on the body of a woman giving birth. Some authors recommend placing four electrodes from the very beginning of delivery until the end [14, 16]. One paper gave an example of 1 pair of electrodes that was placed between Th10 and S2 [9]. Our own study showed a statistically significant difference in pain at cervix dilation of 3 fingers, when women who used TENS during childbirth rated pain as less than those in the control group. There were no differences in the assessment of pain between TENS and control groups in the second period of delivery. Other studies also indicated a significant reduction in labour pain [11].

The most likely reason for this is the inadequate methodology of the procedure in the second period. It is consistent with the theoretical assumptions but does not work in practice. To obtain the full effect of the current you must constantly feel the maximum, painless tingling or shock caused by electrostimulation. When delivering, women often forget to adjust the current and change programs. Therefore, during the second period of labour, it seems practical to set the electrostimulator on a conventional program and set the maximum unbearable current and maintain it throughout the whole course of the second period of labour. Changing-programs of the device unnecessarily distracts women from the tasks they must perform when pushing.

Some of the delivering women noticedthat using the electrostimulator distracted their attention from pain and helped them concentrate on breathing.

Perhaps the lack of knowledge about TENS, as well as its unreliability, increases the stress of being in hospital and giving birth to the first child. The need for additional research in this field is worth noting.

Our research shows that the use of water immersion reduces labour pain during dilation of 4 fingers.

Water immersion is not offered in all hospitals, because of the lack of a bathtub. Often, only a shower is available, which does not give exactly the same effects as water immersion. Relaxation in the shower is also often limited by the number of showers available in delivery rooms.

In futurethe positive effect of water immersion should be considered in designing delivery rooms andsupplying the delivery rooms with bathtubs. TENS stimulation is shown to have a similar effect to water immersion. Both non-pharmacological methods significantly reduce labour pain [13]. However, there are many advantages of using TENS stimulation. It is a simple, non-invasive, non-pharmacological, inexpensive, free of side effects method which gives satisfaction in useand can be used during delivery [12]. Its beneficial effects are maintained throughout labour. A particularly important advantage is the possibility of using electrostimulation from the very beginning of delivery, when the woman is still at home. In the case of water immersion, the analgesic effect is mainly apparentduring the immersion. In addition, the size of the electrostimulator allows it to be used in even the smallest delivery room and it can be operated by the patient. Considering the above arguments, it may be necessary to consider increasing the popularity of transcutaneous electrical nerve stimulation in delivery rooms.

CONCLUSIONS

TENS stimulation and water immersion are good methods for dealing with labour pain and are especially helpful during the first period of labour.

TENS stimulation and water immersion are alternative, non-pharmacological methods for reducing labour pain, safe for both mother and child.

Thanks to TENS stimulation and water immersion, primiparas can have less painful childbirth.

Acknowledgemnets

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Conflict of interest

None.

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Fresh insight into premature ovarian insufficiency

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ABSTRACT

Premature ovarian insufficiency (POI) is one of the vital reasons of anovulatory infertility among women under 40 years old. However, because of the unacknowledged causative factor in most cases, it still remains a huge challenge in gynecology. Recently, the most promising opportunities in diagnosing are connected with the use of some serum biomarkers, such as interleukin-17 (IL-17), Frizzled-5 protein, Soggy-1 protein and other cytokines. Additionally, environmental toxicants such as chemicals and heavy metals might be relevant in the near future when investigating the causes of premature ovarian insufficiency. One of the main aims of the therapy is to focus on maintaining fertility among women with POI, since it is essential for patients considering their young age. Among the newest approaches listed there are different types of stem cells, oocytes donation and in-vitro activation, all of which are recently gaining in importance.

Key words: premature ovarian insufficiency; premature ovarian failure; menopause; cytokines; hormone replacemet therapy; infertility; oncofertility

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INTRODUCTION

Premature ovarian insufficiency (POI) is defined as cessation of menstruation before the age of 40. Principal symptoms include increased levels of follicle stimulating hormone (FSH) and primary or secondary amenorrhea/oligomennorhea prior to the age of 40. Thus, the condition leads to a hypoestrogenism and decline of residual ovarian follicles [1].

Premature ovarian insufficiency was originally known as premature ovarian failure or premature menopause, but these terms are considered as stigmatizing and suggesting irreversible infertility. In the guidelines of European Society of Human Reproduction and Embryology (ESHRE) from 2015 regarding this issue "premature ovarian insufficiency" was proposed [1]. The following paper includes a literature review of most recent studies published in English in Pubmed/MEDLINE database from January 2014 to December 2020 regarding POI.

EPIDEMIOLOGY

The prevalence of premature ovarian insufficiency in adults under 40 years old is estimated at approximately 1.1% of women [2]. Results of cross-sectional multi-ethnic research show that incidence varies depending on ethnicity and is higher among women from Africa and Latin America [1]. The prevalence of POI in Sweden is 1.9% (90% of cases are non-iatrogenic), whereas in China it is 2.75% [1, 3]. The study conducted in Israel states that the incidence rate of new POI diagnoses per 100,000 person/year doubled (4.5 vs 2.0) during the years 2009–2016, compared with 2000–2008, which may explain the difference in prevalence between past and up-to-date studies [4].

ETIOLOGY

The etiology of premature ovarian insufficiency is abundant. However, the causative factor in most cases of the syndrome still remains unknown. Chromosomal and genetic defects can cause POI, including chromosome X defects, fragile-X syndrome, and autosomal monogenic and oligogenic defects. POI may be also associated with autoimmune disorders or infections or have an iatrogenic cause, including surgery, radiotherapy, or chemotherapy. Environmental impact is included in causative factors of POI as well [5, 6]. Incidence rates of idiopathic POI have increased by 2.6-fold and other etiologies by 3.0-fold, while the incidence of genetic disorders such as Turner's syndrome remained constant during the years 2009–2016, compared with 2000–2008 [4].

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Genetic causes

Chromosomal abnormalities and defects can be causation of POI, their frequency is approximately 10–13% [7]. Chromosome X aneuploidies including: Turner syndrome (45,XX), mosaic forms (45,X/46,XX and 45,X/47,XXX), trisomy X (47,XXX), X-deletions, X-autosomal translocations may lead to premature ovarian insufficiency. Another rearrangement is CGG repeat in the 5′ regulatory region of the FMR1 gene, which causes Fragile-X Syndrome [6]. The premutation of FMR1 gene should be investigated in women suffering from POI, because approximately 20–30% carriers of this expansion will develop fragile X-associated POI [6, 8]. What is more, the region from Xq13.3 to Xq27 has been shown to be a critical for normal ovarian function [POI1 (Xq23–Xq27) and POI2 (Xq13–Xq21)], therefore balanced X-autosome translocations or harboring point mutations in this region have been associated with POI [6].

Due to an expansion of Next Generation Sequencing (NGS), allowing to evaluate numerical changes or genetic defects, there are found many novel genes causing non-syndromic POI, that are summarized in Table 1. There are multiple studies on novel genes associated with premature ovarian insufficiency, however most of them are performed on small sample sizes and restricted to a single ethnic group or even single pedigree line. The cytogenetic, cytogenomic (array comparative genomic hybridization) and exome sequencing approaches have revealed a genetic causation in ~20–25% of POI cases [7].

Summing up, chromosomal analysis should be performed in all patients with non-iatrogenic Premature Ovarian Insufficiency, but autosomal genetic testing is not indicated in women with POI, unless there is an evidence suggesting a specific mutation [5].

Table 1. Selection of the novel genes involved in non-syndromic POI etiology classified into groups according to their functions

Genes	Mechanism	References
NANOS3, EIF4ENIF1, NOTCH2	Germ cell development	[6]
FSHR, LHCG, GJA4	Oogenesis and folliculogenesis	[6]
NR5A1, STAR, ALOX12B	Steroidogenesis	[6, 10]
BMP15, BMPR2, BMPR1A, BMPR1B, GDF9, SOHLH1, SOHLH2, FIGLA, LHX8, NOBOX, ATG7, ATG9A POLR3A, POLR3B	Hormone signaling	[6, 7, 11]
MSH4, MSH5, SPIDR, FANCM, FANCL, BNC1, WDR62, BRCA2, TP63, MCM8, MCM9, STAG3, PSMC3IP, HFM1, NUP107, SYCE1, SYCP2L	Meiosis and DNA repair	[6, 7, 9, 12]
POLR2C, MRPS22	Metabolism and protein synthesis	[6]

Autoimmune causes

Evidence for an autoimmune etiology is based on the presence of lymphocytic oophoritis, association with other autoimmune disorders, and autoantibodies to ovarian antigens. Isolated lymphocytic oophoritis in POI is rare, occurring only in three percent of patients. Autoimmune oophoritis is characterized by cellular infiltration of the theca cells of growing follicles by macrophages, natural killer cells, T-lymphocytes, plasma cells, and B-lymphocytes. The prime target of the autoimmune attack is the steroid-producing cells, without damaging the primordial and primary follicles.

Approximately 20% of patients with POI have been already diagnosed with other concomitant autoimmune endocrine diseases like autoimmune thyroid disease (Grave's and Hashimoto's disease), Addison's disease, hypoparathyroidism, hypophysitis, diabetes mellitus type 1 and non-endocrine disorders including chronic candidiasis, idiopathic thrombocytopenic purpura, vitiligo, alopecia, autoimmune hemolytic anemia, pernicious anemia, systemic lupus erythematosus, myasthenia gravis, rheumatoid arthritis, Sjögren's syndrome, primary biliary cirrhosis, chronic active hepatitis, celiac disease and Crohn's disease. Up to 40–50% of the patients with POI are positive for at least one organ-specific autoantibody [13].

Addison's disease and autoimmune polyendocrine syndrome (APS) type II are known as clinically important factors predisposing to ovarian disorders, therefore affected women should be counseled and screened for POI [5]. APS type II consists of primary adrenal insufficiency, diabetes mellitus type 1, autoimmune thyroid disease, celiac disease and myasthenia gravis [13]. POI of adrenal autoimmune origin is the most frequent type observed in 60 to 80% of patients with autoimmune cause of ovarian insufficiency.

Screening for 21-hydroxylase autoantibodies (21OH-Ab) or adrenocortical antibodies (ACA) is recommended in women with POI of an unknown cause or if an autoimmune disorder is suspected [5].

Thyroid autoimmunity is the most prevalent (25–60%) associated endocrine autoimmune disorder reported in patients with POI when adrenal autoimmunity is absent [13]. Although untreated hypothyroidism is not life threatening, it can have severe impact on the fetal neurocognitive development in case of pregnancy. Therefore, according to ESHRE guidelines, screening for thyroid antibodies (TPO-Ab) should be performed in women with POI. In patients with a positive TPO-Ab test, thyroid-stimulating hormone (TSH) should be measured every year [5].

Iatrogenic causes

Chemotherapy affects the granulosa and theca cells of the ovary more than the oocytes. However, the effect of the chemotherapy depends on the drug (Tab. 2), dose, and the age of the patient [14]. Women under 40 years old develop amenorrhea with high serum gonadotropin concentrations during chemotherapy, but menstruation and fertility may return several months to years after the cessation of the chemotherapy [5, 14].

Unlike cytotoxic therapies, oocytes and ovarian stroma are remarkably sensitive to radiation therapy. Ovarian damage also depends on the dose and on the patient's age. In some studies on the dose of radiation that would cause ovarian insufficiency in 97.5% of patients, the required dose at birth was 20.3 Gy, at 10 years old — 18.4 Gy, at 20 years old — 16.5 Gy and at 30 years old — 14.3 Gy. All radiation treatments to the pelvic area will likely result in irreversible ovarian damage [15].

Table 2. Chemotherapeutic drugs divided into groups according to their impact on ovarian insufficiency [14]

Permanent hypogonadism	nitrogen mustard, L-phenylalanine mustard, chlorambucil, cyclophosphamide, melphalan, busulfan, procarbazine, dacarbazine
Likely ovarian damage	vinblastine, cytosine arabinoside, cis-platinum, carmustine, lomustine, etoposide, imatinib
Small or hardly any impact	methotrexate, 5-fluorouracil, 6-mercaptopurine, vincristine, mitomycin

Environmental causes

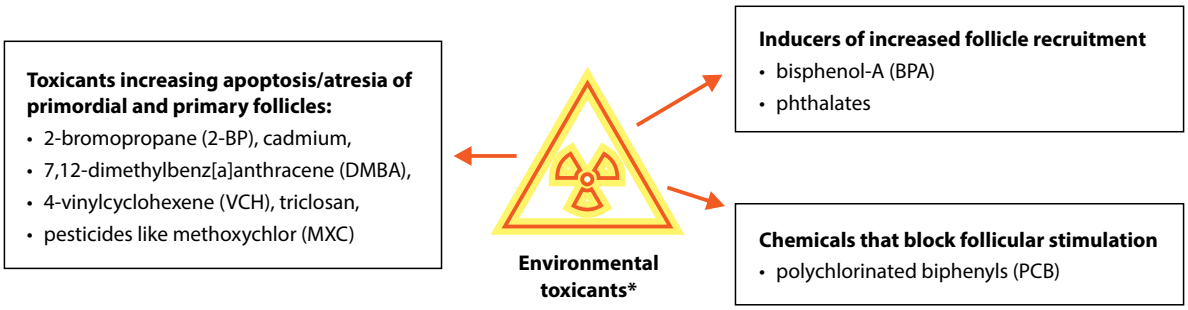
Some studies and meta-analysis indicate an association between POI and environmental toxicants [5, 16]. Environmental causative factors are presented in Figure 1.

DIAGNOSTICS

Clinical features and diagnostic criteria

Diagnostic criteria to establish the diagnosis of the premature ovarian insufficiency are based on both presence of menstrual disturbances and biochemical assessments. It applies to women who are less than 40 years old, including patients older than 40 years, but with symptoms onset before the age of 40.

Therefore, premature ovarian insufficiency should always be excluded in women before 40 with oligomenorrhea/amenorrhea of more than four months duration or estrogen-deficiency symptoms. Primarily, levels of follicle-stimulating hormone (FSH) in serum should be evaluated. The latest recommendations of ESHRE and Polish Society of Reproductive Medicine and Embryology (PTMRiE) proclaim that levels of more than 25 IU/L, obtained twice at



Smoking, alcohol, nutrition, and exposure to **endocrine disruptors** have been also implicated as influencing the earlier menopause but are not yet established as causes of POI [5].

*For most agents, only experimental data are currently available [16]

Figure 1. Environmental causative factors divided into groups by the mechanism of the ovarian damage

Table 3. Proteins candidates for serum biomarkers of POI [20, 23–25]

Protein	Serum levels in POI patients compared to healthy control group	Characteristic
Interleukin 17 signaling family IL-17F IL-17R IL-17C	↓	Prognostic factor in ovarian cancer connected with better prognosis
Interferon gamma receptor 1 (IFN-γ R1)	↓	Prognostic factor in ovarian cancer
Interleukin 29	↓	Involved in autoimmune response
Neurturin	↓	Follicle maturation and ovulation
Frizzled-5	↓	Receptor for Wnt5a protein - FSH inhibitor
Soggy-1	↓	Impacts testicular development and spermatogenesis, but there is poor evidence for role in female fertility
Heparin Cofactor II (Serpin D1)	↓	Coagulation factor and a cofactor for heparin and dermatan sulfate
Matrix-metalloproteinase -7 (MMP-7)	↓	Involved in the breakdown of extracellular matrix during ovulation and menstruation
Intercellular Adhesion Molecule 3 (ICAM3)	↓	Plays role in cell adhesion, phagocytosis and immune response regulation
Afamin	↑	Marker for oxidative stress

least four weeks apart, indicate POI [5, 17]. Whereas according to previous recommendations the FSH level needed to be greater than 40 IU/L. Anti-Mullerian Hormone (AMH) is an important indicator of diminished ovarian reserve, however, it is not used to establish the diagnosis. Nonetheless, in the absence of those symptoms, the change in regular menstruation in every case should be a reason to do the diagnostic work-up [18, 19].

Besides the fact clinicians should enquire about symptoms of estrogen deficiency. Additionally, radiotherapy, surgical interventions on ovaries and cigarette smoking should always raise the doctor's vigilance. Thus, conscientious inquiry into patients' medical history seems to be crucial. Once the diagnosis is established, further assessments need to be done to find a potential cause of the disease.

Serum biomarkers

The most promising opportunities are connected with the diagnostic use of a serum biomarkers. Jian Liu et al. (2020) suggested that there are many proteins which take part in pathogenesis of premature ovarian insufficiency and may constitute novel biomarkers of this condition [23]. Serum specific POI proteins profile in patients with POI, healthy fertile women and menopausal women were compared. Interestingly, in each group the array profile of twelve biomarkers was different (Tab. 3).

The level of cytokines from interleukin 17 (IL-17) signaling family (IL-17F, IL-17R, IL-17C) was lower in the serum of POI patients compared to healthy control group. They are involved not only in immune response, but they are also a crucial part of development of cancers. Elevated level of IL-17 in ovarian cancer is connected with better prognosis, so decreased level in patients with POI can suggest ovarian disease. Another protein, which is a prognostic factor in ovarian cancer is a receptor of Interferon gamma (IFN-γ), IFN-γ R1. Its level was also decreased in POI. Overexpression of a dominant-negative mutant of IFN-γ R1 lead to a decline in immunogenicity in animal studies and the same mechanism could appear in patient suffering from POI. Downregulation of interleukin 29 (Il-29) may be involved in autoimmune response [23].

Decreased level of neurturin protein could be connected with problems with follicle maturation or ovulation, as it is involved in these processes [23].

Furthermore, in POI serum the level of Frizzled-5 protein was decreased. Frizzled-5 is a receptor for Wnt5a protein. Abedini et al. (2016) [24] emphasized the influence of Wnt5a on women's fertility, because of suppression gonadotropin signaling. Furthermore, Liu et al. [20] suggested that Wnt5a may inhibit FSH due to interaction with its receptor. A decline in amount of Frizzled-5, a receptor for Wnt5a, increases the level of FSH.

There is no evidence that Soggy-1 have a role in female fertility, but there are studies about its impact on testicular development and spermatogenesis, and thus also male fertility. Level of the Soggy-1 protein decreased in women with POI. The results of clinical trial have shown that the level of the Serpin D1 protein, MMP-7 enzyme, Intercellular Adhesion Molecule 3 (ICAM-3) was lower in the serum of POI patients when compared with healthy control group [23, 26].

Interestingly, afamin protein was the only one marker, which increased in women with POI. Elevated level of afamin occur not only in POI but also in oxidative stress [23].

The clinical trials conducted by Liu et al. have identified several potential premature ovarian insufficiency biomarkers, which can have greater diagnostic value and applicability in clinical practice. Diagnosis of POI based on the detection of genetic abbreviation is extremely expensive and complicated, so these results of papers are promising and give us hope for easier diagnosis. However, Liu et al. [20] emphasize that further studies are needed to confirm their result, because it was the first study, which suggested this association and other studies proving their result should be conducted.

TREATMENT

Hormone replacement therapy

The British Menopause Society and Women's Health Concern, ESHRE and the American College of Obstetricians and Gynecologists (ACOG) indicate that management of POI should include sex steroid replacement (per os or transdermal)–hormone replacement therapy (HRT) or a combined hormonal contraceptive until the average age of natural menopause is reached, unless they are contraindicated. HRT and combined oral contraceptives are offered to women with POI to decrease risk of breast cancer, cognitive decline, dementia and cardiovascular diseases, to prevent osteoporosis, urogenital atrophy and to improve the quality of a patient's life. Achieving the physiological level of estradiol is the aim of the HRT. Although the frequency of spontaneous pregnancy in women with POI is low and ranges from 5 to 10%, patients should be advised that the HRT is not any contraceptive. For patients avoiding pregnancy combined hormonal contraceptives are more favorable instead of HRT. Levonorgestrel intrauterine device insertion is recommended for women who want highly effective contraception concurrently preferring some non-contraceptive HRT [21, 22, 27].

17β-estradiol, ethinyl estradiol and conjugated equine estrogens can be used in the therapy. However, estradiol is preferred to ethinyl estradiol or conjugated equine estrogens considering bone health and cardiovascular health in women with POI. The delivery of progestogen is required unless the uterus is absent. Oral cyclical micronized natural progesterone is related to the lowest risk of cardiovascular disorders and breast cancer with the endometrial protection compared to the synthetic progestogens [21, 23]. Route of administration depends on the patient›s preferences, however if specific risk factors are present, the transdermal route is preferred [5]. Continuous estrogen replacement is recommended to avoid hypoestrogenism's symptoms. However, cyclical regimens that stimulate active functioning of the endometrium are required for patients desiring pregnancy by oocyte donation, despite the slightly higher risk of the endometrial hyperplasia and carcinoma [22].

Appropriate management of reduced bone mineral density in POI consists of HRT, calcium and/or vitamin D supplementation for women with inadequate vitamin D status and/or calcium intake. Bisphosphonates are not the first-line therapy in women with primary ovarian insufficiency [22, 27].

Hypertension, migraine with aura, history of prior venous thromboembolism (VTE), obesity, Turner's syndrome, BRCA1/BRCA2 mutation (without a history of breast cancer after prophylactic bilateral salpingooophorectomy) and fibroids are not contraindications to the HRT, however transdermal delivery of estradiol is preferred. Women with the VTE or thrombophilic disorders should be referred to a hematologist before the HRT prescription.

Hormone replacement therapy is absolutely contraindicated for breast cancer survivors [21, 27]

If there are any contraindications for hormonal treatment, patient should be provided with management of hypoestrogenism's symptoms, cardiovascular diseases prevention and bone protection [21].

Androgen treatment could be also put into consideration for women with POI, however there are limited studies on long-term effects. Androgen replacement therapy is suggested for indications such as memory disorders, neurological complaints, diminished sexual functions and decreased bone density. Evaluation of the therapy is recommended after 2–3 months. Route of administration is similar to the treatment with estrogen and progesterone — depending on the patient's preferences [27].

Non-hormonal therapy

Cessation of smoking, moderate alcohol intake, balanced diet, maintaining healthy body weight and regular weight-bearing exercises are recommended for the prevention and the therapy of some POI sequelae, especially osteoporosis and cardiovascular disorders [27].

Stem cells therapy is considered to be effective in POI and infertility due to their self-renewal and regeneration potential. There are different types of stem cells used in premature ovarian insufficiency therapy such as mesenchymal stem cells, stem cells from extra-embryonic tissues, induced pluripotent stem cells and ovarian stem cells. Many studies confirmed that stem cell transplants in mice with POI cause a production of ovules and may treat the POI-related infertility [25]. Another approach to the treatment of POI includes the oocytes donation and in vitro activation [29].

Since the diagnosis of POI has a negative impact on emotional and psychological wellbeing, the discussion with the patient is recommended to identify the need for ap-

propriate psychological support and counseling or other types of therapy provided either on a group or individual basis [21, 27].

FERTILITY AND PREGNANCY

One of the principal outcomes of premature ovarian insufficiency are fertility problems. There is a small chance of spontaneous pregnancy. Bidet et al. (2011) revealed that 25% of examined women with idiopathic POI presented features, which indicate resumption of ovarian function. However, pregnancy occurred in only 4.4% cases [26, 27].

Hitherto the solution recommended is *in vitro* fertilization and embryo transfer (IVF-ET) with the use of donor eggs. Frequently, near relatives donate oocytes, though it may be donated also from unknown donors. However, in group of oocyte donation pregnancies are at high risk of obstetric complications e.g., there is a high prevalence of miscarriage (40%), in cases of single gestational sac [28].

In vitro activation (IVA) is a novel method, which enables patients suffered from POI to activation of their residual dormant follicles. Procedure of IVA consist of ovarian cryopreservation, therapy of PTEN (phosphatase and tensin homolog) inhibitor and PI3K (phosphatidylinositol-3-kinase) activator and followed auto-transplantation [28].

The procedure begins with ovariectomy of one or both ovaries, then medulla of ovary is cut into strips. Histological analysis is performed to detect residual follicles. If researcher finds any, the analysis is terminated. Therefore, ovarian strips are fragmented into cubes and treated with a PTEN enzyme inhibitor or a PI3 K stimulator. Next step is the transplantation of ovarian cubes beneath the serosa of one or both Fallopian tubes, this procedure is performed under laparoscopic surgery. This site was chosen, because of high vascularization and convenient monitoring by transvaginal ultrasound and ease for oocyte retrieval for IVF-ET. When preovulatory stage is reached by antral follicles IVF is done [28, 29].

The results of studies by Kawamura [28] and Suzuki [29] consist of 37 women, but histological analysis revealed that only 20 of them had residual follicles. Follicle growth was noticed in about 50% of patients with residual follicles. In some cases, preovulatory stage are detected after six months or longer. IVF and following IVF-ET was done in four patients, but pregnancies were detected in three patients. The outcomes were one miscarriage and two successful deliveries. Endometriosis as a side effect of IVA was detected more frequently in patients with residual follicles and follicle growth.

Suzuki [29] suggested that histological analyses are a better prognosis parameter for predicting *in vitro* activation success than serum AMH levels. Their results suggest that high level of serum AMH is associated with a better IVA outcome. However, some patients with undetectable AMH levels responded to in vitro activation treatment.

The results have been promising, but future studies are needed to develop a non-invasive method to predict the presence of residual follicles and due to that avoid ovariectomy in several cases. Procedure of *in vitro* activation could be also a solution for women suffering from other ovarian dysfunction, as well as girls in prepubertal age [28].

Oncofertility is a medical procedure, which aims fertility preservation in women prepared to cancer treatment (radiation or chemotherapy). The choice of appropriate method depends on age of patient, diagnosis and type of treatment. One of the most popular methods is embryo cryopreservation (as a result of in vitro fertilization). This is an appreciated form of preserving fertility, which is gaining popularity, and best if started within 3 days of the onset of cycle. Nevertheless, it is proved that starting the therapy in any moment of the cycle should be equally successful. There is also a possibility to cryopreservation nonfertilized oocytes, recommended in cases, when a patient doesn't have a partner [30, 31].

Ovarian transposition is another method, characterized by surgical repositioning during laparotomy or laparoscopy. It is especially recommended to patients prepared for radiotherapy, because ovaries could be moved well beyond the planned radiation field [30].

CONCLUSIONS

Premature ovarian insufficiency is a condition of wide-ranging etiology that is expanding even more. Nonetheless, most causative factors are still not established. Fresh approaches of management are deliberated considering not only fertility but also patient's sexuality and novel markers related to the development of premature ovarian insufficiency. The most recent studies suggest that there are some cytokines, which may be novel serum biomarkers for POI. However, it must be confirmed in other studies. Expansion of the Next Generation Sequencing contributes to increasing the number of novel genes associated with POI etiology. In the future sequencing techniques are expected to enable discovering new genetic causes of premature ovarian insufficiency. However, genetic studies should be performed on bigger samples of patients and on different ethnic groups. Currently most studies on novel genes apply only to specific ethnic groups. Therefore, doctors should be aware during counselling patients that some data about genetic causes of POI could be obtained from another ethnic group. Fertility problems are of the most serious difficulties for women with POI. Several approved methods of fertility preservation are available to the patients. However, further research on experimental methods (e.g., *in vitro* activation) is in progress.

Conflict of interest

The authors declare no conflict of interest.

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The role of anti-Müllerian Hormone (AMH) in girls and adolescents

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ABSTRACT

Anti-mullerian hormone (AMH) is produced by the granular cells of primary, preantral and antral follicles. The circulating levels of AMH in adult women reflect the number of remaining primordial follicles. AMH determination plays an increasingly important role in diagnostics in endocrinology and gynecology in adult women. Although the determination of AMH levels is used in pediatric practice, still little is known about its role in various pubertal disorders in girls. This article presents the clinical use of AMH in girls and adolescents.

Key words: Anti-Müllerian Hormone; AMH; adolescents; puberty

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INTRODUCTION

Anti-Müllerian Hormone (AMH), also known as the factor that inhibits the development of the Müllerian ducts, is a dimeric glycoprotein that belongs to the family of transforming growth factors β (TGFβ family) [1, 2], which has been predominantly known for its role in male sexual differentiation. The gene encoding AMH in humans is located on chromosome 19 p13.3 and it contains five exons. The gene for the AMH receptor type 2 is located on chromosome 12p13. The biological action of AMH depends on binding to the specific AMH type II receptor (AMH-RII), which expression has been demonstrated in the mesenchymal cells surrounding the Müller ducts, in testes (Sertoli and Leydig cells), and in granular and TEIC cells of the ovary. The receptor is a single transmembrane protein with serine- threonine kinase activity [2]. AMH expression and secretion are inhibited by androgens and estrogens, and in the situation of their deficiency or receptor defect also by gonadotrophins [1, 2].

Until about the fifth week of pregnancy (in the non-sexually differentiated phase), both sexes have buds of both male and female genital structures, Wolff tubes and Müller tubes. In Y chromosome fetuses carrying the SRY gene, around seven weeks of gestation, testes begin to develop, and then Sertoli cells begin to secrete AMH, which causes the Müllerian ducts to overgrow. Leydig cells begin to produce testosterone, which is responsible for transforming the Wolff's ducts into epididymis, seminal vesicles, ejaculatory ducts, and the abdominal part of the prostate. The external male genitalia develop under the influence of dihydrotestosterone (DHT) [3, 4]. The maximum production of this hormone is observed between 12 and 16 weeks of gestation, which persists at a high level until reaching sexual maturity, then it significantly decreases in adult men [2]. In female fetuses, the lack of the SRY gene and the lack of AMH secretion determine the differentiation of the Müllerian ducts, the atrophy of the Wolff ducts and the development of the female genital organs in the fetus. The Müllerian ducts properly develop into the fallopian tubes, uterus, cervix and the upper part of the vagina [3, 5]. In female fetuses, the production of AMH does not start until around 36 weeks of gestation, which is much later than the period of Mullerian duct sensitivity to AMH.

AMH is produced by the granular cells of primary, preantral, and early antral follicles. The highest concentration of AMH is shown by small antral follicles (2–4 mm in diameter). Even though the concentration of AMH in the blood is much lower than the concentration in the follicle, it correlates very well with it, which relates to usefulness in practice [6].

The role of AMH in adult women

AMH determination can be performed regardless of the phase of the menstrual cycle and the use of hormonal

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contraception. AMH determination plays an increasingly important role in diagnostics in endocrinology and gynecology in adult women [2, 4, 7–10]. With age, the number of ovarian follicles in a woman decreases, which translates into a decrease in AMH concentration in the blood (up to undetectable values after menopause), so the level of AMH reflects the aging process of the ovary [4]. Therefore, AMH is considered one of the best indicators of ovarian reserve, and therefore it is also considered a marker of the assessment of a woman's reproductive potential [7, 9]. Reduced AMH concentrations are observed not only in the physiological aging of the ovary, but also in the premature ovarian failure (POF) [11]. There are also reports on the usefulness of monitoring AMH levels in predicting the age at which a woman will reach menopause [11]. Currently, many studies on the concentration of AMH concern its role in polycystic ovary syndrome (PCOS). The concentration of AMH was 2–3 times higher in women suffering from PCOS than in women with ovaries with a normal number of follicles [10, 11]. Research shows that AMH may also be a marker of hyperandrogenism in PCOS [10]. According to some reports, the concentration of AMH may also be useful in predicting the return of ovulatory cycles in obese women with PCOS after weight loss [2]. Although there is currently no clearly defined upper cut-off point of the AMH level, it is postulated to include this test in PCOS diagnostics.

Moreover, AMH may be a useful marker of granulosa-cell tumors (folliculoma) and their recurrence. In these clinical situations, AMH levels can be very high and correlate with tumor size [11].

The role of AMH in girls

After birth, in female infants, blood levels of AMH are very low (lower than in male fetuses), even undetectable. Research on the changes in AMH levels in the early stages of puberty is quite limited and reports remain inconsistent. A few studies AMH levels rise during infancy and they are stable from childhood Hagen et al. conducted a study in which they tried to determine the individual concentration of AMH in each of the examined girls. They found that circulating AMH shows only slight fluctuations during childhood and adolescence, and a random measurement of AMH appears to be representative. The negative AMH-FSH correlation in pre-pubertal girls supported the statement that AMH is a quantitative marker of ovarian follicles even in young girls. The mean AMH levels ranged between 5 and 54 pmol/L. 10 girls had a mean AMH level below the cut-off of 8 pmol/L, of which four had not yet entered puberty. However, the relationship between the AMH level and the period since menarche has not been assessed [12, 13]. A later study by Hagen et al. shows that three years before the onset of puberty, AMH increases, while within two years after the beginning of puberty, AMH decreases by 30% [14].

The increased concentration of circulating AMH in the pre-pubertal period allowed for the recognition of the hormone as a marker of ovarian follicle growth because its growth occurs in the period when the hypothalamic-pituitary-ovary axis is still inactive [15]. Some statistical models suggest that the highest rate of recruitment of nongrowing follicles takes place between birth and 14 years of age which is an age of menarche in most girls [16].

Precocious puberty

The concentration of AMH may be a marker of the onset as well as the progression of sexual maturation in girls. Chen et al., in their study which comprised 83 girls with diagnosed central precocious puberty (CPP), found out that AMH and inhibin levels are potential biomarkers for distinguishing various progression rates in girls with CPP and they can assist in the distinction of progressive CPP and slowly progressive CPP at the time of diagnosis [17]. Also, Lashen et al. support the thesis that the rise of AMH and inhibin B levels in prepubertal childhood may suggest the onset of central puberty [16]. Xue et al., in their study about AMH use in precocious puberty progression conclude, that although AMH may not be a good indicator for early diagnosis, it has significance in the auxiliary diagnosis, differential diagnosis, treatment and prognosis of sexual puberty disorders in children [18].

PCOS

AMH levels in adolescents have been also proved to have a clinical impact in young patients with PCOS. Kim et al. states that AMH may be a useful biomarker for the diagnosis of PCOS in obese girls, as AMH concentrations are twice higher in obese PCOS girls and correlate with hyperandrogenemia with the cut-ff point of 6.26 ng/mL [19]. Efthymiadou et al. proved that girls with premature adrenarche, especially those from mother with a history of PCOS, could have a higher risk of developing PCOS later in life, because they have increased serum AMH [20].

Premature ovarian insufficiency

Low or even undetectable level of AMH is a good marker of premature ovarian insufficiency (POI) in girls. At young age, POI occurs mostly in girls with Turner Syndrome and in girls receiving gonadotoxic treatment [21].

Granulosa cell tumors

Although only a few percent of folliculomas are seen in girls in adolescents, we cannot forget about this pathology. Granulosa cell tumors may present as precocious puberty. High (masculine) levels of AMH in girls should be considered

a manifestation of ovarian pathology, however, we should not exclude ovarian tumor in girl with AMH levels within the reference range [21]. As mentioned previously, AMH may be an indicator of tumor recurrence.

Determination of the presence of testicular tissue

AMH concentrations within the male reference range are highly indicative of testicular tissue. Low or undetectable levels of AMH indicate either anorchia or dysgenetic testicular tissue or presence of ovarian tissue. This clinical implication is used when a child is born with bilaterally absent testes or ambiguous genitalia [21].

Other pathologies

Codner et al. conducted the study, which showed that AMH levels are increased in girls with type 1 diabetes (T1D) during childhood and decrease during puberty, which suggests, that T1D modulates ovarian follicle growth differently once gonadotrophin levels rise. What is more, Codner et al. suggest, that girls with T1D exhibit similar endocrine findings to other groups at increased risk of developing PCOS [13].

Even though the literature provides information on the use of AMH in the diagnosis of many of the above-mentioned pathologies, the reference values of AMH concentration in prepubertal and postmenarcheal girls are still poorly detailed. The knowledge of AMH norms in girls would enable further research on various types of pathologies occurring in them. AMH could become much more useful in the diagnosis of premature puberty, delayed puberty, thelarche praecox, menarche praecox, and the diagnosis of ovarian tumors in girls.

Conflict of interest

The authors declare no conflict of interest

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Robot-assisted donor hysterectomy in uterus transplantation — a modality to increase reproducibility

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ABSTRACT

Uterus transplantation is a non-lifesaving vascularized composite allotransplantation procedure requiring immunosuppression until removal of the graft. The focus of uterus transplantation is changing regarding refining individual treatment procedures included in this complex treatment of absolute uterine factor infertility, such as robot-assisted donor hysterectomy. The inferior hypogastric nerve plexus should be preserved during robotic dissection of the ureter and uterine vessels to prevent postoperative complications such as urine and fecal evacuation disturbances and sexual disorders. As most uterus transplantations have been performed in living donor concepts, robot-assisted donor hysterectomy should contribute to increased availability of uterus transplantation, particularly because it uses the precise blood-less technique of surgical dissection in the deep pelvis and has cosmetic benefits among living donors.

Key words: robot-assisted surgery; hysterectomy; uterus; transplantation; living donor.

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INTRODUCTION

Absolute uterine factor infertility (AUFI) due to an absent or non-functional uterus has been a long-neglected form of female infertility highlighted at the beginning of the 21st century by Swedish researchers in pioneering studies on animal and human uterine transplantation (UTx) [1, 2]. UTx is a temporary vascularized composite allotransplantation technique requiring immunosuppressive therapy until removal of the graft (after cesarean deliveries or approximately up to five posttransplant years). As adoption and gestational surrogacy are not available in many countries worldwide owing to legal, financial, ethical, religious, and social reasons, UTx could be a solution for infertile women with congenital or acquired AUFI. Although 20 years have passed since the first human UTx attempt in Saudi Arabia [3], and eight years since the onset of the first human living donor UTx study in Sweden [2], the overall number of UTx procedures performed worldwide is still only around 70. Thus, UTx seems to be a low-volume transplant procedure in the future. However, approximately 20 children born from transplanted uteri over the last six years indicate the potential of this infertility treatment.

The focus of UTx research is changing with respect to refining procedures associated with this complex treatment of infertility, such as robot-assisted donor hysterectomy. Minimally invasive surgical approaches using conventional or robot-assisted laparoscopy play an important role in gynecologic surgery, particularly in oncological treatment and surgery for complicated endometriosis. The first ever laparoscopic-assisted retrievals of uterus in two living donors (mothers) and the successful transplantations to recipients (daughters) were performed by Puntambekar et al. in Pune, India in 2017 [4, 5]. Similarly, to conventional laparoscopy performed by skilled surgeon, the technical advantage of robot-assisted surgery is the use of a 3-dimensional camera and instruments that allow for both fine tissue dissection and optimal surgical access to the deep pelvis. Based on the experience with both UTx and oncologic operations in gynecology [6–8], in this article, we discuss robot-assisted donor hysterectomy with regard to minimizing surgical

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morbidity and invasiveness in living donors of the uterus due to the less traumatic dissection of the vascular and other anatomical structures in the retroperitoneal space, particularly concerning the tedious dissection of the uterine veins to isolate them from the firm attachments to paracervical tissue and ureters.

MAIN ASPECTS OF UTERINE GRAFT PROCUREMENT

No serious surgical problems were reported in previous acquisitions of the uterine arteries during living donor hysterectomies using the open approach [2, 6]. This aspect of uterine graft procurement is well known to gynecologists who are specialized in radical hysterectomy, regardless of the abdominal, laparoscopic, or robotic nature of cervical cancer surgery. At the beginning of the uterine graft retrieval, the paravesical and the medial and lateral pararectal spaces are opened after division of the round ligaments. Next, the large flap of the bladder peritoneum is dissected for the fixation of the uterus in the recipient. Thereafter, the bladder is dissected from the cervix and vagina. Dissection of the common and internal iliac arteries up to the area of the obliterated umbilical artery precedes the dissection of the uterine artery between its exit from the internal iliac artery up to the uterine edge. Internal iliac arteries should be preserved in living donors of the uterus to avoid the risk of postoperative gluteal claudication after ligation. To ensure optimal blood inflow to the graft, patches of the internal iliac vessels (or parts of their anterior branches) should be utilized when harvesting the uterine arteries [6, 9, 10].

Pre-procurement insertion of ureteral stents is helpful but optional. The ureter should be dissected up to the parametrial ureteric channel and its inlet into the urinary bladder. During open procurement surgery, the uterine veins are poorly visible without magnifying loupes or a surgical microscope. A skilled surgeon experienced in microsurgical techniques dissects these small veins up to their inlet in the internal iliac vessels. However, dissection of the uterine veins is technically challenging as they may have individual variations and over- and under-ride the ureters. The uterine vein is usually created from two to three veins that come from the uterine body and converge into a common uterine vein or have separate small inlets to the internal iliac vein. Separation of the uterine vein from the vaginal cuff and the ureter between its inlet to the bladder and the crossing with the uterine artery is usually the most time-consuming part of graft procurement. Separation is difficult to perform using both open and robot-assisted surgical techniques, particularly because of the variations in the uterine veins. In contrast, separation of the ovarian veins (or their utero-ovarian segments) that can be utilized for venous outflow from the transplanted uterus is technically less complicated and, as such, usually faster than the complex dissection and retrieval of the uterine veins.

After the uterus is completely mobilized from the adjacent tissues and organs and the uterine vasculature is dissected, the vagina is transected approximately 15 mm caudal to the vaginal vault. Thereafter, the internal iliac vessels are clamped, uterine vessels are divided, and, finally, the uterus is removed from the donor.

THE POTENTIAL ADVANTAGES OF ROBOT--ASSISTED DONOR HYSTERECTOMY

Using open, laparoscopic, and robot-assisted nerve-sparing radical hysterectomies, the hypogastric and pelvic splanchnic nerves as well as the pelvic plexus with vesical branches can be spared [8]. The inferior hypogastric nerve plexus can be preserved during laparoscopic dissection of the ureters, uterine arteries, and utero-sacral ligaments to avoid postoperative complications such as urinary and fecal evacuation disturbances and sexual disorders. This can be also done during laparotomy using surgical loupes. One Czech living uterus donor was found to have prolonged bladder hypotonia immediately after open procurement surgery requiring three months of suprapubic drainage and bladder training to reach normal spontaneous micturition without residual urine [6]. As both laparoscopic and robot-assisted retrieval surgery allows for good visibility of the nerve structures in the deep pelvis like surgical microscope in open surgery, laparoscopic and robot-assisted techniques of nerve-sparing dissection can be used to avoid damage to the above nerve structures.

Most previous open uterus retrievals were performed with minimal tissue trauma and without endangering the adjacent anatomical structures in the parametria. However, both robot-assisted and conventional laparoscopic procurement performed by an experienced surgeon might simplify the dissection of the uterine vessels between the internal iliac vessels and uterine edges as well as the dissection of the ureters. Both approaches show the same results. The laparoscopic dissection of the connective tissues, vessels, and ureters in the deep pelvis is safer than the laparotomy approach when performed by skilled surgeons trained in minimally invasive operative techniques, particularly because of the excessive use of diathermy dissection in the retroperitoneal space when performing open procurement surgeries [2, 6].

In addition to the above advantages of the laparoscopic approach, the comfort of the surgeon is an important benefit of the robot-assisted surgery. Comfortable sitting position with appropriate setting of individually coded robotic console is convenient particularly in long procedures such as radical hysterectomy with lymphadenectomy for cervical cancer and procurement of uterus in living donor.

However, robot-assisted surgery has also several limitations, particularly time-consuming setting of robotic surgical system which can be shortened with the number of performed procedures; use of complex instruments that increase the overall cost of UTx; and 3-dimensional visualization that can cause surgeon's discomfort (*e.g.*, headache), especially when using robot-assisted technique daily and not alternating between different surgical approaches on a regular basis.

FULLY ROBOTIC AND COMBINED ROBOTIC/ /OPEN APPROACHES IN ROBOT-ASSISTED DONOR HYSTERECTOMY

As the main purpose of robot-assisted approach is a less traumatic, more precise, and blood-less surgery than conventional methods, fully robot-assisted donor hysterectomy seems to be a better option than the combined option. Moreover, to minimize the burden on living donors, the uterus should be extracted through the vagina in a sterile bag to prevent bacterial contamination, as observed in the first Chinese robot-assisted uterus procurement for the subsequent transplantation in 2015 and five robot-assisted donor surgeries performed recently in the USA [11, 12]. Of course, contusion of the uterus should be avoided when transvaginal removal of the graft is the preferred option. However, a combined robotic/open approach to donor hysterectomy involving robotic dissection of the uterine vessels and mobilization of all vascular and nerve structures in the parametria including ureters followed by the subsequent removal of the uterine graft after conversion to open surgery, as has been performed in 2017–2019 in Sweden, should also be justified, particularly during the learning-curve period [13, 14]. The Swedish robot-assisted retrieval surgeries showed gradually reducing durations throughout the trial. The last operation had the shortest duration, which was still 10 hours. The length of their donor surgeries was based particularly on the study protocol to separate both uterine veins to be prepared for anastomosis to the internal iliac vessels as the main drainage option from the transplanted uterus. The proximal parts of the utero-ovarian veins were harvested to be used only for the salvage outflow when the uterine veins were of poor quality and seemed unusable.

In five fully robotic retrievals of the uterus in the USA, the study protocol required harvesting of the proximal parts of both utero-ovarian veins together with both uterine veins. However, only 5 out of 10 uterine veins were successfully harvested [12]. Moreover, only 2 out of 5 harvested uterine veins were used for the anastomosis to external iliac veins in the recipient, while all 10 utero-ovarian veins were utilized for the graft's venous outflow. While in the Swedish donors of the uterus, both uterine veins were successfully harvested in all eight retrievals, the team from the USA probably had some technical difficulties that led to only 50% success of robotic dissection of the uterine veins. As live birth after UTx without the outflow via utero-ovarian veins has been reported only by the Dallas research team [15], complete surgical as well as reproductive data of further UTx studies with different venous outflows will shed light on the optimal venous drainage from the transplanted uterus.

While the cosmetic reasons for the preference of robot-assisted hysterectomy in living donors of the uterus are obvious, the prevalence of both ureteric lesions in three (23%) and reversible pressure alopecia (very likely due to duration of the surgery) in two donors (15%) out of 13 women who underwent robotic retrievals of the uterus in Sweden and the USA seems relatively high [12,14]. Further experience with robot-assisted retrieval of the uterus for transplantation is required to identify the risk factors associated with urological complications of donor hysterectomy.

CONCLUSION

Moving UTx to the clinical setting requires comprehensive practical guidelines to ensure a high degree of consistency and safety. If the results of the pioneering studies on robot-assisted donor hysterectomy confirm satisfactory surgical and reproductive results, this less-invasive procurement option should become preferable for the majority of living donors of the uterus. However, further research is needed to confirm the applicability and safety of the robot-assisted procurement of the uterus in clinical practice.

Conflict of interest

The authors declare that they have no conflicts of interest regarding the publication of this article.

Contributions of authors

We confirm that all the co-authors have been included, have contributed to the final manuscript, and have approved it. RCjr and RC designed the study, analyzed the data, and wrote the manuscript. ZP and MN designed the study and critically reviewed the manuscript.

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The usefulness of CrystalVue™ technique in the diagnosis of abnormally invasive placenta

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Key words: abnormally invasive placenta; CrystaVue; USG; 3D ultrasound

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Abnormally invasive placenta (AIP) is a clinical term used to describe abnormal adherence of placenta to the underlying myometrium [1]. Prior caesarean section, placenta praevia, assisted reproduction techniques and other uterine surgeries are all risk factors [1, 2]. AIP is associated with a greater risk of maternal and perinatal morbidity and mortality [1]. The diagnosis of AIP is based on ultrasound imaging. Magnetic resonance imaging is used to confirm the diagnosis [3]. The development of imaging techniques has enabled the creation of new technologies such as CrystalVue™ (Samsung's Ultrasound Imaging Technology). It is a technology-based image-contrast enhancement that allows processing and rendering of acquired three-dimensional volumes.

A 36-year-old pregnant woman, 34 weeks with history of previous caesarean delivery, was hospitalized due to vaginal bleeding with suspicion of placenta praevia. Subsequent ultrasound examination was performed after admission to the hospital. The placenta percreta with invasion into the urinary bladder wall was visualized by CrystalVue™ ultrasound reconstruction. Based on ultrasound images taken at the 12th week of pregnancy presented by the patient, the authors hypothesized that the current clinical situation is the result of an undiagnosed early stage of the caesarean scar pregnancy (Fig. 1). Cardiotocography did not show any abnormalities. Laboratory tests reported HGB 8.3 g/dL and HCT 24%, suggesting haemorrhagic anaemia. After antenatal corticosteroid therapy in order to prevent respiratory distress syndrome, the patient had no other symptoms and vital parameters appeared within normal range. Due to the overall condition and possibility of arising complications, the patient was qualified for a caesarean section. The precise diagnosis with the use of CrystalVue™ allowed surgery to be scheduled in a hybrid operating theatre with the assistance of an interventional radiologist. A healthy male newborn was delivered prematurely at thirty-four weeks of gestational age. After delivery, embolization of uterine arteries and vessels supplying the placenta was performed. Despite the absence of active bleeding in control angiography, several foci of active bleeding appeared after the removal of the placenta from the uterine cavity. The second embolization did not bring the expected results and the residual bleeding was still visible. Respectively the patient was qualified for hysterectomy. During the procedure the vascular sheath became unsealed, which resulted in considerable blood loss. The course of action was expanded to include removal of the left uterine appendages. The sheaths were sealed and no active bleeding sites were visualised during the control angiography. The intraoperatively damaged urinary bladder, which the placenta percreta had grown into, was sutured. During the laparotomy, seven units of fresh frozen plasma, eight units of red blood cell concentrates and two units of platelet concentrates were substituted. In the postoperative period the patient was in a stable condition.

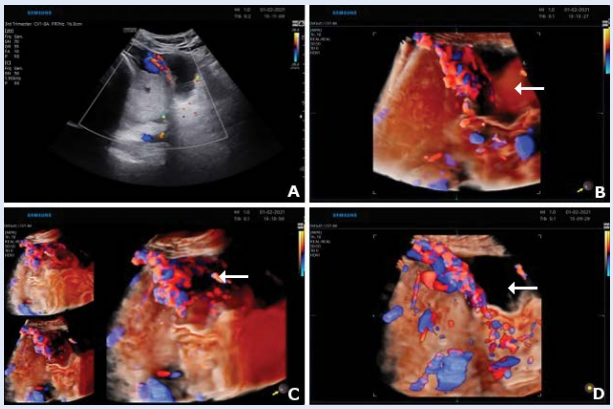

Figure 1. Transvaginal ultrasound examination showing; A — The two-dimensional ultrasound — the placenta in the lower uterine segment; B, C, D — The CrystalVue™ technique showing numerous blood in the wall of the urinary bladder documenting an abnormally invasive placenta (arrows)

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Only early diagnosis of AIP can prevent the occurrence of possible serious complications such as vesicovaginal fistula, life-threatening haemorrhage or even death [4]. Therefore, there is a need to use modern technologies enabling precise visualization of anatomical anomalies. This method is highly sensitive and specific in the prenatal diagnosis of AIP and allows the individual management of delivery, which minimizes possible complications.

Conflict of interest

The authors declare no conflict of interest.

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Water intoxication in the course of stimulation of labor with oxytocin

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ABSTRACT

The antidiuretic attribute of oxytocin can cause many side effects. Water intoxication is one of the most serious complications. The authors describe a case of water intoxication with neurological symptoms and severe hyponatraemia in the course of natural labor stimulated by oxytocin in a low-dose regimen.

Key words: oxytocin; antidiuretic effect; water intoxication

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The use of oxytocin has been indicated in obstetrics to induce or stimulate labor or miscarriage. Apart from having a powerful uterotonic effect, oxytocin is known to possess antidiuretic properties (a hundred-fold weaker than ADH), due to its similarity to vasopressin. This effect is noticeable even at low doses, as early as approximately 10–15 minutes after administration has been initiated.

We present a case of a primipara whose uterine contractions in the first stage of labor were stimulated by oxytocin using a low-dose regimen for a short period of time (5 h). Labor complications included water intoxication with severe hyponatremia and an episode of generalized convulsions in both, the mother and the newborn.

A 26-year-old primipara with non-significant medical history was admitted at 40 weeks of gestation due to amniotic fluid leakage and spontaneous irregular uterine contractions. Obstetric examination revealed the following: effacement of the vaginal part of the cervix, soft cervix, dilation of approximately 4.0 cm, with cervical anterior position of +1, in the axis of the birth canal. The Bishop score was calculated at 11 points. After cardiotocography, a decision was made to administer oxytocin in a low-dose regimen to stimulate uterine contractions. Next, the patient received epidural anesthesia.

To achieve full dilatation, the patient received a total of approx. 20 mLU of oxytocin diluted in 20 mL 0.9% NaCl within the next 5 hours. She had free access to oral rehydration with clear fluids.

The course of the first stage of labor was uncomplicated and dynamically stable, continuous cardiotocographic supervision with electronic analysis revealed no irregularities. During the second stage, the obstetric examination revealed an abnormal position of the fetal head (posito capitis recta alta). A decision was made to perform an emergency caesarean section.

Spinal anesthesia was performed in a semi-sitting position. After being placed on the operating table, the patient had a tonic-clonic (grand-mal) seizure, with loss of consciousness, salivation and trismus. A Mayo oropharynx tube was used to maintain patent airway (GCS — 10 points, auscultated FHR — about 100 bpm).

A full-term viable newborn (male, weight: 3500 g, length: 53 cm) in average overall condition was delivered (Apgar 6–6–7; cord blood pH 7.07, Na concentration in arterial cord blood 113 mmol/L (Tab. 1). A seizure occurred at 20 min. of neonatal life, stopped with phenobarbital. An infusion of glucose and sodium bicarbonate was administered, selective hypothermia was induced.

The patient was transferred to an Intensive Care Unit (ICU). Laboratory tests revealed severe hyponatremia (118 mmol/L). Head computed tomography (CT) reveled no focal lesions or signs of intracranial bleeding. Abdominal CT was also normal. Analgosedation, electrolyte supplementation and diuretic therapy were initiated, resulting in gradual resolution of the symptoms and improvement of the laboratory parameters.

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Table 1. Umbilical-cord blood gas analysis

Temperature	**37.0**	**Cel**		
pH	7.062		L	7.250–7.450
pO2	23.4	mmHg	L	83.0–108.0
pCO2	52.4	mmHg	H	27.0–40.0
ctHb	15.7	g/dL		13.5–20.7
sO2	33.3	%	L	54.0–69.0
FO2Hb	32.5	%	L	94.0–99.0
FCOHb	1.0	%		0.5–1.5
FHHb	65.1	%	H	0.0–2.0
FmetHb	1.4	%		0.0–1.5
FHbF	?...	%		2.0–77.0
cK+	5.2	mmol/L	H	3.5–5.0
cNa+	113.0	mmol/L	L	136.0–146.0
cCa2+	1.5	mmol/L	H	1.2–1.3
cCl-	87.0	mmol/L	L	98.0–106.0
cGlu	95.0	mg/dL	H	40.0–90.0
cLac	9.8	mmol/L	H	0.5–1.6
ctBil	0.4	mg/dL		0.3–1.2
SBE	-15.4	mmol/L		
cHCO-(P,st),c	12.0	mmol/L	L	23.0–27.0

On day five, after cesarean section, the patient was conscious (GCS — 15 points), not requiring electrolyte supplementation, with normal plasma osmolarity and diuresis. During the patient's stay at the ICU, the husband - who had been present during labor — was interviewed and reported that the patient had drunk five liters of low-sodium mineral water during labor. The overall clinical picture and the results of the additional tests lead to the diagnosis of water intoxication caused by the antidiuretic effect of oxytocin.

The problem of water intoxication has been known since the 1960s and the literature offers over a dozen reports of such cases, mainly oxytocin-induced miscarriages or termination of pregnancy up to 24 weeks of gestation. Typically, the protocol was to administer high doses of oxytocin (from 50 to even 140 IU) in large volumes of the carrier (usually 5–10 l 5% dextrose) over a prolonged period (10–36 hours) [1– 4]. The first symptoms included disturbances of consciousness (sometimes challenging to diagnose during labor), tremor, and grand mal convulsions [1, 3]. The problem seems to be significant because it leads to electrolyte disturbance not only in the mother, but also the newborn [3]. In order to minimize the risk of water intoxication, close supervision of the oxytocin dose as well as monitoring of the substances administered in analgesia [2], fluid intake/output, and maternal electrolyte levels [2–5] are recommended. Importantly, despite the availability of prostaglandins [4] used to induce labor or miscarriage and reduced need for oxytocin, the problem of water intoxication has not been eliminated. The rarity of the incidence and the dramatic course of water intoxication make us reflect on the need for an individualized approach to the affected patients.

Conflict of interest

The authors declare no conflict of interest.

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