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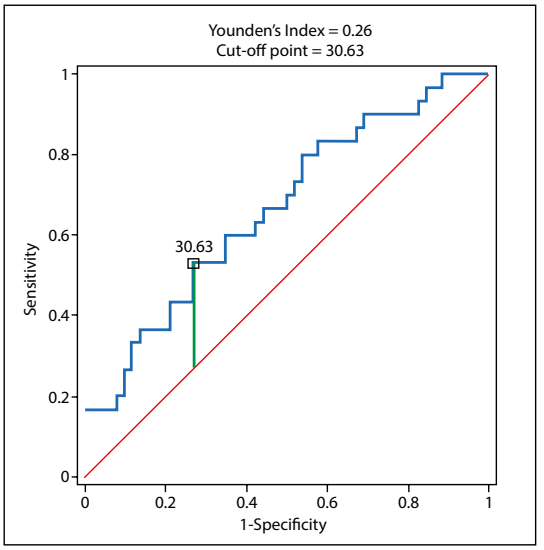

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EDITORIAL

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Editorial

Miroslaw Wielgos

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One of the greatest achievements of perinatology is intrauterine therapy, also known as fetal therapy or fetal surgery. Thanks to well-developed ultrasound screening there is an increasing number of congenital abnormalities diagnosed prenatally; therefore, routine ultrasound examination are believed to play a significant role in fetal surgery. Some of fetal therapies enable to correct identified anomaly before birth; in other cases, intrauterine therapy reduces perinatal morbidity and is a prelude for a proper postnatal treatment.

Intrauterine blood transfusion (IUT) is the most commonly performed in utero therapeutic procedure. An indication for IUT is severe fetal anaemia, that in most cases is caused by red cell alloimmunization and less frequently by intrauterine infection (above others by Parvovirus B19).

The second most frequent intrauterine procedure is fetoscopic laser photocoagulation (FLP), which is used as a treatment of twin-to-twin transfusion syndrome (TTTS). The other indications for FLP are twin anaemia polycythaemia sequence (TAPS), twin reversed arterial perfusion (TRAP), bronchopulmonary sequestration (BPS), sacrococcygeal teratoma (SCT) and amniotic band syndrome (ABS).

One of the prenatal interventions is also fetal shunt placement, for which indications are hydrothorax, congenital cystic adenomatoid malformations (CCAM) and lower urinary tract obstruction (LUTO).

Fetal spina bifida surgery is a strongly expanding field of prenatal therapy; there are a few techniques of the procedure – open repair, minimally-invasive (fetoscopic repair) and hybrid fetoscopic (Belford) technique. Studies have shown, that prenatal surgery of spina bifida significantly improves hindbrain herniation, ventriculoperitoneal shunting, motor defects and reduces the risk of neurogenic lower urinary tract dysfunction.

Fetoscopic endoluminal tracheal occlusion (FETO) is another prenatal surgical procedure, that is performed as a treatment of severe congenital diaphragmatic hernia (CDH). The aim of this therapy is to substantially improve perinatal mortality and consequently increase the chance of proper postnatal surgery.

Fetal cardiac intervention (FCI) is the next branch of intrauterine therapy. Indications for FCI are critical aortic stenosis (CAS), critical pulmonary stenosis (CPS) and foramen ovale restriction.

It should be emphasised that all the above-mentioned procedures are currently performed in Poland. Our leading perinatal centers offer all range of the described fetal therapies for patients diagnosed with the congenital abnormalities.

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The effect of experience on the outcomes of total laparoscopic hysterectomy surgery: 1295 cases

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ABSTRACT

Objectives: To reveal the effect of surgeon's experience on the outcomes of the total laparoscopic hysterectomy (TLH) surgery.

Material and methods: Design: Retrospective case series. Setting: A tertiary university hospital. Patients: 1295 cases with indication for hysterectomy. Interventions: Total laparoscopic hysterectomy.

Results: All cases were grouped according to the surgeon's experience. For 30 different surgeons, their first 20 operations constituted Group A, 21st–50th operations Group B, 51st–100th operations Group C, and their operations after the 100th surgery Group D. Demographic data and post-operative results were compared between the groups. There were no statistical differences in terms of demographic data and major complications. A statistically significant decrease was observed in the post-operative hemoglobin drop and the duration of hospitalization in the groups with increased experience ($p = 0.021$, $p < 0.001$, respectively). There was no increase in uterine specimen weight with increased experience ($p = 0.267$).

Conclusions: We obtained that the peak value in the learning curve could not be evaluated according to the operation time or complication rates. Although the complication rate seems unaffected by surgical experience, concerns about complications may decrease as experience increases. As the trend of minimally invasive surgery will continue to increase in the next century due to higher patient comfort, all gynecologists should gain competence in endoscopic surgery.

Key words: complications; hysterectomy; laparoscopy; learning curve; outcomes

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INTRODUCTION

Hysterectomy is the most common gynecological surgery after cesarean section. There are three main surgical approaches: total abdominal hysterectomy (TAH), vaginal hysterectomy (VH), and total laparoscopic hysterectomy (TLH). Indications for hysterectomy in benign cases include myoma uteri (uterine fibroid), abnormal uterine bleeding, endometriosis, pelvic organ prolapse, and other causes of chronic pelvic pain [1].

Hysterectomy types have certain advantages over each other. Postoperative pain and infection are less common in TLH, but the operative time is longer than in TAH [2]. A wide viewing angle can be obtained in TLH. Shorter operation time and less pain are observed in VH [3]. VH is the most cost-effective type among all operation types [4]. In TAH, the operation time is shorter and although a good visual angle can be achieved thanks to the incision made, post-operative pain and length of hospitalization are increased [2]. Although VH may be considered preferable, the vaginal capacities of the patients and the uterine mass size determine the limits of surgery. The general approach of surgeons when choosing the operation type is the method of hysterectomy that is suitable for the patient's current condition and in which clinicians have more experience.

Major complications of hysterectomy are genitourinary injury, gastrointestinal injury, bleeding more than 1000 mL, wound dehiscence, sepsis, and anesthesia related complications. The trend towards minimally invasive surgery, especially because of the lower rates of major complications, has changed the trend worldwide from abdominal hysterectomy to vaginal hysterectomy and then to laparoscopic hysterectomy. [5, 6]. Although there has been a decrease

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in TLH operation rates after the U.S. Food and Drug Administration mentioned the drawbacks of using morcellators in large mass surgery in USA, minimally invasive surgery reduces the morbidity of patients [7]. In Turkey, there is an increase in TLH surgeries that do not require morcellation [6].

Laparoscopic hysterectomy is dependent on technology and affected by the economic power of the countries. The difficulties in this regard make the training of gynecological endoscopists more difficult. The ability to achieve precision in movements required in minimally invasive surgery is highly influenced by the experience of the surgeon.

In this study, it was aimed to classify 1295 TLH operations performed by surgeons in our tertiary referral hospital according to the experience of surgeons and to investigate how the operation outcomes were affected by experience.

MATERIAL AND METHODS

A total of 1523 patients who underwent total laparoscopic hysterectomy in our tertiary referral hospital between January 2013 and July 2019 were retrospectively examined. Patients who underwent TLH surgery with or without salpingo-oophorectomy were included in the study. Patients who underwent another operation (sling procedures, Burch, perineorrhaphy etc.) and those who were operated due to a malignant indication were excluded from the study. The study continued with the remaining 1295 cases. Ethical approval was obtained from the institutional ethics committee.

Demographic data such as the patients' age, body mass index (BMI), history of abdominal surgery were reviewed using the hospital archives. Patient diagnosis, duration of the operation (time between the beginning and end of anesthesia), the weight of the removed specimen (g), whether adnexectomy was performed, major complications observed during the surgery, drop of hemoglobin (Hb) level and duration of hospital stay were recorded. Complications were classified into massive hemorrhage (more than 1000 mL), ureteral injury, bladder injury, and intestinal injury (full thickness damage) as major peroperative complications. Patients who underwent laparotomy due to inadequate uterine manipulation, uncontrolled bleeding and complication management were determined.

The operations performed by 30 different surgeons were listed in order of surgeons' experience. The first 20 operations of the surgeons were included in Group A, 21st to 50th operations were included in Group B, 51st to 100th operations were included in Group C, and operations after the 100th were included in Group D. While 30 surgeons were included in Group A, only five surgeons were included in Group D. With this arrangement, Group A consisted of 339 cases, Group B 312, Group C 421, and Group D 223 cases. All variables were compared between these groups and the effect of experience on the surgical outcomes was evaluated.

Statistical analysis: Means were expressed as mean (± SD). The number of subjects and rates were given as n (%). Descriptive statistics were applied to all data. All variables between the groups were evaluated in terms of normality and homogeneity. Kruskall Wallis test was performed for non-parametric continuous variables, and Anova test was performed for parametric continuous variables. Statistically, $p < 0.05$ was considered significant. In post-hoc analysis, Bonferroni test was performed for variables that were homogeneously distributed, and Tamhane test was performed for variables that were not homogeneously distributed. Chi-Square test was performed for categorical variables. Statistical analysis was performed with SPSS 22.0 Edition (Chicago, Ill).

RESULTS

A total of 228 out of 1523 patients who underwent additional procedures or had gynecological malignancies were excluded from the study. The mean age of 1295 patients was 50 ± 7 years, and their BMI was 25 ± 7.

The three most common reasons for performing TLH in the patients were fibroids (34.2%), endometrial hyperplasia (27.7%), and abnormal uterine bleeding (19.3%), respectively. Of all patients, 178 (13.7%) had a history of abdominal surgery (Tab. 1). The mean operative time was 130 ± 50 minutes in all patients. Adnexectomy was performed in 1090 (84.2%) of the patients. The mean decrease in the hemoglobin level was 1.8 ± 0.8 mg/dL. The weight of uterus removed during hysterectomy was 172 ± 95 g. Duration of hospitalization after surgery was 2.4 ± 1.1 days.

Major complications occurred in 45 (3.5%) of the patients. Massive hemorrhage occurred in 16 (1.2%) patients. Intestinal injury was detected in five (0.4%) patients. Bladder injury was observed in 17 (1.3%) patients, and ureteral injury was detected in seven (0.5%) patients. Laparotomy was performed in 15 (1.2%) patients for management of complications or due to insufficient operative capability.

Table 1. Operation indications of 1295 cases with TLH performed

Indication	n (%)
Fibroid	443 (34.2%)
Endometrial hyperplasia	358 (27.7%)
Abnormal uterine bleeding	250 (19.3%)
Adnexal mass	108 (8.4%)
Uterine prolapse	44 (3.4%)
Cervical intraepithelial neoplasia	42 (3.2%)
Chronic pelvic pain	23 (1.8%)
Endometrial polyp	15 (1.2%)
Endometriosis	8 (0.6%)
Pelvic abscess	4 (0.3%)

The operations performed by surgeons were arranged based on their experience, and the demographic data were compared between the four groups. No statistically significant difference was found in terms of age, BMI, or history of abdominal surgery (p = 0.082, p = 0.059, p = 0.464, respectively) (Tab. 2).

The most common indication for operation was fibroids in each group. There was no statistically significant difference between adnexectomy rates (p = 0.784). A statistically significant difference was found between the groups in terms of the decrease in hemoglobin level (p = 0.021). The mean decrease in hemoglobin values were 1.95 ± 0.81, 1.92 ± 0.87, 1.88 ± 0.83, and 1.74 ± 0.73 mg/dL in groups A, B, C, and D, respectively. When the post hoc analysis was performed, a statistically significant decrease was found only between groups A and D (p = 0.017). Mean operative times were 138 ± 47, 123 ± 44, 135 ± 56, and 122 ± 48 minutes in groups A, B, C, and D, respectively, and the difference was statistically significant (p < 0.001). In post hoc analysis, a statistically significant decrease was found between A–B, A–D, B–C, and C–D (p < 0.001, p = 0.001, p = 0.009, p = 0.014, respectively). Mean length of hospital stay was 2.6 ± 1.1, 2.6 ± 1.2, 2.3 ± 1, 2.2 ± 1 in groups A, B, C, and D, respectively, and a statistically significant difference was found (p < 0.001). A statistically significant decrease was found between A–C, A–D, B–C, and B–D in post hoc analysis (p = 0.001, p < 0.001, p = 0.004, p < 0.001) (Tab. 3). There was no statistical difference between uterine specimen weights after TLH procedure (p = 0.267). There was no statistically significant difference between the groups in the rates of major complications related to the surgery (p = 0.075). Major hemorrhage occurred in 4 (1.2%), 7 (2.2%), 3 (0.3%), and 2 (0.9%) patients in groups A, B, C, and D, respectively. Bladder injury was detected in 3 (0.9%), 5 (1.6%), 4 (1%), and 5 (2.2%) patients in groups A, B, C, and D, respectively. While ureteral injury did not occur in group A, it occurred in 3 (1%), 2 (0.5%), and 2 (0.9%) patients in groups B, C, and D, respectively. While no intestinal injury was observed in group A, it occurred in 1 (0.3%), 2 (0.5%) and 2 (0.9%) patients in groups B, C and D, respectively. Laparotomy was performed during the operation in 5 (1.5%), 4 (1.3%), 4 (1%), 2 (0.9%) patients in groups A, B, C, and D, respectively.

DISCUSSION

According to our study, it was observed that the results of TLH surgeries performed in our tertiary hospital were affected by experience only in some areas. A statistically significant decrease was observed in the hemoglobin drop especially after the 100th operation. There was no increase in the hysterectomy material size as experience increased. Length of hospital stay decreased statistically significantly after the 50th operation.

When the major complications were examined, no ureteral and intestinal injury was detected among the first 20 TLH operations. We believe that in our hospital's protocol, performing the first surgeries under the control of professional endoscopists prevents significant complications. Effective bleeding control improved with experience. Rates of major hemorrhage, ureteral and intestinal injury were less than one percent after the 50th surgery. It was observed that the need for laparotomy decreased with increased experience. Bladder injury was found to be increased especially after the 100th operation. This may be due to the increase in surgical self-confidence. Although the total complication rate seems unaffected by surgical experience, concerns about complications may decrease as experience increas-

Table 2. Demographic data and operational outcomes in all groups

	All case (n = 1295)	Group A (n = 339)	Group B (n = 312)	Group C (n = 421)	Group D (n = 223)	p-value
Age (year)	50 ± 7	49 ± 7	50 ± 8	49 ± 7	50 ± 8	0.082 β
BMI [kg/m^2]	25 ± 7	25 ± 5	25 ± 4	25 ± 5	26 ± 6	0.059 β
History of abdominal surgery	178 (13.7%)	38 (11.2%)	47 (15.1%)	61 (14.5%)	32 (14.3%)	0.464 ×
Operation duration (min)	130 ± 50	138 ± 47	123 ± 44	135 ± 56	122 ± 44	< 0.001 α
Hemoglobin drop [mg/dL]	1.8 ± 0.8	1.95 ± 0.81	1.92 ± 0.87	1.88 ± 0.83	1.74 ± 0.73	0.021 β
Adnexectomy	1090 (84.2%)	291 (85.8%)	259 (83%)	353 (83.8%)	187 (83.9%)	0.784 ×
Uterine specimen (g)	172 ± 95	163 ± 85	166 ± 92	178 ± 97	183 ±112	0.267 α
Hospital stay (day)	2.4 ± 1.1	2.6 ± 1.1	2.6 ± 1.2	2.3 ± 1	2.2 ± 1	< 0.001 α
Major complication	45 (3.5%)					0.075 ×
Major hemorrhage	16 (1.2%)	4 (1.2%)	7 (2.2%)	3 (0.3%)	2 (0.9%)	N/A
Bladder injury	17 (1.3%)	3 (0.9%)	5 (1.6%)	4 (1%)	5 (2.2%)	N/A
Ureteral injury	7 (0.5%)	–	3 (1%)	2 (0.5%)	2 (0.9%)	N/A
Intestinal injury	5 (0.4%)	–	1 (0.3%)	2 (0.5%)	2 (0.9%)	N/A
Transition to laparotomy	15 (1.2%)	5 (1.5%)	4 (1.3%)	4 (1%)	2 (0.9%)	N/A

α = Kruskal Wallis; β = Anova; × = Pearson Chi-Square; N/A — not applicable

Table 3. Post hoc analysis

	A–B	A–C	A–D	B–C	B–D	C–D	p-value
Operation duration	< 0.001 μ	0.955 μ	0.001 μ	0.009 μ	1 μ	0.014 μ	< 0.001 α
Hemoglobin drop	1 Ω	1 Ω	0.017 Ω	1 Ω	0.082 Ω	0.228 Ω	0.021 β
Hospital stay	1 μ	0.001 μ	< 0.001 μ	0.004 μ	< 0.001 μ	0.501 μ	< 0.001 α

α = Kruskal Wallis; β = Anova; μ = Tamhane; Ω = Bonferroni

es. The ability to complete the operation laparoscopically increases in parallel with experience.

The literature was reviewed about when the plateau in the TLH learning curve is reached. There are authors who have argued that this plateau occurs in the 20th, 25th, or 75th patients [2, 8, 9]. We classified our groups according to similar values. In the literature, when evaluating the time to reach the plateau of the learning curve, the reduction in the operation time or a decrease in complications has been taken into account. Since we could not observe a homogeneous and normal distribution in our study, it was not possible to create a learning curve based on the decrease in complication rates. The rate of major complications observed in TLH surgeries in the literature varies between 1% and 11.1% [8, 10–12]. In the present study, we found this rate to be 3.5%.

We could not create a learning curve based on the reductions in operative time either, because there was no steady decrease. As in a study by Mavrova et al. [8], increases and decreases can be observed in the duration of surgery regardless of experience. Despite the increasing level of experience in their study, the mean operative time was 136, 118 and 122 minutes, respectively. Similar results were obtained in our study. We do not find it appropriate to determine the plateau time in the learning curve according to this parameter, which is affected by individual surgical skills and surgical instruments.

There is a need for rapid circulation of patients in our clinic, and thus we prefer laparoscopic and vaginal hysterectomies to reduce the length of hospital stay. When Walsh et al. [13] examined the results of TAH and TLH surgeries in a meta-analysis, it was found that the duration of hospital stay was reduced in laparoscopic hysterectomies and the operating time was 22 minutes longer in TLH. In our clinic, patients who underwent TLH are discharged on the second postoperative day and the operation takes an average of two hours, including anesthesia. Primary findings for discharge; general condition of the patient, vital stability, and normalization of bowel and urinary functions.

In the literature, the most common indications for TLH are fibroids and abnormal uterine bleeding as they usually occur together [14]. The most common TLH indication was fibroids in each group in our study.

One of the problems in laparoscopic surgery is taking the uterine specimen out of the abdomen. The most important method for gynecologists to avoid this problem is to remove the specimen from the vagina. It is difficult to remove masses over 10 cm in diameter through the vagina after hysterectomy. In these cases, it is necessary to remove the mass by reducing it with a cold scalpel via vaginal orifice or to perform morcellation in an endobag. We do not use the morcellator in our clinic due to the possibility of pathological implantation.

A study by Cianci et al. [15], evaluated the outcomes of TLH operation performed by surgeons with an experience of at least 100 TLH surgeries using a morcellator for uteruses larger than 300 g. They found the mean uterine size to be 622 (301–3882) g, and the major complication rate was 3.5%. When they divided the cases according to the experience of the surgeons, they found that experience did not affect the rate of major complications. Transition to laparotomy was required in 9.8% of the cases [15]. In our study, when the operation outcomes of surgeons with an experience of more than 100 TLH surgeries were evaluated, the rate of major complications was 0.05%, and the rate of transition to laparotomy was 0.9%. We consider that the reason for the lower rate of complications compared with the study by Cianci et al. [15] is directly related to the size of the uterine mass. In addition, we think that it is the main reason for transition to laparotomy. We hypothesise that it is necessary to pay attention to eligibility of the patients for TLH in order to reduce morbidity. In our group consisting of surgeons who were specialized in TLH and performed more than 100 operations, the mean uterine mass size was 183 (range: 60–740) g.

In our clinic, cystoscopy is not routinely performed after TLH operation. We perform it after selected procedures. We prefer to perform it in patients who underwent incontinence surgery, prolapse surgery, and in patients with large cervical myoma. In the series of Vakili et al. [16] consisting of 471 cases, urinary system injuries were detected at a rate of 4.8% after TLH, and the injury was detected without performing cystoscopy in 35.3% of bladder injuries and in only 12.5% of ureteral injuries. There are also articles arguing that not performing routine cystoscopy may delay

the diagnosis of urinary tract injuries for two to 20 days [17]. Visco et al. [18] investigated the cost-effectiveness of performing cystoscopy and it was found to be cost-effective when the rate of urinary tract injury was above two percent in TLH patients.

Laparoscopic surgery is currently very popular in malignant indications as well as benign indications. There are clinics that accept it as a safe approach especially in obese patients with endometrial carcinoma. Due to the requirement of lymph node sampling, a longer operative time is observed in malignant indications compared to TLHs performed due to benign indications [19]. In patient groups undergoing laparoscopic surgery, especially longer operative time, shorter hospital stay, and less wound infections have been detected compared with those undergoing laparotomic surgery [20]. In a study examining the outcomes of TLH operation in obese and non-obese patients, complication rates were found to be similar [12]. We believe that TLH is the primary procedure, especially in cases of increased risk of wound infection, such as diabetes, inadequate self-care, and obesity.

CONCLUSIONS

The strength of our study was the large patient series consisting of 1295 cases in which the same surgical technique was applied in a single center, and its limitation was that we had insufficient data on post-operative long-term complications, because it was a retrospective data search. In addition, differences in surgical skills and periodic surgical instrument changes caused inconsistency in the results for operative time.

As the trend of minimally invasive surgery will continue to increase in the next century due to higher patient comfort, all gynecologists should gain competence in endoscopic surgery.

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Statement of ethics

Local ethics committee approval was obtained.

This study was carried out in consensus with our university´s ethics guidelines.

Conflict of interest

The authors declare that they have no conflict of interest.

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Validation of the Numerical Anxiety Rating Scale in postpartum females: a prospective observational study

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ABSTRACT

Objectives: Perinatal anxiety is important for the quality of life of mothers and their offspring. The Numerical Anxiety Rating Scale (NRS-A) allows the level of anxiety in patients to be quickly assessed. Until now, the NRS-A has not been validated in the postpartum female population. The aim of this study was to assess the accuracy and reliability of the NRS-A when compared with the reference methods for measuring anxiety.

Material and methods: The observational prospective study included a group of 200 adult postpartum females of a hospital maternity ward. The validity between the Numerical Rating Scale for Anxiety (NRS-A) and the State and Trait Anxiety Inventory (STAI), and between the NRS-A and the Hospital Anxiety and Depression Scale (HADS-A), was determined. The detection thresholds for high anxiety were examined.

Results: Both measurements showed a positive high correlation between the NRS and STAI-S (in T1 rho = 0.807, in T2 rho = 0.778; $p < 0.001$), and a comparable relationship of both scales (STAI-S and NRS-A) with the STAI-T and HADS-A. The analysis of the ROC curve indicated that the value of the NRS-A equal to 3.5/10 can be considered the threshold that allows for a differentiation of patients with high anxiety from those without high anxiety in the studied population.

Conclusions: The NRS-A is an accurate tool for measuring anxiety in Polish postpartum females. Routine anxiety measurements using the NRS-A can be used to identify people with high anxiety in order to provide emotional support to patients in the early postpartum period.

Key words: anxiety; postpartum period; patient-oriented outcomes; emotional support

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INTRODUCTION

The perinatal symptoms of anxiety and mood are common and important for the long-term and short-term quality of life of mothers and their offspring. High perinatal anxiety can lead to anxiety and affective disorders. In the postpartum period, women experience generalized anxiety disorder and panic attacks. In addition, obsessive-compulsive disorder, as well as acute and post-traumatic stress disorder symptoms may occur [1–4].

In populations of women evaluated in the perinatal period, anxiety and depressive disorders coexist [5, 6]. In the group of women diagnosed with postpartum depression, anxiety disorders were also found in 82.9% of them, and vice versa — in women with primary anxiety disorders, coexisting depressive disorders were found [7]. Some evidence shows that the incidence rate of perinatal anxiety is about 22%, which is higher than the incidence rate of perinatal depression (13%) [8].

Conclusions from studies conducted on populations of women in the perinatal period include recommendations for high-quality prenatal care systems regarding the routine control of anxiety and mood levels in this period [9, 10]. The Polish standard of perinatal care only recommends examining the perinatal risk of depression [11]. Moreover, it is standard in hospital care that patients are informed about their right to pain treatment. However, there

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are no such recommendations for anxiety, even though studies show that pain coexists with anxiety [12–14].

The study of anxiety among women in the postpartum period may not only be important for the selection of anxiety and depressive disorders in perinatal patients, but above all for the description and normalization of anxiety emotions in this population. According to the authors of Acceptance and Commitment Therapy, anxiety, as well as pain, loss, regret and disappointment, are inseparable elements of human life [15]. However, in order to discuss maternal anxiety in the postpartum period on the basis of scientific evidence, maternity staff should have a simple and relevant tool to measure it. A study by the Silverwood team (2019) [16] shows that there is insufficient understanding of what perinatal anxiety is among healthcare professionals. Employees declare that they lack knowledge concerning "normal perinatal anxiety", as well as simple tools for its screening. In turn, patients with perinatal anxiety declare that they do not receive sufficient support. The recommendations of the National Institute for Health and Care Excellence (NICE) include a provision concerning the recommendation of the assessment of the support needed by women with mental health problems, as well as the women at risk of developing them [17].

Commonly used scales to assess anxiety levels include descriptive scales, such as: Hospital Anxiety and Depression Scale (HADS) for measuring anxiety (A) and depression (D), Beck Anxiety Inventory, and State-Trait Anxiety Inventory (STAI) for measuring two separate anxiety concepts: state anxiety (S) and trait anxiety (T) [12, 18]. STAI-S, due to its high accuracy and reliability in various populations, is the recommended tool for measuring state anxiety [18, 19]. The results of testing the level of state anxiety are sensitive to the variability of anxiety, which depends on situations related to external stimuli [20]. The listed questionnaires contain multiple items. The filling in of them by postpartum females may be difficult due to the lack of time that is related to having to care for their newborns. In the case of limited time possibilities, it is reasonable to use quick measurement scales, e.g., a single 0 to 10 numerical rating scale (NRS), which is commonly used to measure pain. Despite its simplicity, its validity and reliability have also been demonstrated [21]. The twin NRS for anxiety (NRS-A) has been tested in the dental and pediatric patient population [22, 23]. Until now, the NRS-A has not been validated in the postpartum female population.

Therefore, the aim of this study is to answer the question of whether NRS-A is a valid and reliable measurement tool for assessing state anxiety in postpartum women in the first days of puerperium when compared to the reference STAI-S method. An additional goal is to test the detection threshold of high anxiety using the NRS-A, as well as to compare the anxiety of patients in two independent groups: those declaring a need for emotional support versus those declaring no need for emotional support.

MATERIAL AND METHODS

Population and settings

The place of study was the maternity ward in the 2nd Department of Gynaecology and Obstetrics of the Wroclaw Medical University, Poland. 200 women during their first and second postpartum days were included in the study. The data was collected in the period from 27/12/2020 to 04/30/2021. Adult patients, who gave conscious consent to the study and who gave birth at term (i.e., ≥ 37 hbd) to a single newborn in good condition (from 8–10 Apgar points), both by caesarean section and naturally, were enrolled in the research. The condition for inclusion in the study was also the good condition of the mother after childbirth (patient mobilized, with physiological blood loss during childbirth, no blood transfusion, qualified to "rooming" (maternity ward) with their newborn, and with no diagnosed mental, psychological, or orthopaedic dysfunctions).

Data concerning the patient's postpartum condition, medical history, and the health of their newborn were obtained from the medical history of the patient and newborn. The study was confidential. Access to the collected data was secured, and each of the studied participants was given an identification number, which enabled the data to be anonymized.

Tools

Numerical Rating Scale for anxiety (NRS-A)

The raw anxiety scores on a numerical scale from 0 to 10 were categorized as: 0 – not anxious, 1–3 — little/slightly anxious, 4–6 — medium/fairly anxious, 7–9 — a lot/very anxious, 10 — worst imaginable/extremely anxious [22, 23].

State-Trait Anxiety Inventory (STAI)

The STAI, which was developed from its original version, was adapted to the Polish population by the Spielberger team [20, 24]. It consists of two separate scales, which both have 20 questions. The total continuous scores range from a minimum of 20 to a maximum of 80. The higher the total score, the higher the level of state anxiety [at a given time on the X-1 scale (STAI-S)] and trait anxiety [on the X-2 scale (STAI-T)]. The obtained results are interpreted on three levels: low anxiety (1–4 sten), moderate anxiety (5–6 sten) and high anxiety (7–10 sten). The cut-off point for high state anxiety starts above 40 [20]. Cronbach's alpha in our study was for state anxiety (STAI-S) tested on the first day (T1) — 0.956 and second day (T2) — 0.958, and for trait anxiety it was (STAI-T) — 0.850.

Hospital Anxiety and Depression Scale (HADS)

The HADS questionnaire by Zigmond and Snaith (1983) [25] enables the level of anxiety and depression of patients

Table 1. Individual measurements of the observed variables during the study, and the number of correctly completed questionnaires for a group of 200 postpartum females

Variable	Questionnaire	Measurement T1	Measurement T2
State anxiety	STAI-S-X1	X (n = 200)	X (n =200)
Trait anxiety	STAI-T-X2	X (n = 200)	–
State anxiety	NRS-A	X (n = 200)	X (n = 200)
Anxiety	HADS-A	–	X (n = 187)
Need for emotional support	NES	X (n = 200)	X (n = 200)

X — presence of measurement; – — lack of measurement

in hospital conditions to be assessed. The Polish adaptation of the questionnaire was made by the Majkowicz team (2000).[26] Anxiety can be assessed using the independent subscale of the Hospital Anxiety and Depression Scale-Anxiety (HADS-A), which consists of seven questions. For each of them, 0 to 3 points (the maximum number of points is 21) can be achieved. The cut-off point for an anxiety disorder is a score greater than 10 points. Cronbach's alpha for HADS-A in the present study — 0.829.

Need for Emotional Support (NES)

The need for emotional support was tested using the question developed by authors: "In my current situation, I need emotional support." The answers were given on a 6-point Likert scale (1 — "I strongly disagree", 2 — "I disagree", 3 — "I disagree a little", 4 — "I agree a little", 5 — "I agree", and 6 — "I strongly agree"). Single-question scales that fit the specific clinical situation of patients are used in scientific publications [27]. For the purpose of selecting patients who declared a need for emotional support vs those that did not need support, answers from 1 to 3 were included in the group of patients who did not need emotional support, and answers from 4 to 6 were included in the group of patients who declared a need for emotional support.

Bioethics committee

A written informed consent to participate in the study was obtained from all the patients. The study was approved by the Bioethics Committee at Wroclaw Medical University, Wroclaw, Poland (KB No. 747/2020).

The presentation of measurements at both timepoints

After giving informed consent to participate in the study, the patients were asked to fill in questionnaires at two timepoints: on the first postpartum day (T1) and on the second postpartum day (T2). On both days, the patients completed NRS-A, STAI-S-X1 and NES. Additionally, on the first postpartum day (T1), they completed STAI-T-X2, and on the second day (T2) they completed HADS-A. The individual measurements over time are presented in Table 1. Incomplete, or blank questionnaires were considered as missing data. In T2, there were 13 deficiencies for anxiety measured using HADS-A.

Statistical analysis

The IBM SPSS Statistics 26 program (IBM Corp., Armonk, NY, USA) was used for statistical analysis. Due to the non-Gaussian distribution of all the variables, non-parametric tests were used for the analysis. The relationship between NRS-A, STAI and HADS-A is shown by Spearman's correlation coefficient (rho). The non-parametric Mann-Whitney U test was used to compare independent groups, and the Wilcoxon test was used to compare dependent groups. NRS-A thresholds of differentiation with regards to anxiety or non-anxiety (defined by the reference STAI-S cut-off point equal to 40, and HADS equal to 10) were determined based on Receiver Operating Characteristic (ROC) curves and their related area under the ROC curve (AUC). The significance of the measurements was assumed for the value of $p < 0.05$.

The sample size, with an estimated mean effect size and an alpha error probability of 0.05, was determined according to literature [23].

Participants

In the study, 200 women aged Mdn = 32 (range: 21–43) took part. Most of the patients (83%) declared higher education, a good financial situation (87.1%) and living in a formal relationship (78%). In the study group, 56% of patients gave birth to a child by caesarean section (Tab. 2).

RESULTS

The descriptive statistics for the tools used in the study are presented in Table 3. The Wilcoxon test showed no differences in the measurements between the first (T1) and the second (T2) day in the case of anxiety measured using STAI-S ($Z(199) = -0.658$; $p > 0.5$) and in the case of anxiety measured using NRS-A ($Z(199) = -1.928$; $p > 0.5$).

Correlations of comparable strength were shown between the dependent measurements (T1 with T2). They

were calculated separately for NRS-A (rho = 0.708; p < 0.001) and for STAI-S (rho = 0.701; p < 0.001).

Correlations between the NRS-A, STAI and HADS-A measurements

The correlations between STAI-S and NRS-A were positive and high in both measurements (p < 0.001). They amounted to in T1 rho = 0.807, in T2 rho = 0.778. A graphical representation of the relationship between STAI-S and NRS-A for individual measurements is shown in Figure 1.

Table 2. Characteristics of the studied group

Parameter	Total (n = 200)
Age	
20–30 years old	81 (40.5%)
31–40 years old	113 (56.5%)
41–50 years old	6 (3%)
Type of childbirth	
Natural childbirth	88 (44%)
Childbirth by caesarean section	112 (56%)
Education	
Higher	166 (83%)
Secondary	19 (9.5%)
Vocational	11 (5.5%)
Lower secondary	3 (1.5%)
Primary	1 (0.25%)
Financial status	
Good	175 (87.5%)
Average	23 (11.5%)
Poor	2 (1%)
Marital status	
Formal relationship	156 (78%)
Informal relationship	33 (16.5%)
Single	11 (5.5%)

The correlation between STAI-T and NRS-A, and STAI-T and STAI-S, as well as between HADS-A and NRS-A and HADS-A and STAI-S showed positive correlations of similar strength and significance (p < 0.001) for both scales (Tab. 4).

Cut-off points on the NRS-A scale

Analysis of the ROC curve for the 200 patients suggested a value of 3.5/10 on the NRS-A scale as the threshold for high anxiety (defined by the reference STAI-S cut-off of 40) in both measurements (in T1 AUC = 0.886; p < 0.001 and in T2 AUC = 0.860; p < 0.001). Both measurements showed acceptable values of sensitivity (T1 — 0.803; T2 — 0.702) and specificity (T1 — 0.843; T2 — 0.849) (Fig. 2).

The analysis of the ROC curve for 187 patients suggested a value of 4.5/10 on the NRS-A scale for T1 and T2 (for STAI-S the value of 42.5/80 in T1, and the value of 50.5/80 in T2) as a threshold to indicate the risk of an anxiety disorder (defined by the HADS-A reference cut-off of 10). The model adjustment values on the first day (T1) for NRS-A were: AUC = 0.852; p < 0.001; sensitivity = 0.895; and specificity = 0.678; and for STAI-S they were: AUC = 0.842; p < 0.001, sensitivity = 0.947, and specificity = 0.617. The model adjustment values on the second day (T2) were for NRS-A: AUC = 0.880; p < 0.001, sensitivity = 0.842, and specificity = 0.792; and for STAI-S: AUC = 0.863; p < 0.001, sensitivity = 0.711, and specificity = 0.846 (Fig. 3).

Levels of anxiety by the need for emotional support

From the group of 200 patients, 101 (50.5%) declared a need for emotional support on the first day (T1), and 96 (48.0%) patients on the second day (T2). The Mann-Whitney U test showed, in both the NRS-A and STAI-S scores, a higher (p < 0.001) level of anxiety in the group of women declaring a need for emotional support when compared to the group of women not declaring a need for emotional support (Tab. 6).

Table 3. Descriptive statistics for NRS-A, STAI, HADS-A, and NES in T1 and T2

Questionnaire and the measurement (T)	n	Mdn	IQR	Min	Max
NRS-A_T1	200	4	4	0	10
NRS-A_T2	200	3	3	0	10
STAI-S_T1	200	42.5	16	20	79
STAI-S_T2	200	42	17.75	20	77
STAI-T_T1	200	37	10	21	68
HADS-A_T2	187	7	6	0	20
NES_T1	200	4	3	1	6
NES_T2	200	3	3	1	6

HADS-A — Hospital Anxiety and Depression Scale-Anxiety; IQR — interquartile range; Mdn — median; Min — minimum value; Max — maximum value; n — number of subjects; NES — need for emotional support; NRS-A — Numerical Rating Scale for Anxiety; STAI-S — State and Trait Anxiety Inventory-State Anxiety

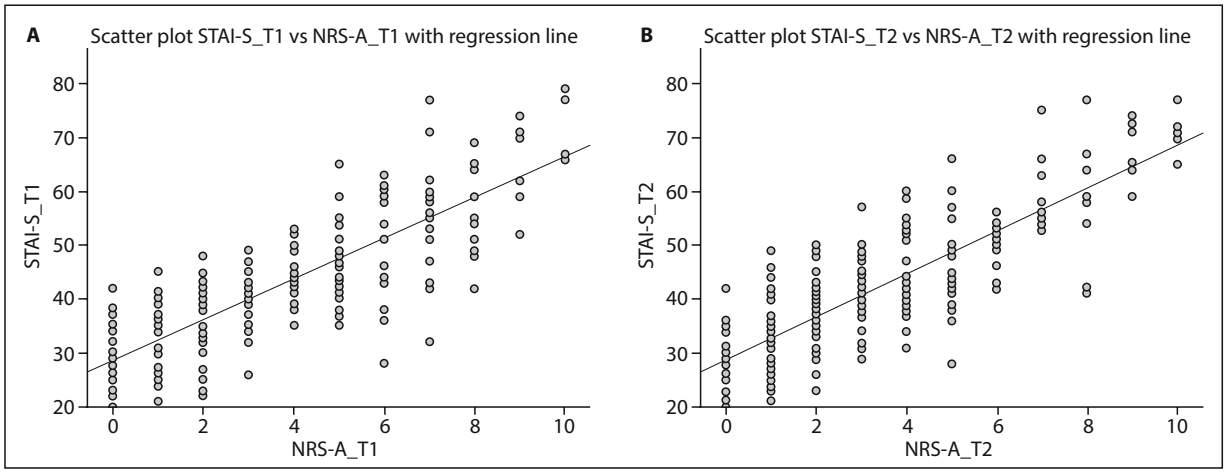

Figure 1. Scatter plots for correlations between STAI-S and NRS-A for both timepoints; **A.** Scatter plot for STAI-S_T1 *vs.* NRS-A_T1 with a regression line [Y = 3.769 (± 0.193)·X + 28.670 (± 0.927); p < 0.001; R2 = 0.658]; **B.** Scatter plot for STAI-S_T2 vs NRS-A_T2 with a regression line [Y = 3.990 (± 0.200)·X + 28.620 (± 0.901); p < 0.001; R2 = 0.667]

Table 4. Correlation between trait anxiety measured using STAI-T (n = 200) and HADS-A (n = 187) with state anxiety measured using NRS-A and STAI-S for the measurements at two timepoints

Spearman's correlation coefficient	T1		T2	
	NRS-A	STAI-S	NRS-A	STAI-S
STAI-T_T1	0.336	0.387	0.354	0.406
p-value	0.000	0.000	0.000	0.000
HADS-A_T2	0.716	0.733	0.686	0.691
p-value	0.000	0.000	0.000	0.000

HADS-A — Hospital Anxiety and Depression Scale-Anxiety; NRS-A — Numerical Rating Scale for Anxiety; STAI-S — State and Trait Anxiety Inventory-State Anxiety; STAI-T — State and Trait Anxiety Inventory-Trait Anxiety

DISCUSSION

Internal consistency of the results for state anxiety on the STAI-S scale in the present study, in both measurements (evaluated by Cronbach's alpha), was high (above 0.9) and comparable to the reliability of the STAI-S results for Polish women in the age range of 21–40 years (0.89) [20]. This value is comparable to Cronbach's alpha STAI-S value in scientific literature [28–30]. The high reliability of measurements using the STAI-S questionnaires in the study allows these tools to be used as a reference for NRS-A validation. The other standardized anxiety measuring tools (STAI-T and HADS-A) were also highly reliable.

The results of both measurements carried out in the present study showed a high positive correlation between NRS-A and STAI-S. They suggest a high convergence validity between the NRS-S and STAI-S tools. Although there is little evidence in the literature, the relationship between NRS-A and STAI-S was shown to be stronger than reported by other researchers. This corelation in our study was stronger than that obtained in the group of adult dental patients (rho = 0.6563; p < 0.05) [23], as well as in the group of pediatric patients (r from 0.424 to 0.639) [22]. In the present study, the corelation between NRS-A and STAI-S was stronger than this in studies which also compared other single-item scales, such as VAS-A to STAI-S in patients undergoing surgical procedures (r = 0.555 to 0.593) [31]. It was also similar or stronger when compared to the corelation measured with VAS-A and STAI-S in three timepoints (at admission to the operation theatre: r = 0.76, p < 0.001; at skin closure: r = 0.60, p < 0.001; two hours after the procedure: r = 0.65, p < 0.001) [32] in patients undergoing cesarean section [32]. The strength of the correlation between NRS-A and STAI-T was slightly weaker than the strength of the correlation between STAI-T and STAI-S, and slightly stronger than the correlation between NRS-A and STAI-T (r = 0.3456, p < 0.05) obtained the study by Walawender et al. [23]. Positive correlations between NRS-A and HADS-A of a similar strength as between STAI-S and HADS-A were obtained. The above results enable NRS-A to be considered as a relevant tool for measuring state anxiety in Polish postpartum females.

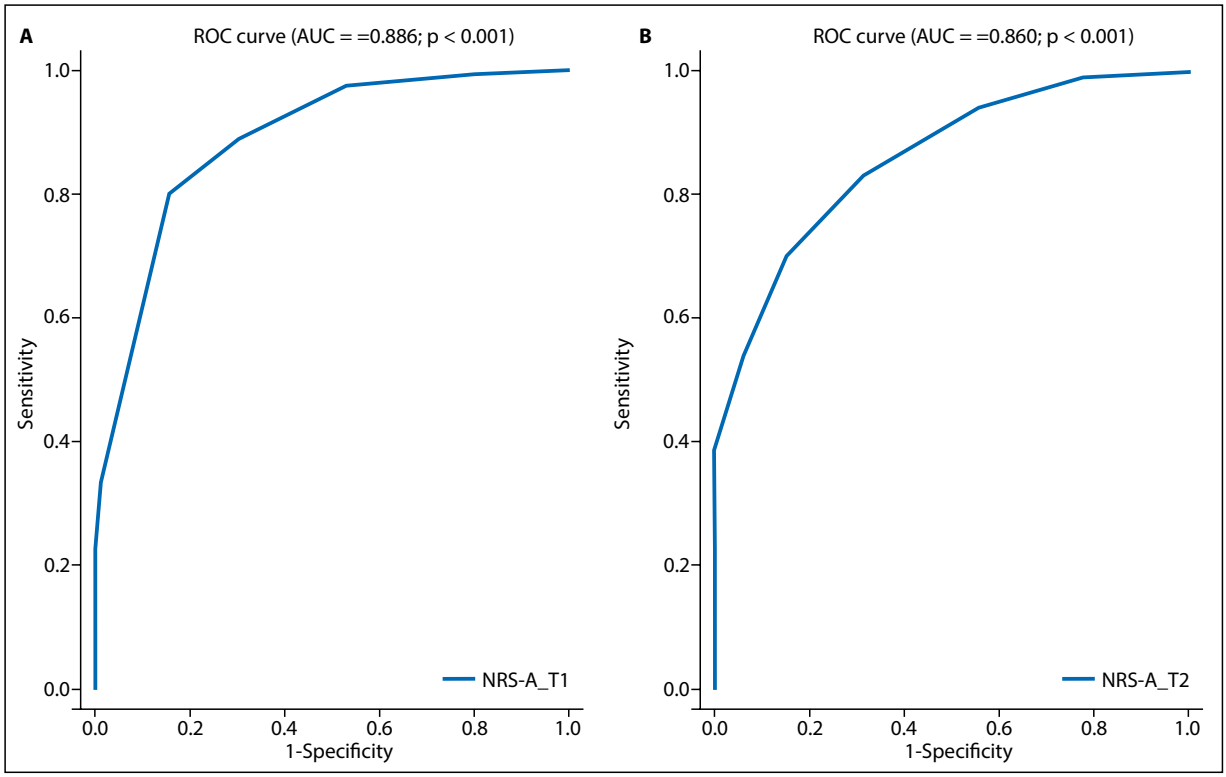

Figure 2. ROC curves; **A.** ROC curve calculated for NRS-A_T1 using STAI-S_T1 where a score of more than 40 was selected as an indicator of high anxiety. A NRS-A cut-off value of 3.5/10 reflected the best combination of sensitivity (80%) and specificity (84%); **B.** ROC curve calculated for NRS-A_T2 using STAI-S_T2 where a score of more than 40 was selected as an indicator of high anxiety. A NRS-A cut-off value of 3.5/10 reflected the best combination of sensitivity (80%) and specificity (85%)

The absolute stability values for state anxiety measured using STAI-S in two measurements with an interval of 3–4 weeks for women and men of different ages range from 0.39 to 0.81. In the group of 25 Polish women aged 21–40, the absolute stability is r = 0.59 [20]. Obtaining a similar high strength of dependent measurements (using the absolute stability method with the retest test) of state anxiety between the first day and the second day on both scales (NRS-A — rho = 0.708 and STAI-S — rho = 0.701), as well as obtaining a lack of differences in the anxiety level measured on both scales, allows NRS-A to be considered as a reliable tool.

No studies concerning the determination of the cut-off point were found for patients with high anxiety on NRS-A. The present research filled this gap. The cut-off points for separating patients with high anxiety using STAI-S equal to 40 was selected according to the recommendation of the manual for the Polish version of STAI-S for the group of women in the age range of 21–40. This is similar to the age of the studied population in the author's previous study [20], and also similar to the studies that validate the single visual analogue scale for anxiety (VAS-A) from 0 to 100 [31, 33].

The obtained (on the basis of the ROC curve analysis) cut-off point of 3.5/10 on NRS-A is similar to the values obtained by Labaste et al. on VAS-A with a shift of one decimal place (34/100) [31], and lower than the values obtained by Facco et al. (46/100) [33]. Measurements were conducted at two points (using the test-retest method). In both measurements, the values of the cut-off point coincided with each other. The range for high anxiety on NRS-A should therefore be 4 and above (considering that the STAI-S cut-off point is equal to 40). However, it should be noted that in the group of 90 women, which is a group that normalizes the sten in the Polish STAI adaptation for 21-40 years old, the mean state anxiety was 36.80 (the median was not given), i.e. it considered the group of patients without high anxiety [20]. In the author's study, for 200 women after childbirth, the median of anxiety in the first day was 42.5, and in the second day was 42. Both medians are in the high anxiety group. For this reason, the value of 3.5/10 on NRS-A for identifying patients with high anxiety should be treated as a starting point for further research concerning the identification of high anxiety in women during the puerperium.

Additional evidence of the reliability of the measurement using NRS-A in relation to STAI-S is the comparability of the similar values of the AUC, sensitivity and specificity of both ROC curve models for the thresholds that indicate the risk of an anxiety disorder in patients (defined by

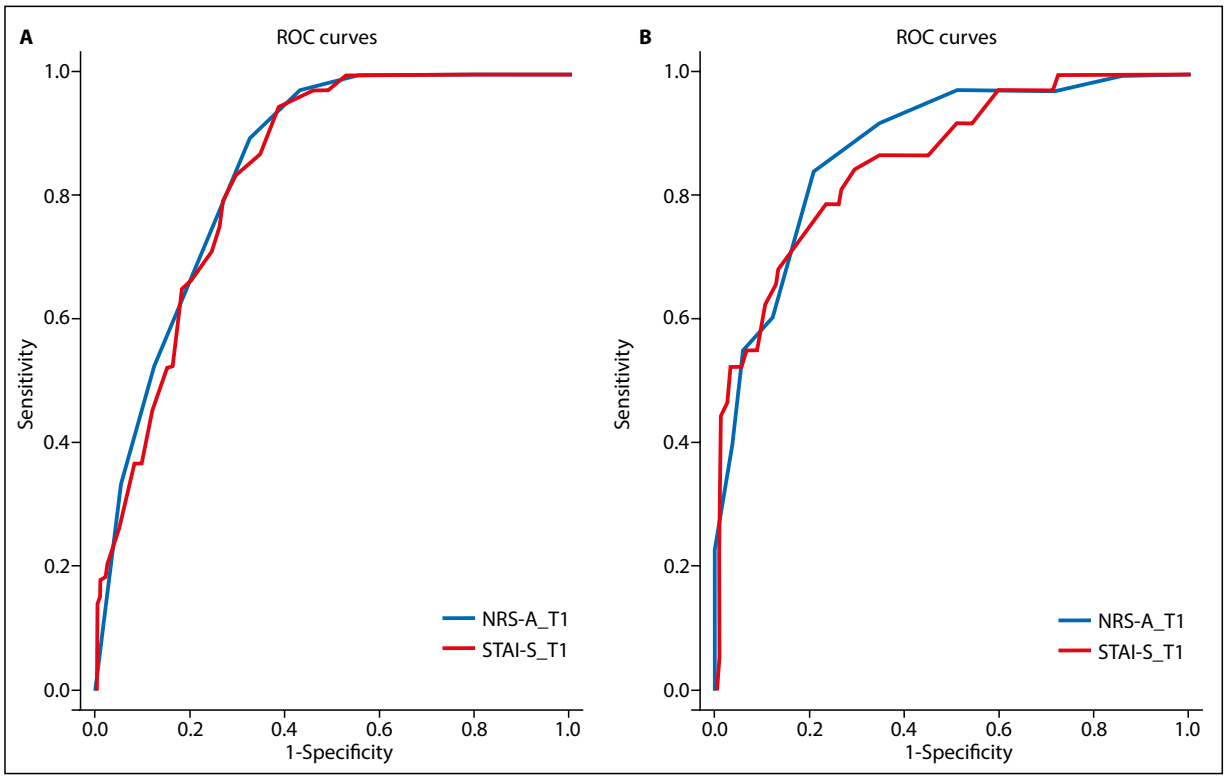

Figure 3. ROC curves; **A.** Calculated for NRS-A_T1 (AUC = 0.852; p < 0.001) and for STAI-S_T1 (AUC = 0.842; p < 0.001) using HADS-A, where a score of more than 10 was selected as an indicator of anxiety disorders. A NRS-A cut-off value of 4.5/10 reflected the best combination of sensitivity (89%) and specificity (69%). A STAI-S cut-off value of 42.5/80 reflected the best combination of sensitivity (95%) and specificity (62%); **B.** Calculated for NRS-A_T2 (AUC = 0.880; p < 0.001) and for STAI-S_T2 (AUC = 0.863; p < 0.001) using HADS-A, where a score of more than 10 was selected as an indicator of anxiety disorders. A NRS-A cut-off value of 4.5/10 reflected the best combination of sensitivity (84%) and specificity (79%). A STAI-S cut-off value of 50.5/80 reflected the best combination of sensitivity (71%) and specificity (85%)

Table 5. Anxiety (measured using NRS-A and STAI-S) in the group of patients declaring no need for emotional support (NES1) vs the group of patients declaring a need for emotional support (NES2) on the first (T1) and the second (T2) day

	Mdn	Mrang	Mdn	Mrang	Z(U)	p
	NES1_T1 (n = 99)		NES2_T1 (n = 101)			
NRS-A_T1	2	75.21	5	125.29	–6.155	< 0.001
STAI-S_T1	37	72.66	49	127.79	–6.739	< 0.001
	NES1_T2 (n = 104)		NES2_T1 (n = 96)			
NRS-A_T2	2	75.43	4.5	127.66	–6.422	< 0.001
STAI-S_T2	37	77.46	46.5	125.46	–5.863	< 0.001

Mdn — median; NRS-A — Numerical Rating Scale for Anxiety; STAI-S — State and Trait Anxiety Inventory-State Anxiety

the reference cut-off point on HADS-A equal to 10). Marking the cut-off point on a straight line using the NRS-S scale allows for the quick identification of patients with a high level of anxiety during the puerperium.

The innovative implementation of dividing patients in the author's study into those reporting a need for emotional support or those reporting a lack of such a need made it possible to assess the levels of anxiety in these groups on both scales (NRS-A and STAI-S). Similar results of the Mann-Whitney U test on both scales confirmed a significant difference in the levels of anxiety in both groups. In the group of patients reporting a need for emotional support in both measurements, the mean level of anxiety was above the cut-off point for patients with high anxiety in the case of both tools (over 3.5 on NRS-A and over 40 on STAI-S). In turn, in the group of patients reporting no need for emotional support in both measurements, the average level of anxiety was below the cut-off point for patients with high anxiety in the case of both tools.

The ability to measure anxiety in a simple way allows for a quick preliminary qualification of patients for emergency interventions. Considering both days of puerperium, the need for emotional support was declared by nearly half of the patients. The NICE guidelines[17] recommend the monitoring of the emotional state of women in the perinatal period and the use of evidence-based relief interventions. The NRS-A scale, tested in terms of its accuracy and reliability, may facilitate the assessment of puerperal anxiety. An additional advantage of NRS-A is its free availability and its similarity to the well-known NRS for assessing pain, which is recommended for use in hospitals [12, 34]. It takes a few seconds for the respondent to provide a one value for anxiety experienced at a given moment [22]. Taking into account the period of early puerperium, in which postpartum females may feel discomfort caused by pain and in which they also have a limited time to fill in time-consuming questionnaires (due to the need of caring for their newborn), NRS-A gives the opportunity to assess anxiety in a simple, quick, accurate and honest way.

The limitation of the study is the fact that patients from only one clinical centre were examined, and that the evaluated population was homogenic in terms of the patients' health, education and economic situation, as well as the health of their children.

CONCLUSIONS

The present study showed that NRS-A is a valid and reliable tool for measuring anxiety in postpartum females. Routine anxiety measurements with a numerical single-item postpartum scale can be used to identify patients with high anxiety in order to provide emotional support to patients in early postpartum.

Conflict of interest

All authors declare no conflict of interest.

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Psychometric properties and cultural adaptation of Polish version of Gynecological Cancers Awareness Scale (GCAS)

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ABSTRACT

Objectives: Cancer of the female genital organs is one of the most common causes of death of women in Poland. The aim of the study was to translate and analyze the psychometric properties of the Polish version of the Gynecological Cancers Awareness Scale (GCAS).

Material and methods: Cross-sectional study and questionnaire technic were used to collect data. The study was conducted from June 10th to July10th 2021 among 443 adult women in Poland.

Results: The Cronbach Alpha measure was used to assess the internal consistency of the scale. Cronbach's Alpha values greater than 0.7 indicates that the scale has high reliability.

Conclusions: The analysis confirms that the Polish version of Gynecological Cancers Awareness Scale has a very high reliability to assess the women's cancers awareness and knowledge of cancers.

Key words: gynecological cancers; GCAS; women; cancer prevention

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INTRODUCTION

Cancer has been one of the most common causes of death in Poland for many years, and the number of cases of malignant cancer has more than doubled in recent decades [1]. According to statistics, in 2018 there were quite a few numbers of new cases of malignant tumors of the female genital organs. the incidence rate was 14.5%, which is second only to breast cancer (22.5%). In addition, female genital malignancies caused 13.5% of cancer deaths in women (ovarian cancer — 6.1%, uterine shaft cancer — 3.9%, cervical cancer — 3.5%) [2].

The problem in the early detection of this group of cancers is the lack of characteristic clinical signs at their initial stage and the unsatisfactory participation of women in recommended preventive studies [1]. Prevention allows early detection of the disease, which increases the chances of their faster and more effective treatment. In order to improve the situation, measures should be taken to raise women's awareness of health-promoting behavior, including their participation in screening. Early diagnosis of gynecological cancers with effective and common screening programs is very important in reducing mortality and morbidity rates [3–9].

The analysis will allow for the preparation of a Polish version of a standardized tool for recognizing women's awareness of female genital cancers. Identifying knowledge deficits can be useful in practice in the implementation of educational programs aimed at women.

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Objectives

The aim of the study was to translate and analyze the psychometric properties of the Polish version of the Gynecological Cancers Awareness Scale (GCAS).

MATERIAL AND METHODS

Design and Participants

The study was conducted using a diagnostic survey method and survey technique. The subject of this study consisted of women who applied to two gynecology outpatient clinics in south-eastern Poland. The sample size required for a reliable factor analysis during the adaptation of a scale to a different culture, is classified as follows: 100 "poor", 200 "medium", 300 "good", 500 "very good", and 1000 "perfect" [10, 11]. Based on this classification, it was aimed to reach 500 women, 443 of whom agreed to participate and were included in the study. Women meeting the inclusion criteria were selected from the relevant population by random sampling method. Inclusion criteria: sexually active women in aged over 18 years no communication problems and voluntary consent to participate in the study. The method of sample selection and data collection as well as the sample size were agreed with the author of the original version.

Gynecological Cancers Awareness Scale (GCAS)

GCAS was developed by Alp Dal and Ertem in 2017 to assess women's awareness of gynecological cancers and it is addressed to women aged 18–65 [12]. Given the cultural differences, the Polish version of the scale is addressed to sexually active adult women.

This GCAS scale consists of 41 statements divided on four subscales:

1. Awareness of Early Diagnosis and Knowledge of Gynecologic Cancers — items 1, 2, 12, 13;
2. Awareness of Gynecologic Cancer Risks — items 3–11;
3. Awareness of Gynecologic Cancer Prevention — items 14–19;
4. Awareness of Regular Control and Severe Disease Perception on Gynecologic Cancers — items 20–41.

It is a five-point Likert-type scale (1 = strongly disagree, 2 = disagree, 3 = neither agree not to disagree, 4 = agree, and 5 = strongly agree). GCAS is evaluated against the overall result. The minimum score is 41 and the maximum score is 205. The higher the score, the higher the awareness of women. On the end of questionnaire, respondents were asked about socio-demographic data including age, place of residence and the level of education.

Tool translation procedure

The GCAS was translated into Polish by two independent translators, they then compared the two versions and created a single version of the translation. The English version has been retranslated into English by another translator. The main purpose of this process was preparation of a Polish version of the scale ready for practical use [13–15].

Ethical consideration

Prior to the study, permission was obtained to conduct the study from the researchers who developed the scale. The research tool was used with the authors' consent and prepared according to the rules adopted for the language adaptation process. Ethical approval (Decision No: 7/06/2021) was received from the Bioethics Committee at the University of Rzeszow Poland. Informed consent was obtained from the women included in the study.

Pilot study

The pilot study was carried out with 35 women to ensure that the prepared version of the tool was understandable. The data obtained from this pilot study was not included in the main sample. The pilot application determined that there were no misunderstood questions, and the Polish form of the scale was applied to the participants.

Data collection

The data was collected from June 10th to July10th 2021 by midwives among women who applied to the gynecology polyclinics in Rzeszow for a routine check-up, and who agreed to participate in the study. The interviews were conducted on weekdays using an anonymous questionnaire and took approximately 10 minutes to complete.

Psychometric analysis of the scale

Validity analysis

The adequacy and size of the sample were tested before factor analysis for the construct validity of the scale was done. Kaiser–Meyer–Olkin (KMO) test was used to determine the adequacy of the sample. Bartlett's Test of Sphericity analysis was conducted to determine whether the scale is suitable for factor analysis. KMO values used to decide whether the data is suitable for factor analysis or not are interpreted as follows; 0.90–1.00 "perfect", 0.80––0.89 "very good", 0.70–0.79 "good", 0.60–0.69 "medium", and 0.50–0.59 "poor". The desired KMO value to conduct factor analysis should be over 0.60 [16].

Principal Component Analysis was used to examine the factor structure of the GCAS, and the results were evaluated according to the opinion that the factor loads of the questions obtained as result of the analysis should be at least 0.30 [17]. Confirmatory Factor Analysis (CFA) was applied to support the accuracy of the results obtained by explanatory factor analysis (EFA). As a result of CFA, the lower limits of the data fit index of the model were accepted as ≤ 5 for X^2/sd, ≤ 0.08 for RMSEA, and a value higher than 0.90 for GFI, CFI, and IFI [18].

Table 1. Statistical tests used in data analysis

Test Used	Technique
Content Validity	Davis Technique
Explanatory Factor Analysis	KMO and Bartlett Coefficients, Principal Components Analysis
Explanatory Factor Analysis	x^2/SD value, GFI, AGFI, CFI, RMSEA, SRMR fit indices, and PATH diagram
Internal Consistency	Cronbach α coefficient, item total correlation, bottom top 27% slice comparison

Reliability analysis

The reliability value of the GCAS was determined through the Cronbach Alpha (α) coefficient. The Cronbach α reliability coefficients range from 0 to 1. As the value approaches 1, the reliability of the internal consistency of the scale increases. According to this, a value below 0.50 is unacceptable, values between 0.50–0.60 are weak, values between 0.60–0.70 are questionable, values between 0.70–0.80 are acceptable, values between 0.80–0.90 are good, and values between 0.90–1.00 are perfect [19].

The item-total correlation coefficients were examined to determine the relationship between the scores obtained from the scale items and the total score of the GCAS. The correlation values calculated between the items were above 0.20, which was accepted as a sufficient value for the reliability of the scale [20].

Data evaluation

The data was analyzed with SPSS for Windows 22 package program and LISREL 8.80 package program. Numbers, percentages, minimum and maximum values, mean, and standard deviations as well as statistical analyzes stated in the Table 1 below were used in the analysis of the data.

RESULTS

There were 443 women in the study. A majority the respondents had secondary (48.3%) or higher (34.1%) education level. Residents of villages constituted 55.1% of the respondents, while 44.9% were from the city. The participants mean age was 33.64 ± 11.19 years, and their age differed from 18 to 65 years. The scale was examined in three different categories: content validity, construct validity, and internal validity, to determine whether the GCAS is valid and reliable in the Polish language.

Findings regarding content validity

The GCAS, whose validity and reliability were examined after the translation process was completed, was submitted to the opinion of 10 experts for evaluation regarding cultural equivalence to ensure content validity. The CVI scores of the items of the GCAS, whose content validity was evaluated using the Davis technique in the presence of expert opinions, are shown in Table 2.

CVI scores of all items belonging to the GCAS vary from 0.90 to 1.0. Therefore, no item was excluded from the scale in terms of content/scope validity (Tab. 2).

Findings regarding construct validity

After content validity, factor analysis was performed to determine the construct validity of the GCAS to obtain clearer findings in the study. KMO and Bartlett's tests were applied before factor analysis to evaluate the adequacy of the sample and the suitability of the data for factor analysis.

As shown in Table 3, the KMO value was determined as 0.896, and this value shows suitability for principal components analysis. Similarly, the Bartlett test results ($x^2 = 83922.644$, $p = 0.000$) showed that the data correlate with each other and are suitable for factor analysis. In addition, the anti-image correlations of the scale items were also examined to evaluate whether the study data is suitable for factor analysis (Tab. 4). As seen in the table, all items meet the sampling adequacy criterion.

The items, factor loading and explained variance of the GCAS are shown in Table 5.

Routine Control and Serious Disease Perception in Gynecological Cancers Subdimension

1. Gynecological Cancer Risks Awareness Subdimension;
2. Protection from Gynecological Cancers Awareness Subdimension.

Early Diagnosis and Information Awareness in Gynecological Cancers Subdimension

Table 5 shows that the GCAS consists of four subdimensions, which is similar to the original structure. The factor loads of all the items of the scale are above 0.40 and the variance explained is 20.411% for Routine Control and Serious Disease Perception in Gynecological Cancers Subdimension, 9.185% for Gynecological Cancer Risks Awareness Subdimension, 8.101% for Protection from Gynecological Cancers Awareness Subdimension, 7.550% for Early Diagnosis and Information Awareness in Gynecological Cancers Subdimension, and 45.247% for the Total Gynecological Cancers Awareness Scale. Therefore, no item was removed from the scale at this stage and the four subdimensions were accepted. Structural equation modeling was established with confirmatory factor analysis after explanatory factor analysis to obtain more precise findings.

Findings regarding confirmatory factor analysis

the fit index values found for the GCAS, and normal and acceptable values are shown in Table 6.

As seen in Table 6, many indexes were used to examine the fit of the model of the Gynecological Cancers Awareness

Table 2. CVI Scores of GCAS Items

Items		4	3	2	1	CVI Score
1	Ovarian cancer is a female genital organ cancer	9	1	–	–	1.00
2	Uterine cancer is a female genital organ cancer	10	–	–	–	1.00
3	Not giving birth increases the risk of ovarian cancer	10	–	–	–	1.00
4	Menstruating at a young age (before the age of 9) and going through menopause at an older age (after the age of 52) increases the risk of ovarian and uterine cancers	7	3	–	–	1.00
5	The drugs used in the *in-vitro* fertilization treatment increase the risk of ovarian cancer	10	–	–	–	1.00
6	Receiving hormone therapy after menopause increases the risk of ovarian and uterine cancers	8	2	–	–	1.00
7	Being overweight increases the risk of ovarian and uterine cancers	10	–	–	–	1.00
8	Being over the age of 50 increases the risk of uterine cancer	10	–	–	–	1.00
9	Diabetes mellitus increases the risk of uterine cancer	10	–	–	–	1.00
10	Not giving birth increases the risk of uterine cancer.	10	–	–	–	1.00
11	Using contraceptive pills increase the risk of uterine and cervical cancers	10	–	–	–	1.00
12	Early diagnosis is important in the female genital organ cancer	10	–	–	–	1.00
13	Having HPV (the virus causing cervical cancer) test is important for early diagnoses of cervical cancer	10	–	–	–	1.00
14	For the early diagnosis of cervical cancer, I have a cervical swab test performed	10	–	–	–	1.00
15	For the early diagnosis of the female external genital organ, I make self-examination for the external genital organ	7	3	–	–	1.00
16	I do not smoke in order to reduce the risk of female genital organ cancer	10	–	–	–	1.00
17	In order to reduce the risk of female genital organ cancer, I do not use contraceptive pills for a long period	8	2	–	–	1.00
18	I keep away from stress in order to reduce the risk of female genital organ cancer	8	1	1	–	0.90
19	I regularly get examined by a gynecologist	10	–	–	–	1.00
20	If I have pain in my abdomen, I go to a gynecologist	10	–	–	–	1.00
21	Abdominal distention may be a serious symptom	10	–	–	–	1.00
22	Abnormal vaginal bleeding may be a serious symptom	10	–	–	–	1.00
23	Bleeding after sexual intercourse may be a serious symptom	10	–	–	–	1.00
24	Too much menstrual bleeding may be a serious symptom	10	–	–	–	1.00
25	Weight loss may be a serious symptom	10	–	–	–	1.00
26	A palpable mass in the genital area may be a serious symptom	10	–	–	–	1.00
27	A wound in the genital area may be a serious symptom	10	–	–	–	1.00
28	Bleeding between menstruation periods may be a serious symptom	10	–	–		1.00
29	I go to a doctor if I have a sudden and irregular weight loss	10	–	–	–	1.00
30	If I have a long-term diarrhea without a reason, I go to a doctor	10	–	–	–	1.00
31	If there are people with ovarian cancer in my family, I go to a gynecologist	10	–	–	–	1.00
32	If I have bleeding between menstruation periods, I go to a gynecologist	10	–	–	–	1.00
33	If I have brown discharge, I go to a gynecologist	10	–	–	–	1.00
34	If I have back pain, I go to a doctor	10	–	–	–	1.00
35	If I have problem with urination, I go to a doctor	10	–	–	–	1.00
36	If I have pain during sexual intercourse, I go to a gynecologist	10	–	–	–	1.00
37	If I have continuous discharge, I go to a gynecologist	10	–	–	–	1.00
38	If I have a problematic itch in my genital area, I go to a gynecologist	10	–	–	–	1.00
39	If I have pain in my genital area, I go to a gynecologist	10	–	–	–	1.00
40	If I have burning in my genital area, I go to a gynecologist	10	–	–	–	1.00
41	If I have watery bloody discharge, I go to a gynecologist	10	–	–	–	1.00
CVI mean		0.99				

Table 3. KMO and Bartlett test values for scale items

KMO	0.896
Bartlett	$x^2 = 8322.644$, p = **0.000**

Table 4. Anti-image correlations

	S20	S21	S22	S23	S24	S25	S27	S28	S29	S30	S31	S32	S33	S34	S35	S36
S20	0.920[a]															
S21	–0.224	0.932[a]														
S22	–0.092	–0.028	0.954[a]													
S23	–0.028	0.033	–0.219	0.930[a]												
S24	0.007	–0.174	–0.040	–0.212	0.923[a]											
S25	0.032	–0.114	–0.063	–0.164	–0.301	0.914[a]										
S27	0.042	0.026	–0.027	–0.051	–0.073	–0.139	0.922[a]									
S28	0.056	–0.073	0.022	–0.099	0.075	–0.003	–0.263	0.928[a]								
S29	0.039	–0.057	0.065	–0.012	–0.002	–0.072	0.024	–0.063	0.938[a]							
S30	–0.231	–0.121	0.069	0.075	–0.162	0.060	–0.086	–0.027	–0.150	0.882[a]						
S31	0.007	0.076	–0.010	0.052	0.069	–0.049	0.011	–0.045	0.004	–0.179	0.930[a]					
S32	–0.008	0.042	–0.106	–0.022	0.003	–0.114	0.042	–0.182	–0.089	–0.004	–0.230	0.930[a]				
S33	–0.092	0.028	–0.001	0.038	–0.013	0.009	0.070	–0.100	–0.054	0.028	0.063	–0.305	0.926[a]			
S34	–0.054	–0.170	0.068	–0.068	0.011	–0.029	–0.044	–0.006	–0.227	–0.060	–0.036	0.045	–0.078	0.909[a]		
S35	–0.005	0.000	–0.060	0.075	–0.081	0.053	0.030	0.000	–0.054	0.020	–0.074	–0.101	–0.075	–0.244	0.914[a]	
S36	0.058	–0.037	–0.046	–0.197	0.009	0.190	–0.118	0.075	–0.064	0.058	–0.092	0.036	–0.125	–0.050	–0.225	0.909[a]

Table 4. Anti-image correlations (continued)

	S37	S38	S26	S39	S40	S41	S4	S5	S6	S7	S3	S8	S9	S10	S11	S14	S17
S37	0.908[a]																
S38	–0.186	0.920[a]															
S26	0.085	0.019	0.939[a]														
S39	–0.002	–0.394	–0.292	0.931[a]													
S40	–0.084	–0.317	–0.072	–0.199	0.941[a]												
S41	–0.045	0.067	–0.041	–0.158	–0.279	0.951[a]											
S4	–0.148	0.098	0.048	–0.015	0.006	–0.012	0.822[a]										
S5	0.020	0.087	0.008	0.014	–0.028	–0.022	–0.213	0.857[a]									
S6	–0.048	–0.016	0.069	0.022	–0.029	0.082	0.069	–0.160	0.934[a]								
S7	–0.034	0.013	–0.045	–0.026	0.025	–0.053	–0.133	0.047	–0.125	0.870[a]							
S3	0.061	–0.081	–0.052	0.050	0.029	0.027	–0.271	–0.130	–0.133	–0.023	0.798[a]						
S8	0.077	–0.068	–0.027	0.004	–0.036	0.043	–0.104	–0.015	–0.050	–0.208	–0.004	0.903[a]					
S9	0.015	0.045	–0.003	0.028	–0.068	–0.009	0.008	0.010	–0.041	–0.332	–0.040	–0.223	0.836[a]				
S10	0.028	–0.132	0.012	0.024	0.036	–0.075	–0.126	–0.071	–0.012	–0.100	–0.470	–0.004	–0.026	0.817[a]			
S11	–0.092	0.037	–0.052	0.052	0.055	–0.025	0.012	–0.109	–0.123	0.040	0.038	–0.032	–0.134	–0.154	0.814[a]		
S14	0.045	–0.014	–0.002	0.047	–0.007	–0.016	–0.023	0.010	–0.051	0.094	0.046	–0.097	–0.139	–0.005	–0.018	0.891[a]	
S17	0.079	–0.038	0.026	0.007	0.053	–0.019	–0.024	–0.037	–0.014	–0.078	–0.013	–0.066	0.133	0.068	–0.358	–0.007	0.768[a]

→

Table 4. Anti-image correlations (continued)

	S15	S16	S18	S19	S1	S2	S12	S13
S15	0.895[a]							
S16	–0.142	0.855[a]						
S18	–0.056	–0.151	0.876[a]					
S19	–0.132	–0.051	–0.145	0.904[a]				
S1	0.086	–0.049	0.051	0.026	0.737[a]			
S2	–0.064	0.013	–0.095	0.043	–0.777	0.730[a]		
S12	0.065	–0.109	–0.033	–0.127	0.019	–0.127	0.748[a]	
S13	–0.138	–0.035	0.035	0.039	–0.251	0.077	–0.601	0.795[a]

[a]Measures of Sampling Adequacy (MSA)

Table 5. Factor analysis findings for the GCAS

Item no	Items	Factor/subdimension			
		1	2	3	4
S20	If I have pain in my abdomen, I go to a gynecologist	0.520	0.158	0.185	–0.054
S21	Abdominal distention may be a serious symptom	0.444	0.180	0.303	–0.115
S22	Abnormal vaginal bleeding may be a serious symptom	0.601	–0.081	0.406	0.132
S23	Bleeding after sexual intercourse may be a serious symptom	0.571	0.021	0.397	0.076
S24	Too much menstrual bleeding may be a serious symptom	0.507	0.075	0.336	–0.039
S25	Weight loss may be a serious symptom	0.547	0.094	0.349	0.113
S26	A palpable mass in the genital area may be a serious symptom	0.659	0.004	0.315	0.183
S27	A wound in the genital area may be a serious symptom	0.509	0.147	0.240	0.184
S28	Bleeding between menstruation periods may be a serious symptom	0.438	0.133	0.278	0.173
S29	I go to a doctor if I have a sudden and irregular weight loss	0.535	0.296	0.077	–0.084
S30	If I have a long-term diarrhea without a reason, I go to a doctor	0.489	0.263	0.042	–0.164
S31	If there are people with ovarian cancer in my family, I go to a gynecologist	0.543	0.029	0.137	0.056
S32	If I have bleeding between menstruation periods, I go to a gynecologist	0.656	–0.007	0.146	0.077
S33	If I have brown discharge, I go to a gynecologist.	0.666	0.036	0.043	0.027
S34	If I have back pain, I go to a doctor	0.524	0.175	–0.010	–0.090
S35	If I have problem with urination, I go to a doctor	0.652	–0.047	0.003	0.000
S36	If I have pain during sexual intercourse, I go to a gynecologist	0.623	–0.014	0.003	0.046
S37	If I have continuous discharge, I apply to a gynecologist	0.587	0.143	–0.090	–0.017
S38	If I have a problematic itch in my genital area, I go to a gynecologist	0.788	–0.001	0.046	0.114
S39	If I have pain in my genital area, I go to a gynecologist	0.820	–0.051	0.077	0.096
S40	If I have burning in my genital area, I go to a gynecologist	0.774	–0.017	0.017	0.153
S41	If I have watery bloody discharge, I go to a gynecologist	0.692	0.022	0.047	0.182
S3	Not giving birth increases the risk of ovarian cancer	0.008	0.761	0.006	0.145
S4	Menstruating at an early age (before the age of 9) and going through menopause at a later age (after the age of 52) increases the risk of ovarian and uterine cancers	0.028	0.721	–0.081	0.124
S5	The drugs used in the *in-vitro* fertilization treatment increase the risk of ovarian cancer	0.029	0.628	0.055	–0.096
S6	Receiving hormone therapy after menopause increases the risk of ovarian and uterine cancers	0.211	0.539	0.223	–0.014
S7	Being overweight increases the risk of ovarian and uterine cancers	0.065	0.541	0.281	0.239
S8	Being over the age of 50 increases the risk of uterine cancer	0.134	0.447	0.212	0.262
S9	Diabetes mellitus increases the risk of uterine cancer	0.056	0.485	0.288	0.107
S10	Not giving birth increases the risk of uterine cancer	0.032	0.735	0.082	0.033

→

Table 5. Factor analysis findings for the GCAS (continued)

Item no	Items	Factor/subdimension			
		1	2	3	4
S11	Using contraceptive pills increases the risk of uterine and cervical cancers	0.039	0.449	0.372	–0.023
S14	For the early diagnosis of cervical cancer, I have a cervical swab test done	0.124	0.089	0.521	0.306
S15	For the early diagnosis of the female external genital organ, I make self-examination for the external genital organ	0.162	0.180	0.482	0.159
S16	I do not smoke in order to reduce the risk of female genital organ cancer	0.022	0.036	0.664	0.221
S17	In order to reduce the risk of female genital organ cancer, I do not use contraceptive pills for a long period	0.019	0.226	0.628	–0.072
S18	I keep away from stress in order to reduce the risk of female genital organ cancer	0.157	0.145	0.567	–0.004
S19	I regularly get examined by a gynecologist	0.310	0.070	0.417	0.111
S1	Ovarian cancer is a female genital organ cancer	0.136	0.168	0.020	0.803
S2	Uterine cancer is a female genital organ cancer	0.117	0.165	0.030	0.762
S12	Early diagnosis is important in the female genital organ cancer	–0.016	–0.001	0.227	0.769
S13	Having HPV (the virus causing cervical cancer) test is important to early diagnose cervical cancer	0.066	0.065	0.197	0.791
Variance explained (%)		20.411	9.185	8.101	7.550
Total variance explained (%)		45.247			

Table 6. Fit index values found for the Gynecological Cancers Awareness Scale, and normal and acceptable values

Index	Normal value	Acceptable value	Found value
x^2/SD	< 2	< 5	3.78
GFI	> 0.95	> 0.90	0.94
AGFI	> 0.95	> 0.90	0.93
CFI	> 0.95	> 0.90	0.94
RMSEA	< 0.05	< 0.08	0.056
SRMR	< 0.05	< 0.08	0.071

Scale. Of these, the x^2/SD value was found as 3.78, GFI as 0.94, AGFI as 0.93, CFI as 0.94, RMSEA as 0.056, and SRMR as 0.071. As a result of the relevant fit index values, it was decided that the model is acceptable in this state.

Findings Regarding Internal Validity

Table 7 presents item means, item total correlations, and Cronbach α coefficients if item is deleted from the GCAS.

As seen in Table 7, the Cronbach α coefficient is 0.943 for Total Gynecological Cancers Awareness Scale, 0.920 for Routine Control and Serious Disease Perception in Gynecological Cancers Subdimension, 0.814 for Gynecological Cancer Risks Awareness Subdimension, 0.719 for Protection from Gynecological Cancers Awareness Subdimension, and 0.849 for Early Diagnosis and Information Awareness in Gynecological Cancers Subdimension. Item-total correlations for all items of the scale are positive and the deletion of any item did not cause a significant increase in the Cronbach α coefficient of the scale. Therefore, no item was removed from the scale at this stage, either.

As seen in Table 8, the comparison results of the bottom and top 27% slice of the GCAS are statistically significant ($p < 0.05$). This result shows the discriminatory power of the scale.

The distribution of the min, max, and mean scores taken from the GCAS and its subdimensions is presented in Table 9.

As seen in Table 9, the participants' mean scores were as follows: 84.27 ± 12.02 for Routine Control and Serious Disease Perception in Gynecological Cancers, 29.84 ± 5.19 for Gynecological Cancer Risks Awareness, 22.88 ± 4.02 for Protection from Gynecological Cancers Awareness, 17.80 ± 2.94 for Early Diagnosis and Information Awareness in Gynecological Cancers, and 154.79 ± 17.85 for the Total Gynecological Cancer Risks Awareness Scale.

DISCUSSION

It is very important to have knowledge about gynecological cancers. With increasing awareness of gynecological cancer, incidences can be reduced by enabling their prevention and early diagnosis [21]. For this purpose, valid

Table 7. Item total correlations and Cronbach α coefficients of the Gynecological Cancers Awareness Scale

no	Item	n	Mean	SD	Item total correlation	Cronbach α if an item is deleted
S20	If I have pain in my abdomen, I go to a gynecologist	443	30.37	10.152	0.488	0.911
S21	Abdominal distention may be a serious symptom	443	30.44	10.031	0.478	0.911
S22	Abnormal vaginal bleeding may be a serious symptom	443	40.16	0.878	0.579	0.910
S23	Bleeding after sexual intercourse may be a serious symptom	443	30.93	0.859	0.578	0.910
S24	Too much menstrual bleeding may be a serious symptom	443	30.81	0.946	0.499	0.911
S25	Weight loss may be a serious symptom	443	30.94	0.901	0.576	0.910
S26	A palpable mass in the genital area may be a serious symptom	443	40.15	0.805	0.624	0.909
S27	A wound in the genital area may be a serious symptom	443	30.88	0.871	0.542	0.910
S28	Bleeding between menstruation periods may be a serious symptom	443	40.13	0.715	0.506	0.911
S29	I go to a doctor if I have a sudden and irregular weight loss	443	30.34	10.037	0.499	0.911
S30	If I have a long-term diarrhea without a reason, I go to a doctor	443	30.13	10.184	0.415	0.912
S31	If there are people with ovarian cancer in my family, I go to a gynecologist	443	40.06	0.828	0.457	0.911
S32	If I have bleeding between menstruation periods, I go to a gynecologist	443	40.07	0.818	0.528	0.910
S33	If I have brown discharge, like broth, I go to a gynecologist	443	30.93	0.913	0.502	0.911
S34	If I have back pain, I go to a doctor	443	30.16	10.060	0.408	0.912
S35	If I have problem with urination, I go to a doctor	443	30.88	0.818	0.439	0.911
S36	If I have pain during sexual intercourse, I go to a gynecologist	443	30.86	0.803	0.440	0.911
S37	If I have continuous discharge, I go to a gynecologist	443	30.82	0.872	0.418	0.912
S38	If I have a problematic itch in my genital area, I go to a gynecologist	443	40.03	0.755	0.591	0.910
S39	If I have pain in my genital area, I go to a gynecologist	443	40.03	0.730	0.601	0.910
S40	If I have burning in my genital area, I apply to a gynecologist	443	40.01	0.757	0.570	0.910
S41	If I have watery bloody discharge, I go to a gynecologist	443	40.14	0.728	0.549	0.910
S3	Not giving birth increases the risk of ovarian cancer	443	30.16	10.042	0.313	0.913
S4	Menstruating at an early age (before the age of 9) and going through menopause at a later age (after the age of 52) increases the risk of ovarian and uterine cancers	443	30.35	0.906	0.276	0.913
S5	The drugs used in the *in-vitro* fertilization treatment increase the risk of ovarian cancer	443	30.14	0.827	0.242	0.913
S6	Receiving hormone therapy after menopause increases the risk of ovarian and uterine cancers	443	30.23	0.738	0.438	0.911
S7	Being overweight increases the risk of ovarian and uterine cancers	443	30.44	0.974	0.410	0.912
S8	Being over the age of 50 increases the risk of uterine cancer	443	30.66	0.856	0.404	0.912
S9	Diabetes mellitus increases the risk of uterine cancer	443	30.26	0.862	0.352	0.912
S10	Not giving birth increases the risk of uterine cancer	443	30.13	0.957	0.323	0.913
S11	Using contraceptive pills increases the risk of uterine and cervical cancers	443	30.47	0.996	0.338	0.913
S14	For the early diagnosis of cervical cancer, I have a cervical swab test done	443	40.15	0.907	0.402	0.912
S15	For the early diagnosis of the female external genital organ, I make self-examination for the external genital organ	443	30.90	0.967	0.421	0.912
S16	I do not smoke in order to reduce the risk of female genital organ cancer	443	30.98	10.070	0.353	0.913
S17	In order to reduce the risk of female genital organ cancer, I do not use contraceptive pills for a long period	443	30.57	10.083	0.333	0.913
S18	I keep away from stress in order to reduce the risk of female genital organ cancer	443	30.32	10.082	0.401	0.912
S19	I regularly get examined by a gynecologist	443	30.96	10.113	0.444	0.911
S1	Ovarian cancer is a female genital organ cancer	443	40.47	0.854	0.369	0.912

→

Table 7. Item total correlations and Cronbach α coefficients of the Gynecological Cancers Awareness Scale (continued)

no	Item	n	Mean	SD	Item total correlation	Cronbach α if an item is deleted
S2	Uterine cancer is a female genital organ cancer	443	40.47	0.843	0.348	0.912
S12	Early diagnosis is important in the female genital organ cancer	443	40.51	0.913	0.269	0.913
S13	Having HPV (the virus causing cervical cancer) test is important to early diagnose cervical cancer	443	40.35	0.933	0.349	0.912
Routine Control and Serious Disease Perception in Gynecological Cancers Cronbach α					0.920	
Gynecological Cancer Risks Awareness Cronbach α					0.814	
Protection from Gynecological Cancers Awareness Cronbach α					0.719	
Early Diagnosis and Information Awareness in Gynecological Cancers Cronbach α					0.849	
Total Gynecological Cancers Awareness Cronbach α					0.913	

Table 8. Bottom top 27% slice comparison results

	n	Mean	SD	Significance
Bottom 27%	120	133.73	12.16	t = –31.130 p = **0.000**
Top 27%	120	176.05	8.59	

Table 9. Distribution of scores obtained from Gynecological Cancers Awareness Scale and subdimensions

Subscales	n	Min.	Max.	Mean	SD
Routine Control and Serious Disease Perception in Gynecological Cancers	443	24.00	110.00	84.27	12.02
Gynecological Cancer Risks Awareness	443	16.00	45.00	29.84	5.19
Protection from Gynecological Cancers Awareness	443	6.00	30.00	22.88	4.02
Early Diagnosis and Information Awareness in Gynecological Cancers	443	4.00	20.00	17.80	2.94
Total Gynecological Cancers Awareness	443	72.00	203.00	154.79	17.85

and reliable measurement tools are needed to determine gynecological cancer awareness. This section discusses the findings obtained from the research conducted to ensure the validity and reliability of the GCAS under the following headings:

Validity is the degree to which a measurement tool can measure the property that it aims to measure accurately without reflecting the effect of any other feature on the measurement. [22, 23]. To test the validity of the GCAS, it was first adapted to Polish. Language validity, content validity, and a pilot application were carried out in this regard. In the adaptation phase of the GCAS to the Polish culture, it was first translated from its original language Turkish into English and then from English into Polish. Then, the scale items, which were translated into Polish, were examined by expert linguists, and the original scale was compared to the Polish translation. The Polish form of the scale was presented to 10 academicians who are experts in their fields to evaluate the content validity.

After language validity, content validity, and pilot application, the study proceeded with the construct validity. Construct validity is performed to evaluate how accurately an abstract concept or behavior can be measured by the tool [23, 24]. Factor analysis method, one of the most frequently used methods, was used to ensure construct validity. Prior to factor analysis, KMO analysis was performed to test the sample size sufficiency and appropriateness. The KMO value of the GCAS was determined as 0.896 (Tab. 3). The KMO value of the Turkish version of the Scale was found as 0.943 [12]. The sample size analysis value $x^2 = 8322.644$, $p = 0.000$ tested in the study showed that the sample size was quite sufficient and suitable for factor analysis (Tab. 3).

Varimax rotation was used in the EFA stage of factor analysis. The variance explained for the scale was found as 45.24% (Tab. 5). As a result, it was determined that the variance explained according to the EFA findings was at a satisfactory level. The original GCAS consists of 41 items. In the literature, the lower value for the factor loading of the items in the measurement tool was specified as 0.30–0.40. As a result of EFA in this study, it was determined that the Gynecological Cancers Awareness Scale was gathered under

four factors as in the original. As a result, the Polish version of the Gynecological Cancers Awareness Scale consisting of 41 items was obtained (Tab. 5).

According to the CFA results, the x^2/SD value was found as 3.78, GFI as 0.94, AGFI as 0.93, CFI as 0.94, RMSEA as 0.056, and SRMR as 0.071 (Tab. 6). According to the relevant fit index values, it was decided that the model was acceptable in this state.

Reliability shows the invariance of the measurement tool, consistency, the ability to reach similar results in measurements made at different times and is used to determine the true value levels. If the reliability of a measurement tool is found to be low, its scientific value is also considered low [25]. Cronbach's alpha internal consistency coefficient and item total correlation were used to determine the reliability of the Polish version of the GCAS.

In this study, the Cronbach's alpha internal consistency coefficient of the GCAS was found to be 0.913 (Tab. 7). The Cronbach's alpha internal consistency coefficient of the original scale was 0.944 [12].

CONCLUSIONS

Since the Gynecological Cancer Awareness Scale, which was developed by Alp Dal and Ertem (2017) to measure the Gynecological Cancer Awareness of women and which we have made valid and reliable in Polish, is harmonious with the original scale, it was determined that it is a valid and reliable tool for evaluating the gynecological cancer awareness of Polish women.

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Conflict of interest

All authors declare no conflict of interest.

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Prognostic value of systemic inflammation response index in patients with persistent human papilloma virus infection

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ABSTRACT

Objectives: Persistent human papilloma virus (HPV) infection is a risk factor for the progression of cervical neoplasia into invasive carcinoma. Many inflammatory markers obtaining from hemogram parameters as platelets, monocytes, lymphocytes, and neutrophils or their ratios are still under investigation in recent decades, especially in the oncology era. Indeed, there have not been enough data about the relationship between these parameters and cervical cancer in the literature. Our primary aim was to investigate the possible relationship between the persistent HPV, which is one of the significant risk factors of cervical cancer, and these inflammatory markers. Further, we can add an easy follow-up parameter in women with persistent HPV infection.

Material and methods: The study included patients between 30–65 years old, tested positive for HPV, and afterward had an HPV control test between January 2015 and June 2020.

Results: The study included 114 HPV DNA-positive patients. The mean age was 43 (standard deviation 8.7), and 41 of them (36%) had persistent HPV, but the remaining 73 (64%) did not. The baseline neutrophil/lymphocyte ratio (NLR) value was 2.1, platelet/lymphocyte ratio (PLR) was 133, monocyte/lymphocyte ratio (MLR) was 0.28, and systemic inflammation response index (SIRI) was 0.9. All the parameters were significantly higher in the persistent HPV group compared to the non-persistent group. Patients who had 0.65 and under this had a significantly lower risk of persistent HPV.

Conclusions: Persistent HPV disease can be predicted with an elevated SIRI, NLR, and other hematologic parameters. So, we can closely follow up with these patients with different algorithms to prevent cervical cancer.

Key words: systemic inflammation response index; neutrophil to lymphocyte ratio; platelet to lymphocyte ratio, persistent HPV

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INTRODUCTION

Human papilloma virus (HPV) is a DNA virus that affects the epidermis and mucosa, and it has been transmitted by skin-to-skin contact. There are more than 100 different types of HPV; the two major groups are high and low risks for cancer [1]. The prevalence of HPV infection was around 5% in Turkey, published by Gultekin et al., including more than 4 million women [2]. Other studies found different ranges according to the region and age between 13–45% [3, 4]. Most HPV infections disappear within two years, but some persist, causing pre-malign cervical lesions as well as cervical cancer [5].

Persistent HPV infection is a risk factor for the progression of cervical neoplasia into invasive carcinoma [6]. Many studies showed that the persistence of HPV for a long time is crucial for cervical carcinogenesis. A systematic review found that HPV persistence is substantially linked to cervical intraepithelial neoplasia (CIN2-3) and, high-grade squamous

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intraepithelial lesions (HSIL). Moreover, Longer durations of infection, longer test intervals for HPV, and higher-grade cervical illness all increased the magnitude of the effect of HPV persistence [7, 8].

Virchow found the connection between inflammation and cancer in 1863. Many hematologic parameters such as monocyte/lymphocyte ratio (MLR), neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR), systemic inflammation response index (SIRI) have been studied further [9–12]. Although some studies showed a relationship between cervical cancer and hematologic parameters, there was no study about persistent HPV relation and these parameters above, especially SIRI in the literature. Thus, this research aims to find a relation between persistent HPV with SIRI and other classic parameters.

Objectives

Persistent HPV infection is a risk factor for the progression of cervical neoplasia into invasive carcinoma. Many inflammatory markers obtaining from hemogram parameters as platelets, monocytes, lymphocytes, and neutrophils or their ratios are still under investigation in recent decades, especially in the oncology era. Indeed, there have not been enough data about the relationship between these parameters and cervical cancer in the literature. Our primary aim was to investigate the possible relationship between the persistent HPV, which is one of the significant risk factors of cervical cancer and these inflammatory markers. Further, we can add an easy follow-up parameter in women with persistent HPV infection.

MATERIAL AND METHODS

This study was designed in two gynecology centers in Turkey: Afyonkarahisar Health Sciences University and Sakarya Training and Research Hospitals. The research is a retrospective study approved by the ethics committee, including HPV positive female patients. The study included patients who were between 30–65 years old, tested positive for HPV, and afterward, had an HPV control test between January 2015 and June 2020. Patients who had an active infection had been vaccinated for HPV or had a history of malignancy were not included in this study.

All patients underwent HPV genotyping and liquid smear tests (Roche Cell-IVD) while having a gynecologic examination. The Bethesda System was used to report the cervical cytopathologic examination. Abnormal results in this system are squamous cell carcinoma, adenocarcinoma in situ (AIS), atypical squamous cells of undetermined significance (ASC-US), atypical squamous cells cannot exclude HSIL (ASC-H), low-grade squamous intraepithelial lesion (LSIL), high grade squamous intraepithelial lesion (HSIL), atypical glandular cells not otherwise specified (AGC-NOS), atypical glandular cells, and suspicious for AIS or cancer (AGC-neoplastic). Our study used LGSIL and HGSIL because most of our pathology reports included these two scores, so we excluded the other rare score. Cervical intraepithelial neoplasia (CIN) classification shows the abnormal growth of cervical surface cells. We accepted CIN 1 lesion as LSIL and CIN 2/3 lesion as HSIL according to The College of American Pathology and the American Society of Colposcopy and Cervical Pathology reports to reduce the heterogeneity of centers and pathologists [13]. All patients controlled for HPV, in case the result was positive, the patient was followed up for at least 12 months and a retest was performed. In case of the same type of HPV being positive again, we accepted the patient as persistent for HPV.

Measurement of hematologic parameters

Complete blood counts and related parameters were obtained from the peripheral blood of patients before the diagnosis of HPV. An automated hematology analyzer counted peripheral neutrophils, lymphocytes, platelets, and monocytes. NLR and PLR were defined as absolute neutrophil/platelet count, respectively, divided by absolute lymphocyte count. MLR was defined as an absolute monocyte count divided by absolute lymphocyte count. SIRI was calculated as neutrophil count multiplied by monocyte count divided by lymphocyte count (SIRI = N × M/L).

Statistical analysis

All analyses were done with SPSS version 22.0 (IBM Corporation, New York, USA). Women who had positive HPV results were being followed up, and in case the second test was positive, the patient was accepted as persistent for HPV. Otherwise, if the control test was negative, it was accepted as non-persistent HPV infection. Co-infection with another type of HPV, was not considered as persistent type. A normality test was performed for all data and determined with standard deviation or interquartile range as appropriate. Qualitative variables were analyzed with the chi-square test, and quantitative data analyzed with the Student *t*-test. Roc curve analysis calculated the cut off value for the SIRI score. P values lower than 0.05 were considered statistically significant.

RESULTS

The study included 114 HPV DNA positive patients. The mean age was 43 [standard aviation (SD) 8.7], and 41 of them (36%) had persistent HPV, but the remaining 73 (64%) did not. Persistent HPV types were shown in Figure 1. The most common three types of persistent HPV were 16, 31, and 35 in our population. In this study, the mean hemoglobin level was 12.8 g/dL, white blood cell number was 7.7 $mm^3 \times 1{,}000$,

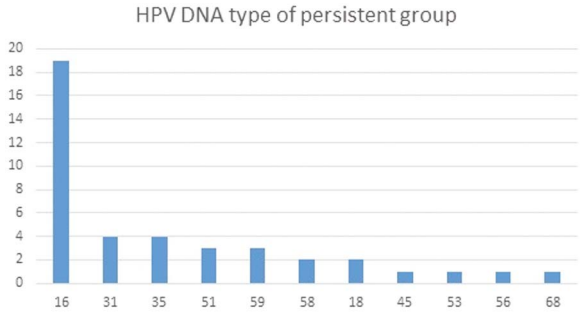

Figure 1. Persistent Human papilloma virus (HPV) DNA types

the neutrophil count was 4.6 mm^3 × 1,000, and platelet count was 295 mm^3 × 1,000.

The baseline NLR value was 2.1, PLR was 133, MLR was 0.28, and SIRI was 0.9. When we compare persistent and non-persistent groups, all four variables were significantly different and shown in Table 1. All the parameters were significantly higher in the persistent HPV group. The persistent HPV group had a significantly higher rate of HSIL/LSIL ratio (27/30 vs. 14/44) and the chi-square statistic is 6.7624. The p value is 0.00931.

Roc-curve analysis for SIRI with 0.65 value has 95% sensitivity and 79% specificity with AUC 0.71, shown in Figure 2. Patients who had 0.65 and under this SIRI value had a significantly lower risk of persistent HPV disease. One of 16 patients had a positive HPV in patients who had SIRI scores lower than 0.6 but, 40 of 98 patients had persistent HPV disease in a patient with a higher SIRI score (The chi-square statistic is 7.1359. The p value is 0.0075).

DISCUSSION

This study found significantly higher NLR, PLR, and MLR values in patients with persistent HPV than the non-persistent HPV group. Although this is the first time in the literature, according to our research, SIRI scores are significantly higher in the persistent HPV group. This score could predict the persistence risk of HPV; therefore, it can be a valuable hematologic marker to follow up HPV-positive patients.

One of the most common causes of sexually transmitted infection is HPV in women and men. According to DNA sequence data, there are more than a hundred types of HPV, and they can be divided into high and low-risk types based on their association with pre-malign lesions and cervical cancer [14, 15]. The connection between HPV and cervical cancer has become well defined, and its contribution is more prominent than lung cancer with smoking [16]. It is accepted worldwide that more than 99% of cervical squamous cell cancer cases are related to HPV [17].

The systemic inflammation response index is a new biomarker calculated with peripheral blood neutrophil, monocyte, and lymphocyte counts. It can be used for the prognosis of patients with cancer, for instance, pancreatic [12], esophageal [10], and nasopharyngeal [18]. In a recent study, Chao et al. [9] found that SIRI was correlated with cervical cancer prognosis. They found a 1.25 cut-off value for SIRI. Above that, values were had worse outcomes, such as overall survival and recurrence. Higher NLR, PLR, and MLR values were significantly correlated with decreased overall survival for cer-

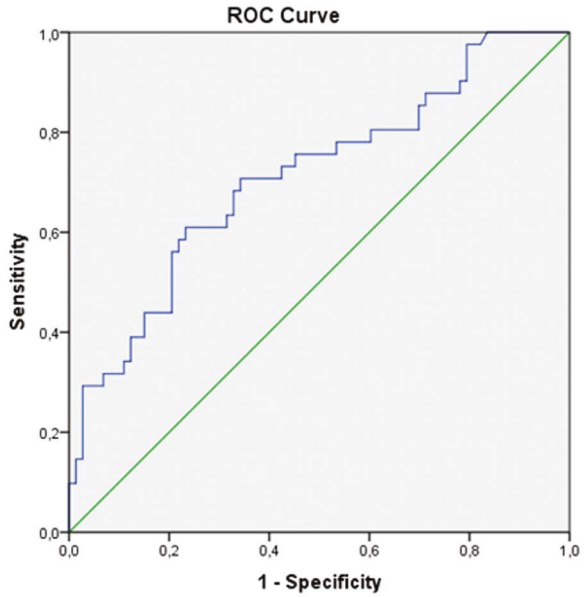

Figure 2. Receiver operating characteristic (ROC) curve anaylsis for systemic inflammation response index score

Table 1. Comparison of hematologic parameters in persistent and non-persistent human papilloma virus (HPV) groups

Variable	Persistent HPV	Non-persistent HPV	p value
Number	41	73	
NLR	2.6 (1.2)	1.8 (0.5)	0.0001
PLR	149 (54)	125 (34)	0.005
MLR	0.28 (0.1)	0.2 (0.05)	0.0001
SIRI	1.2 (0.5–5.7)	0.85 (0.3–2.6)	0.0001

NLR — neutrophil/lymphocyte ratio; PLR — platelet/lymphocye ratio; MLR — monocyte/lymphocye raito; SIRI — systemic inflammation response index

vical cancer. The cut-off value was 2.8, 135, and 0.29, respectively [9]. Another large cohort study found higher NLR, PLR, and MLR values significantly related with worse overall survival in cervical cancer, cut-off values were 2.4, 118, 0.26, respectively [19]. Our research also supports these results, and besides, as a new marker, SIRI could be predictive for persistent HPV infection. Our study's cut-off values were 2.6, 149, and 0.28, respectively, and 0.6 for SIRI. Nearly 10% of HPV infections tend to persist, most of them could clear spontaneously, and about 2% of them persist as a chronic disease and proceed to heterogenous dysplastic changes as LSIL or HSIL. The etiologic role of persistent infection with high risk-HPV in pre-malign lesions and cervical cancer is well known [20, 21]. That's why determining high-risk HPV types and follow-up for persistence are essential to diagnose cancer and early treatment if possible. This study found that SIRI is an easy and cheap method to predict the disease's persistence.

Increased neutrophil counts following chemotherapy can cause a worse prognosis in biliary tract cancer [22]. Furthermore, peripheral absolute lymphocyte count has a predictive value for tumor shrinkage and survival in cervical cancer patients following the definitive chemoradiation. Besides, post-treatment lymphopenia was correlated with decreased overall survival [23, 24]. In a meta-analysis including 26 studies and more than 10.000 patients diagnosed with gynecologic cancers, reported that NLR higher than 2.95 was correlated with worse overall survival (OS) [hazard ratio (HR) 1.65, 95% confidence interval (CI), $p < 0.001$] [25]. To our knowledge, there is no study found any relation between the HPV and hematologic parameters other than oropharyngeal cancer. Our research found that persistent HPV can cause higher NLR, PLR, MLR, and SIRI values than the non-persistent type. We can all agree that it is easy to check these parameters while screening for HPV in the general population. According to the results, recommendations can be given to the patients such as short-term follow-up periods, different vaccination schedules, or detailed histologic analyses because of the higher value of those hematologic parameters more risk for cervical cancer.

It was not our primary aim, but there are much recent data about molecular and inflammatory pathways. HPV viruses aid carcinogenesis by exacerbating the accumulation of UV-induced DNA breaks and somatic mutations with the expression of viral oncoproteins E6 and E7. E6 oncoprotein make a complex with p53 tumor suppressor protein, E7 protein binds to retinoblastoma (Rb) protein and both deploy the cell cycle checkpoints and cause a genomic instability then increase transformation rate of cells [26]. Furthermore, CD8+ T cells were limited to the stroma of dysplastic epithelium. They were missing in the lesioned epithelium of persistent cervical lesions and HPV-related malignancies; the presence of a cytotoxic CD8+ T cell infiltration correlates with increased patient survival [27]. In addition, Patients with chronic HPV infection had greater local and circulating Treg frequencies than those with regressed lesions. E-cadherin, an adhesion molecule, plays a glue role in persistent HPV infection between the Langerhans cells and keratinocytes [28]. Lastly, more recent mechanism investigated keratinocytes (KCs) and antigen-presenting cells (APC). KCs are a component of the innate immune system and express several toll-like receptors (TLRs) which trigger type I interferon (IFN) release and proinflammatory cytokines such as tumor necrosis factor α (TNF-α) and interleukin 1 β (IL1-β) [29]. Active HPV infection and/or expression of E6/E7 oncoproteins were linked to depletion of intraepithelial LCs in cervical precancerous lesions and invasive malignancies.

Furthermore, collecting LCs in biopsy specimens is significantly associated with clearance of HPV infection in the cervix [30]. Also, it has shown that APCs were gradually disappeared through the epidermis in HPV-related skin warts [31]. Taken together, all these data can show that LCs has unique role to control the HPV-induced lesions, and inhibition of LC function and infiltration might be an immune escape mechanism of HPV infections [32].

We have some limitations, such as the retrospective study, and we did not compare it with the healthy control group. Still, our primary aim was to investigate differences between the persistent and non-persistent group of HPV. HPV colonization was only limited to the cervix. It does not consider anal or oral colonization. Also, a relatively small number of patients was another limitation of this study.

On the other hand, there is no standardization for the screening and follow-up of HPV infection. P16 detection is a helpful method for differentiating HSIL and LSIL in cervical lesion [33]. Besides, predicting persistent HPV infection to prevent cancer progression is not easy, and DNA based methods such as p16 detection are not usable worldwide. That's why our research is valuable, as the test is easily applicable in most clinics, and it could lead the way to plan the follow-up for the patients. However, prospective studies with larger patient populations are still needed.

CONCLUSIONS

In conclusion, persistent HPV disease can easily be predicted with elevated SIRI, NLR, and other hematologic parameters. Managing these patients should include different algorithms to prevent cervical cancer.

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Conflict of interest

None.

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Do women play sports while pregnant?

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ABSTRACT

Objectives: The aim of the study was to evaluate the relationship between sociodemographic factors, perinatal data and physical activity in pregnancy, to determine the sources of information about physical health that pregnant women got from and preferred types of sport activities before and during gestation.

Material and methods: The study included 247 pregnant women who fulfilled a questionnaire.

Results: 73.7% of respondents declared doing sport in pregnancy. The preferred types of pre-pregnancy activities were walking, riding a bicycle and swimming. It did not change during pregnancy, but more women declared swimming than cycling. In general, the females chose each type of activity less often in pregnancy than before, except pilates, of which that frequency did not change. The respondents declared that they ran, swam, did aerobics, roller skating and rode a bike significantly less often in pregnancy in comparison to the pregestational period. The sociodemographic factors that influence the physical activity were age, education and net income. The incidence of cesarean section was significantly higher among physically inactive women comparing to those, who declared physical activity during pregnancy. Fifty-five point one percent of survey respondents declared barriers precluding sport activities. The most of women got the information about physical activity from the Internet, books or magazines and an obstetrician.

Conclusions: Pregnancy has an impact on the type of chosen physical activity. The sport activities are dependent on age, education and salary. The active women have 30% lower risk for cesarean section in comparison to inactive respondents. Finally, a great group of women gets the information about proper physical activities during pregnancy from unreliable sources.

Key words: physical activity; sport; pregnancy; perinatal outcomes

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INTRODUCTION

Physical activity in pregnancy has not only minimal risk but primarily is related with many benefits for both mother and fetus [1]. The regular and supervised exercise program throughout pregnancy does not affect fetal well-being, but above all improves maternal physical condition and cardiovascular efficiency [2]. However, due to the changes in women's body during pregnancy, some modifications should be made regarding the physical activity. From a medical point of view, also pregnancy complications should be considered. According to the American College of Obstetricians and Gynecologists Committee opinion, the pregnant women should implement the exercises of moderate intensity for at least 20 to 30 minutes a day for the most or even all days a week [1].

Recommended forms of physical activity during pregnancy are as follows: aerobic, cross-country skiing, Nordic walking, pelvic floor exercise, stationary cycling, strengthening, stretching, walking, water exercise, swimming and yoga [3]. Moreover, Spanish recommendations give an example of activity to do with a caution which include bowling, cross-country skiing, horseback riding, golf, gymnastics, mild jogging and racquet sports [4].

Regular physical activity in gestational period helps to maintain proper weight and physical fitness, reduces the risk of diabetes mellitus and ensures the mood stability [5–7]. It improves glycemic and gestational weight control and decreases the risk of preeclampsia [8]. Furthermore, physical activity during gestation may increase the success rate of vaginal birth after previous cesarean section [9].

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Table 1. The general characteristics of survey respondents

Characteristics	Physically active (n = 182)	Physically inactive (n = 65)	p-value
Age (years, Mean ± SD)	30 ± 5	31 ± 5	ns
BMI (kg/m^2, Mean ± SD)	22.7 ± 3.7	23.2 ± 6.1	ns
Gestational weight gain (kg/m^2, Mean ± SD)	11 ± 6	9 ± 8	ns
Gravidity (n, Median; Min-Max)	1 [0–6]	1 [0–6]	ns
Parity (n, Median; Min-Max)	1 [0–5]	1 [0–4]	ns
Work activity (%) before pregnancy during pregnancy	 89.6 63.7	 81.5 50.8	 ns ns

Table 2. The diseases and pregnancy complications of survey respondents

Diseases and pregnancy complications (%)	Physically active (n = 182)	Physically inactive (n = 65)	p-value
Chronic arterial hypertension	4.4	4.6	ns
Pregnancy induced arterial hypertension	4.9	3.1	ns
Gestational diabetes mellitus	9.3	10.8	ns
Anaemia	8.8	4.6	ns
Polyhydramnion	2.2	1.5	ns
Oligohydramnion	1.1	4.6	ns
Premature membrane rupture	3.8	4.6	ns
Fetal growth restriction	3.8	3.1	ns
Cervical insufficiency	5.5	3.1	ns
Threatening preterm delivery	20.3	15.4	ns
Threatening miscarriage	7.7	4.6	ns
Spinal pain	70.3	55.4	**< 0.05**

Objectives

The aim of the study was to evaluate the association between sociodemographic factors and physical activity in pregnancy. Moreover, the objective was to determine the preferred types of physical activity before and during gestation, comparison of perinatal data between physically active and inactive women. Furthermore, we would like to check the sources of information about physical health and barriers to do sports among pregnant respondents.

MATERIAL AND METHODS

The study included 247 pregnant women who delivered a child in the Obstetrics and Gynecology Hospital University of Medical Sciences in Poznan. The patients signed informed consent and fulfilled a questionnaire. The survey included general questions concerning the age, place of residence, education, type of work, net income and pregnancy complications. The next part of the questionnaire referred to the kind of physical activity before and during pregnancy, subjective assessment of physical condition, sources of information about exercises during pregnancy and perinatal data. The patient's characteristics and diseases were presented in the Tables 1 and 2.

The calculations were made in Microsoft Excel 2010 and in Statistica Statsoft 13.1. The Gaussian distribution was checked using Kolmogorov-Smirnov test and Lilliefors test. If the data met the assumptions of normal distribution the t-Student test was used, if not the Mann-Whitney test was performed. The data in nominal scale were calculated using Chi-square statistic or Fisher's exact test if the expected values were less than five. In reference to the Fisher's exact test the two-sided p-value was considered. The data that fulfilled the assumptions of Gaussian distribution were described as Mean (M) and Standard Deviation (SD), otherwise as Median and Minimal and Maximal value. The results in nominal scale were presented in percentages. The significance level was assumed as p-value below 0.05. The data collected in the Tables 2 and 3 were the multiple questions.

RESULTS

Seventy-three-point three percent of survey respondents declared doing sport in pregnancy. The preferred

Table 3. Kind of physical activity before and during pregnancy

Physical activity (%)	Before pregnancy (n = 247)	During pregnancy (n = 247)	p-value
Walking	75.3	72.1	ns
Running	10.1	1.2	**< 0.0001**
Roller blading	6.5	2.4	**< 0.05**
Riding a bicycle	29.1	10.5	**< 0.0001**
Swimming	19.0	11.3	**< 0.05**
Team games	2.0	0.8	ns
Nordic walking	3.2	2.0	ns
Aerobics	13.8	4.9	**< 0.001**
Gym	4.0	1.2	ns
Pilates	2.0	2.0	ns
Yoga	5.3	4.0	ns
Other	3.2	0.8	ns
None	16.6	26.3	**< 0.01**

types of pre-pregnancy activities were walking (75.3%), riding a bicycle (29.1%) and swimming (19.0%). It did not change significantly during pregnancy, but more women declared swimming (11.3%) than cycling (10.5%). In general, the females chose each type of activity less often in pregnancy than before, except pilates that frequency did not change (2.0%). The respondents declared running (10.1 vs 1.2%, $p < 0,0001$), swimming (19.0 vs 11.3%, $p < 0.05$), doing aerobics (13.8 vs 4.9%, $p < 0.001$), roller blading (6.5 vs 2.4%, $p < 0.05$) and riding a bike (29.1 vs 10.5%, $p < 0.0001$) significantly less often in pregnancy in comparison to the pregestational period (Tab. 3).

The sociodemographic factors that influence the physical activity were age, education and net income. The most active women were between 26 and 30 years old (78.5%), the least between 31 and 35 (68.8%). The significant differences according to the percentage of women who were active during pregnancy were observed between all age groups. The women with higher education level were significantly more physically active than those with basic, vocational or secondary one (78.0% vs 63.5%, $p < 0.05$). The most of active females were in group who earned between 3000 and 6000 Polish Zloty (78.2%) and the number of active women was significantly higher in comparison to those with lower salary (78.2 vs 69.3%, $p < 0.05$). Any significant association according to the place of residence or type of work' performed and physical activity was observed (Tab. 4).

The incidence of cesarean section was statistically higher among not exercising women comparing to those who were physically active during pregnancy (58.5 vs 40.7%, $p < 0.0001$). The physically inactive women were nearly two-fold [OR 2.05 (95% CI: 1.15–3.65); $p < 0.05$] more likely to have cesarean section with about 40% of higher relative risk [RR 1.43 (95% CI: 1.09–1.88); $p < 0.01$] for this mode of delivery than active respondents. Because the frequency of cesarean section did not correlate with age, BMI, gestational weight gain, term of delivery, newborn birth weight, gravidity, parity, arterial hypertension, gestational diabetes mellitus and fetal growth restriction, we did not evaluate the aOR. Any significant difference according to the term of delivery, duration of the first and the second stage of labor, perineal excision, oxytocin administration, the other modes of deliveries, fetal weight or length and Apgar score in the first and in the fifth minute was observed (Tab. 5).

Fifty-five-point one percent of survey respondents declared barriers precluding sport activities during pregnancy. The patients listed pregnancy complications (32.0%), feeling unwell (19.0%) and aversion to physical activity (4.1%).

The most of pregnant women got the information about physical activity from the Internet (51.0%), books or magazines (45.3%) and doctors (31.1%). Moreover, the other pointed sources of knowledge were schools of childbirth (20.6%) and midwifes (15.8%). They gained information from TV (13.0%), family or friends (8.5%) and physiotherapists (3.2%) the least often. Even about one tenth of women (9.3%) had no information about proper physical exercises during gestation.

DISCUSSION

The increasing rate of obesity and its consequences is one of the major public health concerning problem. Pregnant women belong to the high risk's group of excessive weight gain so regular physical activity and its protective benefits constitutes a fundamental part of both the mother and fetus well-being [10]. We checked the behaviors

Table 4. Association between physical activity in pregnancy and sociodemographic factors

Parameter	Physically active (n = 182)		Physically inactive (n = 65)		p-value
	n	%	n	%	
Age [years]					
≤ 25	30	75.0	10	25.0	
26–30	73	78.5	20	21.5	**< 0.0001**
31–35	55	68.8	25	31.2	
> 35	24	70.6	10	29.4	
Place of residence					
Urban areas	120	74.1	42	25.9	ns
Rural areas	62	72.9	23	27.1	
Education					
Basic, vocational or secondary	47	63.5	27	36.5	**< 0.05**
Higher	135	78.0	38	22.0	
Marital status					
Unmarried	25	13.7	14	21.5	ns
Married	153	84.1	50	76.9	
Divorced	4	2.2	1	1.5	
Type of work					
Sitting	122	75.3	40	24.7	
Physical	51	70.8	21	29.2	ns
Student	6	75.0	2	25.0	
Unemployed	3	60.0	2	40.0	
Net income [PLN]					
≤ 3000	61	69.3	27	30.7	
3000–6000	86	78.2	24	21.8	**< 0.05**
6001–10000	24	70.6	10	29.4	
> 10000	11	73.3	4	26.7	

Table 5. The association between physical activity in pregnancy and perinatal data

Perinatal data	Physically active (n = 182)	Physically inactive (n = 65)	p-value
Term of delivery (week, Mean ± SD)	39 ± 2	38 ± 2	ns
1st stage of labour (hours, Mean ± SD)	7 ± 6	6 ± 3	ns
2nd stage of labour (minutes, Mean ± SD)	46 ± 54	33 ± 21	ns
Episiotomy [%]	42.9	45.9	ns
Oxytocin administration [%]	24.2	16.9	ns
Mode of delivery [%] Spontaneous	49.5	38.5	ns
Cesarean secion	40.7	58.5	**< 0.0001**
Instrumental vaginal	9.9	3.1	ns
1-minute Apgar score (points, Median; Min-Max)	10 [1–10]	10 [7–10]	ns
5-minute Apgar score (points, Median; Min-Max)	10 [3–10]	10 [10–10]	ns
Birth weight (g, Mean ± SD)	3328 ± 589	3408 ± 585	ns
Birth length (cm, Mean ± SD)	55 ± 4	55 ± 3	ns

and attitude to physical activity of women hospitalized in the tertiary care center.

In our study, from all physical activities, the respondents preferred walking (72.1%), swimming (11.3%) and riding a bicycle (10.5%). The most common types of physical activity during pregnancy in Stadnicka et al. [11] study were walking (38.2%), fitness (27.6%), yoga (18.4%) and pilates (32.9%). Moreover, in contrast to the cited study, only small amount of our respondents declared aerobic (4.9%), yoga (4.0%) and pilates (2.0%).

Our study revealed the association between doing sport and age, education, salary. The most active group were women between 26 and 30 years old (78.5%). The high educated females declared doing sport activities statistically more often (78.0%). Moreover, the group of women, who earned between 3000 and 6000 Zloty was more ac-

tive (78.2%) than females with the lowest salary (69.3%). According to the study of Stadnicka et al., physical activity in pregnancy was dependent on education, place of residence, professional status and age. The most active women were below 25 (59.3%) and between 26 and 30 (58.6%) years old. The respondents with higher education and from urban areas were more active during gestation. Moreover, the professionally active females and students did different types of sport more often than non-working women [11]. Furthermore, Lindqvist et al. observed that women, who achieved recommended level of physical activity in pregnancy had lower BMI, very good or good self-rated health and higher educational level [12]. Szatko et al. [13] observed that higher education was associated with greater awareness of the beneficial impact of physical activity on the course of pregnancy, while no relationship was noted between respondents' place of residence and physical activity, like in our study, but both pregnant and non-pregnant women participated in the survey.

Our analysis revealed that inactive females had statistically more often cesarean section. Other perinatal data were comparable in both groups. Stadnicka et al. revealed that physical activity had significant influence on the mode of delivery, onset of spontaneous contractions and close to the statistical significance impact on the rate of perineum damage during delivery. The active women had spontaneous contractions (57.0%) and delivered physiologically (55.6%) more often. Perineum incision or rupture was observed less often among active females, but it was a result on the verge of statistical significance (45.0%) [11]. Many studies checked the association between physical activity and perinatal data. Clapp et al. noticed decreased rate of cesarean sections among active women [14–15], what our study proved. Most studies did not show any relationship between frequency of cesarean section and sport activities [14, 16–24]. Clapp et al. observed significantly lower occurrence of vaginal operative delivery [14, 15], whereas other researchers did not notice such observation [14, 16, 17, 19–21, 24–26]. Melzer et al. revealed lower rate of vaginal operative labor after adjusting for parity, maternal weight gain and newborn birth weight [14, 23]. Takami et al. observed that instrumental delivery rate increased among group with very low physical activity level's group compared to the medium one. Furthermore, the occurrence of cesarean section in the low active group and instrumental delivery in the high active group were higher than the risks in the group of medium activity [27]. The shorter labor was observed by Clapp et al. [14, 15]. Moreover, Melzer et al. and Dias et al. observed shorter second stage of labor without differences in duration of the first stage [14, 23, 24]. Contrary, Ghodsi et al. noticed shorter first stage of the labor but similar duration of the second stage [14, 28]. Interestingly, Megann et al. observed prolongation of the labor among heavy exercise group. Other studies did not reveal differences according to the labor length [14, 16, 19, 20, 25, 26] as in our study. Most researchers did not observe significant differences in frequency of episiotomy [14, 16, 19, 21, 23, 24, 28] as in our study but Clapp et al., Kardel et al. and Salvesen et al., independently, noticed decreased rate of this procedure among active women [14, 15, 25, 26]. Our study did not show any difference in Apgar score according to physical activity in pregnancy, what is compatible with many other studies [14, 20, 23, 26]. On the other hand, Clapp et al. observed higher Apgar score among active women [14, 15].

Forty-six-point two percent of our respondents declared permanent or temporary barriers to sport activities because of pregnancy complications (32.0%), feeling unwell (19.0%) and aversion to physical activity (4.1%). Some women had more than one reason for restricting their sport activity. According to the study of Stadnicka et al., the causes of physical inactivity during pregnancy were lack of time (51.4%), barrier of access to physical classes (44.6%), fear of losing pregnancy (23.0%) and other (14.9%) [11]. On the other hand, the most frequent contraindications reported by Wojtyła et al. included uterine contractions (39.0%), cervical incompetence (11.0%) and past obstetrical history (10.0%). Nearly two-fold more of females declared barriers to sport activities than in our study (96.0 vs 55.1%) [29]. In independent Wojtyła et al. study, 69.4% of women had limitations to physical activity in pregnancy and the most often causes to avoid sport were fear of normal course of pregnancy (59.9%) and doctor's recommendations (32.3%) [30].

The most of our respondents got the information about proper physical activities in pregnancy from the Internet (51.0%), books or magazines (45.3%) and doctor (31.1%). The above-mentioned sources of information were also the most common in the study of Szatko et al. [13]. Torbé et al. [31] observed similar preferences, but the survey respondents based on knowledge from the doctor only in 2%. Basing on the other persons experience was placed on the third position. In the study of Mercado et al. most women received information from books (60.6%) or the Internet (58.3%). Physicians, dietitians or nurses advice were declared by 55.6%, 48.2%, and 33.9% of respondents, respectively [32], so the percentage of probably reliable knowledge was much higher than observed.

CONCLUSIONS

Our study revealed that pregnancy has an impact on the type of chosen physical activity. The pregnant women chose running, roller blading, riding a bicycle, swimming and aerobic less often than before. The most popular physical activity is walking both before and during gestation. Statistically more women resign from doing sport in pregnancy comparing to the periconceptional period. Moreover, the level

of physical activity during gestation are dependent on age, education and salary. Women aged 26–30 years old, higher educated and with income between 3000–6000 Zloty are more active during gestation. Furthermore, the physically inactive women have appropriately two-fold higher chance of cesarean section with about 40% of higher relative risk for this mode of delivery than active respondents. Almost half of pregnant women declares permanent or temporary barriers for physical activity because of pregnancy complications, bad mood and aversion to exercises. Finally, a great group of women gets the information about proper physical activities from unreliable non-medical sources or do not achieve it at all. Because of the importance of physical activity both for mother and fetus well-being, physicians should implement programs for appropriate planning of exercises after considering contraindications and complications of pregnancy.

Conflict of interest

All authors declare no conflict of interest.

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A study on non-invasive prenatal screening for the detection of aneuploidy

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ABSTRACT

Objectives: To explore the feasibility of clinical application of non-invasive prenatal screening to detect aneuploidy diseases.

Material and methods: A total of 14,574 singleton pregnant women who underwent Non-invasive prenatal testing (NIPT) in the Southern Hospital from 2015 to June 2017 were selected, and 6471 pregnant women with twin pregnancy who underwent NIPT in the laboratory of Bei Rui He Kang Southern Hospital from June 2016 to October 2017 were included in this study. We analyzed NIPT screening efficiency (sensitivity, specificity) in twin pregnancies and singleton pregnancies, compared the positive detection rate of NIPT in patients with or without clinical symptoms. All NIPT high-risk results were validated by karyotyping, which were further verified by the follow-up physical examination of the neonatal.

Results: A total of 68 cases of twin pregnancy abnormalities were detected by NIPT, including 18 cases of trisomy 21, 6 cases of trisomy 18, 1 case of trisomy 13, 39 cases of Spinocerebellar ataxias (SCAs), and 4 cases of other chromosomal abnormalities. The sensitivity for trisomy 21, 18, and 13 and sex chromosome abnormality was 100%; the specificity for trisomy 21, 18, and 13 and sex chromosome abnormality was 99.97%, 99.95%, 99.97%, and 99.91% respectively. The screening efficiency was similar to that of singleton pregnancy, indicating that the NIPT technology in our laboratory for screening for aneuploidy diseases in twin pregnancy has reached the accuracy level of singleton pregnancy screening. There was a statistical difference between the risk group and the non-risk group in pregnant women with singleton pregnancy. The screening efficiency of NIPT was higher in pregnant women in the risk group, which implies that the clinical application of NIPT is inclined to detect high-risk group.

Conclusions: Non-invasive prenatal testing (NIPT) is a rapid and safe screening method with high efficiency. Non-invasive prenatal testing (NIPT) is used for the screening of aneuploidy in twin pregnancy. The efficiency is similar to that of singleton pregnancy, indicating the feasibility of clinical application. However, the efficiency of NIPT screening tends to favor the detection in high-risk groups.

Key words: twin pregnancy; non-invasive prenatal test (NIPT); chromosomal aneuploidy

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INTRODUCTION

With the implementation of the second-child policy and the application of assisted reproductive technology, 20––30% of live births related to assisted reproductive technology are twins, and the number of twin pregnancies is increasing rapidly [1]. Traditional serological screening for singleton pregnancy has a better performance than twin pregnancy, so there is an urgent need for a reliable twin pregnancy screening method [2]. Non-invasive prenatal test (NIPT) is a method using massively parallel sequencing technology to sequence free fetal DNA fragments in maternal plasma. Previous studies have shown that NIPT has high sensitivity and specificity for trisomy 21, 18, 13 and sex chromosome abnormalities in singleton pregnancies [3]. However, there is a very limited studies applying NIPT to twin pregnancy screening, especially the ones with large sample size [4]. Multiple health organizations are calling for the need of NIPT in twin pregnancy screening for aneuploidy research [5–7]. This study aimed to describe the effectiveness of NIPT in detecting aneuploidy in 6471 cases of twin pregnancy,

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and to provide statistical basis for the feasibility of NIPT in clinical detection of aneuploidy in win pregnancy.

MATERIAL AND METHODS

Research subjects

From 2015 to 2016, a total number of 6471 pregnant women who carried twin pregnancies in Bei Rui He Kang Southern Hospital database. The inclusion criteria: gestational week of blood collection 12–24 weeks (median gestational week 16.83 weeks); early pregnancy ultrasound determined to be double Fetal pregnancy; pregnant woman weight ≤ 100 kg; no history of chromosomal abnormalities in both spouses; no allogeneic blood transfusion, transplantation, cell therapy or immunotherapy within one year. This study has been approved by the Ethics Committee of Southern Medical University, and all pregnant women who participated in the study signed an informed consent form.

Methods

After genetic counseling, pregnant women with twins voluntarily chose NIPT. When the result was high-risk, invasive prenatal diagnosis was further performed for verification. If the result was low-risk, follow-up examination was performed regularly until the newborn was born. If the ultrasound results were abnormal, an invasive prenatal diagnosis was performed to confirm the chromosome karyotype, and the newborn was subject to routine physical examination.

Procedures

NIPT high-risk results were subject to cell chromosome karyotype analysis and verification, or first interrogating the newborn's physical examination record and then completed the chromosome karyotype test to clarify chromosomal abnormalities with the consent of the parents; all non-invasive prenatal screenings were independently completed on the experimental platform of the Bei Rui He Kang Southern Hospital, and the karyotype results were independently examined in the cytogenetic laboratories; the low-risk results were followed up by telephone interrogation.

Non-invasive prenatal screening and data analysis

1) Sample extraction: extract 10 mL of peripheral blood from pregnant women, centrifuge at 1600 rpm for 10 min at 4°C, and distribute the supernatant to 2.0 mL centrifuge tubes; 2) Automated library construction: Extract DNA with magnetic beads, fill in the ends, connect the adapters, 3) Library purification: magnetic bead purification; 4) Library quality inspection: automated fluorescence quantitative PCR for library quality inspection, quality control qualified libraries were automatically pooled to obtain the mixed library required for sequencing, and then proceed to the next step of on-machine sequencing using sequencing platform: illumina NextSeq CN 500; 5) Data analysis: transfer the computer data to the Bebian data analysis system, perform sequence comparison and statistical analysis of the data, and obtain the Z value. The cutoff for the positive was Z = 3.0, when the absolute value of Z less than 3, the risk of chromosome aneuploidy was considered low; and the absolute value of Z was greater than 3, and the risk of chromosome aneuploidy was considered high.

Verification of non-invasive prenatal screening results

All high-risk results were verified by chromosomal karyotyping. If the patient had not undergone prenatal diagnosis, the conditions of the newborn was followed up by telephone until delivery. The electronic record of the medical conditions was also checked, and the type of aneuploidy was determined according to the physical examination of the neonatologist. In other cases, the karyotype results of the newborn were re-collected.

The follow-up

The follow-up of the newborns was jointly completed by Southern Hospital and Bei Rui He Kang Southern Hospital. The content of the follow-up included the content of color Doppler ultrasound structure screening during pregnancy, and abnormal appearance, development, and intellectual development of the newborn after birth. Because the aneuploidy disease also displayed typical characteristics in the appearance, it can be judged whether it is a true positive case through the physical examination of the newborn.

Statistical analysis

SPSS22.0 statistical software was used for statistical analysis. Quantitative data were expressed as mean ± standard deviation, and count data were expressed as rate. The sensitivity, specificity, false positive rate and other indicators of non-invasive prenatal screening were calculated.

RESULTS

Results of NIPT

Demographic information is as follow: in the total 6471 cases of twin pregnancy pregnant women, the average age of pregnant women was 30.91 years, of which the percentage of samples (≥ 35 years old) is 24.32%, and the percentage of samples (< 35 years old) was 75.68%. The average gestational week of blood sampling for pregnant women was 16.83 weeks. A total of 68 abnormalities were detected, including 18 cases of trisomy 21, 6 cases of trisomy 18, 1 case of trisomy 13, 39 cases of Spinocerebellar ataxias (SCAs), and 4 cases of other chromosomal abnormalities (Tab. 1).

Table 1. Non-invasive prenatal screening data of 6471 pregnant women with twin pregnancy

Chromosome Abnormality	Ture positive	True negative	False negative	False positive	Sensitivity	Specificity	Rate of false negative	Rate of false positive	PPV*	NPV*	Yorden Index
T21	18	6451	0	2	100.00	99.97	0.00	0.03	90.00	100.00	99.97
T18	6	6462	0	3	100.00	99.95	0.00	0.05	66.67	100.00	99.95
T13	1	6468	0	2	100.00	99.97	0.00	0.03	33.33	100.00	99.97
Sum of above three	25	6439	0	7	100.00	99.89	0.00	0.11	78.1	100.00	99.89
SCAs	39	6426	0	6	100.00	99.91	0.00	0.09	86.67	100.00	99.91
Abnormality-other chromosomes	4	6466	0	1	100.00	99.98	0.00	0.02	80.00	100.00	99.98
Sum	68	6389	0	14	100.00	99.78	0.00	0.22	82.93	100.00	99.78

*PPV — positive predictive value; *NPV — negative predictive value

Table 2. Non-invasive prenatal screening data of 14,574 singleton pregnant women in Southern Hospital from 2015 to June 2017

Chromosome Abnormality	Ture positive	True negative	False negative	False positive	Sensitivity	Specificity	Rate of false negative	Rate of false positive	PPV*	NPV*	Yorden Index
T21	45	14525	1	3	97.83	99.98	2.17	0.02	93.75	99.99	97.81
T18	9	14562	0	3	100.00	99.98	0.00	0.02	75.00	100.00	99.98
T13	4	14569	1	0	80.00	100.00	20.00	0.00	100.00	99.99	80.00
Sum of above three	58	14508	2	6	96.67	99.96	3.33	0.04	90.63	99.99	96.63
Sex chromosomes	17	14532	1	24	94.44	99.84	5.56	0.16	41.46	99.99	94.28
Others	2	14559	0	13	100.00	99.91	0.00	0.09	13.33	100.00	99.91
Sum	77	14447	3	43	93.90	99.70	3.75	0.30	64.17	99.98	93.60

*PPV — positive predictive value; *NPV — negative predictive value

Table 3. Comparison of detection rate of abnormality by NIPT in singleton pregnant women with high and low risk group

Risk group	Detected (case)	High risk (case)	Positive rate(%)	True Positive (cases)	Abnormality detection rate (%)
High-risk	10953	94	0.86	50	53.19
Low-risk	3621	17	0.47	8	47.05
Sum	14574	111	0.76	58	52.25

Statistics — $x^2 = 5.441$; $p = 0.020$

The sensitivity of NIPT for the detection of the three major chromosomal aneuploidies of twin pregnancy is 100%, the specificity is above 99%, and the highest false positive rate is 0.05%. Compared with the NIPT used in the screening of the three major chromosomal aneuploidies in singleton pregnancies, screening results in twins were more sensitive (100%/96.6%) and showed the same specificity (99.9%/99.9%) as the results of singleton pregnancy. Positive predictive value (PPV) for twins was much lower (78.1/ /90.6%) (Tab.1 and 2).

The positive rate (0.86%) of the three major chromosomes (13, 18, 21) of pregnant women in the risk group was higher than that in the non-risk group (0.47%), and the difference was statistically significant. Binomial test: The total positive rate of the test was 0.76%, which was not significantly different from the national positive rate (0.75%) ($p = 0.448$) (Tab.3).

DISCUSSION

Non-invasive prenatal testing (NIPT) has a good performance in single fetal aneuploidy [8]. A current meta-analysis of NIPT for twin pregnancy showed that: T21 detection has a sensitivity 99% and a specificity 100%, T18 has a sensitivity 85% and a specificity 100%, the screening performance of T13 cannot be judged since there was only three cases being detected [9]. The sensitivity of traditional early pregnancy serological screening + Nuchal translucency (NT) combined screening for T21 in twin pregnancy is 89.3% and specific-

ity is 94.6%. Although the screening results are acceptable [10], However, there are also reports that under the same false positive rate, combined screening in the first trimester does not have a higher detection rate than NT screening alone, and it also increases the economic burden of the parents [11]. The second trimester serological screening is used for the detection rate of twin pregnancy aneuploidy diseases and has a high false positive rate. It cannot provide screening for trisomy 13. Therefore, it is not recommended that the second trimester serological screening be used solely for the detection of aneuploidy in twin pregnancies [12]. Serological screening in the first trimester combined with NT and serological screening in the second trimester is an optional program, but more prospective studies are needed for validation [13]. Therefore, the screening of aneuploidy in twin pregnancy, especially for high-risk pregnant women with difficulty in pregnancy, assisted reproductive pregnancy, advanced age, and with high risk of miscarriage, demands for a non-invasive, accurate and simple method.

This study provides a clinical basis for the feasibility of non-invasive prenatal screening for twin pregnancy. The sensitivity of NIPT for the detection of the three major chromosomal aneuploidies of twin pregnancy is 100%, the specificity is above 99%, and the highest false positive rate is 0.05%, which is consistent with the results published in previous studies [14, 15]. Compared with the NIPT used in the screening of the three major chromosomal aneuploidies in singleton pregnancies, screening results in twins were more sensitive (100%/96.6%) and showed the same specificity (99.9%/99.9%) as the results of singleton pregnancy. Positive predictive value (PPV) for twins was much lower (78.1%/90.6%). The screening result of twin pregnancy in this study showed consistent performance with that in singleton pregnancy, which achieved high sensitivity and specificity that are superior to traditional serological screening. However, the positive predictive value of the test for aneuploidy in twins is lower, which may be due to the variable factors such as fetal DNA ratio of twins, chronicity and laboratory technical operations. In fact, the DNA concentration of normal fetuses in twins is higher, which can easily mask abnormal fetal DNA and lead to false results. In 2013, Professor Liang Deyang applied Single Nucleotide Polymorphism (SNP) technology to determine the genomic regions of fraternal twins and derived the proportion of each fetus's DNA to estimate the aneuploidy risk of each fetus. However, this study has a small sample size and future work involving a larger sample size is required to validate the findings [14–16].

In addition to T21, T18, and T13, we also evaluated the effectiveness of NIPT in detecting other chromosomal aneuploidies. In the detection of twins' sex chromosomes, NIPT has achieved high detection efficiency like that of T21, T18, and T13, even higher than that of singletons. It may be because the number of sex chromosomal aneuploidy cases in this study is too low to accurately assess the efficiency of NIPT screening. Zhang, et al. [17], reported that the overall positive predictive value of NIPT for SCA was 54.54%, and Turner syndrome (45, X) was 29.41%. Many organizations such as ISPD have issued guidance on the application of NIPT in sex chromosome aneuploidy [18]. Fetal free DNA sequencing can be used to screen for sex chromosome abnormalities, but the detection rate and false positive rate are not as good as those of the three major chromosomes. Pregnant women should be informed that the positive result may be the mother's fetal sex chromosome abnormalities, and further invasive prenatal examination of maternal chromosomes is needed. However, pregnant women have the right to refuse to do fetal sex chromosome aneuploidy screening [17].

In this study, there were false-positive and false-negative results in single-twin pregnancies, three false-negative cases and 43 false-positive cases were screened out of 14574 singleton pregnant women; 14 false-positive cases were screened out of 6471 twin-born pregnant women. There are many reasons for NIPT false positive and false negative results: 1) Low fetal DNA concentration; 2) Maternal chromosomal abnormalities; 3) Restricted placental mosaicism; 4) Fetal mosaicism; 5) Disappearance of twins. In this study, the total cell-free DNA concentration of twin pregnancies was above the standard required by NIPT, in the massively parallel sequencing, the cell-free DNA concentration of individual fetus could not be measured separately. From the results of placental chromosome karyotype, abnormal maternal copy number and placental mosaicism are the main reasons for inconsistent results. Moreover, the NIPT data analysis method cannot clarify whether the abnormality is caused by maternal copy number abnormality or fetal mosaicism. Therefore, for NIPT copy number abnormalities or chimera results, maternal leukocytes, amniotic fluid cells, and multiple placental tissues should be collected for verification. In addition, the current NIPT based on SNP and targeted sequencing technology has not been routinely used for clinical twin pregnancy screening for aneuploidy.

The overall sensitivity of NIPT for the detection of the three major chromosomal aneuploidies of singletons is 96.67%, and the false positive rate is the highest 0.04%, which are consistent with other reports [3]. Risk factors for singleton detection in this study contain: Tang Si high risk and borderline risk, abnormal fetal ultrasound structure, abnormal fetal ultrasound soft index, and age ≥ 35 years due to delivery. According to statistical analysis, the positive rate of the three major chromosomal aneuploidies in pregnant women with high-risk factors is significantly higher than that

of pregnant women without high-risk factors. More suspected cases can be found in the group of pregnant women with high-risk factors. Therefore, it is advisable that standard guideline for NIPT incorporating risk factors and clinical indications should be established.

In addition, in this study, NIPT also detected a total of six cases of other abnormalities in single and twin pregnancy, including copy number abnormalities, mother or fetus origin, etc., which have also been reported in previous studies [19]. Therefore, non-invasive prenatal screening cannot be used as a prenatal diagnosis method. This point should be explained when genetic counseling is given to patients.

CONSCLUSIONS

At present, NIPT as a prenatal screening technology has been widely used in singleton pregnant women in China. Our research confirms that in twin pregnancy pregnant women, NIPT can still achieve similar detection efficacy and the performance seems to be better than traditional screening. The number of cases of sex chromosome aneuploidy in this study is too low to accurately assess the screening efficiency. However, NIPT can effectively detect aneuploidy of the three major chromosomes and can be included in the current screening system under the premise of strict control of laboratory technical procedures.

Conflict of interest

All authors declare no conflict of interest.

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Evaluation of inflammatory markers in threatened abortions and spontaneous abortions

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ABSTRACT

Objectives: To evaluate the relationship between threatened abortion and inflammation markers such as procalcitonin, neutrophil-lymphocyte ratio and platelet-lymphocyte ratio.

Material and methods: This was a prospective, controlled study. Serum procalcitonin, neutrophil-lymphocyte ratio (NLR) and platelet-lymphocyte ratio (PLR) results of 60 threatened abortions were compared with the results of 60 spontaneous abortions and 60 healthy pregnancies. ROC analyses of procalcitonin, NLR and PLR were performed for threatened abortions. In addition, the threatened abortion group with ongoing pregnancy was divided into two groups according to the presence of hemorrhage area in ultrasonography and re-evaluated in terms of serum procalcitonin levels, NLR and PLR.

Results: Procalcitonin and NLR levels were significantly higher in the threatened abortion group than the abortion and control groups ($p < 0.05$). There was no significant difference between the control and abortion groups. The area under the curve in ROC analysis was within the 95% confidence interval for procalcitonin and NLR and was statistically significant ($p < 0.05$). Among the abortus imminens, which were divided into two groups according to whether there was hemorrhage area on ultrasonography, procalcitonin, NLR and PLR were higher in patients with bleeding area than without bleeding, but this was not significant ($p > 0.05$).

Conclusions: There is an association between procalcitonin and NLR and threatened abortion. Procalcitonin and NLR may support the diagnosis of threatened abortion.

Key words: abortion; neutrophil-lymphocyte ratio; platelet-lymphocyte ratio; procalcitonin; threatened abortions

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INTRODUCTION

Threatened abortion is defined as uterine bleeding without cervical dilation up to the first 20 weeks of pregnancy. It occurs in 16–25% of pregnancies [1]. Only 50% of threatened abortion cases can be treated with current conservative methods. At the end of the first trimester, bleeding in 95–98% of pregnancies with a positive heartbeat by ultrasonography can occur up to the 20th gestational week [2].

Although the etiology of threatened abortion is unknown, there are many hypotheses put forward. Among these hypotheses, it is thought that threatened abortion is triggered by various mechanisms and causes obstetric and neonatal complications in the later stages of pregnancy [2]. One of the hypotheses put forward in threatened abortion is that intrauterine bleeding results from the disruption of the contractile-relaxing mechanisms of the uterus by various uterotonic mediators [3]. The other hypothesis is that a chronic inflammatory reaction develops in the decidua with bleeding. According to this hypothesis, it is stated that this chronic inflammation causes placental development disorders in the later stages of pregnancy and causes obstetric complications (such as preterm labor, premature-preterm rupture of membranes and preeclampsia) [4].

Procalcitonin is the precursor of the calcitonin hormone and is present at undetectable levels in healthy individuals. Its level increases with cytokines released with bacterial infection [5]. In addition, it has been shown that the level is significantly increased in many diseases in which the inflammation process plays a role (end-stage renal disease, congestive heart failure, cirrhosis, acute kidney injuries, intracerebral hemorrhages, post-operative anastomotic leaks) [6–8].

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Like neutrophils, platelets increase the secretion of cytokines at the onset of inflammation, and increased cytokines contribute to the increase in inflammation by increasing the synthesis of new neutrophils and platelets. Like NLR, PLR shows a significant relationship with cancer and inflammatory diseases [9].

Objectives

Since chronic inflammation is thought to play a role in the pathophysiology of threatened abortion, we wanted to evaluate the relationship between threatened abortions and inflammation markers such as procalcitonin, neutrophil-lymphocyte ratio and platelet-lymphocyte ratio in this study.

MATERIAL AND METHODS

Ethical approval for this study was obtained from the Ethics Committee of Amasya University (protocol #121). The results of 60 patients diagnosed with threatened abortion who came to the Amasya Sabunçuoğlu Şerefeddin Training and Research Hospital Gynecology and Obstetrics Clinic between 15 June 2020 and 15 August 2021 were compared with the results of 60 patients who spontaneously aborted after threatened abortion diagnosis and 60 healthy pregnancies. The threatened abortion group was formed from pregnant women who were diagnosed with threatened abortion between six weeks and 20 weeks with vaginal bleeding but no cervical dilation. The abortion group was formed from those who were diagnosed with threatened abortion and then spontaneously aborted. The control group consisted of 60 healthy pregnancies between six and 20 weeks who came to the outpatient clinic for normal controls. Those with hypertension, diabetes, thrombophilia, those diagnosed with hyperemesis gravidarum, those with autoimmune, renal, cardiac or hepatic disease, those with a history of threatened abortion, preeclampsia, gestational diabetes, hellp syndrome in previous pregnancy, those with diseases that may trigger inflammation (such as infectious diseases, collagen tissue disease) and those with fetal anomalies were not included in the study and control groups. Pregnant women with positive fetal cardiac activity and diagnosed with threatened abortion were included in the study. Those with no positive fetal cardiac activity were not included in the study. Pregnant women included in the study with the diagnosis of threatened abortion were not re-evaluated in their subsequent vaginal bleeding. Pregnant women who met the study criteria for threatened abortion, and abortion and control groups were included in the study after they were informed about the study and their consent was obtained.

A Mindray DC-7 ultrasound device was used in the evaluation of pregnancy in the study. Obstetric ultrasonography was performed by a single clinician (S.M.A.). The week of pregnancies, their development, fetal cardiac activity, whether amniotic fluids were normal or not, and whether there was a hemorrhage area around the gestational sac were evaluated by ultrasonography. Age, parity, height, weight, last menstrual period, education level, previous surgery, and whether they had chronic diseases were questioned in terms of demographic characteristics of all three groups. A blood sample was taken into a hemogram tube to evaluate serum neutrophils, lymphocytes, platelets, NLR and PLR, and into a biochemistry tube to evaluate parameters such as procalcitonin, liver and renal functions. In total, blood samples were taken into two separate tubes. Blood samples were taken within the first two hours after spontaneous abortions or diagnosis of threatened abortion.

Neutrophil, lymphocyte and platelet levels were evaluated with laser optics (X N-1000, Siemens, Japan) and procalcitonin with electrochemiluminescence immunoassay (Cobas e 411, Roche, Japan).

The groups were compared in terms of serum procalcitonin, neutrophil, lymphocyte and platelet levels, NLR and PLR. ROC analysis of procalcitonin, NLR and PLR was performed for threatened abortion. The threatened abortion group was divided in two according to the presence of hemorrhage area in ultrasonography and these two groups were also compared in terms of NLR, PLR and procalcitonin.

Power analysis of the study

The sample size of the study was made with the G*Power 3.1 program. It was calculated according to the effect width ($d = 0.66$) and the two-tailed hypothesis method, considering that the incidence of threatened abortion was 16–25% in the study of Farrell et al. [1] and the number of women who gave birth in 2020 in the health institution where the research was conducted ($n = 2154$). It was determined as $1-\beta = 0.95$ and $\alpha = 0.05$. As a result of the calculation, it was determined that there should be 60 women for the control group, 60 women for the experimental group, and a total of 120 women.

Statistical analysis

Data were analyzed with IBM SPSS V23 program. Conformity to normal distribution was examined with Kolmogorov-Smirnov test. Chi-square test and Fisher's Exact test were used to compare categorical variables according to groups. Mann-Whitney U test was used for comparing non-normally distributed data according to paired groups and independent two sample t-test was used for comparison of normally distributed data. One-way analysis of variance (ANOVA) was used to compare normally distributed data for three or more groups, and Kruskal Wallis test was used for non-normally distributed data. ROC analysis

Table 1. Demographic characteristics of the groups

		Threatened abortion n = 60	Spontaneous abortion after threatened abortion n = 60	Healthy pregnancies n = 60	p-value
Age [year]		27.38 ± 5.75	29.58 ± 5.52	28.17 ± 6.29	0.1118
Height [cm]		161.62 ± 5.12	162.23 ± 5.91	160.17 ± 6.06	0.130
Weight [cm]		64.38 ± 12.46	69.38 ± 16.09	66.07 ± 14.38	0.156
BMI [kg/m^2]		24.76 ± 5.30	26.38 ± 5.95	25.76 ± 5.49	0.280
Parity	Nulliparity	29 (48.3%)	25 (41.7%)	23 (38.3%)	0.530
	Multiparity	31 (51.7%)	35 (58.3%)	37 (61.7%)	
Education	Primer school	6 (10.0%)	11 (18.3%)	11 (18.3%)	0.388
	Midlee school	16 (26.7%)	23 (38.4%)	17 (28.4%)	
	High school	18 (30.0%)	12 (20.0%)	18 (30.0%)	
	Univercity	20 (33.3%)	14 (23.3%)	14 (23.3%)	
Previous operation	Yes	14 (23.3%)	17 (28.3%)	11 (18.3%)	0.432
	No	46 (76.7%)	43 (71.7%)	49 (81.7%)	
Chronic disease	Yes	67 (11.7%)	5 (8.3%)	3 (5.0%)	0.418
	No	53 (88.3%)	55 (91.7%)	57 (95.0%)	
Diagnosis week (week)		9.69 ± 3.80	10.11 ± 3.51	10.59 ± 11.16	0.784

P-values were calculated with the One-Way ANOVA Test (age, height, weight, BMI, diagnosis week) and Chi-square test

Table 2. Comparison of procalcitonin, neutrophil, lymphocyte, platelet, NLR and PLR of the groups

	Threatened abortion n = 60	Spontaneous abortion after threatened abortion n = 60	Healthy pregnancies n = 60	p-value
Procalcitonin [ng/mL]	0.050 ± 0.011^a	0.042 ± 0.013^b	0.041 ± 0.015^b	< 0.001
Neutrophil [×10^9/L]	6.40 ± 1.79	6.00 ± 1.92	5.79 ± 1.24	0.130
Lymphocyte [×10^9/L]	2.28 ± 1.76	2.28 ± 0.72	2.24 ± 0.64	0.974
Platelet [×10^9/L]	236.90 ± 48.21	252.78 ± 52.25	249.91 ± 51.97	0.193
NLR	3.17 ± 1.01^a	2.76 ± 0.95^b	2.72 ± 0.74^b	0.012
PLR	121.56 ± 44.62	122.23 ± 47.0	120.04 ± 41.38	0.962

One Way ANOVA Test was used, $^{a-b}$ — there is no difference between groups with the same letter
NLR — Neutrophil Lymphocyte Ratio; PLR — Platelet Lymphocyte Ratio

was used to determine the cut-off values for procalcitonin, NLR and PLR for threatened abortion. The significance level was $p < 0.05$.

RESULTS

The groups were homogeneous in terms of demographic characteristics ($p > 0.05$) (Tab. 1).

Serum procalcitonin level and NLR were significantly higher in the threatened abortion group than in the control and abortion groups ($p < 0.05$). There was no significant difference between the control and abortion groups in terms of these parameters ($p > 0.05$). There was no significant difference between the groups in terms of PLR, neutrophils, lymphocytes and platelets ($p > 0.05$) (Tab. 2).

Serum procalcitonin levels, NLR and PLR for threatened abortions were evaluated by ROC analysis (Tab. 3). In the ROC curve for procalcitonin and NLR, the area under the curve (AUC) was within the 95% confidence interval and was statistically significant ($p < 0.05$) (Fig. 1). Procalcitonin and NLR can therefore be used as suitable parameters for diagnostic decision making in predicting disease. In the ROC curve for PLR, the AUC was not within the 95% confidence interval and was not statistically significant ($p > 0.05$) (Fig. 1).

The threatened abortion group was divided into two groups according to the presence or absence of hemorrhage area on ultrasonography and compared in terms of serum procalcitonin levels, NLR and PLR. Serum procalcitonin levels, NLR and PLR values were higher in those with hemorrhage areas on ultrasonography than those without, but there was no significant difference between the groups ($p > 0.05$) (Tab. 4).

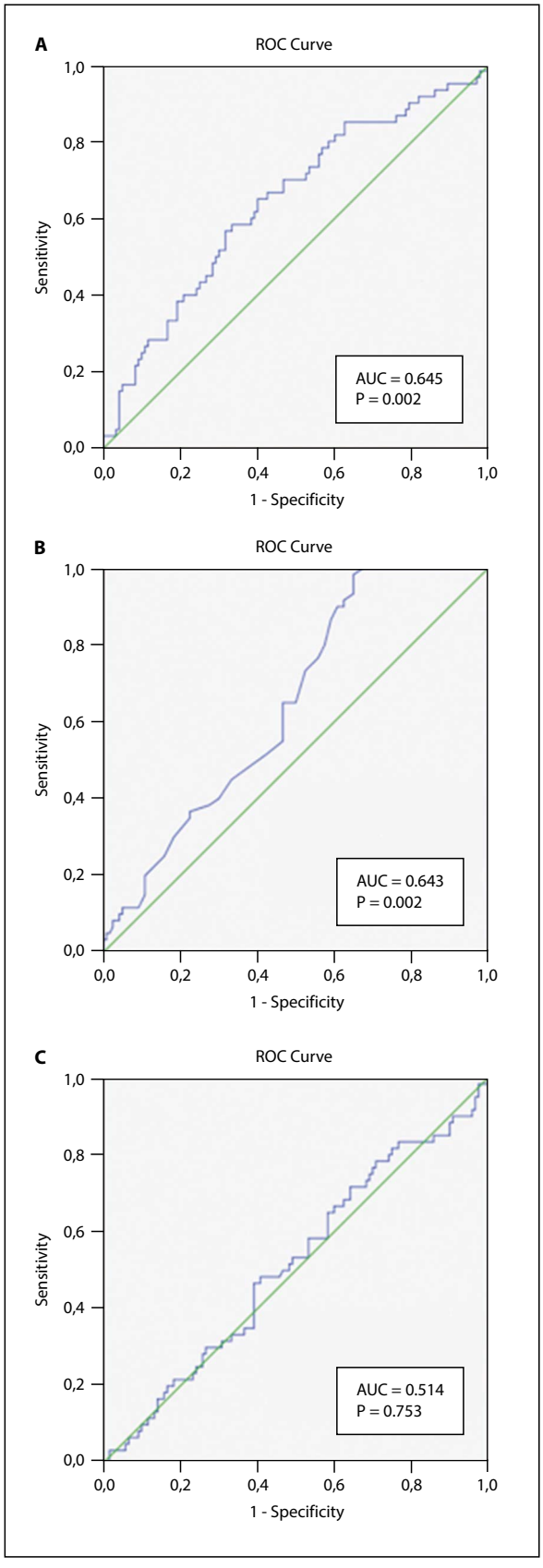

Figure 1. A. ROC curve for procalcitonin; **B.** ROC curve for NLR; **C.** ROC curve for PLR

DISCUSSION

In our study, we evaluated the relationship between procalcitonin, NLR and PLR, which are known inflammatory markers, and threatened abortion due to the chronic inflammatory reaction, which is one of the hypotheses suggested to play a role in the pathophysiology of threatened abortion. For this purpose, we compared the results of 60 threatened abortions with results of 60 spontaneous abortions (after threatened abortion diagnosis) and 60 healthy pregnancies.

In many studies, it has been shown that various obstetric and neonatal complications develop in the later stages of pregnancy due to threatened abortion [4, 10]. The reason for this is that the pathological mechanism that usually causes the underlying threatened abortion causes these various complications in the later stages of pregnancy. If the pathophysiological mechanism causing threatened abortion becomes clear, these complications secondary to threatened abortion could be prevented. For example, in a meta-analysis including 31 studies, it was stated that first trimester bleeding causes very important obsteric complications such as prematurity, intrauterine growth retardation and increased risk of perinatal death [10]. Most of these complications are conditions that increase maternal and fetal morbidity and mortality. Predicting these complications that may occur due to threatened abortion and taking the necessary precautions will reduce this maternal-fetal morbidity and mortality, and thus reduce the cost spent on this issue [11]. One of the hypotheses put forward in the pathophysiology of threatened abortion is the development of a chronic inflammatory reaction in the decidua with bleeding [4]. Inflammation of the fetus or placenta may cause an inflammatory response in the mother [12]. Therefore, in this study, we wanted to evaluate the levels of procalcitonin, NLR and PLR, which are known inflammatory markers and have been shown to be related to diseases based on chronic inflammation, in patients with threatened abortion and spontaneous abortion.

The normal level of procalcitonin is < 0.5 ng/mL [13]. Procalcitonin is produced in large quantities, especially by macrophages and monocytic cells, by up-regulation of the CALC-1 gene, mostly in bacterial infections. The rise of procalcitonin occurs immediately due to its cytokine-like behavior [14]. It reaches a detectable level in 2–3 hours, peaking at the sixth hour. Procalcitonin is also elevated in various non-infectious conditions such as cirrhosis, pancreatitis, mesenteric infraction, burns and aspiration pneumonia [15, 16]. Studies differ in what appropriate negative cut-off points should be used for procalcitonin [15, 17]. For example, serum procalcitonin levels above 0.06 ng/mL in acute heart failure, and in another study, serum procalci-

Table 3. Sensitivity, specificity, positive predictive and negative predictive values for procalcitonin, NLR, and PLR

	Area	P	Cutt-off	Lower	Upper	Sensitivity	Specificity	PPV	NPV
Procalcitonin	0.645	0.002	0.048500	0.565	0.725	0.550	0.467	83.5	65.1
NLR	0.643	0.002	2.8083	0.557	0.729	0.600	0.392	85.0	68.2
PLR	0.514	0.753	114,9604	0.425	0.604	0.517	0.483	73.2	59.7

p-values were calculated according to ROC analysis; NPV — negative predictive value; PPV — positive predictive value

Table 4. Comparison of the two groups formed by separating the threatened abortions as with and without hemorrhage area on ultrasound in terms of procalcitonin, NLR and PLR

	Threatened abortions with hemorrhage area on ultrasound n = 11	Threatened abortions without hemorrhage area on ultrasound n = 49	p-value
Procalcitonin [ng/mL]	0.053 ± 0.004	0.050 ± 0.012	0.117
NLR	3.48 ± 0.99	3.10 ± 1.00	0.257
PLR	135.19 ± 50.34	118.50 ± 43.21	0.266

Independet T Test and Mann-Whitney U test (procalcitonin) were used; NLR — neutrophil lymphocyte ratio; PLR — platelet lymphocyte ratio

tonin levels above 0.05 ng/mL in patients with cirrhosis were found to be significant [8, 18]. In our study, procalcitonin levels were significantly higher than in the abortion and control groups. They were at the same levels in the abortion group and the control group (0.050 ± 0.011, 0.042 ± 0.013, 0.041 ± 0.015 ng/mL, respectively). The significantly higher serum procalcitonin levels in the threatened abortions group confirms the hypothesis of chronic inflammation. The fact that the procalcitonin level was similar in the abortion group and the control group may suggest that this inflammation is impaired by abortion and therefore procalcitonin may be decreased. The half-life of procalcitonin of 24 hours may support this idea [19].

Studies have reported that serum procalcitonin levels differ according to the gestational week. In one study, serum procalcitonin level was 0.043 µg/L at 24–28 weeks of pregnancy, 0.061 µg/L at 36–40 weeks, 0.068 µg/L at birth, 0.200 µg/L on postpartum day 2–3, and 0.060 µg/L on postpartum day 10 [20].

In our study, we found the serum procalcitonin level to be 0.041 ± 0.015 ng/mL in healthy pregnant women in the first trimester. In the threatened abortion group, it was 0.050 ± 0.011 ng/mL and was significantly higher than the healthy pregnancy group. It was also statistically significant in the ROC analysis. In other words, procalcitonin can be used as a suitable parameter as a diagnostic decision maker in predicting threatened abortion. Serum procalcitonin levels were higher in the threatened abortion group with a hemorrhage area on ultrasonography compared to without, but this was not significant. The fact that the serum procalcitonin level was higher in the group with threatened abortion with a hemorrhage area may be due to the persistence of bleeding for a certain period of time and increased triggering of the chronic inflammatory reaction [4].

Most of the studies on NLR and PLR in early pregnancy are studies that compare pregnancies that result in abortion with control groups, in order to evaluate the utility of these parameters as precursors of early miscarriages. In the literature, there is a rare study evaluating NLR and PLR in threatened abortion and spontaneous abortion (after threatened abortion). In the study of Ata et al. [21], NLR and PLR levels were compared between healthy pregnancies, threatened abortions and abortions at early gestational weeks. While there was no difference between the three groups in terms of NLR levels, PLR levels were found to be higher in early pregnancy loss and threatened abortions. In our study, NLR was significantly higher in the threatened abortion group compared to the abortion group and the control group. There was no significant difference between the groups in terms of PLR.

In a study in which NLR in abortions were compared with the first trimester NLR of patients who had a healthy delivery, no significant difference was found between the two groups [22]. While it was reported in another study that low NLR and PLR values were associated with early pregnancy losses, on the contrary, in another study, it was concluded that high PLR and NLR values were associated with early pregnancy losses [23, 24]. In our study, there was no significant difference in terms of NLR and PLR levels in the comparison of abortions with healthy pregnancies.

As in our study, there are other studies evaluating other biomarkers to confirm the presence of an inflammatory process in the etiopathogenesis of threatened abortion. Vascular endothelial growth factor (VEGF), soluble VEGF

receptor-1 (sVEGFR-1) and VEGF/SVEGFR-1 ratio were found to be associated with threatened abortion pathogenesis [25]. Apolipoprotein A-1, amniotic immune biomarkers (IL2β receptor, IL6, IL8, IL10, IL1β and TNFα) have been associated with threatened abortions [26, 27]. A systematic review and meta-analysis of prospective studies have highlighted the role of the biochemical markers' serum progesterone, hCG, pregnancy associated plasma protein A, estradiol and cancer antigen 125 (CA 125) in the prediction of outcome in women with threatened miscarriage. According to the results of this review, serum CA 125 was determined as the marker with the highest predictive value in determining 'probable to continue' pregnancies. Although serum hCG and progesterone biomarkers are most used, they are not useful in predicting the outcome of a pregnancy with a viable fetus [28]. Low PAPP-A values in threatened abortion women is associated with pregnancy failure [29].

The fact that the number of cases in our study is equal to the number of cases detected in the power analysis can be considered as a limitation of the study. As a matter of fact, if the number of our cases were greater, it would have increased the power of our study. The strength of our study is the simultaneous evaluation of the relationship between both abortus immines and abortions, and procalcitonin, NLR and PLR.

CONCLUSIONS

In summary, in this study an association between procalcitonin and NLR and threatened abortion was found. This supports chronic inflammation having a role in the etiopathogenesis of threatened abortion. In addition, an increase in serum procalcitonin and NLR levels in pregnancies may indicate an increase in risk of threatened abortion, and in contrast, a decrease in serum procalcitonin and NLR in threatened abortions may herald spontaneous abortion.

Conflict of interest

All authors declare no conflict of interest.

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Mode of vaginal delivery in breech presentation and perinatal outcome

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ABSTRACT

Objectives: To compare a perinatal outcome in breech presentation depending on different modes of vaginal breech delivery (VBD).

Material and methods: Over the course of 13 years (2005–2018), perinatal outcome of newborns was compared among 98 singleton pregnancies (64 term pregnancies and 34 preterm pregnancies) completed with VBD divided into six groups depending on the mode of delivery used (Bracht, Müller, Thiessen, classical arm release, Mauriceau-Levret-Veit-Smellie (MLVS), and Vermelin´s spontaneous vaginal delivery). Also, maternal demographic parameters were observed.

Results: Of 98 singleton pregnancies, the most frequently used mode was Thiessen (35.71%), followed by MLVS technique (25.51%), Bracht (22.45%), Vermelin (13.27%), classical arm release (2.04%) and Müller (1.02%). Newborns with Apgar score ≤ 7 at 5 min. were transferred to the neonatal intensive care unit (NICU), which included 15.31% of newborns (total 15 newborns: 1 term and 14 preterm newborns). The incidence of episiotomy was 63.27%. Seventy-point five percent of women included in the study were ≤ 35 years of age, and 37.76% were multiparas. Delivery was induced in 7.14% cases.

Conclusions: Less- traumatizing actions during VBD have less harmful consequences and better perinatal outcome. Lower Apgar score was noted with the aggressiveness of the mode of VBD.

Key words: vaginal delivery; breech presentation; delivery mode; perinatal outcome

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INTRODUCTION

Breech presentation occurs in 3–5% of term newborn. While that percentile is higher for preterm newborns (about 20% of newborns), vaginal delivery of breech presentation (VBD) has been the tradition since the 1st century AD. Contemporary vaginal delivery of breech presentation began in the middle of the 20th century with Bracht who published a new method, which was named after him, with minimal interventions for delivering breeches [1]. After that, more and more research had begun in the field of minimal invasive methods in vaginal breech delivery. Later, Vermelin and Thiessen introduced the technique of passive breech management with spontaneous or supported VBD without obstetric intervention [2]. Known methods of delivery according to Müller, Bickenbach, Mauriceau- Lovret- Veit- Smellie and Lövset are used in case of hand and head retention [3, 4]. The Term Breech Trial in 2000 showed a bad perinatal outcome and maternal outcome after VBD [5]. After that study, the number of caesarean deliveries increased rapidly in more countries. Recent studies show that there is no difference in perinatal outcome between vaginal and caesarean delivery [6]. Moreover, they show that elective caesarean delivery is related to abnormal immune response in a newborn, which could possibly explain why children and adults delivered by caesarean section are at greater risk of developing immune diseases and a long-term morbidity (Mb. Chron, allergic diseases, diabetes mellitus, attention deficit hyperactivity disorder (ADHD), autism, etc.) [7, 8]. Also, elective caesarean delivery increases the risk of maternal complications (bleeding, infection, thromboembolism) and complications in other pregnancies (invasive malplacentation, scar pregnancy, uterine rupture, hysterectomy) [9]. The aim of this study was to compare perinatal outcome depending on the mode of VBD.

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MATERIAL AND METHODS

The perinatal outcomes of 98 VBD were reviewed retrospectively from 2005–2018 at the Department of Gynecology and Obstetrics, Clinical Hospital 'Sveti Duh', Zagreb.

Criteria for VBD at term pregnancy included:

- Normal pelvimetry ;
- Ultrasonographical estimated fetal weight (< 3,800 g);
- Completed or frank breech presentation;
- Absence of fetal and maternal comorbidity (gestational diabetes mellitus (GDM), hypertension, oligohydramnios, intrauterine growth restriction (IUGR));
- Fetal head flexion.

All deliveries were observed by a senior obstetrician and a pediatrician- neonatologist in the delivery room with continuous cardiotocographic (CTG) fetal monitoring. Pregnant women and newborns were divided into six groups depending on the mode of VBD used (Bracht, Müller, Thiessen, classic arm release, Mauriceau-Levret-Veit-Smellie (MLVS) and Vermelin). Also, the incidence of episiotomy, the course of labor (spontaneous, induced), maternal age and parity were observed. In perinatal outcome of newborns, birth weight and length of newborns, gestational age and an Apgar score at 1 and 5 minutes after delivery were observed. Statistical analysis made by Kruskal-Wallis test with a statistical value of $p < 0.001$ included a percentage calculation and a multivariant analysis.

RESULTS

During the period of 2005–2018, there were total of 1,510 singleton breech deliveries at the Department of Gynecology and Obstetrics Clinical Hospital "Sveti Duh". By caesarean section, 1,412 newborns were delivered while 98 newborns were delivered vaginally.

Twenty-three out of the 1,412 newborns delivered by caesarean section required transfer to neonatal intensive care unit (NICU). Most women in this group were < 35 years (78%). Also, most women were multiparas (71%).

The most frequently used breech delivery mode during vaginal delivery was Thiessen (35.71%), followed by MLVS (25.51%), Bracht (22.45%), Vermelin (13.27%), classical arm release (2.04%) and Müller technique (1.02%).

Table 1 shows maternal demographic parameters (age and parity), the course of labor (spontaneous, induced) and the incidence of episiotomy depending on the mode of vaginal delivery. Seventy-point five percent of women included in the study were ≤ 35 years of age, and 37.76% were multiparas. There is no statistically significant difference between the years or parity of pregnant women in groups of different methods of assistance during VBD. Seven-point fourteen percent of labors were induced because fetal growth restriction without hypoxia, uterine inertia in term pregnancy and oligohydramnios and the incidence of episiotomy was 63.27% with the top of incidence by Thiessen mode.

Table 2 shows perinatal outcomes depending on the mode of VBD. This includes birth weight and length, gestation age and an Apgar score at 1- and 5-minute marks after labor. More than half of the newborns were born in term, 38–42 gestation week (65.31%). Seventy-four-point forty-nine percent of newborns had a weight > 2,500 g and 47.96% had a length 46–50 cm.

An Apgar score > 7 at the 5-minute mark had 100% of newborns delivered by Thiessen mode, 90.9% by Bracht, 76.00% by MLVS, 61.5% by Vermelin, 50% by classical arm release and 0% by Müller technique. There were 34.69% of preterm newborns delivered between 22–37 gestation week. The most preterm newborns were delivered by Thiessen (29.41%) and MLVS technique (29.41%) followed by Bracht (17.65%), Vermelin (17.65%), Müller (2.94%) and classical arm release (2.94%). Fifteen-point thirty-one per-

Table 1. Maternal demographic data

		Delivery mode					
		Bracht	**Thiessen**	**Müller**	**MLVS**	**Classical arm release**	**Vermelin**
Total of cases	98	22 (22.45%)	35 (35.71%)	1 (1.02%)	25 (25.51%)	2 (2.04%)	13 (13.27%)
Maternal age							
≤ 35	69 (70.50%)	14	26	1	20	2	6
> 35	29 (29.50%)	8	9		5		7
Parity							
nultipara	37 (37.76%)	8	13	1	8	1	6
multipara	61 (62.24%)	14	22		17	1	7
Course of labor							
spontaneous		22	30	1	23	2	13
Induced			5		2		
Episiotomy	62 (63.27%)	14 (63.64%)	26 (74.29%)	0 (0%)	18 (72.0%)	0 (0%)	4 (30.77%)

Table 2. Perinatal outcome

	Delivery mode					
	Bracht	**Thiessen**	**Müller**	**MLVS**	**Classical arm release**	**Vermelin**
Birth lenght, cm						
< 40	3	4	1	3	1	5
41–45		3		4		1
46–50	13	21		6	1	6
> 51	6	7		12		1
Birth weight, g						
500–999	3	2	1		1	4
1000–1499		1		4		1
1500–1999		2		1		1
2000–2499	1	2		1		
> 2500	18	28		19	1	7
Gestational age, week						
22–28	2	3	1	3	1	5
29–32				3		1
33–37	4	7		4		
38–42	16	25		15	1	7
Apgar score						
1 min > 7	17	30		13	1	7
1 min ≤ 7	5	5	1	12	1	6
5 min > 7	20	35		19	1	8
5 min ≤ 7	2		1	6	1	5

cent (15/98) of all included newborns were transferred to the NICU, all who had an Apgar score ≤ 7 at the 5-minute mark. Fourteen out of 15 newborns transferred to NICU were preterm. Most newborns transferred to NICU were delivered by MLVS (40%).

With classical arm release, transfers of newborns to the NICU was 50%, MLVS (24%), Vermelin (38.46%) and Bracht mode (9.09%). Only one newborn transferred to the NICU was a term. It was delivered by the Bracht method. Reason for a low Apgar score in 5 minutes was a result of complicated obstetrics techniques (MLVS, Müller, classical arm release) and early maladaptation. All other newborns were preterm, and it is an increased risk for a necessary transfer to the NICU.

Higher Apgar scores and less transfers to the NICU were noticed with less-traumatizing assistance during VBD. 100% of the newborns delivered by the Thiessen mode required no other treatment. The percentage decreased in other more active delivery modes ($p < 0.001$) and the lowest was through delivery by the Müller technique.

During vaginal delivery, intrapartum complications (impossible head extraction, cervical spasm, the use of forceps, umbilical prolapse, etc.) or traumatic injury to newborns (intracranial hemorrhage, musculoskeletal lesion, bone fracture, etc.) were not recorded.

DISCUSSION

In 2002, there was a trend in the US and EU to perform caesarean delivery for term singleton fetus in a breech presentation [10]. Eighty-six-point nine percent of newborns in the United States were delivered by elective caesarean section. According to that, the number of obstetricians with experience and skills required to VBD has reduced. This problem is also present in major medical clinics where education is conducted because there is not enough VBD which would enable an adequate education of future obstetricians [11].

The trend related to the increased number of elective caesarean sections in breech presentation has initiated by the major international multicenter randomized clinical trial published by the Canadian obstetricians (Term Breech Trial Collaborative Group) in 2000 [5]. The study included 2088 pregnant women in 121 institutions from 26 countries. Their results showed a higher risk of neonatal mortality and morbidity in vaginal delivery compared to elective caesarean section. Considering its size and controlled implementation, this study is somewhat revolutionary when

it comes to the current attitude towards delivery in breech presentation.

After a few years, additional publications have been written that modify the original conclusions of the 2000 Term Breech Trial [6]. The same researchers have published three follow-up studies with maternal outcomes at three months after delivery and children's' outcomes two years after labor. Those studies showed that the risk of urinary incontinence was lower for women in the planned caesarean delivery group at three months postpartum, and after two years, there was no difference between the groups. Furthermore, at two years postpartum, most women (79.1%) did not report a difference in most maternal parameters, including breastfeeding, menstrual problems, depression, pain and distressing memories of the birth experience. Also, the studies showed that there was no difference in the risk of death or neurological damages between the elective caesarean group and the planned vaginal delivery group. Goffinet et al., concluded that different countries have different obstetric practices and there are better outcomes in vaginal delivery in the country where that mode is used more often [12–14].

In 2018, The American College of Obstetricians and Gynecologists made the following recommendations for the VBD [11]:

- Obstetrician-gynecologists and other obstetric care providers should offer external cephalic version as an alternative to planned caesarean for a woman who has a term singleton breech fetus, and she has no contraindications for that. In that case caesarean delivery services must be readily available;
- The decision regarding the mode of delivery should consider patient wishes and the experience of the health care provider;
- Planned VBD of a term singleton breech fetus may be reasonable, but under specifical guidelines;
- If VBD is planned, a detailed informed consent should be documented — including risks that perinatal or neonatal mortality and short-term neonatal morbidity may be higher than if a caesarean delivery is planned.

The VBD can be recommended if certain criteria are met. Consistent international recommendations are still missing, so several different characteristics are used as exclusion criteria for vaginal planned breech deliveries [15, 16]. Criteria for planned vaginal breech delivery at term pregnancy included the expected normal vaginal delivery, ultrasonographic estimated fetal weight < 3,800 g, fetal head flexion, normal pelvimetry of a maternal pelvis, absence of a comorbidity (hypertension, gestational diabetes mellitus, intrauterine growth restriction, oligohydramnios), completed or frank breech presentation, a term pregnancy (38–42 gestation week) and the educated obstetrician. Also, The English breech guideline uses a birth weight of 3,800 g or more as an indication for a cesarean section. Contraindications for planned vaginal delivery in breech presentation include [17–19]:

- Cord — breech presentation (compound presentation);
- Footling breech presentation (1 or both hips extended);
- Fetal growth restriction or macrosomia (newborn weight more than 4,000 g);
- Fetal anomaly likely to interfere with vaginal labor;
- Fetal head — hyperextended;
- Clinically inadequate maternal pelvis.

Recent studies have suggested possible association of immunological diseases such as asthma, inflammatory bowel disease, type 1 diabetes in children born by caesarean section [7, 8]. Moreover, a maternal 6 morbidity after a caesarean section is three times higher than after vaginal delivery. Also, long- term neurological infant outcomes (including cerebral palsy) do not differ by planned vaginal delivery or caesarean section. Keag et al. [19], and authors in their meta-analysis and systematic review described that there is no statistically significant association of mode of delivery with perinatal mortality. Their meta- analysis described eight studies showing an association between allergies, hypersensitivity, dermatitis, or atopic conditions with cesarean section. Caesarean section was also associated with increased odds of childhood obesity up to five years when compared with vaginal delivery. Also, their research shows many disadvantages of caesarean section for further pregnancy and labor such as increased odds of placenta previa, placental abruption, ectopic pregnancy and increased odds of miscarriage or hysterectomy. The mechanics of VBD pose a greater risk of perinatal injury than caesarean section, but short- term injury often resolves and reliable estimates of permanent damage are lucking [20]. A newborn in breech presentation has a higher risk of cord presentation and a higher risk of cord prolapse during delivery than a newborn in cephalic presentation. That risk varies from < 1% to 10% and is higher for so- called "footling breech presentation" [21]. As mentioned, footling breech presentation is indication for caesarean section. But a fetus with feet presentation with flexed hips and flexed knees is known as a complete breech. Also, an incomplete breech is a fetus with flexed hips, one extended knee and one flexed knee. Both, fetus in completed breech and in incomplete breech presentation are qualified for VBD [22].

A retrospective cohort study published by Finnish authors compare neonatal and maternal outcomes in spontaneous onset preterm VBD after trial of labor (BTOL) and elective caesarean section (BCS) and between BTOL and vertex control deliveries, in singleton fetuses at 32 + 0 — 36 + 6 weeks of gestation [20]. Results showed that no mortality was observed and severe morbidity was rare.

Sixteen-point five percent of neonates in the BLOT group, 23.3% in the BCS group and 7.8% in the vertex control group needed support after delivery in the neonatal intensive care unit (NICU). Lower gestation age and small for gestation age were associated with the need for support in the NICU. This study showed that maternal morbidity was similar across the groups. Median blood loss was more pronounced in the BCS group compared to the BTOL group. So, in breech deliveries at 3 + 0 — 36 + 6 gestational weeks, BTOL did not increase neonatal morbidity compared to BCS [23, 24]. Our study included 14 preterm newborns who were transferred to NICU. Twelve out of 14 were extremely premature and they were delivered due to some complications (placenta defects, abruptio placentae, preterm premature rupture of membranes (PPROM), anhydramnios). All newborns transferred to NICU, independent of gestational age, survived and were discharged from NICU.

Minimal assistance delivery is used in vaginal delivery in breech presentation. With some method of minimal assistance delivery it was possible to successfully complete 70% of the breech presentation. In case of some complications, the newborn should be delivered by some method for the release of the head and/or shoulder or by a caesarean section. As shown in our study, delivery by Thiessen had the best perinatal outcome. Also, the most newborns transferred to NICU were delivered by MLVS technique. It shows that the more traumatizing method being used, the worse perinatal outcome and more transfers to NICU result. Also, most vaginal delivery in breech presentation is uncomplicated and can be completed with no assistance (Vermelin) or with minimal assistance at delivery (Thiessen). Such cases are highest at vaginal delivery in breech presentation. Sometimes complications occur, such as stagnation of the shoulder or the head, and more complicated methods are needed. Fortunately, this is not very common. This is why there is such a difference in the number of the deliveries with different delivery modes. Unfortunately, the difference in the number of deliveries between groups may be increasing the likelihood of a mistake. So, this study should be compared with other such studies. [25, 26]. The best conclusion would be made by meta- analysis of all study that research vaginal delivery in breech presentation.

In 2016, Louwen et al., and a group of authors published study about perinatal outcomes in breech presentation depending on maternal position during the delivery (upright, on their back or caesarean section). Results showed a non — significant increased risk of mortality and serious morbidity for planned vaginal deliveries in the maternal dorsal position, but much smaller differences in risk with upright delivery, or planned vaginal birth ending in caesarean, when compared with planned caesarean. Also, with the mother in an upright position then in a dorsal position the length of second stage of vaginal delivery was significantly shorter — 42% shorter. The study compared the first years of research, then the dorsal position was used almost 1/3 of the time and the last 2.5 years of study, when all VBD were done upright — the comparison shows the caesarean rate reduced by 32%. Researchers from Austria did an analysis limited to 41 VBD with the woman on her hands and knees and after that a retrospective cohort of classic VBD. They concluded that upright delivery seemed to be "safe for the fetus with reduced maternal morbidity". According to that, VBD in the upright position was associated with shorter second stages, reduced maneuvers and neonatal injuries, less serious perinatal laceration than was the dorsal position, less caesareans during labor, suggesting potential advantages of maternal upright position for VBD [27, 28]. Vaginal delivery in breech presentation in a position other than a dorsal position also requires obstetric care providers with a lot of a knowledge and an experience. So, that is only implement in some European centers.

Induction of labor in breech presentation has rarely, but recently, been reported. Finnish authors published a retrospective observational study of induction of labor in breech presentation [29]. Results showed no statistical differences between the induction group and the spontaneous group regarding neonatal and maternal morbidity and mortality. Indications for induction are diverse: delayed labor after spontaneous rupture of membranes, preeclampsia, postterm pregnancy, diabetes, etc. The labor can be induced with prostaglandins, a balloon catheter, an oxytocin infusion and an amniotomy. The mode of induction has no effect the success rate of the VBD. In the study published by Finnish obstetricians, they observed two groups of deliveries: in the induction group the second stage of delivery was significantly longer, furthermore there were more cases of diabetes, and the gestation age was higher in that group of deliveries. The study also showed that the induction of labor was not associated with an increased risk of neonatal morbidity. The vaginal delivery rate in induction VBD at term is like the rate of induced deliveries with the fetus in cephalic presentation. Another group of obstetricians compared the induction of labor with the elective caesarean section. Results showed that there was no significant difference between the groups for the primary neonatal outcome in the planned caesarean section versus in the induction of labor. Consequently, the induction of labor might be an additional tool after unsuccessful external version to prevent a primary caesarean section [29–31].

In 2018, study in Australia and New Zealand showed that experience and confidence in VBD increased with the number of procedures performed and were significantly higher among Fellows [32]. Despite the level of confidence,

responders felt confidence in managing vaginal twin delivery more than managing vaginal breech deliveries, and only 32.7% (67/205) of respondents intended to offer vaginal breech delivery in their practice. The main reasons reported were the risk of adverse outcomes and potential medico-legal consequences (43.4%) and not enough experience (57.2%). The encouragement of older obstetricians, more practice and an adequate birth room are necessary to young obstetrician- gynecologist fore achieves self- confidence in managing vaginal delivery in breech presentation.

The Swiss clinical study implements VBD in its clinical guidelines, naming that the renaissance in delivery in breech presentation [33]. Our study shows that the newborns delivered by Thiessen and Bracht method had the best perinatal outcomes. These two methods are also referred in other studies as the two methods of assistance with the best perinatal outcome. The method of assistance has direct impact on the perinatal outcome in VBD, regardless of a parity and a gestation age, and better outcomes are related with less-traumatizing methods. Also, obstetricians and obstetric care providers with enough experience and knowledge are indispensable.

The results of our study showed that the better perinatal outcome of newborns was during vaginal delivery by Thiessen method compared to other methods of assistance during vaginal delivery. Also, very good outcomes were at newborns delivered by Vermelin and Bracht methods. Those three methods are methods with minimal assistance, and it brings a lot of benefit during vaginal delivery in breech presentation. Sixty-four out of 98 pregnancies were completed between 38 and 42 gestation weeks.

Comparing percentages of newborns who were transferred to NICU, the number is higher in VBD. On the other hand, 14/15 newborns delivered vaginally who were transferred were preterm and that was additional 8 reason for transfer to the NICU. With caesarean section, 20/23 newborns who were transferred to the NICU were preterm. The most common condition in NICU transfer in vaginal delivery were placenta defects, abruptio placenta, PPROM, anhydramnion and polyhydramnion while in caesarean section these were preeclampsia, placenta defects, Rh– immunization and hypoxio detalis.

Following the criteria for VBD is not necessarily planned elective caesarean section in pregnancy with fetus in breech presentation. Perinatal outcome, as show in this study and in many other studies, does not differ between caesarean section and vaginal delivery. Better outcomes were detected at newborns delivered vaginally by method with minimal assistance. These results indicate that the assisted delivery technique has an impact on perinatal outcome of newborns delivered by vaginally.

CONCLUSIONS

According to our study, it is necessary to know that better outcomes are related to less- traumatizing methods of assistance. Some recommendation for vaginal breech delivery needs to be followed for the best perinatal outcome and a minimally maternal injury. To sum up, vaginal delivery in breech presentation (VBD) is a safe option in the centers where there is enough experience and knowledge among obstetric care providers.

Statement of ethics

This research has the approval of an Ethics Review Committee.

Conflict of interest

The authors have no conflicts of interest to declare.

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Can FMR1 CGG repeat lengths predict the outcome in ICSI cycles?

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ABSTRACT

Objectives: The aim of this study was to assess relationship between CGG repeat lengths and ovarian reserve and response to controlled ovarian stimulation (COH).

Material and methods: This prospective cohort study was carried out on patients (n = 49) who were admitted to the *in vitro* fertilization (IVF) clinic of the Zeynep Kamil Women's and Children's Diseases Training and Research Hospital, University of Health Sciences. Women under 40 years of age with premature ovarian insufficiency underwent genetic analysis to determine CGG repeat lengths. Ovarian reserve was assessed for each participant and participants underwent ovarian hyperstimulation and intracytoplasmic sperm injection (ICSI) cycle. Relationships between ovarian reserve, cycle outcome and CGG repeat lengths were assessed. Variables including fertility assessment including ovarian reserve tests [Follicle stimulating hormone (FSH), Luteinizing hormone (LH), Estradiol (E2), Prolactin (PRL), Thyroid stimulating hormone (TSH), Antimullerian hormone (AMH), antral follicle count (AFC) tests] and some IVF cycle characteristics were assessed in relation to number of CGG repeat numbers.

Results: None of the ovarian reserve tests and cycle characteristics was found to be correlated with CGG repeat lengths. Comparison of ovarian reserve tests and cycle characteristics revealed no difference between groups of women with CGG repeat length > 55 and CGG repeat length ≤ 55. Antimullerian hormone (AMH) was a significant predictor for cycle cancellation (AUC = 0.779, P = 0.008). AMH level > 0.035 was found to be the optimal cut off value to predict cycles reaching to embryo transfer with 71% sensitivity and 85% specificity. The rate of cycle cancellation was 71% in cases with AMH ≤ 0.035 whereas it was 20% in cases with AMH > 0.035 (p = 0.001). No difference was determined between groups with and without cycle cancellation in terms of CGG repeat lengths (55.3 vs 53.9, p = 0.769). Among cycles reaching to embryo transfer stage, 3 (13.6%) pregnancies were achieved.

Conclusions: Our data showed no relationship between CGG repeat lengths and ovarian reserve and response to controlled ovarian stimulation. This data also showed that no clinical difference between FMR gene mutation related POI and other etiologies.

Key words: CGG repeat length; pragile X; premature ovarian insufficiency; ICSI

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INTRODUCTION

Premature ovarian insufficiency (POI) is seen in approximately 1% of the general female population before the age of 40 [1]. Although the main cause of this disease is unknown, common etiologies include genetic causes [2–6] and autoimmune diseases [7–9]. Among all the genetic causes, Fragile X is the most frequently blamed for this disorder. The premutation allele interval (55–200 CGG repetition interval) is important because of the risk of POI and the risk of being transmitted as a full mutation to subsequent generations [10]. Shamilova et al. [11], reported that the < 28 CGG repeat interval is associated with anti-ovarian antibodies. Making this distinction in the etiology may be important in terms of affecting ovarian response to ovarian stimulation in POI patients in the future [11].

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Many population studies have evaluated the relationship between FMR1 premutation (55–200) and POI. While a meta-analysis reported an increased risk of POI in pre-carriage carriers, particularly those of European origin [12], some researchers did not show a significant difference in populations.

FMR1 CGG repeat lengths are examined in four categories according to their stability: normal (< 44); intermediate or gray zone (45–54); premutation (55–200); and full mutation (> 200 repetitions) [13, 14]. FMR1 premutations are thought to account for ~5% of all POI cases [15]. The clinical significance of these ranges for ovarian function is highly controversial. Studies have investigated the relationship between FMR1 CGG repeat lengths in the normal range and the intermediate range (gray zone) and the presence of POI or low ovarian reserve. Some investigators reported increased frequency of POI with FMR1 CGG repeat alleles in the intermediate range [16, 17], while other investigators failed to demonstrate this association [18, 19]. In addition, some studies have reported a relationship between low-ovarian reserve and FMR1 CGG repeat alleles in the normal range [20, 21], whereas in other publications [22, 23] the low over-overexpression of the normal range FMR1 CGG alleles was reported. The relationship with the reserve has not been shown. There is no consensus on the effect of CGG repeat lengths in the normal and intermediate range on ovarian reserve.

Objectives

Normally, only premutations have a definite relationship with POI, but some studies have shown that POI can develop in normal or gray zone cases. Discussion continues in the literature on the exact relationship between the detection of CGG repeat intervals in the normal and intermediate range with POI, unlike premutation. As we know, 5–10% spontaneous pregnancy can be seen in patients with premature ovarian failure. In patients with normal AMH and AFC, it will be possible to direct the patients in terms of clinical follow-up by looking at the number of CGG repetitions instead of waiting for spontaneous pregnancy. In the light of these data, the aim of our study was to evaluate the relationship between FMR 1 CGG repeat lengths and ovarian reserve and response to ovarian stimulation.

MATERIAL AND METHODS

Patient population

In order to evaluate the relationship between the number of CGG and ovarian reserve and ovarian response to stimulation, this prospective cohort study was carried out on patients (n = 49) who were admitted to the IVF clinic of the Zeynep Kamil Women's and Children's Diseases Training and Research Hospital, University of Health Sciences, Istanbul with infertility between June 2017 and January 2018. This study was conducted in accordance with the Declaration of Helsinki. Approval for this study was obtained from the Institutional Review Board (2017/41). A written informed consent was obtained from all participants.

POI was diagnosed according to ESHRE criteria [24]; under 40 years; cases with oligo-amenorrhea for at least four months and with a high follicle stimulating hormone (FSH) level > 25 IU/L twice every four weeks. Although oocyte donation was reported as the first choice in WHO type III anovulatory patients, since oocyte donation program is not legal in our country, patients were directed to ART. All of these patients underwent initial fertility assessment, conventional fertility assessment include ovarian reserve tests (FSH, Luteinizing hormone (LH), Estradiol (E2), Prolactin (PRL), Thyroid stimulating hormone (TSH), Antimullerian hormone (AMH) Antral follicle count (AFC) tests). Since the relationship between Fragile X carriage and POI is well known, Fragile-X permutation test was requested for all patients not only to reveal the cause of POI, but also because the presence of mutation could have significant effects for the patient and his/her family. Patients were referred to the genetic clinic of our hospital prior to controlled ovarian hyperstimulation (COH) cycle for Fragile X premutation screening.

To avoid multiple comparison statistical bias, only information regarding the initial stimulation cycle of each patient was included. The age of patients during stimulation was also recorded. Initial gonadotropin dose was calculated according to patients' age, AMH and number of antral follicles. Initial gonadotropin doses were between 300 and 450 IU/day (75–150 H LH was added to each case as gonadotropin in total dose). A flexible antagonist protocol was applied for inhibition of the premature LH surge during the COH cycle. For this purpose, when the dominant follicle reached a diameter of 13 mm, 0.25 mg Cetrorelix (Cetrotide; Merck Serono, Switzerland) was started subcutaneously once a day in the morning. Ovulation was triggered with 250 µgr of recombinant hCG (Ovitrelle; Merck-Serono, Switzerland) subcutan was applied when at least one follicle diameter reached ≥ 18 mm. Oocyte aspiration was performed 36 hours after hCG injection under transvaginal ultrasound guidance. The number of mature oocytes obtained in response to stimulation was evaluated as a measure of ovarian response.

Fragile X evaluation was performed using a commercially available kit "Fragile X GScan Kit" (Gene Link-Hawthorne, NY, USA), a standard test procedure mentioned by Sherman et al in their 2005 study [25]. Fragile X genotyping was performed with a DNA sequencer (ABI-310 DNA Sequencer; Applied Biosystems, USA) for direct fluorescent PCR amplification of the CGG trinucleotide repeat region and fragment analysis.

FSH, E2 and AMH concentrations were evaluated by commercial experiment (Diagnostic System Laboratories Inc, Texas, USA) using enzyme-linked immunosorbent assay. All comparisons were performed per participant instead of cycle. The variation coefficients for these three tests were between 2.4% and 8.6%. Individuals with approximately 55–200 CGG repeats were considered premutation carriers. The primary aim of this study was to figure out any association between number of CGG repeat length and cycle outcome. The secondary outcome was to assess possible relationship between number of CGG repeat length and ovarian reserve markers.

Statistical analysis

The statistical analysis was performed with using the Statistical Package for the Social Sciences version 21.0 (SPSS Inc., Chicago, IL, USA). The continuous variables were expressed as the mean ± standard deviation. The categorical variables were expressed as the number and percentage. Mann-Whitney U test was used for nonparametric data. Statistical significance was defined as $p < 0.05$.

RESULTS

None of the ovarian reserve tests and cycle characteristics was found to be correlated with CGG repeat length (Tab. 1). Comparison of ovarian reserve tests and cycle characteristics revealed that no difference between groups of women with CGG repeat lengths ≤ 55 and > 55 (Tab. 2). Comparison of groups with and without cycle cancellation did not show any significant difference between groups in terms of age ($p = 0.8$), FSH ($p = 0.06$), CGG repeat number ($p = 0.6$) and total antral follicle counts ($p = 0.2$) but serum AMH ($p = 0.007$) was significantly lower in group with cycle cancellation. AMH was a significant predictor for cycle cancellation (AUC = 0.779, $p = 0.008$). AMH level > 0.035 was found to be the optimal cut off value to predict cycles reaching to embryo transfer with 71% sensitivity and 85% specificity. AMH > 0.035 is associated with cycle cancellation [OR = 0.1, 95% CI (0.02–0.5, $p = 0.001$)]. The rate of cycle cancellation was 71% in cases with AMH ≤ 0.035 whereas it was 20% in cases with AMH > 0.035 ($p = 0.001$, Tab. 3). No difference was determined between groups with and without cycle cancellation in terms of CGG repeat lengths (55.3 vs 53.9, $p = 0.769$). Among cycles reaching to embryo transfer stage 3 (13.6%) pregnancies were achieved.

DISCUSSION

The main reason for investigating triple CGG repeats on the FMR1 gene has been the prevention and/or diagnosis of psychiatric and/or neurological conditions that have historically been associated with extremely high triple re-expansion and full mutation (Fragile X syndrome > 200 CGG repetition) intervals [26, 27]. The current classification of CGG repetition extends to typical (normal), intermediate (gray zone), premutations, and full mutation, so it is based solely on a screening process for psychiatric and neurological risks. Therefore, these risk ranges have nothing to do with other potential risks associated with triple CGG repeats in the FMR1 gene, such as the risk for premature ovarian aging.

The aim of this study was to assess relationship between CGG repeated numbers and ovarian reserve and response to gonadotropin stimulation. Our data showed no relationship between CGG repeat lengths and ovarian reserve and response. This data also showed no clinical difference between FMR gene mutation related POI and other etiologies.

In studies of markers of ovarian function in populations, a relationship was found between the premutation carriers, which was largely based on the family history of fragile X syndrome and both FSH and AMH [28]. No correlation was found between medium number CGG repeats and POI. Therefore, a role of up to 55 repetitions for FMR1 CGG repeat sizes in the ovarian aging process can be questioned. Furthermore, the diagnostic study of women affected by POI shows a limited value for the assessment of normal and moderate FMR1 repeat size or for prognostic purposes in women at risk of developing POI [29]. Some cut off values for CGG repeat length have been proposed in the context of ovarian function, normal values were suggested to be between 26–34, whereas > 34 repetitions were considered to be high and < 26 repeat was considered to be low. These values were suggested to be associated with weaker embryo morphology and an accelerated decrease in functional ovarian reserve [30]. Tang et al. [31], evaluated the relationship between the number of CGG repeats in FMR1 in Chinese patients with POI and DOR. The authors found that the frequency of FMR1 premutation did not differ between

Table 1. Correlation between ovarian reserve tests and cycle characteristics with the number of CGG repeats

		Age [years]	FSH	LH	AMH	Total AFC	Total Gonadotropin dose	Stimulation day at oocyte trigger	Peak estradiol	Total oocyte number
CGG repeat #	Correlation coefficient (r)	–0.115	0.079	0.048	0.153	–0.009	–0.072	–0.106	0.282	0.258
	p value	0.437	0.595	0.751	0.413	0.949	0.625	0.638	0.228	0.203

FSH — follicle stimulating hormone; LH — luteinizing hormone; AMH — antimullerian hormone; AFC — antral follicle count

Table 2. Comparison of ovarian reserve tests and cycle characteristics between groups of women with CGG repeat lengths ≤ 55 and > 55

	Groups	Mean	Std. Deviation	p value
Age [years]	CGG ≤ 55	29.8	6.3	
	CGG > 55	29.9	5.2	0.866
FSH [mIU/mL]	CGG ≤ 55	37.7	35.4	
	CGG > 55	31.6	33.8	0.867
Estradiol [pg/mL]	CGG ≤ 55	42.2	42.6	
	CGG > 55	40.3	52.7	0.810
Progesterone [ng/mL]	CGG ≤ 55	0.4	0.5	
	CGG > 55	0.5	0.2	0.031
TSH [mIU/L]	CGG ≤ 55	1.7	1.09	
	CGG > 55	1.7	0.7	0.652
Prolactin [20 ng/mL]	CGG ≤ 55	15.4	9	
	CGG > 55	17.2	9.7	0.702
LH [mIU/mL]	CGG ≤ 55	18.1	17.5	
	CGG > 55	17.1	20.06	0.982
AMH [ng/mL]	CGG ≤ 55	0.4	0.8	
	CGG > 55	0.8	2.1	0.724
Total_AFC	CGG ≤ 55	6.09	4.01	
	CGG > 55	5.4	4.3	0.484
Total gonadotropin dose [IU]	CGG ≤ 55	3584.03	1493.7	
	CGG > 55	3604.8	994.3	0.765
Menstrual day at ovulation trigger	CGG ≤ 55	10.9	3.2	
	CGG > 55	11.2	2.8	0.748
Peak estradiol level [pg/mL]	CGG≤55	673.3	435.3	
	CGG > 55	967.5	359.01	0.274
Total number of oocytes	CGG ≤ 55	0.7	0.8	
	CGG > 55	1	0.8	0.497
Total number of mature oocytes	CGG ≤ 55	0.4	0.5	
	CGG > 55	0.6	0.5	0.572

FSH — follicle stimulating hormone; TSH — thyroid stimulating hormone; LH — luteinizing hormone; AMH — antimullerian hormone; AFC — antral follicle count

Table 3. The rates of cycle cancellation of women with antimullerian hormone (AMH) ≤ 0.035 and AMH > 0.035

	AMH ≤ 0.035	AMH > 0.035	Total	p value
Uncancelled	10	12	22	
	29.4%	80%	44.9%	
Cancelled	24	3	27	
	70.6%	20%	55.1%	P < 0.001
Total	34	15	49	
	100.0%	100.0%	100.0%	

POI or DOR and normal menopausal controls; they reported that the most common CGG repeats were 29 and 30, and the repeat length for allele 2 had a secondary peak around 36–39 repeats. In addition, the researchers reported that mean FSH and AMH values did not show any association with different CGG repeats in both the POI and DOR groups [31]. In our study population, there was only one case with CGG repeat length of 2, among all the remaining cases the lowest number of repeat numbers was 38.

Whether the FMR1 CGG repeat length can be used clinically to predict IVF outcome is a controversial issue. In a study performed by Banks et al. [32], with 4690 fresh

transfer cycles, FMR1 CGG repeat lengths was associated with ART response; however, this relationship has been reported to be weak for use during clinical management [32]. The authors argued that CGG repeat lengths do not have a higher predictive ability beyond classical predictors such as age, AMH, FSH, AFC. Banks et al. [32], data reveals a possible role of FMR1 CGG repeat length in the normal zone in ovarian response but failed to demonstrate clinical significance as a predictor of ART results. In another study conducted by Fıçıcıoğlu et al. [33], they suggested that the triple repeat numbers of CGG can predict a reduced ovarian reserve before the onset of ovarian aging, and that in clinical practice CGG repeats can be used to predict premature ovarian aging (FSH > 12–50IU/mL) and ovarian reserve.

A recent study by Batiha et al. [34], evaluated the relationship between short CGG repeats (< 26; 26–34; > 34) and poor ovarian response. The researchers reported that CGG median allele sizes differed significantly between cases and controls, and poor ovarian responders carried shorter CGG repeats compared to healthy controls. The authors also noted that women with < 26 alleles showed twice as poor ovarian response as compared to controls. However, the authors also reported that they did not find a significant relationship between CGG repeats and ovarian reserve markers, similar to our study. The authors concluded that although low CGG repeats appeared to be associated with POR as a result of their study, the clinical use of FMR1 to predict ovarian response needs further research [34].

Lledo et al., [19] evaluated the results of oocyte donation cycle. The study cases were examined in three groups with CGG repeat lengths of 35–39 (n = 34), 40–45 CGG (n = 12) and > 45 CGG (n = 17) and the ovarian response was found to be similar between the groups. This study is the first to evaluate the ovarian response in subjects with a normal and intermediate repeat lengths. As a result of this study, the authors recommended that CGG repeats in the intermediate zone does not adversely affect the ovarian response, so fragile X genetic screening should not be taken into account in predicting ovarian response. In a study conducted by Rehnitz et al. [35], they evaluated the COH response in three groups as poor responder, normoresponder and hyperresponder, and divided the patients into six genotypes according to CGG repeat lengths. The authors reported that the ovarian response could be adversely affected by low CGG alleles. They even argued that this poor ovarian response associated with a low CGG allele might be impaired during folliculogenesis independent of stimulation.

In a study conducted by Gustin et al. [36], with 566 patients, it was found that the relationship between CGG repeat length and AMH changes with age in an analysis using a multivariate regression model. In our study mean age of whole study population was 29 years and our data analysis revealed no association with AMH level and CGG repeat length. We used AMH level to be reference predictor for cycle outcome and AMH significantly predicted cycles reaching to embryo transfer among cycles with high rate of cancellation, overall cancellation rate was 55.1% in all the study groups. In a past study by Pastore et al. [37], the cycle characteristics of seventy-nine women with a diagnosis of low ovarian reserve and no family history of fragile X syndrome were evaluated. As a result of the study, the authors reported that women with a CGG repeat length ≥ 35 had a higher rate of follicular loss starting at later ages.

The impact of smaller repeats at the boundary of premutation and normal is less clear. Eslami et al. [38], compared the FMR1 CGG repeat lengths with the intermediate and premutation group in a study they included the POI, DOR, and healthy control group. In the study, the frequency of premutation was found to be higher in patients with POI and DOR than in control patients; intermediate allele frequency was similar between groups. Based on the results of the study, the authors concluded that FMR1 CGG repeat alleles in the intermediate zone do not pose a high risk for POI and DOR.

Ranisavljevic et al. [39], investigated that ovarian response to controlled ovarian stimulation in premutation and full mutation carriers and compared the clinical results. They reported that significantly higher FSH doses were needed for ovarian stimulation in premutated patients. However, the researchers found no correlation between the number of oocytes collected and the number of CGG repeats [39].

A current meta-analysis of Pastore [40] revealed no association within subcategories of normal repeat length (< 45 CGG) and IVF pregnancy rates. It was shown that, premutation carriers (CGG 55–200) may have reduced success with IVF treatment than women with a normal CGG repeat length or a full mutation [40]. According to these cited researches, there is no consensus on this issue, majority of the investigations showed no predictive value of CGG repeat lengths and reproduction, while some showed lower number of repeats to be risk factor for poor outcome, on the other hand some showed higher repeat number may be responsible for poor response in IVF. For this reason, we conducted this prospective study, in our study, we included consecutive women diagnosed to have POI, major disadvantage of this study was small sample size and lack of data regarding other etiologies of POI.

CONCLUSIONS

In conclusion, our study showed no relationship between CGG repeat lengths and ovarian response to ovarian stimulation. Despite the small number of patients, the results of our study are consistent with the current literature.

Conflicts of interest

All authors declare that they have no conflict of interest.

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Twin anaemia polycythaemia sequence: a complicated target for prenatal diagnosis, a current state of knowledge

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ABSTRACT

Objectives: Processing of available information on TAPS with a focus on the evaluation of the most sensitive and most specific prenatal diagnostic test.

Material and methods: Retrospective analysis of available publications on TAPS with their meta-analytical processing through available electronic medical databases. Evaluation of the most sensitive and specific prenatal diagnostic test with graphical processing of sensitivity and specificity values depending on the TAPS diagnostic criteria used.

Results: In total, we found 165 available articles, the oldest from 2007 and the most recent from 2020. Based on the available articles, we evaluated the determination of MCA-PSV with a sensitivity of 83% and a specificity of up to 100% for the currently generally accepted diagnostic criterion TAPS — Delta MCA-PSV > 0.5MoM as the most sensitive and specific method of prenatal diagnosis.

Conclusions: The serial determination of MCA-PSV represents the most sensitive and specific prenatal diagnostic test to date (2020) based on available knowledge. Serial measurement of the MCA-PSV since gestational week 20 every two weeks until delivery represents a potential TAPS screening test for all monochorionic pregnancies. The late, or postnatal diagnosis of TAPS can have serious consequences in the form of intrauterine death of the foetus(es) and increased perinatal mortality and morbidity.

Key words: TTTS (Twin-twin Transfusion Syndrome); TAPS (Twin Anaemia Polycythaemia Sequence); MCA-PSV (Middle Cerebral Artery Peak Systolic Velocity); sensitivity; specificity

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INTRODUCTION

The presence of a single placenta, together with the presence of a variable number of interfetal vascular connections of various diameters, provides a basic structural substrate for the development of many intrauterine pathologies typical of monochorionic pregnancy [1]. The angioarchitecture of the monochorionic placenta and the size of the shunting blood volume are the essential determinant of clinical manifestations and possible morphological changes in the affected foetuses [2].

Histopathological examinations of human monochorionic placentas showed three types of vascular connections that differ in their lumens, the type of vessels connected, the size and direction of the shunting blood volume. These three types are arterioarterial (AA), venovenous (VV), and arteriovenous (AV) anastomoses. AA and VV anastomoses are located on the chorionic plate's surface and are bidirectional in terms of blood flow. AV anastomoses are located deep in the placental tissue and are unidirectional [3–6].

TAPS (Twin Anaemia Polycythaemia Sequence), in contrast to TTTS (Twin-twin Transfusion Syndrome), which has been known as a syndromological unit since the 19th century, represents a relatively new syndrome described for the first time in 2007 by Lopriore et al. [7–11]. The main pathophysiological principle of both conditions is the presence of unequal blood distribution between the two foetuses with the formation of a donor-recipient circuit [1, 12, 13]. Compared to TAPS, TTTS is characterized by the shunting of a larger amount of blood, which in addition to changes in the concentration of haemoglobin, is also reflected in changes

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in the amniotic fluid volume. It is the change in amniotic fluid volume that represents the basic morphological difference between TTTS and TAPS. In TTTS, imbalanced blood flow occurs through AV anastomoses in the simultaneous absence of AA anastomoses, which, according to the latest findings, represents a protective factor before its development. In the case of monochorionic placentas examined in pregnancies not complicated by TTTS, the presence of AA anastomoses was demonstrated in up to 90%, while in the case of TTTS only 20–25% [6, 7, 14]. Placental preparations in TAPS are characterized by only a few minuscule AV anastomoses in the absence of AA anastomoses. The absence of AA anastomoses is not a prerequisite for the development of TAPS, as there have been described cases where the presence of AA anastomoses has been demonstrated [15–18]. Based on several TAPS cases treated with intrauterine transfusions, it was possible to calculate the approximate amount of shunting blood via AV anastomoses, which was determined to be 5–15 mL/24h [7, 19, 20]. Such a small amount of shunting blood provides sufficient time for haemodynamic compensation in both foetuses and prevents the development of differences in the amniotic fluid volume (Fig. 1) [21, 22].

TAPS occurs in two forms: spontaneous (primary) and post-ablative (secondary) in terms of aetiopathogenesis. The spontaneous (primary) form is rarer and occurs without prior intrauterine surgery on placental vessels. In contrast, the post-ablative form, more frequent, occurs iatrogenically based on foetoscopic laser ablation treatment with occlusion of AV anastomoses in TTTS cases. The development of the post-ablative form of TAPS is therefore interpreted as a complication of intrauterine treatment of TTTS when several minuscule AV anastomoses persist [23–25].

The incidence of the post-ablative form of TAPS is very different and, according to most authors, is around 13%, while the incidence of the spontaneous form of TAPS is relatively constant and is about 3–5% [23].

Diagnosis is possible based on several direct and indirect diagnostic methods, prenatally and postnatally. Postnatally, the diagnosis of TAPS can be made by determining the concentration of haemoglobin, haematocrit, and the number of reticulocytes or their ratio in both foetuses. There are different opinions among the authors on the values of blood count in foetuses, confirming TAPS diagnosis. Lewi's working group defined TAPS as the haemoglobin concentration in the anaemic foetus < 111g/L with the concurrent haemoglobin value in the polycythaemic foetus > 200 g/L. The disadvantage of such strictly determined cut-off values of the red blood component is that they do not include the dynamics of foetal haemoglobin concentration in relation to particular gestational weeks [26–29]. Slaghekke et al., considered the above and tried to correlate the values to gestational weeks. They defined TAPS as anaemia in the donor, with a haemoglobin value < 5 percentile for a given gestational week with concomitant polycythaemia in the recipient, defined as a haematocrit value > 65% [2]. Eurofoetus criteria define TAPS based on the difference in haemoglobin values between the donor and recipient > 80 g/L [2]. The disadvantage of a solitary criterion such determined lies in the fact that in monochorionic pregnancies, even in the absence of TAPS, relatively significant differences in haemoglobin levels can occur in both foetuses due to the development of acute intrapartum TTTS or acute foetoplacental shunting after the birth of the first foetus. Therefore, most authors point to the possibility of using different re-

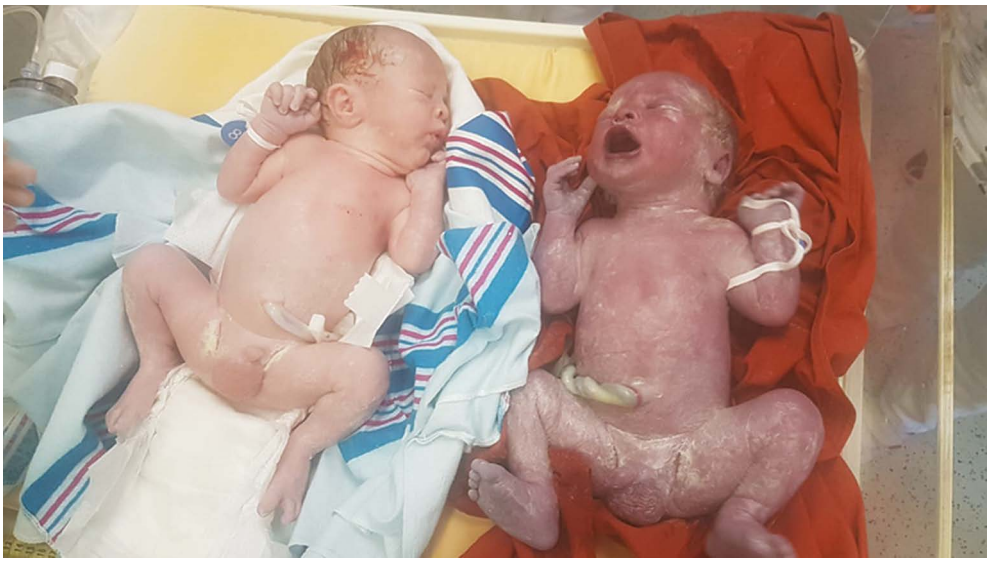

Figure 1. Monochorionic twins complicated by TAPS, gestational week 36, donor twin — anemia, recipient twin — polycythemia

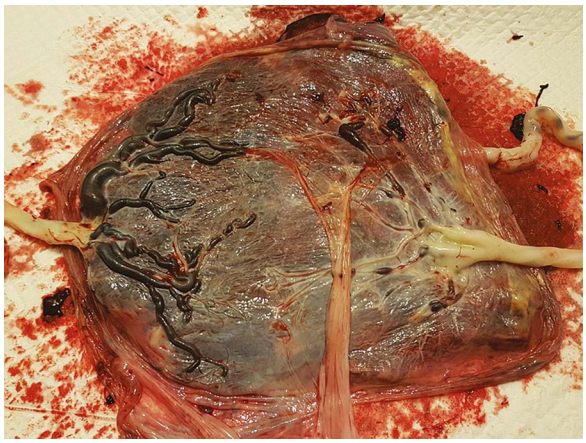

Figure 2. Fetal side of the monochorionic placenta complicated by TAPS — hyperemic vessels belong to recipient twin, collapsed to donor twin

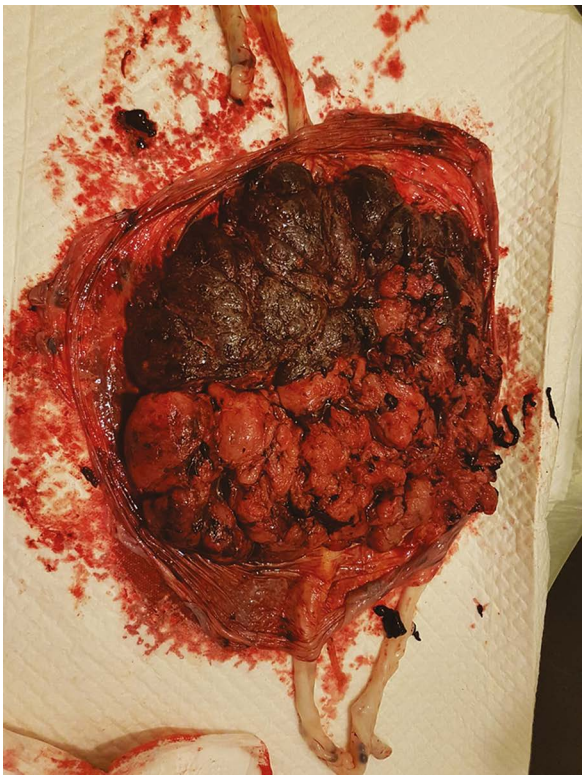

Figure 3. Maternal side of the monochorionic placenta complicated by TAPS — hyperemic part belongs to recipient twin, anaemic to donor twin

ticulocyte counts in both foetuses, representing a general marker of physiologically or pathologically enhanced haematopoiesis. Slaghekke et al., report a difference in reticulocyte count > 3.5% for monochorionic twins as diagnostic for TAPS. The ratio can also express significant changes in reticulocyte levels typical of TAPS. The value of the mutual ratio of the number of donor-recipient reticulocytes > 1.7 is pathognomonic for the diagnosis of TAPS [30, 31].

The latter method, which is rarely used in most clinical workplaces, is a histopathological examination of the placenta, accompanied by injection studies and visualization of particular types of vascular connections. Strict criteria and histopathological characteristics of "physiological" monochorionic placentas do not currently exist, but TAPS is characterized by a small number of AV anastomoses in the concurrent absence of AA anastomoses. The absence of AA anastomoses in monochorionic placentas is frequent in TAPS, but not pathognomonic, since TAPS cases with AA anastomoses have been reported (Fig. 2, 3) [15, 32–34].

In the case of prenatal diagnosis of TAPS, ultrasound examination is the only practically available modality. Ultrasound examination of monochorionic twins suspected of the presence of TAPS evaluates morphological as well as flow criteria. Since TAPS represents a relatively new syndromological unit, its ultrasound criteria are not yet completely uniform. In general, from a morphological ultrasound finding, the absence of amniotic fluid discordances between foetuses is essential for the diagnosis of TAPS. Its presence certainly rules out the diagnosis of TTTS and suggests the presence of TAPS [35, 36].

The available literature also describes the so-called " minor" ultrasound, morphological criteria such as the image of placental dichotomy (demarcation of placental tissue with hyperechogenic, thicker, hydropic tissue on donor side and physiological finding on recipient side) [37] and the image of hepatic parenchyma of starry sky appearance, "starry sky liver" (hypoechogenic hepatic parenchyma of the recipient with hyperechogenic dilated portal venules) [38]. Their more extensive application in prenatal diagnosis has yet to be supported by enough studies.

However, measuring the peak systolic flow velocity in the cerebral artery in both foetuses, in the Anglo-Saxon literature referred to as middle cerebral artery peak systolic velocity (MCA-PSV), is crucial for the diagnosis of TAPS and, in part, the quantification of the severity of the disorder. Changes in MCA-PSV reflect changes in foetal blood viscosity that is predominantly affected by foetal haematocrit. MCA-PSV values expressed in multiples of medians (MoM) for a given gestational week represent an indirect reflection of the number of foetal erythrocytes in the circulation of both foetuses. MCA-PSV values > 1.5 MoM are diagnostic for the presence of anaemia, while values < 0.8 MoM are diagnostic for the presence of polycythaemia in the foetus in cases of single-foetal pregnancies. The value of the difference in MCA-PSV between the donor and the recipient is more critical for TAPS diagnosis than their absolute values in individual foetuses (Tab. 1) [39–41].

Despite the relatively wide application of MCA-PSV in the diagnosis of foetal anaemia in single-foetal pregnancies, the sensitivity and specificity of the above criteria in mul-

Table 1. TAPS stages - diagnostic criteria — 2019 [53]

Stages	Diagnostic criteria
1.	Delta MCA-PSV > 0.5 MoM, with no signs of haemodynamic risk to the foetuses
2.	Delta MCA-PSV > 0.7 MoM, with no signs of haemodynamic risk to the foetuses
3.	Stage 1 or 2 with signs of haemodynamic risk to the donor*
4.	Signs of hydrops in the donor
5.	Intrauterine demise of one or both foetuses preceded by TAPS

*Absence or reversibility of end-diastolic flow in the umbilical artery, pulsatile flow in the umbilical vein, and/or increased pulsatile index or reverse flow in the ductus venosus. MCA-PSV — Middle Cerebral Artery Peak Systolic Velocity, MoM — Multiple of Medians, TAPS — Twin Anaemia Polycythaemia Sequence

ti-foetal pregnancies are still being investigated. The validity and the interpretability of the measurements can be significantly biased, especially in the third trimester of pregnancy, due to the foetuses' spatial presentation. TAPS, analogously to TTTS, can be stratified into several stages based on the degree of severity (Tab. 1) [27].

Therapeutic options for confirmed TAPS are diverse and include observation, induction of labour, intrauterine transfusion, laser, ablation therapy, and controlled selective feticide. The choice of treatment is strictly individual, with the dominant factors being the gestational age at the time of diagnosis and the severity of the disorder. Observation and monitoring are appropriate in late gestational weeks and a milder form of the disorder with relatively good haemodynamic compensation. Cases of post-ablative form of TAPS with spontaneous improvement have been reported. According to the currently available literature, the mortality rate associated with the individual therapeutic modalities is approximately the same. However, observational or expectant management is associated with higher neonatal and perinatal morbidity compared to intrauterine transfusion or laser ablation treatment [42–45].

Administration of intrauterine transfusions is a suitable option for the manifestation of the disorder in the early gestational weeks, as it allows temporary improvement in the condition of the anaemic foetus, delay of premature birth, and prolongation of pregnancy. However, intrauterine transfusions are not a causal treatment, and despite a temporary correction of anaemia in the donor, most cases of TAPS recur within one week. In addition, repeated administration deteriorates the condition of the polycythaemic foetus [46–48]. In the case of transfusion therapy, some authors prefer intraperitoneal to intraumbilical administration, as erythrocytes persist longer in the abdominal cavity with slower release and less overload of the recipient circulation [49].

Laser ablation therapy is the only causal treatment for TAPS, but sporadically presented cases indicate different results. Performing fetoscopic laser ablation in the case of TAPS is more technically demanding compared to ablation in the case of TTTS, as there is no intrauterine working window in the form of polyhydramnios and vascular connectors in the form of AV anastomoses are minuscule, deeply located and difficult to visualize [28].

Assessing short-term and long-term mortality and morbidity in TAPS cases is challenging, as many cases remain prenatally undiagnosed. Slaghekke et al., report the results of a randomized controlled trial of 19 TAPS cases (38 foetuses). The incidence of neonatal mortality and morbidity was comparable in both groups — TAPS 3% (1/38) *vs.* control group 1% (1/76), TAPS (24% 9/38) *vs.* control group (28% 21/76). Severe brain damage occurred in one foetus in the TAPS group (5%), and a similar result was reported in the control group (2%). In the TAPS group, transfusion was reported in 80% of donors (15/19) and partial exchange transfusion in 68% of recipients (13/19) [2]. Due to the insufficient size of the groups of children from pregnancies complicated by TAPS, long-term mortality and morbidity are still the subject of research with preliminary results showing that approximately 9% of foetuses are affected by long-term developmental impairment [50]. Han et al., published a retrospective comparative study of preterm (24–27 gestational week) foetuses from monochorionic pregnancies where they recorded an incidence of spontaneous TAPS in 6.4% based on the postnatal determination of haematocrit in foetuses. Foetuses from TAPS-affected pregnancies had a lower gestational age at delivery, with perinatal mortality and morbidity not different from the control group. The incidence of a severe cerebral lesion in neonatal age and persistent sensorimotor deficit at two years of age was not statistically significantly different in the TAPS and the control group [51]. One Dutch study compared the incidence of neurodevelopmental disorders between donors and recipients in pregnancies complicated by spontaneous TAPS occurrence. According to published findings, donors have a 4-fold higher risk of neurodevelopmental disorders, cognitive delay, and a high rate of deafness [52].

MATERIAL AND METHODS

Based on the available literature (04/2020) using electronic research databases (PubMed, Google Scholar, Dyna Med, Web of Science, Scopus), we created a meta-analytical review of up-to-date knowledge on TAPS with a focus on current options for early detection and subsequent effective management. We analysed the available prenatal diagnosis modalities with an emphasis on the effective TAPS screening in the management of monochorionic pregnancies. The quality of MCA-PSV as a main diagnostic modality pub-

Table 2. Sensitivity and specificity of MCA-PSV in the diagnosis of TAPS

Study	Defined criteria	Sensitivity (95% CI)	Specificity (95% CI)	Positive predictive value (95% CI)	Negative predictive value (95% CI)
Slaghekke et al. 2015 [55]	MCA-PSV ≥ 1.5 MoM — donor MCA-PSV ≥ 1.0 MoM — recipient	**94%** (85–98%) **97%** (87–99%)	**74%** (62–83%) **96%** (89–99%)	**76%** (65–85%) **93%** (81–97%)	**94%** (83–98%) **99%** (93–100%)
Veujoz et al. 2015 [59]	MCA-PSV > 1.5 MoM — donor and simultaneously MCA-PSV < 1.0 MoM	**71%** (29–96%)	**50%** (1–99%)	**83%**	**33%**
Tollenaar et al. 2019 [53]	MCA-PSV > 1.5 MoM — donor and simultaneously MCA-PSV < 1.0 MoM MoM — recipient Delta MCA-PSV > 0.5 MoM	**46%** (30–62%) **83%** (67–92%)	**100%** (92–100%) **100%** (92–100%)	**100%** (81–100%) **100%** (88–100%)	**70%** (58–80%) **88%** (77–94%)

CI — Confidence Interval; MCA-PSV — Middle Cerebral Artery Peak Systolic Velocity; MoM — Multiple of Medians

lished in defined papers was graphically recorded using a table depending on the established diagnostic criteria of TAPS in individual studies (Tab. 2). Data on sensitivity and specificity with various MCA-PSV cut-off values were mostly calculated by use of standard binominal 2 x 2 tables with a determination of 95% Confidence Interval (95% CI) based on the Wilson interval method. The nature of the continuous variables was corrected using Mann-Whitney U-test. However, the exact methods are stated in the original papers cited.

RESULTS

After entering key words (Twin Anaemia Polycythaemia Sequence), we obtained 165 articles, the oldest from 2007 and the most recent from 2020. Due to a low incidence of TAPS, currently the only described methodology in prenatal diagnosis is the determination or secondary comparison of given MCS-PSV values in individual foetuses. Some papers describe morphological organ changes in individual foetuses but without exact determination of sensitivity and specificity values due to an insufficiently large cohort regarding statistical evaluation. Based on the available articles, we evaluated the determination of MCA-PSV with a sensitivity of 83% and a specificity of up to 100% for the currently generally accepted diagnostic criterion TAPS — Delta MCA-PSV > 0.5MoM as the most sensitive and specific method of prenatal diagnosis. Data on sensitivity 83% and specificity 100% with a cut-off value – delta MCA-PSV > 0.5 was for the first time determined in paper published by Tollenaar et al., in 2019 (Tab. 2) [53].

DISCUSSION

TAPS, as a phenomenon known for almost 13 years, is still an underestimated complication of monochorionic pregnancies. The absence of unambiguous morphological markers during the ultrasonographic examination, combined with a relatively low incidence, is the leading cause of low disease detection [50].

Even though some papers report the occurrence of some so-called "minor" ultrasonographic morphological markers, the frequency of their presence has not yet been clearly assessed through large, randomized studies. Tollenar's working group monitored the prevalence of minor markers in 91 cases of monochorionic pregnancies complicated by the occurrence of a spontaneous and post-ablative form of TAPS, recording the prevalence of placental dichotomy in 44% and a so-called "starr sky liver" in 66%. Based on the above, these markers can be considered a complementary and active search for them should be included in a comprehensive second-trimester morphological examination of monochorionic pregnancies [8, 20].

Based on published studies, the only non-invasive technique enabling early, prenatal diagnosis of TAPS is serial examinations of MCA-PSV of individual foetuses at regular intervals [18, 21]. The sensitivity and specificity of this examination in cases of monochorionic pregnancies complicated by the occurrence of TAPS depends on the set diagnostic criteria (Tab. 2) as it was found that cut-off values for the detection of foetal anaemia in single-foetal pregnancies (MCA-PSV > 1.5 MoM) may not be of diagnostic value in TAPS cases. Originally applied criteria defined for the diagnosis of anaemia or polycythaemia in single-foetal pregnancies showed reduced sensitivity and specificity in TAPS diagnosis. Currently, the difference in MCA-PSV in both foetuses > 0.5 MoM is considered diagnostic for TAPS (Delta MCA-PSV > 0.5 MoM) [53].

Despite the documented sensitivity, specificity, non-invasiveness, safety, and cost-effectiveness of MCA-PSV, no clear recommendations are currently issued for its widespread use as a potential screening method for TAPS in the diagnosis of monochorionic pregnancies.

In the United States, according to the recommendations of the Society for Maternal-Fetal Medicine (SMFM), routine serial measurement of MCA-PSV in monochorionic pregnancies is not suitable, as the Society declares that despite early detection of potential TAPS, perinatal mortality and foetal morbidity are not reduced. The Society admits measurement in TTTS cases after ablation treatment where there is a high probability of TAPS prevalence

Table 3. Therapeutic algorithm of TAPS proposed by Tollenaar et al. [28]

Treatment modality	Indication criterion
Expectant management	TAPS Stage 1 regardless of the gestational week TAPS Stage 2 without signs of progression in the period > 28th gestational week
Laser bichorionization of placenta	TAPS Stage ≥ 2 and gestational age < 28 weeks
Intrauterine blood transfusion with laser ablation treatment	TAPS Stage ≥ 3 or Stage 2 with signs of progression in the period between 28–32 gestational weeks
Induction of labour	TAPS Stage ≥ 3 or Stage 2 with signs of progression in the period after the end of the 32nd gestational week

TAPS — Twin Anaemia Polycythaemia Sequence

but does not specify the time intervals between individual examinations [8].

NICE (National Institute for Health and Care Excellence) similarly recommends serial measurements only in the presence of pathology and likewise does not specify the time intervals between individual examinations [57].

ISUOG (The International Society of Ultrasound in Obstetrics & Gynaecology) recommends serial determination of MCA-PSV in all monochorionic pregnancies from gestational week 20 with two-week intervals until delivery [58].

Despite incoherent recommendations, many of which have the character of a so-called "expert opinion", part of the authors in the clinics of maternal and foetal medicine, especially in the United States of America, sets the MCA-PSV from gestational week 16 despite technical difficulties in measuring and difficulty to interpret results [50].

Since serial measurement of MCA-PSV remains the only diagnostic modality for early diagnosis of TAPS to date, according to some authors, its widespread use is suitable for early detection and possible therapeutic intervention in verifying this complication [50]. The above view is also supported by Hill and colleagues' work, which states that expectant management is associated with poorer perinatal outcomes than laser ablation therapy and administration of intrauterine transfusions.

Based on meta-analytical evaluation of the available literature, the authors of the publication are inclined to the opinion supporting the importance of determining MCA-PSV in monochorionic pregnancies. The serial assessments of MCA-PSV allow for the early detection of the disorder and provides sufficient information to patients with the possibility of the next therapeutic procedure's initial planning. According to the authors, serial MCA-PSV measurements should be performed in all monochorionic pregnancies as a TAPS screening test from gestational week 20 every two weeks until delivery.

Many published case studies confirm the need for serial measurement of MCA-PSV to determine the prenatal diagnosis of TAPS [1, 6].

The modality of treatment and the method of its application depend mainly on the severity of the condition (TAPS Stage 1–5), the gestational age of the foetuses, and the patient's preferences. In general, with decreasing gestational age and increasing severity of the disorder, a significant shift from conservative management to invasive procedures regarding laser bichorionization of the placenta can be observed. Minor forms of TAPS diagnosed in advanced gestational age are usually managed conservatively. An indicative chronological arrangement of therapeutic options in the case of pregnancies complicated by the development of TAPS was developed and published by Tollenaar et al. [28], in 2016 (Tab. 3).

Conflict of interest

All authors declare no conflict of interest.

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Respiratory distress syndrome in preterm infants: possible impact of surfactant application techniques

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ABSTRACT

Objectives: Prematurity is one of the most important issues in perinatology. The most frequent postnatal pathology connected with prematurity is respiratory distress syndrome (RDS) caused by surfactant deficiency due to lung immaturity. RDS is one of the most frequent causes of mortality and morbidity with short- and long-term consequences. The aim of the study was to compare the effectiveness of individual surfactant supply techniques in the treatment of respiratory disorders in premature infants.

Material and methods: In the period from the year 2009 to 2013, there were 198 very premature infants that received surfactant included to this retrospective study.

They were divided into three groups based on the surfactant application method:

1. Premature newborns with substitute ventilation, with supply of surfactant through a traditional endotracheal tube — Average gestational age 26.6 weeks; Mean birth weight 911 g; Average Apgar score 4 in 1st minute, 6 in 5th minute.

2. Premature newborns with exogenous surfactant supplementation — InSure method — Average gestational age 28.3 weeks; Average birth weight 1117 g; Mean Apgar score 6 in 1st minute, 7 in 5th minute.

3. Premature newborns with exogenous surfactant supplementation — Less Invasive Surfactant Administration (LISA) method — Mean gestational age 29.9 weeks; Average birth weight 1444 g; Average Apgar score 7 in 1st minute, 8 in 5th minute.

Results: Noninvasive methods of respiratory support and minimally invasive surfactant administration (MISA) significantly reduced the incidence of severe RDS, compared to the traditional method.

Conclusions: Non-invasive methods of respiratory support and MISA like LISA and InSure methods were safe and effective in the treatment of RDS.

Key words: neonatology; continuous positive airway pressure; spontaneous breathing; surfactant; respiratory distress syndrome

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INTRODUCTION

Prematurity is one of the biggest challenges in neonatology. According to the World Health Organization definition, a premature infant is a child born after 22 and before 37 weeks of pregnancy. Newborns born prematurely are at risk of numerous short- and long-term consequences.

Among the short-term consequences respiratory distress syndrome (RDS) is regarded as one of the most crucial. The main causes of RDS are lung immaturity and surfactant deficiency. Untreated RDS could lead to death and is the most common cause of mortality of prematurely born infants.

Until recently, the only standard of management for respiratory failure caused by surfactant deficiency was intubation, endotracheal administration of surfactant and mechanical ventilation, usually continued for many days. All these approaches aim to achieve vital parameters allowing for extubation. This method was associated with damage to the lungs and the development of bronchopulmonary dysplasia.

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Since the beginning of the new millennium, clinicians have started to seek new, less invasive methods for the treatment of respiratory failure in preterm neonates [1, 2]. Implementing noninvasive methods of respiratory support in the early stages after birth has successfully reduced mortality among these patients [3–5] and the incidence of bronchopulmonary dysplasia [6, 7]. These findings were confirmed by the Vermont Oxford Network (VON), Continuous Positive Airway Pressure or Intubation at Birth (COIN) and Surfactant, Positive Pressure, and Pulse Oximetry Randomized Trial (SUPPORT) studies. [8–10].

The use of noninvasive methods of ventilation is insufficient for some patients. These newborns require additional administration of exogenous surfactant because of surfactant deficiency. Research is currently in progress for a method to provide surfactant administration with less invasive methods [11], *i.e.*, inhalation or nebulization [12, 13].

Then, a new method was introduced several years ago: the Intubation, Surfactant Administration and Extubation (INSURE) technique. This method consisted of patient intubation, surfactant administration through thane endotracheal tube and immediate extubation with further use of noninvasive methods of respiratory support, without the need for the continuation of mechanical ventilation [14]. Although great progress has been made, an even less invasive method of administering surfactant was proposed by German researchers: Less Invasive Surfactant Administration (LISA) [1, 15]. In some Australian centers, this technique is called Minimally Invasive Surfactant Therapy (MIST) [11]. The advantage of this method relies on the administration of surfactant without the need for intubation while continuing noninvasive nasal ventilation. This technique reduces the frequency of failure of noninvasive ventilation [7, 11, 16], decreases the duration of mechanical ventilation [15–17], the use of oxygen and the incidence of bronchopulmonary dysplasia [7].

Objectives

The aim of this retrospective study was to compare the effectiveness of each of the three surfactant administration techniques used in the treatment of respiratory failure in premature patients, considering the frequency of complications following each method in the Neonatal Intensive Care Unit (NICU) in a tertiary referral hospital in Lodz, Poland.

MATERIAL AND METHODS

Study design and patients

The study included patients with a gestational age of 25–32 weeks who were hospitalized from 2009–2013 in the Department of Neonatology, 1st Department of Gynecology and Obstetrics in Lodz, Poland.

The study group consisted of 198 newborns with respiratory failure caused by respiratory distress syndrome. We performed a retrospective analysis of the preterm patient treatment results, depending on the type of treatment that had been used, *i.e.*, the surfactant administration method.

Inclusion Criteria:

— Gestational age of 25–32 weeks
— Respiratory Distress Syndrome
— Need of surfactant administration

Exclusion Criteria:

— Gestational age different that 25–35 weeks
— Birth defects impacting the respiratory system

Three study groups were defined:

1. Preterm babies with mechanical ventilation (MV) who received surfactant administration through an endotracheal tube, followed by MV (Group 1).
2. Preterm babies with exogenous surfactant administration — INSURE method (Group 2).
3. Preterm babies with exogenous surfactant administration — LISA method (Group 3).

Patients in the LISA-treated group were given surfactant via a feeding catheter.

The distribution of patients in each group was as follows: 104 infants in the Intubation+MV group, 60 infants in the INSURE group, and 34 infants in the LISA group.

Poractant alfa (porcine-derived surfactant) was the surfactant used in all our patients.

The distribution of the number and gestational age of patients in each group derives from the fact that in the mentioned period, surfactant administration not followed by mechanical ventilation (Groups 2 and 3) was not routine, the LISA method was very innovative, and formal trials were just beginning.

The following parameters were assessed: patient sex, birth weight, status after birth assessed with the Apgar score (after 1 and 5 minutes) and occurrence of intrauterine fetal growth restriction. From the obstetric point of view, additional parameters were analyzed: type (level) of facility where the patient was delivered, method of birth (via cesarean section or vaginal birth), occurrence of premature rupture of membranes (PROM) and administration of prenatal corticosteroids.

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

Assessment and endpoints

We evaluated patient survival rate and the number of complications after treatment of respiratory failure: necessity for surfactant administration, need for oxygen therapy within the first 28 days of life, total length of respiratory support, failure of noninvasive ventilation methods, need

Table 1. Demographic characteristics of the studied groups

	Intubation + MV (n = 104)	INSURE (n = 60)	LISA (n = 34)
Week of pregnancy, average (SD)	26.6 (2.5)	28.3 (1.8)	29.9 (1.9)
Birth weight, average (SD)	911 (400)	1117 (387)	1444 (433)
APGAR 1 min, median (IQR)	4.0 (3.5)	6.0 (2.0)	7.0 (2.0)
APGAR 5 min, median (IQR)	6.0 (2.0)	7.0 (2.0)	8.0 (1.0)
Boys, n (%)	53 (51.5)	31 (53.4)	19 (57.6)
PPROM, n (%)	19 (18.3)	15 (25.0)	9 (26.5)
C-Section, n (%)	76 (73.1)	46 (76.7)	29 (85.3)
Outborn, n (%)	39 (37.5)	9 (15.0)	6 (17.6)
IUGR, n (%)	26 (30.2)	25 (47.2)	4 (14.3)

SD — standard deviation; IQR — interquartile range; PPROM — preterm premature rupture of membranes; IUGR — intrauterine growth restriction; MV — mechanical ventilation; INSURE — Intubation, Surfactant Administration and Extubation; LISA — Less Invasive Surfactant Admnistration

Table 2. Prenatal steroids, surfactant administration information and respiratory distress syndrome stages

	Intubation + MV (n = 104)	INSURE (n = 60)	LISA (n = 34)	p (Insure vs Intubation + MV)	p (LISA vs Intubation MV)
Prenatal steroids, n (%)	40 (39.2)	27 (45.8)	20 (58.8)	0.518	0.073
Preventive surfactant administration, n (%)	57 (54.8)	45 (76.3)	14 (41.2)	0.012	0.237
Early surfactant administration, n (%)	30 (29.1)	12 (20.3)	9 (26.5)	0.298	0.938
Readministration of surfactant, n (%)	18 (17.3)	3 (5.3)	5 (14.7)	0.030	0.930
RDS stage I & II, n (%)	63 (61.2)	47 (78.3)	31 (93.9)	0.140	0.001
RDS stage III, n (%)	40 (38.8)	13 (21.7)	2 (6.1)	0.041	< 0.001

Groups were compared with chi-square or Fisher's exact test; MV — mechanical ventilation; INSURE — Intubation, Surfactant Administration and Extubation; LISA — Less Invasive Surfactant Administration

Table 3. Complications of prematurity

	Intubation + MV (n = 104)	INSURE (n = 60)	LISA (n = 34)	p (Insure vs Intubation + MV)	p (LISA vs Intubation + MV)
BPD, n (%)	44 (44.0)	29 (49.2)	11 (32.4)	0.642	0.322
Pneumothorax, n (%)	16 (15.4)	2 (3.3)	1 (2.9)	0.019	0.071
Pulmonary hemorrhage, n (%)	10 (9.6)	1 (1.7)	2 (5.9)	0.057	0.730
IVH stage I & II, n (%)	36 (35.0)	28 (46.7)	9 (26.5)	0.190	0.482
IVH stage III & IV, n (%)	21 (20,4)	7 (11,7)	1 (2,9)	0.227	0.015
PVL, n (%)	5 (4.9)	7 (11.7)	0 (0.0)	0.202	0.331
PDA, n (%)	43 (41.3)	29 (49.2)	15 (44.1)	0.424	0.933
NEC, n (%)	17 (16.3)	17 (28.3)	6 (17.6)	0.104	> 0.999
ROP, n (%)	26 (25.0)	13 (21.7)	2 (5.9)	0.905	0.014

Groups were compared with chi-square or Fisher's exact test; MV — mechanical ventilation; INSURE — Intubation, Surfactant Administration and Extubation; LISA — Less Invasive Surfactant Administration; BPD — bronchopulmonary dysplasia; IVH — intracranial hemorrhage; PVL — periventricular leukomalacia; PDA — persistent ductus arteriosus; NEC — necrotizing enterocolitis; ROP — retinopathy of prematurity

for endotracheal intubation, duration of mechanical ventilation, and occurrence of bronchopulmonary dysplasia, pneumothorax and lung hemorrhage if occurred at any stage of treatment.

The incidence of other conditions connected with prematurity like intracranial hemorrhage (IVH), periventricular leukomalacia (PVL), persistent ductus arteriosus (PDA), retinopathy of prematurity (ROP), and necrotizing enterocolitis (NEC) was followed.

Two-sided statistical tests with a significance level of 0.05 were used. Depending on whether the data followed a normal distribution, the t-test or Mann-Whitney U test were applied to compare the differences in continuous variables between groups. Discrete variables were compared

between groups with the chi-square test or Fisher's exact test. The statistical package R version 3.5.1 (www.r-project.org) was used for statistical analysis.

Ethics

The study was approved by the Bioethics Committee of Medical University of Łódź (number: RNN/6/14/KE, KE/649/14).

Patients' parents and/or legal guardians were counselled before enrolling to the study and they were free to ask questions concerning all procedures. They were asked to sign informed consent forms.

RESULTS

RDS

The grade of RDS was based on the chest X-ray of the patient.

The difference in the incidence of mild RDS was not statistically significant between the Intubation+MV and INSURE groups (61.2% vs 78.3%, p = 0.14) or between the Intubation+MV and LISA groups (61.2% vs 93.9%, p = 0.001). Statistically significant differences were also observed among groups in the incidence of severe RDS. In the group of MV - treated patients, severe RDS was diagnosed more often (38.8%) than in the remaining groups – INSURE (21.7%, p = 0.041) and LISA (6.1%, p < 0.001).

Such a high occurrence of severe RDS might result from the relatively younger gestational age in Group 1 (26.6 weeks g.a.), as well as the lack of prenatal steroid therapy in some of the patients. The frequency of prenatal steroid therapy was not significantly different among all groups (MV — 39.2%; INSURE — 45.8%; LISA — 58.8%; MV vs INSURE: p = 0.518; MV vs LISA: p = 0.073). However, the number of doses of antenatal steroids differed among groups.

Prophylactic surfactant

Prophylactic surfactant was administered up to 15 minutes after birth in 54.8% of the MV group, in 76% of the INSURE group and in 42% of the LISA group. Preventive surfactant administration was significantly more frequent in the INSURE group than in the MV group (76.3% vs 54.8%; p = 0.012).

On the other hand, no statistically significant difference was found in the rate of early surfactant administration among all study groups (MV 29.1%; INSURE 20.3%; LISA 26.5%; p = 0.298).

Readministration of surfactant

The need for a second dose (readministration) of surfactant in the INSURE group, in which most of the patients had surfactant administered prophylactically, was significantly lower than that in the MV group (5.3% vs 17.3%; p = 0.030).

The number of days patients from the studied groups need oxygen therapy was the lowest in the LISA group, but the difference was not statistically significant (p = 0.514).

Consequences of preterm birth

Bronchopulmonary dysplasia is one of the most common negative outcomes of the use of mechanical ventilation and long-term oxygen therapy. The frequency of this complication was lowest in the LISA-treated group (MV: 44.0%; INSURE: 49.2%; LISA: 32.4%; p = 0.32). Pneumothorax occurred significantly less frequently in both the INSURE and LISA groups than in the MV group (MV: 15.4%; INSURE: 3.3%; LISA: 2.9%; p = 0.019).

Regarding the number of cases of pulmonary hemorrhage, no significant differences were identified among the studied groups (MV: 9.6%; INSURE: 1.7%; LISA: 5.9%; p= 0.73).

Analyzing other late consequences of preterm birth, the incidence of intracranial hemorrhage (regardless of grade) was highest in the INSURE group (MV: 35.0%; INSURE: 46.7%; LISA: 26.5%; p = 0.48). A significant difference was observed in the rate of severe intra- and periventricular hemorrhage (grade III and IV) in favor of LISA patients compared to MV patients (LISA: 2.9% vs MV: 20.4%, p = 0.015).

Periventricular leukomalacia (PVL) occurred more frequently in patients treated with the INSURE method; however, no statistically significant difference was observed compared to the MV group (MV: 4.9%; INSURE: 11.7%; LISA: 0%; p = 0.202). None of the patients from the LISA group presented periventricular leukomalacia.

No significant differences were identified among study groups in the number of cases of patent ductus arteriosus or the need for pharmacological treatment for PDA. It is important to mention that the introduction of pharmacological treatment of PDA for the LISA group was always effective. The need for surgical treatment for PDA was significantly lower in the LISA group than in the MV group (MV: 11.5%; INSURE: 8.3%; LISA: 0%; p = 0.038). None of the patients in the LISA group required surgical PDA treatment.

The occurrence of necrotizing enterocolitis (NEC) was the highest in the INSURE group, but the difference was not significant (MV: 16.3%; INSURE: 28.3%; LISA: 17.6%; p > 0.999).

Retinopathy of prematurity is another late consequence of preterm birth. A significantly high rate of bronchopulmonary dysplasia (BPD) occurred in the INSURE group. The LISA group had a significantly lower ROP rate than the MV group (MV: 25.0%; INSURE: 21.7%; LISA: 5.9%; p = 0.014).

DISCUSSION

Our study showed that both the INSURE and LISA methods of surfactant administration can be considered safe and effective as treatments for RDS. These methods seem to have fewer adverse effects than the classical approach of intubation and the administration surfactant followed by mechanical ventilation.

In our study, [16] both the INSURE and LISA methods significantly reduced the incidence of severe RDS in comparison to the MV method, with LISA being even more effective than INSURE [18]. Although this result might be biased by the lack of antenatal steroid therapy in some of the patients, which was unsatisfactory low in Poland at the time [19], in the MV group as well as the higher percentage of extreme prematurity in the same group of patients, the conclusion agrees with previous studies [16, 18].

Consistent with most previous studies, the duration of oxygen dependence was significantly shorter in the LISA group than in the two other studied groups. Similar to most studies, the LISA group had the lowest rate of BPD. [1, 6, 7, 18, 20].

As underlined in many previous studies, the benefits of the LISA surfactant administration method might come from the fact that the technique allows for noninvasive respiratory support (such as nCPAP) to be continued during the entire procedure of administering surfactant [21]. This might be the factor preventing the lung injuries that result from mechanical ventilation of any duration [15]. This approach allows the infant to breathe spontaneously during the entire procedure instead of relying on repetitive positive pressure inflations, which might cause faster and more thorough surfactant distribution and absorption [22].

We did not notice any significant differences in the incidence of PDA, although the need for surgical treatment was significantly lower in the LISA group than in the other studied groups.

Regarding the number of cases of ROP and NEC, there was a significant difference between the LISA group and INSURE group. In our study, the INSURE group had a higher rate of both of those complications. This stands in contrast to some of the previous studies in which no significant difference was found [5, 7].

In our study, the INSURE patients seemed to have a significantly lower rate of pulmonary hemorrhage, while patients receiving surfactant with the LISA method had less severe intraventricular and periventricular hemorrhage.

Some of the differences between the results of our study and previous studies [5, 7] might come from the previously stated difference in antenatal steroid administration as well as the number of doses received by the patients' mothers. The preventive type of surfactant administration was much more common in the INSURE group.

The other factors causing the differences between this study and other studies [5, 7] might be the average gestational age, birth weight, and the rate of intrauterine growth restriction (IUGR). Each of these factors could affect the rate of preterm morbidities.

Like other studies [23], we found that noninvasive prophylactic surfactant administration immediately after birth in the delivery room is beneficial for patients and can reduce the need for subsequent doses of surfactant.

CONCLUSIONS

1. Noninvasive methods of surfactant administration, such as with the LISA and INSURE methods, are safe and effective in the treatment of respiratory distress syndrome, with no increase in the rate of pneumothorax.
2. The prophylactic administration of surfactant in the delivery room using noninvasive or less invasive methods is beneficial for the patient and reduces the need for subsequent doses of surfactant.
3. Noninvasive methods of respiratory support and surfactant administration significantly reduce the incidence of severe RDS.
4. For patients treated with a noninvasive approach, mainly infants from the LISA group, patent ductus arteriosus was more common; however, pharmacological treatment was shown to be effective. None of the patients in this group required surgical treatment of PDA.
5. Patients who were administered surfactant with use of the LISA method had intraventricular and periventricular hemorrhages of lower grades and a lower rate of ROP. Additionally, the frequency of BPD in the LISA group was lower than that in the other groups.
6. In patients treated with the INSURE surfactant administration method, there was a significantly lower incidence of pulmonary hemorrhage, while necrotizing enterocolitis and retinopathy of prematurity occurred more often.

Conflict of interest

All authors declare no conflict of interest.

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Anti-Mullerian hormone levels in girls and adolescents

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ABSTRACT

Anti-Mullerian hormone (AMH) is a homodimeric glycoprotein which belongs to the TGF-beta superfamily of growth and differentiation factors. There are few studies that present AMH concentrations in premenarcheal and early postmenarcheal girls. The aim of this study is to evaluate AMH levels in girls. A serum AMH increase of 1 pmol/L is related with a higher possibility of menarche occurrence. AMH levels are significantly higher in postmenarcheal girls than in prepubertal girls.

Key words: Anti-Mullerian hormone; puberty; adolescents; pediatric endocrinology

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INTRODUCTION

Anti-Mullerian hormone (AMH) is a homodimeric glycoprotein, with a molecular weight of 140 kDa, which belongs to the TGF-beta superfamily of growth and differentiation factors. The gene encoding AMH is located on the short arm of chromosome 19 in humans, band 19p 13.3.

It plays major role in developing male reproductive tract by activating the regression of male fetal Mullerian ducts [1]. In females it is produced by the granulosa cells of primary, preantral, and early antral follicles. The highest concentration of AMH is shown by small antral follicles (2–4 mm in diameter). AMH has two functions during follicular development. Firstly, it inhibits the transition of primordial follicles to the mature phase and it is through this mechanism that it plays a role in the regulation of the number of follicles resting in the reservoir of primordial follicles. Secondly, it decreases the FSH-sensitivity of the follicles, playing a role in the process of follicle selection.

In recent years, AMH has gained importance in endocrinologic gynecology. Serum concentration of AMH are much lower than the concentration in the follicle, although it correlates with it well. The AMH level determination can be performed independently of the phase of the menstrual cycle. A decrease in the number of follicles correlates with a decrease in AMH concentration. Therefore, serum AMH determination is mainly used to assess the ovarian reserve reflecting AFC and therefore it may be used as a marker during ovarian stimulation strategies [2]. The concentrations of AMH reflect the aging process of the ovary. Reduced AMH levels are also observed in the premature ovarian failure. 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 they correlate with tumor size. What is more, in women with polycystic ovarian syndrome (PCOS) AMH levels are observed to be higher than in healthy females. Although determination of AMH level is not necessary for the diagnosis of PCOS, it may be a useful and valuable marker.

There are few studies that present AMH concentrations in premenarcheal and early postmenarcheal girls. According to such studies, AMH levels rise during infancy and are stable from childhood to early adolescence, as they slightly decline from 9 to 15 years of age and then increase with the peak levels around 25 years of age [3–6]. Hagen et al. have presented data that AMH levels increase three years prior to the start of puberty, while decreasing after pubertal onset by 30% during the first two years [4, 7]. Lee et al. [8] have shown that AMH levels increase at 6-8 years of age and reach a peak during late adolescence.

The aim of this study is to evaluate AMH levels in girls.

MATERIAL AND METHODS

The subjects of this study were consecutive girls who were referred to the Pediatric Endocrinology Depart-

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ment and Outpatient Clinic at Upper Silesian Child Health Center between 1 June 2019 and 31 March 2020 (n = 100). The exclusion criteria were:

— Thyroid, prolactin, androgen, cortisol level disorders
— Chronic systemic illness
— Eating disorders
— Smoking or drug or alcohol use
— Taking medications known to interfere with reproductive hormones/receiving hormonal contraception.

Eighteen girls were excluded from the study and 82 girls were enrolled to undergo further research. Demographic and clinical data were retrieved from medical records.

The study was approved by the Ethics Committee of Medical University of Silesia (KNW/0022/KB1/3/19).

Clinical data

Anthropometric measurements included weight and height measurements. Body mass index (BMI) was calculated for each girl using the standard formula of weight (kg) divided by height (m) squared. The BMI Z-score and BMI percentile for each girl were calculated using The Pediatric Z-score Calculator, which is available on the website of The Children's Hospital of Philadelphia, Research Institute (https://zscore.research.chop.edu/calcbmi.php) and is based on the Center for Disease Control (CDC) growth charts.

Biochemical measurements

Blood samples were drawn from an antecubital vein between 8 am and 10 am after an 8-hour fast for luteinizing hormone (LH), follicle-stimulating hormone (FSH), total testosterone (TTE), inhibin B and anti-Mullerian hormone (AMH). The samples were centrifuged and stored at -20°C until analyses were conducted. TTE, LH, FSH, and AMH were measured with the electrochemiluminescence "ECLIA" method (Elecys, Roche Diagnostics GmbH, Mannheim). Inhibin B was measured with an enzyme-linked immunosorbent assay (ELISA Genie ELISA).

In postmenarcheal girls, the samples were drawn between the 2nd and 5th day of their menstrual cycle.

All measurements were performed in the Laboratory of the Upper Silesian Child Health Center, Katowice, Poland.

Pelvic ultrasound

The subjects underwent a transabdominal pelvic ultrasound. The length, width and volume of the ovaries were measured. Uterus and cervix measurements were also taken.

Statistical analysis

Statistical analysis was performed using StatSoft Statistica version 13.3 software. Quantitative variables are presented as a mean and standard deviation (SD) or median and interquartile range (IQR). The qualitative variables are presented as an absolute value and/or percentage. The between-group differences for quantitative variables were verified using a parametric (t-test or ANOVA) or non-parametric tests (U Mann-Whitney or Kruskal-Wallis), with previous verification of their distribution by the Shapiro-Wilk or Smirnov-Kolmogorov tests. In the case of qualitative variables, the chi-square test or Fisher's exact test was used. A receiver-operating characteristic (ROC) curve analysis was used to assess the diagnostic accuracy of AMH predicting menarche. Logistic regression analysis was conducted in order to assess the power of AMH increase in menarche occurrence. A p value of < 0.05 was considered significant.

RESULTS

A total of 82 healthy girls and adolescents were included. The median age was 142 months (11 years and 10 months) (IQR 111-180). The youngest subject was 87 months old (7 years and 3 months) and the oldest was 215 months old (17 years and 11 months). In addition, 30 girls were after menarche, while 52 girls had not menstruated yet. The clinical, demographic and ultrasound characteristics of the patients are presented in Table 1.

The mean AMH level was 30.47 ± 21 pmol/L. There were significant differences between the group of premenarcheal and postmenarcheal girls (25.2 pmol/L vs 39.6 pmol/L, p = 0.01). Mean TTE, LH, FSH, inhibin B and AMH levels are presented in Table 2.

The variations of AMH depending on age are presented in Figure 1.

ROC analysis was used to determine the cutoff level of AMH. The value of AMH that indicates menarche was

Table 1. Clinical and ultrasound characteristics of the study group

	TOTAL (n = 82)	Premenarcheal (n = 52)	Postmenarcheal (n = 30)
Age [months]	142 (IQR 111–180)	111.5 (IQR 106–140)	194 (IQR 177–205)
BMI	20.24 ± 4.58	17.93 ± 2.8	24.23 ± 4.35
BMI Z-score	0.41 ± 1	0.22 ± 1	0.75 ± 0.95
BMI percentile	60.83 ± 30.22	55.4 ± 30.22	70.23 ± 28.29
Mean ovarian volume [mL]	2.72 ± 3.09	0.82 ± 0.7	6.02 ± 2.85

BMI — body mass index; IQR — interquartile range

Table 2. Laboratory data and comparison of the groups

	TOTAL (n = 82)	Premenarcheal (n = 52)	Postmenarcheal (n = 30)	p-value
AMH [pmol/L]	30.47 ± 21	25.2 ± 16.93	39.59 ± 19.67	p = 0.01
LH [mIU/mL]	4.76 ± 6.6	1.51 ± 4.16	10.38 ± 6.32	p < 0.001
FSH [mIU/mL]	3.91 ± 4	3.31 ± 4.66	4.92 ± 2.23	p < 0.001
TTE [ng/dL]	18.62 ± 21	6.67 ± 9.06	39.33 ± 19.67	p < 0.001
INHIBIN B [jednostka??]	0.45 ± 2	0.31 ± 1.38	0.69 ± 2.8	p = 0.8

AMH — Anti-Mullerian hormone; LH — luteinizing hormone; FSH — follicle-stimulating hormone; TTE — total testosterone

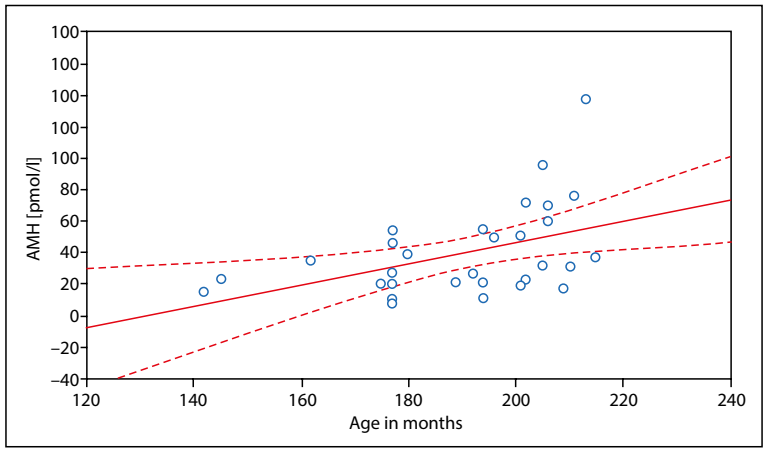

Figure 1. Variations of Anti-Mullerian hormone (AMH) depending on age. AMH was significantly associated with age (p < 0.05)

determined as 30.63 pmol/L with 53% sensitivity and 73% specificity (p = 0.007). The area under the ROC curve was determined as 0.666 (CI 0.545–0.787) (Fig. 2).

Regression analysis was performed in order to assess the relationship between an increase in AMH levels and menarche occurrence. An increase of 1 pmol/L of AMH resulted in 1.03 times higher possibility of menarche (p < 0.005).

The mean AMH level in the group of girls who had been menstruating for more than 24 months (n = 19) was 45.53 ± 29.75 pmol/L. Mean AMH level in the group of girls who had been menstruating for 24 months or less (n = 11) was 29.33 ± 24.1, p > 0.05. In addition, there were no statistically important differences in AMH levels between premenarcheal girls and girls who had been menstruating for less than 24 months.

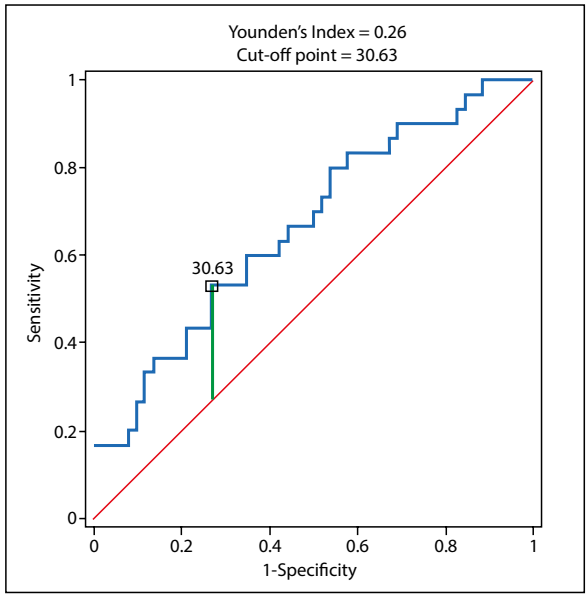

Figure 2. Receiver-operating characteristic curve of Anti-Mullerian hormone (pmol/L)

DISCUSSION

In this single-center study we sought to investigate the fluctuations of AMH in the group of healthy pre- and postmenarcheal girls. There are few studies that report the variations of AMH during childhood and puberty. Ortega et al. [9] report that healthy, early postmenarcheal girls have an average AMH level of 37.13 ± 2.14 pmol/L (5.2 ± 0.3 ng/mL).

Studies describing the variations of AMH show that its levels slightly rise until about 9 years of age, then there is a slight

decline from 9 to about 15 years of age and then they increase [5, 6, 10]. In our study age was significantly associated with AMH levels, there was a significant raise in levels observed from the age of 168 months of age (14 years).

As AMH is considered one of the indicators of precocious puberty and may be useful in differentiation of central precocious puberty (CPP) and premature thelarche (PT), it is important to evaluate the fluctuations of this hormone in healthy girls [11, 12]. Sahin et al. [11] found out that the AMH levels in patients with CPP were lower than in patients with PT. They determined the level of AMH that defines CPP as 9.03 pmol/L. Chen et al. [8] remain consistent with this finding. In this study we focused on investigating the range of AMH levels in healthy young females that can serve as a reference for clinicians in differentiating CPP, PT and other pubertal problems with physiological changes. Chen et al. [12] present that AMH levels can be potential biomarkers for distinguishing progression rates in girls with CPP and they can help in the distinction of progressive CPP and less severe CPP. In addition, Efthymiadou et al. [13] found out that AMH concentration is increased in girls with premature adrenarche compared with healthy girls. In contrary, Utriainen et al. [14] found out that girls with premature adrenarche had lower serum AMH concentrations than the control group. Sahin et al. [11] underlined that AMH may be a marker for diagnosis of CPP and PT. These findings show how important is to establish AMH levels in healthy girls to identify potential endocrinologic disorders.

Our findings show that the mean levels of AMH in premenarcheal girls were 25.2 ± 16.93 pmol/L. Savas-Erdeve et al. [15] reported that average AMH levels in a group of 22 prepubertal girls (22 female cases who were prepubertal before the age of 8) were 14.9 ± 6.1 pmol/l (2.1 ± 0.85 ng/mL).

In our study, there were no significant differences found in the girls who had been menstruating for at least two years and girls who had been menstruating for less than two years (45.53 ± 29,75 pmol/L vs 29.33 ± 24.1, $p > 0.05$, $p > 0.05$, respectively). However, these findings may be due to the small number of girls in both subgroups.

The main limitation of this work is the small number of participants, although it is challenging to gather large representative group of healthy minors who present to the outpatient clinic or hospital ward for diagnostics, as many of them meet the exclusion criteria. Moreover, as the formal consent of their parents is needed, even when a minor meets the inclusion criteria, she may not be included to the study.

However, we hope that this study may be useful for clinicians in pediatric and endocrinologic pediatric wards when interpreting the laboratory examinations of their patients, as well as for the authors of further articles on this topic. Understanding the variations in AMH levels in healthy female adolescents may enable early identification of diminished ovarian reserve, risk of developing polycystic ovarian syndrome or premature puberty.

CONCLUSIONS

In conclusion, a serum AMH increase of 1 pmol/L is related with a higher possibility of menarche occurrence. AMH is significantly connected with age. AMH levels are significantly higher in postmenarcheal girls than in prepubertal girls. No differences were found between the AMH levels in girls who had been menstruating for more than 24 months and girls who had been menstruating for less than 24 months.

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Conflict of interest

All authors declare no conflict of interest.

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Birth before arrival — is there anything to be afraid of?

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ABSTRACT

Over the past centuries maternal and neonatal morbidity and mortality has fallen dramatically. This is mainly due to the fact that we achieved a lot in the field of medicine in a very short amount of time. Evidence, mostly from Europe but also from US, suggested that home birth can be relatively safe provided the appropriate conditions are met. The question is "What if something goes wrong?" How to increase patient safety in the case of birth before arrival (BBA) or it may not be associated with any increased risk?

Our study review nowadays available articles and describes rates, obstetrical characteristics and perinatal and maternal outcome of unplanned out-of-hospital deliveries.

Key words: pregnancy; BBA; OOH; paramedics

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INTRODUCTION

Out-of-hospital birth can occur as planned or unplanned. Most of planned childbirths take place at home in the care of dedicated midwife. However, situation of that sort may happen unplanned. The term — birth before arrival (BBA) — is defined as a delivery of a baby that takes place outside healthcare facilities. It also includes home or enroute to a delivery centre or hospital (in an ambulance, private car or on hospital grounds) and are not attended by a midwife. [1, 2].

The incidence of BBA varies worldwide. Overall, rate of BBA in developed countries is less than in developing countries. It is 0.1–0.44% in Europe [3], 1.36–1.8 % in USA [4], 1.8–4.6% in South Africa [5].

Out-of-hospital birth is connected with adverse perinatal outcome and increased neonatal mortality [6, 7].

Our study aims to review the available articles and describes rates, obstetrical characteristics and perinatal and maternal outcome of unplanned out-of-hospital deliveries.

HISTORICAL VIEW

Undoubtedly, looking at human history — most people who lived on our planet have been born at home or in communities. However, it does not mean that it is the best or the safest idea of giving birth. What it means is that, frankly recently, we managed to achieve plenty in the field of medicine in a very short amount of time. And it changed the idea of labour dramatically. The beginning of the hospital births is estimated for the 18th and 19th century but was not the luxury it might seem to be [8, 9]. Patients who were well-off chose to employ an accoucheur and give birth at home [10]. Hospital births concerned only poor and destitute part of society — in order to provide them with support. Therefore, as is easy to guess, hospital delivery was surprisingly not connected with benefits or increased safety [8, 9].

In the middle of 19th century quite a revolution took place. There has been an understanding of bacterial infection, sepsis, and the development of antiseptic techniques [11]. In 1876, an Italian obstetrician Eduardo Porro described his method of amputating the body of the pregnant uterus and stitching the cervical stump as a way to deliver a baby [12]. In 1882, gynaecologist Max Sänger, described the use of a double layer of sutures to close the uterine incision in order to preserve this organ after delivery. It was beginning of the classical operation era [13].

Increasing perfection of surgical techniques coincided in time with the introduction of blood banks and using antibiotics which together led to further extreme reduction of maternal mortality (Fig. 1) [14, 15].

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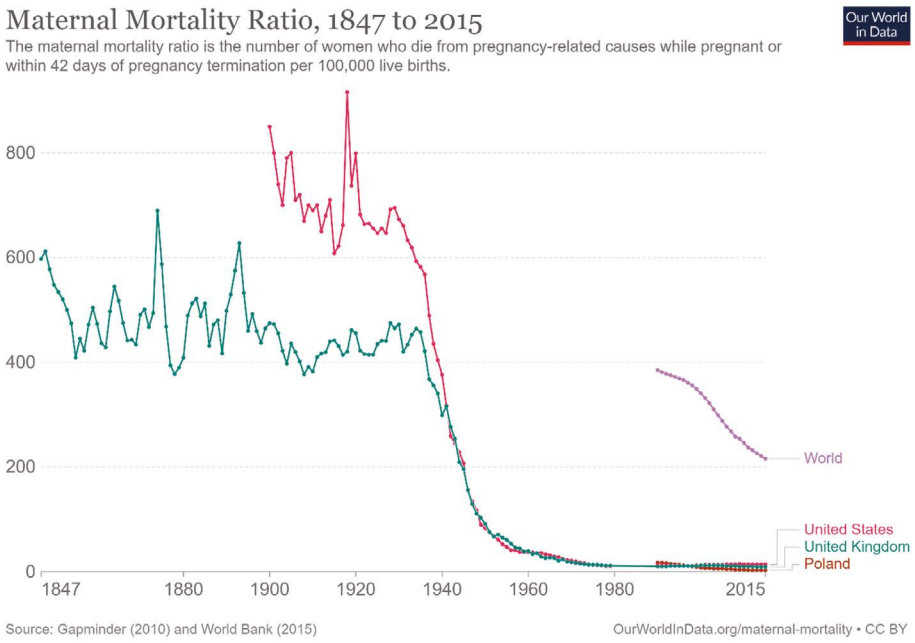

Figure 1. Maternal Mortality Ratio 1847 to 2015

NEONATAL OUTCOMES

Out-of-hospital delivery is indisputably associated with worse perinatal outcomes as well as increased neonatal mortality compared to hospital deliveries [16, 17]. The most unfavourable result described was hypothermia [18, 19]. In most studies, neonatal morbidity and mortality were defined as death or neonatal intensive care unit (NICU) hospitalization at day 7. Neonatal mortality varied widely between the different cohort studies. Moscovitz et al. [20] reported in their study 9 neonatal deaths among 91 out-of-hospital deliveries (9.9%). On the contrary, McLelland [21] reported nine (2.7%) neonatal deaths, including three that were not viable being less than 24 weeks gestation. In a French research study NICU hospitalization or death was recorded in 106 newborns (6,3%) [22]. Ovaskainen et al. [17] found out that out-of-hospital cases were more often admitted to neonatal departments due to infection or hypothermia.

Other complications that have been confirmed in many studies included higher rate of prematurity and lower birth weights [23, 24]. There were also evidence that prolonged transportation time is significant predictor of neonatal mortality among newborns. Moreover, it is clear that proper neonatal intervention before and during transportation significantly decreased neonatal morbidities and mortality [25, 26].

MATERNAL PROFILE AND OUTCOMES

Most previous published papers focused on a neonatal outcome. There have been a few reports of maternal morbidity but the results sometimes contradicted each other [23, 27].

BBA mothers, according to many studies, were characterized by young age and low education. Being multipara, attending antenatal care visits ≤ 4, experiencing preterm birth and rapid labour progression were also named as significant common attributes [28, 29]. An explanation for these factors may be the fact that younger women are less likely to take proper medical care of themselves and that they lack awareness of childbirth. Low education significantly affects their basis and decision about health care. Then, the insufficient number of ob-gyn check-ups effect in poor antenatal education. Furthermore, multiparity and short labour duration are likely to lead to faster childbirth what contributes to BBA.

Women with BBA have increased risk of postpartum haemorrhage and it's the leading cause of maternal death during the immediate postpartum period [23]. In every 4 min one female dies due to massive postpartum haemorrhage [30].

WOMEN'S EXPERIENCES WITH BIRTH SETTING

Research showed that every fifth woman in Western countries is afraid of childbirth. It is simply fear of the unknown. Making effort to reduce this anxiety is essential as it might have a direct negative effect on childbirth process. It is also important to try to minimize stress, to have positive experience of breastfeeding [31]. Access to prenatal medical care and therefore to education seems crucial in this case.

Childbirth may be certainly a beautiful event for many women. However, in the absence of support from medical

professionals and/or family relatives, it can only contribute to negatives. Elina Svedberg et al. [32] in their pilot research described women's experiences of unplanned prehospital births. The results showed that the women are not prepared to give birth to a child outside the hospital, and the course of events usually happen too quickly to adjust. A BBA from the patients' point of view is often described as a tumultuous event. It is also worth highlighting that the patients felt dissatisfaction, frustration, and even shame. Additionally, they blamed themselves and/or their partners for not getting to the hospital in time [32]. In another study, most women despaired of no one being there to help when they understood that they were in labour too advanced to make it to the hospital. Most women described childbirth dramatically, however they were also proud of themselves and/or took responsibility for finding themselves in labour without professional care [33].

TRANSFER TO HOSPITAL

Paramedics play important role in BBA — they provide intrapartum, immediate postpartum and neonatal care. Cases of BBA are described by paramedical staff as "infrequent", yet often "normal" and "uncomplicated". Unfortunately, it turns out that pre-hospital care has not always been carried out properly. For example, several cases documented fundal massage prior to the birth of the placenta. This procedure, is associated with unequal separation of the placenta from the fundus and could contribute to excessive maternal blood loss [34, 35]. Also, as mentioned before, the most common complication among neonates was hypothermia. Despite the existing recommendation of wrapping the baby in cling-wrap or plastic-film with the head exposed without drying beforehand, the paramedic teams did not reported it as their routine [34].

Gayle McLelland et al. [36] reported complications encountered by paramedics at OOH (out-of-hospital) births such as: breech presentation, shoulder dystocia, face presentation, cord prolapse, twins and PPH.

Therefore, the fact that paramedics most often aid BBA patients, it is important to provide sufficient education (including practical skills) to effectively care for them during this period. It is crucial for paramedics to grow confidence that they would be able to secure both the baby's adapting process to the extra-uterine environment and that third stage of labour is progressing without maternal complications. Moreover, ideally, they should have clinical abilities to respond early to any complications that may arise.

CONCLUSIONS

As medical advances were increasing there can be observed the growth of safety for both mothers and their newborns. This contributed to the rising number of patients who decide to give birth at the hospitals. BBA could be the new real problem in the medicine that the paramedics and obstetricians share and face together. In the upcoming years this issue may need more attention due to the popularization of the more natural approach to labour, demedicalization and seemingly safety of home birth. In most studies, the general condition of the mother and newborn after BBA were described as good. For the mother, the greatest risk was postpartum haemorrhage, and for the newborn, hypothermia, which may be effectively prevented by encouraging skin-to-skin contact between mother and child. Undeniably, a tremendous piece of work in this field is done by well-trained emergency medical teams, who are the first to take care of both patients.

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Conflict of interests

Authors declare no conflict of interests.

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