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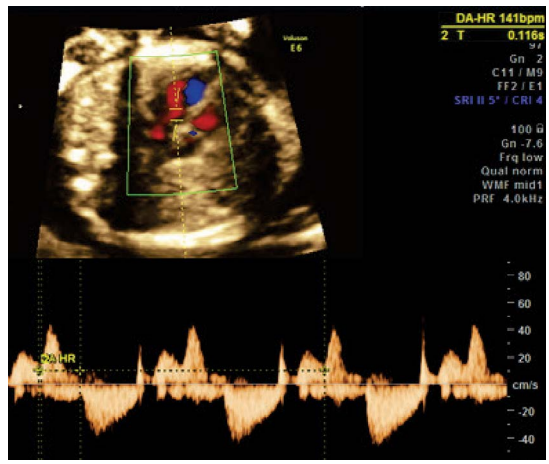

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The impact of motherhood on sexuality

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ABSTRACT

Objectives: Motherhood is a beautiful, extremely satisfying time ina woman's life, but also very challenging at the same time. Forty weeks of pregnancy, delivery, postpartum and breastfeeding periods affect physiological and mental functions that may unfortunately hinder women sexuality.

Material and methods: A longitudinal study was carried out. The questionnaire was developed to include a validated tool as wells as socio-demographic and medical data. The completely self-administered questionnaire was provided to patients twice — before pregnancy and postpartum. Finally, 398 women were included in the study and filled out the survey.

Results: Pregnancy and childbirth significantly ($p < 0.001$) reduce female sexual activity by lowering FSFI score. A similar relationship occurs in the six domains included in the FSFI scale.The number of women who received ≤ 26 points (which may indicate sexual dysfunctions) before pregnancy is 34 (8.54%) and after giving birth it is 167 (41.96%)

Conclusions: Pregnancy and childbirth significantly reduce female sexual activity by lowering FSFI score. The number of women who with sexual dysfunctions increases fivefold after giving birth, and may even reach the value of 40% of young mothers. The role of the medical personnel in maintain women's sexual health is extremely important.

Key words: sexuality; pregnancy; intercourse; desire; motherhood; pain; sexual dysfunction

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INTRODUCTION

Motherhood is a beautiful, extremely satisfying time in a woman's life, but also very challenging at the same time. Forty weeks of pregnancy, delivery, postpartum and breastfeeding periods affect physiological and mental functions that may unfortunately hinder a woman's sexuality.

After childbirth interest in sex and sexual activity decreases. This phenomenon may be caused by vaginal injuries, as well as episiotomy and discomfort provoked by them. Women in puerperium also complain of urinary incontinence, painful relationships due to insufficient arousal after childbirth and organ mismatch feeling.

Sexuality is a complex process, coordinated by the nervous, vascular and endocrine systems. Individually, sexuality incorporates family, societal and religious beliefs, as well as being altered with aging, health status and personal experience [1].

Sexuality is closely related to the concept of sexual health. Until the twentieth century, sexual health was identified with parenthood and vaginal intercourse. In China, sexual health was also correlated with the state of mind and the harmony of nature. In Europe, however, sexuality was a taboo subject, and attempts to talk about it were considered completely unfit, sometimes even referred to as pathology. It was not until 1944 that a new definition of sexual health was published at the United Nations International Conference for Population and Development [2, 3].

According to the current working definition given by the World Health Organization (WHO), sexual health is a state of physical, emotional, mental and social well-being in relation to sexuality; it is not merely the absence of disease, dysfunction or infirmity. Sexual health requires a positive and respectful approach to sexuality and sexual relationships, as well as the possibility of having pleasurable and safe sexual experiences, free of coercion, discrimination and violence. For sexual health to be attained and maintained, the sexual rights of all persons must be respected, protected and fulfilled [4].

The prevalence of sexual dysfunction increases as women age. About 40–45% of adult women have at least one manifest sexual dysfunction. Unfortunately, this number significantly elevates when talking about postpartum period [5].

Sexual intercourse of women in the early period of motherhood is poorly understood, because there is little research in this area. The results of scientific research that have been known so far confirm the fact that women during the postnatal period need sexual contact, but their

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frequency and character vary depending on the course of labor, procedures performed during childbirth, its complications, breastfeeding and of course closeness of the relationship with the partner during this period [6].

Aim

This study investigates the quality of sexual life of women in the first year after delivery compared to the time before pregnancy. Our research also focuses on the self-assessment of women after childbirth and the frequency of side effects of labour such as pain during intercourse, impaired vaginal lubrication and problems in reaching orgasm. A better understanding of the topic of postpartum female sexual disfunction and related factors can also be the basis for improving education and care for women during this period.

MATERIAL AND METHODS

Study group

A longitudinal study was carried out at the Department of Pregnancy Pathology, Department of Woman's Health, School of Health Sciences in Katowice of Medical University of Silesia in Poland, between May 2017 and June 2019. Silesia, located in south-western Poland, is one of the biggest Polish urban areas with a population of 4 548 180 people. Approximately 45 000 children are born there each year.

The questionnaire was developed to include a validated tool as wells as socio-demographic and medical data. To measure of sexual functioning in women, a standardized Female Sexual Function Index (FSFI) questionnaire was used. The completely self-administered questionnaire was provided to patients two times. Initially, the survey was completed by women thinking of pregnancy in future months (n = 500) at random while waiting for their routine medical check-ups. The second time, the patients were interviewed at six months postpartum. At this time, the survey was completed by 418 women. Exclusion criteria were incorrectly completed questionnaire and missing data (n = 6) and lack of sexual activity after childbirth (n = 14). Finally, 398 women were included in the study and filled out the survey.

Questionnaire

The survey was divided into four parts. The first part included questions about socio-demographic characteristics, obstetric history, possible complications and perinatal injuries in previous pregnancies and self-esteem before pregnancy.

In the second part of the questionnaire patients could find the Polish version of the FSFI questionnaire. FSFI is a validated questionnaire containing 19 questions and it measures women's sexual functioning across six domains: desire (questions 1 and 2; score range 1–5), arousal (questions 3, 4, 5, 6; score range 0–5), lubrication (questions 7, 8, 9, 10; score range 0–5), orgasm (questions 11, 12, 13; score range 0–5), satisfaction (questions 14, 15, 16; score range 1–5) and pain (questions 17, 18, 19; score range 0–5) during last 4 weeks. The full– scale score range is 2–36 and lower scores are associated with worse sexual function [7].

The third and the fourth part of the questionnaire were completed by the patients at six months postpartum.

In the third part of survey the same FSFI questionnaire was presented, while in the fourth part of the questionnaire patients were asked about the sexual initiation after delivery, patient's self-esteem, the feel of attractiveness, breastfeeding and its influence on relationship with the partner.

Statistical analysis

The statistical analysis was carried out based on the procedures available in the licensed software Statistica version 13. Quantitative variables are presented in the form of arithmetic mean and standard deviation (SD) or median and interquartile range (IQR). The qualitative variables are presented in the form of absolute value and/or interest. Intergroup differences for quantitative variables were tested using parametric (Student's or ANOVA) or non-parametric tests (U Mann-Whitney or Kruskal-Wallis), previously verifying the nature of their distribution by the Shapiro-Wilk or Smirnov-Kolmogorov test. In the case of qualitative variables, the chi-square test or Fisher's exact test was used. The criterion of statistical significance was $p < 0.05$.

RESULTS

Group characteristics

The median age of the studied group was 28 (IQR = 25–31). Among the 398 patients surveyed, 242 (60.8%) women had vaginal delivery, and 156 (39.2%) were women had the Caesarean section performed. 233 women (58.54%) were primiparas, while 165 women (41.46%) were multiparas

The full group characteristics are presented in Table 1.

Female Sexual Function Index (FSFI) before and after pregnancy

Pregnancy and childbirth significantly ($p < 0.001$) reduce female sexual activity by lowering FSFI score. A similar relationship occurs in the six domains included in the FSFI scale.

Detailed results are presented in Table 2.

The number of women who received ≤ 26 points (which may indicate sexual dysfunctions) before pregnancy is 34 (8.54%) and after giving birth it is 167 (41.96%). Indeed ($p < 0.001$) the number of women with sexual dysfunction in the group of postpartum women increased. The result is shown in Figure 1.

Education, type of relationship, type of birth (vaginal delivery/caesarean section delivery), number of pregnancies, type of feeding does not affect the total score of FSFI and individual domains ($p > 0.05$).

Table 1. The main characteristics of the group

Characteristics	No	(%)
Marital status		
Marriage	304	76.38%
Informal partner	94	23.62%
Education		
Higher education	247	62.06%
Secondary education	113	28.39%
Vocational education	25	6.28%
Basic education	13	3.27%
Place of residence		
Village	103	25.88%
City > 250 k inhabitants	98	24.62%
City 50–250 k inhabitants	134	33.67%
City < 50 k inhabitants	63	15.83%
Childbirth method		
Vaginal delivery	242	60.80%
Caesarean section delivery	156	39.20%
Complications during vaginal delivery	175	72.31%
Epistotomy	105	60%
Perineal trauma	41	23.43%
Epistotomy and perineal trauma	19	10.86%
Vacuum/forceps delivery	10	57.14%
The symbol (%) indicates the percentage presented in a given population		

Table 2. Female Sexual Function Index score

Domain	Before pregnancy	After delivery	p
Desire	4.74 ± 0.93	3.69 ± 1.37	< 0.001
Arousal	5.14 ± 0.78	4.39 ± 1.33	< 0.001
Lubrication	5.46 ± 0.78	4.76 ± 1.23	< 0.001
Orgasm	4.93 ± 1.08	4.54 ± 1.30	< 0.001
Satisfaction	5.20 ± 0.86	4.61 ± 1.22	< 0.001
Pain	5.09 ± 1.04	4.46 ± 1.38	< 0.001
FSFI score	30.57 ± 3.17	26.46 ± 6.20	< 0.001

FSFI — Female Sexual Function Index

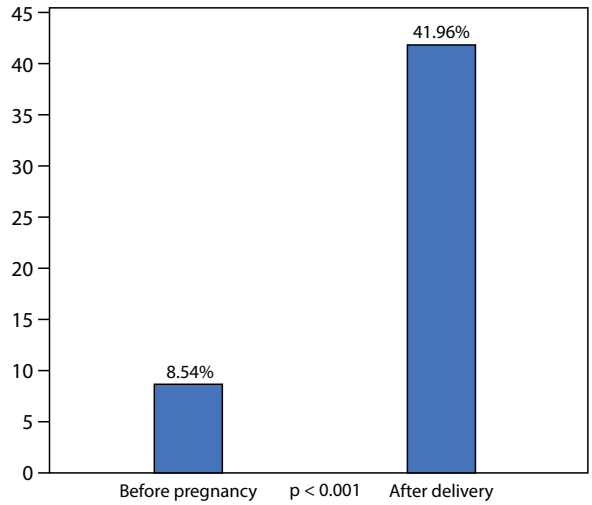

Figure 1. A significant increase in the number of patients with sexual dysfunction after delivery

The exact results gained from the patients about their satisfaction with sexual life before pregnancy and after childbirth is presented in Table 3.

Table 3. Assessment of satisfaction with sexual life

How do you assess your satisfaction with sexual life before becoming pregnant?	How do you assess your satisfaction with sexual life after childbirth?
Very good: 247 (62.06%) Good: 117 (29.40%) Average: 28 (7.04%) Rather bad: 4 (1.01%) Bad: 2 (0.50%)	Very good: 91 (22.86%) Good: 115 (28.89%) Average: 127 (31, 91%) Rather bad: 38 (9.55%) Bad: 27 (6.78%)

Vaginal delivery or Caesarean section delivery

The occurrence of complications during childbirth of the vaginal birth causes a decrease in the total score and in each of the domains. The significant difference is statistically present in the total FSFI score ($p < 0.01$) and in the domains: desire ($p < 0.01$), excitement ($p < 0.05$), orgasm ($p < 0.05$), satisfaction ($p < 0.01$). Does not affect domains: lubrication, pain ($p > 0.05$).

Time of sexual initiation

Almost one-third (n = 118) of patients began sexual initiation before the gynecological examination, recommended six weeks after delivery. It has been checked whether the time of initiation of sexual initiation after childbirth affects the FSFI score. Statistically significant difference appeared only in the domain of "pain" — in the group of women who were waiting six weeks after the birth with sexual initiation the result in this domain was 4.37 ± 1.40, while in the group of women who earlier than six weeks after the birth began sexual initiation, the result in this domain was 4.68 ± 1.34 ($p < 0.05$).

Breastfeeding or modified milk

The type of child's feeding by the surveyed patients is presented in Figure 2. More than half of our patients declare to be breastfeeding (n = 201), while 33.42% feed their babies with modified milk (n = 133). 12.31% of the respondents mixed both techniques (n = 49), while 3.77% choose to bottle feed their babies with only pumped breastmilk. 15.33% of women declare to feel less attractive to their partner

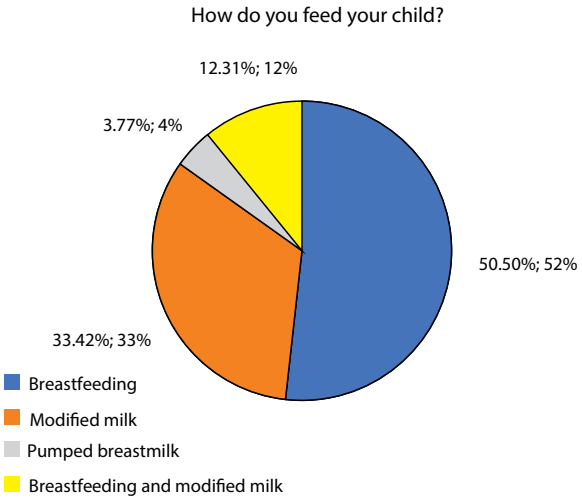

Figure 2. The type of child's feeding by the surveyed patients

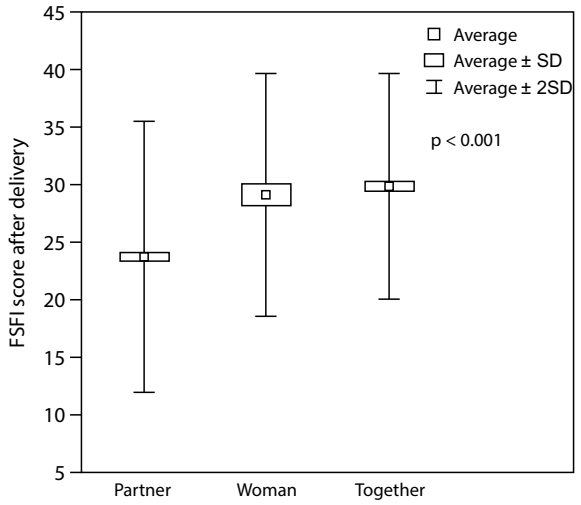

Figure 3. Female Sexual Function Index depending on sex initiator; FSFI — Female Sexual Function Index

through breastfeeding, however the type of baby feeding does not affect the FSFI score ($p > 0.05$).

Tiredness

Women were also asked how often they feel tired from the moment they gave birth. The answers were as follows: 42.96% (n = 171) answered that the feeling of fatigue was very common, whereas 41.96% (n = 167) said it was common. Also, the mood changes since childbirth was very common for 28.64% of patients (n = 114) and common for 37.69% of them (n = 150).

More than 79% (n = 316) of women admitted that fatigue resulting from child-care affected sexual initiation with their partner.

Initiator of sexual intercourse

For the question of "who the most often initiates sexual contact after childbirth?" 8.54% (n = 34) of patients indicated themselves, while 54.77% (n = 218) indicated their partners and 36.68% (n = 146) said both.

Statistically significant differences were found as a result of FSFI depending on which partner initiates sexual intercourse. The result of FSFI when it is initiated by a woman or both partners is significantly higher than in the case when the partner initiate sexual intercourse. The exact parameters are presented in Figure 3.

DISCUSSION

The puerperium is defined in the literature as a six-week period after childbirth during which the pregnancy and childbirth changes withdraw and labor wounds heal. It is also connected with the initiation and maintenance of lactation and the re-initiation of ovarian function. During the puerperium, sexual intercourse is strictly forbidden [8, 9].

Pregnancy process, delivery, postpartum and breastfeeding periods all affect physiological and mental functions that hinder women sexuality.

In the puerperium, women usually do not feel sexual needs. The first relation after giving birth raises fears and anxieties. They are usually associated with fear of pain, fear of becoming pregnant again or fear of damage to the stitched crotch [10, 11].

More physical problems affecting women in the first year of maternity may include diminished vaginal lubrication, pain and discomfort upon intercourse, decreased sense of arousal and difficulty in achieving orgasm. All these symptoms are components of the Female sexual dysfunction (FSD) [12].

Female sexual dysfunction can be subdivided into desire, arousal, orgasmic and sexual pain disorders. Sexual pain disorders include dyspareunia and vaginismus [13].

Desire

In the postpartum period, it is common to find the problem in marital relations and a decrease in desire between partners is noticeable.

In the puerperium, women usually do not feel sexual needs. Motherhood brings close contact between mother and child through, for example, frequent breastfeeding. This usually satisfies the mother's need for intimacy. The first approach between partners usually takes place up to 12 weeks after delivery [14].

Lactation has a significant impact on sexual intercourse after delivery. Many women have reduced sexual excitability, weakness and slowed sexual reactions or decreased libido. The inhibition of libido during breastfeeding is influenced by hormones responsible for lactation [9, 14–16].

The time of lactation may be compared to the period of old age. At this time, insufficient congestion of female

genitalia, sparse cervical mucus secretion, high vaginal sensitivity resulting from thin vaginal epithelium are observed. Women show less interest in sex and even indicate they do not want to have sexual intercourse. The reasons are tiredness, breast hypersensitivity and conflicts between partners [14, 16, 17].

It is also important not to only feel desire but also feel desirable. However, it is often impossible without self-acceptance. From the studies carried out so far, it can be concluded that there are statistical differences between the sense of attractiveness of women before, during and after pregnancy and breastfeeding [18, 19].

It has been proven that during pregnancy the future mother's level of satisfaction increases. It is often connected to the breast enlargement. Body parts such as: hips, abdomen, buttocks, thighs, the appearance of the silhouette, legs or intimate organs are assessed worse than during the preconception period.

Indeed, the assessment of attractiveness is influenced also by the labor and the breast-feeding period. Women showed lower self-esteem concerning selected parts of the body such as: breasts, stomach, hips, buttocks, thighs, silhouette or intimate organs compared to the period before pregnancy. Notwithstanding, a lot of women feel even more attractive in this period due to being more aware of their body [19].

Lack of desire for women's sexual intercourse may also result from maternity blues. It is stated that almost 40% of women suffer from maternity blues, which generally involves symptoms such as: mood lability, tearfulness, mild anxiety and depressive symptoms [20, 21].

However, in 19% of cases, it may evolve into postpartum depression. The disease manifests as sleep disorders, mood swings, changes in appetite, fear of injury, serious concerns about the baby, much sadness and crying, sense of doubt, difficulty in concentrating, lack of interest in daily activities, thoughts of death and suicide. In this extreme case, the sexual life of women is very strongly disturbed, if it exists at all [22].

Arousal and orgasmic

During the first few months of maternity, decreased estrogen levels and elevated prolactin levels are observed. These changes, however, do not remain indifferent to the woman's sexual life. Such variations may lead to important sexual problems including vaginal dryness/insufficient lubrication. Women with this problem often suffer from vaginal irritation after intercourse, painful penetration, pain during sexual intercourse resulting in loss of sexual desire, lack of sexual satisfaction, tiredness and bruises/tear while that of non-resumption of coitus included unavailability of the husband [23].

The method of delivery also affects sexual life. Natural childbirth initially causes stretching of the muscles and, consequently, permanent relaxation of the muscles and fascia of the pelvic floor. The looser vagina, which is a consequence of passing the fetal head through the birth canal, has an adverse effect on achieving orgasm. Vaginal pelvic muscles exercises are recommended for vaginal changes caused by childbirth [9, 14, 24, 25].

An additional point that should be addressed is the role of the male partner that has many emotional, psychological, behavioral and interpersonal issues as a new father. The relationship factors had substantial impact on female sexual function in desire, arousal, orgasm and satisfaction where women's lubrication problems and sexual pain are related predominantly with biological factors [26].

Sexual pain

Natural delivery is not only reported leading to looser the vagina, but also to causing numbers of injuries. Only about 10% of women having a first baby will achieve a vaginal birth with no attendant perineal trauma [27].

Both, spontaneous injuries and the incision of the crotch performed during the labour affects sexual intercourse. Scientific research on the issue of episiotomy has proven its negative impact on the satisfaction with sexual life. In women who engage in sexual activity and who have had an episiotomy performed during childbirth, dyspareunia and secondary vaginismus is more commonly diagnosed [11, 14, 28–30].

Correct suturing of the crotch with attention to detail about anatomy and functionality allows the patient to enjoy better post-pregnancy sexuality [30].

The method of the delivery also seems to play important role in woman's frame of mind. It was confirmed that caesarean sections may reduce the prevalence of urinary incontinence. Also, having vaginal delivery and more than one child group of women has worse sexual function than caesarean delivery and single children group.

One cannot forget that the decreased libido in women in puerperium is usually associated with delivery complications. One of the most common may be postpartum urinary incontinence. Overall, its prevalence seems to be around 30% within the first three months. It can be a key factor causing the woman's reluctance towards sexual intercourse, which greatly decreases self-confidence [31].

CONCLUSIONS

Pregnancy and childbirth significantly reduce female sexual activity by lowering FSFI score. The number of women with sexual dysfunctions increases fivefold after giving birth and may even reach the value of 40% of young mothers.

Childbirth results in lack of libido and sexual satisfaction, tiredness and bruises, dyspareunia and impaired self-ac-

ceptance in order to maintain women sexual health. It is important to prepare young parents for the changes taking place in the body as well as the psyche of the mother after childbirth as well as preparing them for the constant fatigue and changing of the priorities.

Notwithstanding, the role of the medical personnel in maintaining women's sexual health is extremely important. Medics need to ensure the most comfortable course for the pregnancy and delivery, with minimal trauma to the intimate area. Also, try as much as possible to prevent urinary incontinence and to teach patients how to deal with body adversities, such as reduced vaginal arousal, hormones fluctuations or pain.

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Assisted reproductive medicine in Poland, 2013–2016: Polish Society of Reproductive Medicine and Embryology (PTMRiE) and Fertility and Sterility Special Interest Group of the Polish Society of Gynaecologists and Obstetricians (SPiN PTGiP) report

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ABSTRACT

Objectives: The purpose of this publication is to present data on the results and complications associated with infertility treatment using assisted reproductive technology (ART) and intrauterine insemination (IUI) in Poland between 2013 and 2016.

Material and methods: The report was prepared by the Polish Society of Reproductive Medicine and Embryology (PTMRiE) and the Fertility and Sterility Special Interest Group of the Polish Society of Gynaecologists and Obstetrics (SPiN PTGiP) as a part of the European IVF Monitoring program (EIM) for the European Society of Human Reproduction and Embryology (ESHRE). Reporting was voluntary and the data was not subject to external control. The report presents the availability and structure of infertility treatment services, the number of procedures, their effectiveness and complications.

Results: Between 2013 and 2016, a total of 106,718 treatment cycles using ART [64,413 classical *in vitro* fertilization and *in vitro* fertilization with intracytoplasmic sperm injection (IVF + ICSI), 36,041 frozen embryo replacements (FER)] and 51,405 IUI were recorded. The clinical pregnancy rates per embryo transfer in IVF, ICSI and FER were 38.3%, 38.1% and 32.4%, respectively. The effectiveness of IUI with husband/partner's semen (IUI-H) was 11.1% and with donor semen (IUI-D) 16.7%. Multiple delivery rates were 11.3% and 6.2% in IVF + ICSI and IUI, respectively. The most common complication was the ovarian hyperstimulation syndrome (OHSS) (0.34%).

Conclusions: PTMRiE and SPiN PTGiP report is the only national study documenting Polish reproductive medicine. The results of infertility treatment effectiveness in Poland are comparable with the European data, complications are less frequent than in other countries. The low percentage of multiple pregnancies, and so perinatal complications, is especially valuable. However, due to the lack of a central database and register, the possibility of external control and monitoring of pregnancies and births is limited. Thus, a fully reliable assessment of the treatment quality in our country is not possible.

Key words: PTMRiE and SPiN PTGiP report; infertility treatment; assisted reproduction techniques; IVF; ICSI; IUI

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INTRODUCTION

Infertility is a disease and a social condition, defined by the World Health Organization (WHO) as the inability to get pregnant or carry the pregnancy to term after a year of regular intercourse without using contraceptive methods. It is estimated that in Poland about 1.2 million couples face subfertility or absolute infertility. Annually, approximately 2%, *i.e.*, 24 000 couples, require treatment using assisted reproductive technology (ART). WHO warns that the problem of infertility will continue to grow and gain in importance, which means that the percentage of couples who, despite their efforts, cannot have their desired child will be even greater in the future.

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The methods used to treat infertility, and especially ART, have been evaluated for many years for their safety and effectiveness. In Poland, it is the Polish Society of Reproductive Medicine and Embryology (PTMRiE) and the Fertility and Sterility Special Interest Group of the Polish Society of Gynaecologists and Obstetricians (SPiN PTGiP) who are responsible for collecting and processing this data. The reports are made available to the European Society of Human Reproduction and Embryology (ESHRE) as part of the international project — European IVF Monitoring (EIM), and then published in the Human Reproduction [1–19]. The first report was published in 2001 and depicted data for 1997 [1]. The last one was published in February 2020 and presents data for 2015 [19]. Poland has participated in the EIM Program continuously for 18 years, providing data for the years 1999–2016. The last three years of this reporting period (2013–2016) are a breakthrough period for the development of assisted reproductive medicine in Poland:

1. Health program funded by the Polish Ministry of Health "Infertility Treatment by the in vitro fertilization method for the years 2013–2016" reimbursed IVF procedures and increased the availability of ART methods making it accessible to the couples who withhold the therapies because of financial difficulties [20],
2. Some local governments decided to partially reimburse the costs of ART treatment financially supporting the therapy of their residents,
3. On 25th of June 2015, the Act on infertility treatment entered into force, thereby regulating the legal aspects of infertility treatment, including donations of gametes and embryos [21],
4. A national register of medically assisted procreation centres and reproductive cell and embryo banks were established, listing the sites authorized by the Ministry of Health to conduct activities in the field of infertility treatment using ART [22].

OBJECTIVES

The aim of the publication is to present data on the use of assisted reproduction techniques in Poland between 2013 and 2016, including the number of performed procedures, their effectiveness and the most common complications. The collected data is particularly important in the aspect of health policy planning and is also the basis for comparing the quality of treatment in Poland and other European countries.

MATERIAL AND METHODS

The data was made available by 41 centres of medically assisted procreation and included the following methods of infertility treatment:

— classical *in vitro* fertilization (IVF) and *in vitro* fertilization with intracytoplasmic sperm injection (ICSI)
— frozen embryo replacement (FER)
— preimplantation genetic testing (PGT)
— *in vitro* maturation (IVM)
— frozen oocyte replacement (FOR)
— egg donation (ED)
— embryo donation
— intrauterine insemination using husband/partner's semen (IUI-H) or donor's semen (IUI-D).

The report concerns infertility treatment procedures that began between January 1, 2013 and December 31, 2016 and is a continuation of the report with data for 2012, published in 2015 [23]. Data regarding pregnancies and deliveries is derived from observations of the procedures carried out in the above period. The data collection schedule is consistent with the EIM Program, run under the patronage of ESHRE.

Data reporting was voluntary. Clinics were not obliged to participate in the report, and the submitted data was not subject to external control and verification. Only the completeness and mathematical convergence of data between the tables were checked. If an inconsistency was found, the clinic was contacted to make a correction. Based on individual data, a summary report for Poland was prepared, which was sent to ESHRE using dedicated Dynamic Solutions software. Individual data of individual centres remain confidential.

The terminology used in the report is consistent with that proposed by the International Committee for Monitoring Assisted Reproductive Technology (ICMART) [24].

RESULTS

Availability of assisted reproduction methods and number of treatment cycles

The list of IVF and IUI centres that participated in the report is presented in Annex to this publication. Compared to data from 2012 over the following four years, the number of IVF clinics reporting has increased (from 33 in 2012 to 39 in 2016, +18.2%) as well as the total number of ART[1] procedures performed (from 16,849 in 2012 to 31,613 in 2016, +87.6%) [23]. In total, 219 879 IVF + ICSI cycles have been recorded since the beginning of the EIM data collection, of which almost half in the period 2013–2016 — 107,881 (Fig. 1). 17,865 fresh IVF + ICSI cycles were performed in 2016, 67% more than in 2012 (10,714 cycles).

There was also an increase in the number of IUI centres that participated in the report (from 31 in 2012 to 38 in 2016), however, the number of IUI decreased (from 14,727 in 2012 to 13,202 in 2016, –10.4%).

In the years 2013–2016, the most popular techniques were: ICSI (60,440 cycles, 56%) and FER (36,041, 33.4%).

1 ART methods include the following procedures: IVF, ICSI, FER, PGT, ED, IVM, FOR and prenatal adoption

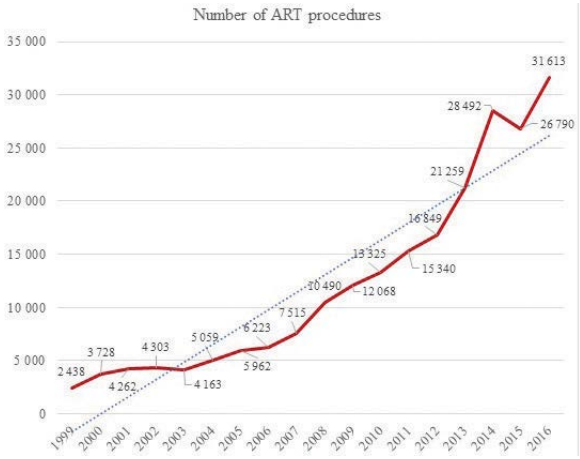

Figure 1. Number of ART treatment cycles in Poland, 1999–2016

Compared to 2012, the number of IVF, PGT, ED, FOR cycles also increased, while the number of IVM procedures decreased (Tab. 1). Of all fresh treatments (IVF + ICSI), 93.8% were cycles using ICSI. The number of ICSI procedures has slightly decreased in the considered period, as compared to the year before, when it amounted to 95.7% (2012).

Availability of advanced infertility treatment increased as demonstrated by the rise in numbers of ART cycles per million inhabitants in Poland from 437 cycles in 2012 to 810 cycles in 2016 (Table 1). As a result, the percentage of newborns born through *in vitro* methods increased from 4,694 in 2012 to 6,484 in 2016. This data is not complete since the course of 627 (in 2012) and 2157 (in 2016) clinical pregnancies[2] is unknown (11.5% and 22.7% of all pregnancies, in 2012 and 2016 respectively). For deliveries with an unknown result, single delivery was used for the calculation (146 deliveries after ART in 2012 and 695 in 2016).

2 Clinical pregnancy based on clinical and ultrasound parameters according to WHO / ICMART definition (fetal vesicle visible in ultrasound), including ectopic pregnancy

Efficiency of treatment

IVF, ICSI, FER

Clinical pregnancy rates per cycle during IVF and ICSI procedures in the years 2013-2016 were comparable and amounted to 28.8% and 29.0%, respectively, and 38.3% and 38.1% per transfer. For frozen embryo replacement (FER), the clinical pregnancy rate was 32.4%. An increase in the effectiveness of FER was recorded in the following years: from 29.1% in 2013 to 36.1% in 2016. Detailed data is presented in Table 2.

In 17.8% of fresh IVF + ICSI cycles (5,912/33,297), the decision was made to freeze all embryos. More than one percent of the cycles ended in freezing of all egg cells (410/33,297).

The effectiveness of treatment based on the percentage of children born after the use of assisted reproductive techniques is not possible to determine due to incomplete pregnancy monitoring, which for IVF, ICSI and FER in the years 2013-2016 amounted to: 10.4% (119/1,143), 20.9% (3,666/17,532), and 19.6% (2,266/11,533). According to the data in the report, there were 142 miscarriages after IVF (12.4%), 2,448 after ICSI (14%) and 1,980 after FER (17.2%). However, it cannot be excluded that the percentage of pregnancy losses is higher. Incomplete monitoring is the reason for the lack of reliable assessment of this phenomenon.

IVF with egg donation (ED)

The effectiveness of treatment using donor eggs, expressed as the percentage of clinical pregnancies per embryo(s) transfer in 2013-2016 was significantly higher when using freshly collected oocytes (46.8%, 599/1,281) than thawed ones (FOR-ED) (34.5%, 427/1,239). The efficiency of transfers of stored embryos derived from freshly collected oocytes (FER-ED) was also higher (41.5%, 592/1,425). Despite the lower efficiency, the number of FOR-ED cycles has increased significantly in recent years - from 65 transfers in 2012 to 505 in 2016 (+677%).

Table 1. Number of ART procedures in Poland, 2012–2016

Year	Number of reporting IVF centres	IVF	ICSI	FER	PGT	ED	IVM	FOR	All	Number of cycles/ million inhabitants
2012	33	461	10 253	4 969	237	713	70	139	16 842	437
2013	34	884	12 525	6 151	253	895	56	197	20 961	545
2014	36	1 158	16 549	9 057	320	934	24	141	28 183	732
2015	33	1 050	14 382	9 458	355	1 031	30	124	26 430	688
2016	39	881	16 984	11 375	487	1 085	33	299	31 144	810
2013–2016		3 973	60 440	36 041	1 415	3 945	143	761	106 718	

IVF — *in vitro* fertilization; ICSI — intracytoplasmic sperm injection; FER — frozen embryo replacements; PGT — preimplantation genetic testing (PGT); ED — egg donation; IVM — *in vitro* maturation; FOR — frozen oocyte replacement

Table 2. Results of ART procedures in Poland, 2013–2016

	2013	2014	2015	2016	2013–2016
	Clinical Pregnancy Rates, CPR [%]	Clinical Pregnancy Rates, CPR [%]	Clinical Pregnancy Rates, CPR [%]	Clinical Pregnancy Rates, CPR [%]	Clinical Pregnancy Rates, CPR [%]
IVF					
Cycle	29.0	29.4	28.3	28.4	28.8
Egg collection	29.6	29.8	29.4	28.6	29.4
Transfer	36.1	37.6	41.0	38.5	38.3
ICSI					
Cycle	32.8	30.9	27.3	25.8	29.0
Egg collection	33.1	31.8	27.7	25.8	29.4
Transfer	38.5	38.9	37.5	37.4	38.1
FER					
Transfer	29.1	30.5	32.0	36.1	32.4

CPR — clinical pregnancy rates; IVF — *in vitro* fertilization; ICSI — intracytoplasmic sperm injection; FER — frozen embryo replacements

Table 3. Results according to the patient's age, 2013–2016

	IVF		ICSI		FER		ED	
Age	Clinical pregnancies/ Egg collection	Clinical Pregnancy Rates, CPR [%]	Clinical pregnancies/ Egg collection	Clinical Pregnancy Rates, CPR [%]	Clinical pregnancies/ Thawing	Clinical Pregnancy Rates, CPR [%]	Clinical pregnancies/ Transfer	Clinical Pregnancy Rates, CPR [%]
≤ 34	794/2511	31.6	10878/32551	33.4	7040/20660	34.1	375/847	44.3
35–39	315/1154	27.3	5697/20421	27.9	3673/11922	30.8	531/1206	44
≥ 40	34/213	16	940/6587	14.3	812/3687	22	711/1878	37.9
unknown	0/12	0	17/55	30.9	8/39	20.5	1/14	7.1

IVF — *in vitro* fertilization; ICSI — intracytoplasmic sperm injection; FER — frozen embryo replacements; ED — egg donation; CPR — clinical pregnancy rates

Age vs effectiveness of treatment

The largest group of patients receiving treatment using IVF, ICSI and FER techniques were patients before 35 years of age (64.7%, 54.7% and 57.0% respectively). ED procedures were performed mainly to older patients over 40 years of age (47.8%).

There was a well-known negative correlation between the patient's age and treatment efficiency in IVF and ICSI procedures. The highest effectiveness was recorded in the group of young patients (≤ 34 years of age) and it was 31.6% for IVF and 33.4% for ICSI. The lowest effectiveness was found in the group of women over 40 years of age — 16% and 14.3% respectively.

A similar relationship was observed for FER; however, the baseline data was higher than in fresh cycles: 34.1% (≤ 34 years of age), 22% (≥ 40 years of age). The results in fresh and frozen cycles are difficult to compare due to the different way of testing the effectiveness — in IVF + ICSI cycles, the effectiveness of treatment was determined upon the percentage of clinical pregnancies calculated per ovarian puncture, and in FER — calculated per embryo(s) transfer.

In ED procedures, age was of not of such significance. Effectiveness of treatment expressed as a percentage of clinical pregnancies per transfer in a group of patients ≤ 34 years of age and in the age of 35–39 years was similar and amounted respectively to 44.3% and 44.0%, and in the group of women ≥ 40 years of age was slightly lower (37.9%).

Detailed data is presented in Table 3.

Number of embryos transferred vs multiple pregnancy

In most cases one or two embryos were transferred in IVF and ICSI cycles (98.9% of fresh transfers performed in 2013–2016). The transfer of a single embryo was reported on average in 53.1% of procedures (42.2% in 2013, 54.4% in 2014, 63.0% in 2015 and 52.8% in 2016) and was more frequent than in previous years (20% in 2011, 24.7% in 2012).

A similar transfer policy applied to FER - in most procedures one (65.9% cycles) or two embryos (32.7%) were transferred. In the subsequent years, an increase in the percentage of transfers using one embryo was observed (from 43.6% in 2013 to 72.7% in 2016). For comparison, in 2012, only 29% of FER cycles were conducted with the

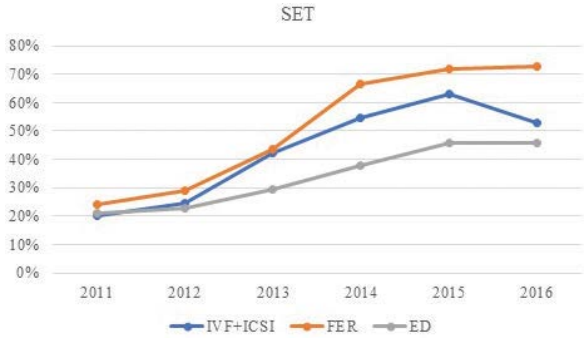

Figure 2. Percentage of single embryo transfers (SETs) after in vitro fertilization and *in vitro* fertilization with intracytoplasmic sperm injection (IVF + ICSI), frozen embryo replacements (FER) and egg donation (ED), 2011–2016

transfer of a single embryo, in 2011 — 23.9%. In egg donation procedures, the proportion of 1, 2, 3 and ≥ 4 transferred embryos within the considered period was, respectively: 40.1%, 58.2%, 1.7%, 0.1%. The percentages of single embryo transfers (SET) in IVF + ICSI, FET and ED cycles in the years 2011-2016 are presented in Figure 2.

As a result of SET, 6,216 children were born after fresh IVF + ICSI cycles, of which 98.2% were single births. The number of multiple deliveries increased with the number of embryos transferred. The percentage of twin and triplet births after the transfer of two embryos (DET) totalled 21.1% and of three embryos — 33.1%. In total, the percentage of multiple deliveries in IVF + ICSI procedures in 2013-2016 was 11.3%.

Adverse events

Preterm delivery

In the years 2013–2016, data on the time of 5,052 deliveries after IVF + ICSI and 2,836 deliveries after FET were collected. According to them, the frequency of preterm births (between 20 and 36 weeks of pregnancy) was in the case of single birth: 27.1% for IVF + ICSI and 23.2% for FET, in the case of twins: 63.5% for fresh cycles and 55% for FET, in the case of triplets: 100% for fresh cycles and 66.7% for FET. Delivery on time (between 37 and 41 weeks of gestation) occurred in 69.6% of single births after IVF + ICSI and in 73% of single births after FET, in 33.6% twin births after IVF + ICSI and in 40.5% after FET, and in 33,3% triplet births after FET.

Other complications

The most common complication in the treatment course was the ovarian hyperstimulation syndrome (OHSS). In total, 228 severe cases of OHSS were reported in 2013-2016, representing 0.34% of all stimulated cycles. A decrease in the percentage of severe OHSS cases was observed in subsequent years, from 0.63% in 2013 to 0.16% in 2016. The most common adverse event associated with the ovarian puncture was bleeding (n = 157, 0.24%) and infections (n = 17, 0.03%).

Intrauterine inseminations

Data on the number, type and effectiveness of intrauterine insemination (IUI) treatment was submitted by 38 clinics. According to the results of reports for the years 2013–2016, a total of 51,405 insemination procedures were performed in these centres, including 43,474 using husband/partner's semen (IUI-H) and 7,931 using donor's semen (IUI-D). Most of the procedures were performed to women under 40 years of age (90.4%).

Treatment effectiveness, defined as the clinical pregnancy rate per cycle, was:

— when husband/partner's semen was used: 11.1% (11.5% in the group of women < 35 years of age, 10% in the group of women aged 35–39 years and 7.4% in the group of women ≥ 40 years)
— when using donor's semen: 16.7% (17.1% in the group of women < 35 years of age, 15% in the group of women aged 35–39 years and 11.5% in the group of women ≥ 40 years of age).

The course of 3,906 clinical pregnancies is known: 93.8% of them ended in a single delivery. The percentage of multiple pregnancies was 6.2%.

DISCUSSION

The effectiveness, safety and availability of assisted reproduction techniques have been monitored in Poland as part of the EIM Program for 18 years continuously. Data from 1999–2015 together with data from other European countries were published in Human Reproduction [1–19]. Data regarding treatment in 2011 and 2012 solely for Poland was also published in 2014 and 2015 [23, 25]. For the first time, in 2019, all Polish centres that performed *in vitro* fertilization procedures in 2016 joined the EIM report (n = 39). Full identification of IVF clinics was possible thanks to the central registry of medically assisted procreation centres and reproductive cell and embryo banks [22]. Unfortunately, the number of centres performing IUI is still difficult to determine — according to the Act of 25th of June 2015 on infertility treatment, the use of procedures that do not require gamete and/or embryo freezing by healthcare entities performing medical services such as stationary and round-the-clock health services does not require the permission of the Ministry of Health [21]. Thus, IUI with "fresh" husband/partner's semen can be performed by centres that are not listed in the central register.

The years 2013–2016 were a period of rapid increase in the number of ART[3] procedures performed. In 2016, their number was by 87.6% higher than in 2012 (31,613 vs

3 IVF (classical in vitro fertilization), ICSI (intracytoplasmic sperm injection), FER (frozen embryo replacement), ED (in vitro fertilization with egg donation), IVM (in vitro maturation), FOR (procedures using frozen egg cells) and PGT (preimplantation genetic testing)

16,849). There was 67% increase in fresh IVF + ICSI cycles (17,865 vs 10,714), most likely thanks to the healthcare program of the Ministry of Health "Infertility Treatment by In vitro Fertilization Method for 2013–2016", which began in July 2013 and ended in June 2016. The program guaranteed free access to treatment using IVF/ICSI for couples who met the qualification criteria, i.e. have already exhausted other methods of infertility treatment during preceding at least 12 months or were diagnosed with the an absolute indication for ART. Exclusion criteria included the woman's age (≥ 40 years) and the potential risk of a lack of proper response to ovulation stimulation (follicle stimulating hormone, FSH > 15 mU/mL on day 2–3 of the cycle, or anti-Mullerian hormone, AMH < 0.5 ng/mL) [20].

Thus, the Ministerial reimbursement program created the possibility of treatment with ART methods for those couples for whom the only reason for delaying the decision about therapy was the financial aspect. This healthcare program also exposed the scale of the problem and the real need for infertility treatment using ART. According to the report of the Ministry of Health of March 5, 2020, 26,062 clinical pregnancies were recorded, and 22,131 children were born. These numbers are constantly increasing due to the ongoing transfers of cryopreserved embryos.

The increase in the number of in vitro fertilization cycles, and thus the number of children born as a result of them meet demographic trends. Poland is one of the countries with the lowest fertility rates (TFR was 1.26, 1.29, 1.29 and 1.36[4] in the subsequent years, from 2013 to 2016) [26]. Since 1980, the number of live births has decreased by 45% (from 695,8 thousand to 382,3 thousand in 2016). This data is worrisome. The low number of deliveries is largely the result of problems with getting pregnant, while the percentage of children born in Poland as a result of ART is still not sufficient, in 2016 it was only 1.7%. For comparison, in Denmark or Spain it amounted to as much as 6.6% and 7.1%, respectively, in Europe it is on average 2.3% [19]. Interestingly, the number of assisted reproduction procedures performed in our country is high. Poland, carrying out 31,613 ART cycles in 2016, took 7th place, after Spain, Russia (which performed over 100,000 procedures), Germany, France, Italy and Great Britain. However, considering the number of inhabitants, Poland is at the end of the list. According to the current report, the number of procedures ART in Poland per million inhabitants in 2016 was 810 cycles. According to data estimated by the ESHRE Capri Group the overall demand for assisted reproduction techniques is almost twice as high and amounts to 1500 cycles per million inhabitants [27]. This fact may constitute an important argument in discussions with the authorities at the national and local level on taking actions to improve access to infertility treatment. The highest application of ART procedures is observed in Denmark and Belgium (over 2500 treatment cycles per million inhabitants), the lowest in Malta (727 treatment cycles per million inhabitants) [19].

Most of the treatment procedures in 2013–2016, as in previous years, were performed by intracytoplasmic sperm injection, classic IVF is performed marginally. However, a slight increase in the number of IVF procedures was observed compared to the previous period (6.2% in 2016 vs 4.3% in 2012). This fact may be related to the implementation of the Ministry of Health program, the regulations of which strictly defined the situations in which ICSI may be performed (male infertility factor, endometriosis, idiopathic infertility). The advantage of ICSI over conventional IVF is evident throughout Europe. The European average in 2015 was: 71.2% for ICSI and 28.8% for IVF. There is also a trend to postpone transfers and freeze all embryos in the so-called 'freeze all' procedures (6.4% of all IVF + ICSI procedures in Europe and 17.8% in Poland) [19].

Poland is a country with one of the highest rates of a single embryo transfer (SET). According to this report, SET has been performed in more than 53% of IVF + ICSI procedures. There is also a steady increase in the number of SETs performed in Europe (from 11.5% in 1997 to 37.7% in 2015). Most SETs are performed in the Scandinavian countries: in Sweden and Finland over 80% of "fresh" *in vitro* cycles end with a transfer of a single embryo. The lowest rates for SET are in Albania - only 5.8% of IVF + ICSI cycles [19].

The policy of transferring a single embryo is a proof of the maturity of Polish ART centres. Such a procedure significantly reduces the risk of multiple pregnancy, and thus allows the achievement of the primary goal of ESHRE, which is to significantly increase the safety of *in vitro* procedures for both mother and child. The most commonly reported complications that occur in newborns from multiple births are malformations and prematurity. According to the presented report, over 63% of twin pregnancies and all triplet pregnancies ended prematurely, i.e., before 37 weeks of pregnancy. SET minimizes the risk of multiple pregnancy. In Poland, in the years 2013-2016 after IVF + ICSI, the percentage of such pregnancies after SET was only 1.8%, while for DET already 21.1%, and in the case of transfer ≥ 3 embryos — 33.1%.

The observed rapid increase in the number of SET in the years 2013-2016 is a result of increased awareness and the development of new therapeutic standards, but also the impact of the government program, which forced the implementers to transfer a single embryo, recommending DET only in clinically justified situations and in patients over 35 years of age [20].

4 The fertility rate that guarantees simple replacement of generations is 2.1-2.15

Single embryo transfer and freezing of all remaining embryos for future use helps to avoid multiple pregnancy - the most important problem of fertility treatment using ART, while not reducing the effectiveness of treatment. The cumulative pregnancy rate resulting from SET and subsequent transfer of the cryopreserved embryo is comparable to the results achieved with DET [28, 29]. According to this report, infertility treatment is highly effective in Poland. The percentage of clinical pregnancies in the analysed period calculated per transfer was on average 38.3% in IVF cycles, 38.1% in ICSI cycles and 32.4% in FER and was dependent on the age of the woman. Comparable data for Europe (available for 2015) showed lower efficiency of 34.6%, 33.2% and 30.4% respectively for IVF, ICSI and FER [19].

The most serious complication during ovarian stimulation was OHSS. However, it was very rare, accounting for only 0.34% of all treatment cycles initiated in the period 2013-2016. During ovarian puncture, the most common complication was vaginal bleeding (0.24%) and infection (0.03%).

In the years 2013–2016 a decrease in the number of *in vitro* fertilization procedures with the use of 'fresh' donor egg cells in favour of thawed cells was observed. Although these procedures are less effective, the availability of this form of treatment has increased because the recipient is prepared for embryo(s) transfer regardless of the donor's procedure - no synchronization of the cycles of both women is required. Undoubtedly, the Act of 25th June 2015 on infertility treatment had an impact on changing the approach of IVF centres to IVF procedures using donor egg cells. The Act introduced a ban on non-anonymous donation and the lack of compensation for the so-called hardships related to treatment [21]. As a result, there was a decrease in interest from altruistic female donors (women who underwent hormonal stimulation and ovarian puncture for the sole purpose of transferring all donated eggs to couples with infertility problems) and development of cooperation between IVF centres and foreign gamete banks. Thus, the transport of frozen egg cells intended for donation in Poland increased. In 2016, the percentage of FOR-ED procedures was 46.5%, FER-ED 40.6%, and fresh ED cycles accounted for only 12.8%. For comparison, in 2012, the number of all *in vitro* procedures with the donor's egg cell was 34.3% lower (713 vs 1085 in 2016), of which FOR-ED cycles only accounted for 9.1% [23]. Procedures with gamete and embryo donation are becoming increasingly available and acceptable in Poland. The largest number of oocyte donation procedures is carried out in Spain — in 2015 over 34,000 such treatments were reported [19].

When discussing the efficiency and safety of infertility treatment, IUI should not be overlooked. Intrauterine insemination is a relatively simple procedure that does not require highly specialized laboratory and medical equipment; therefore, it is widely used. The lack of a central register of all centres offering this therapeutic method does not allow the assessment of the actual scale of IUI use in infertility treatment in Poland. However, the results, based on 51,405 reported treatment cycles, allow an assessment of the effectiveness of this method. A higher percentage of clinical pregnancies was obtained, as expected, in procedures with donor sperm than with husband/partner's semen (16.7% vs 11.1%). The percentage of multiple pregnancies was 6.2%.

CONCLUSIONS

This PTMRiE and SPiN PTG report is the first to be joined by all IVF clinics active in 2016 and is still the only study summarizing the number of ART procedures performed in Poland, their effectiveness and safety. Data obtained thanks to the EIM program show that infertility treatment in Poland using highly specialized assisted reproduction methods is at a high level. Changes in medical standards observed over the years (*e.g.*, increase in SET cycles and cycles ending with freezing of all embryos) have resulted in a low risk of multiple pregnancies and complications while maintaining high effectiveness of treatment. This is an evidence of a conscious and mature approach of IVF centres to conducted ART therapies.

Infertility treatment using *in vitro* methods is becoming more common. The number of ART procedures in Poland is increasing every year, but it is still insufficient. The health program of the Ministry of Health exposed the real need for *in vitro* fertilization procedures and pointed out the main factor limiting access to this method of treatment — the financial factor. Over 17,000 couples were qualified to the Program, and thanks to it more than 22,000 children were born. Significant interest and overwhelming participation in this Program as well as participation in subsequent programs of local governments shows the need for partial or total reimbursement of ART procedures in Poland.

The main weakness of the report is the different quality of data collected by the centres, the inability to verify them externally, and the numerous gaps in monitoring of pregnancy and delivery. The introduction of mandatory electronic databases with real-time reporting should be considered as the necessary solution.

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ANNEX

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The analysis of the prognostic value of the neutrophil/ /lymphocyte ratio and the platelet/lymphocyte ratio among advanced endometrial cancer patients

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ABSTRACT

Objectives: About 20% of endometrial cancer (EC) patients have advanced disease (FIGO III & IV) at the moment of diagnosis. An attempt to evaluate the prognostic value of biochemical markers of inflammation and classic endometrial cancer prognostic factors in the group of advanced EC (aEC) patients has been made in this study.

Material and methods: Records of 266 patients treated in the Maria Sklodowska-Curie Memorial Cancer Centre and Institute of Oncology, Cracow Branch between the year 2006 and 2018 were included in the study. Follow-up ranged from 1 to 138 months. Progression free survival (PFS) and overall survival (OS) have been set as endpoints. Tests such as: chi-squared, Fisher, log-rank, Mann-Whitney, Kruskal-Wallis and Cox proportional hazard ratio were used in the statistical analyses.

Results: In the analysed group high total platelet count (PLT) before operative treatment and high levels of white blood cells (WBC), PLT, neutrophil/lymphocyte ratio (NLR) and platelet/lymphocyte ratio (PLR) before adjuvant therapy (AT) have been significantly associated with shorter PFS and OS. After setting the cut-off values of NLR and PLR a statistically significant correlation between those parameters and PFS as well as OS has been shown. Multivariate analysis has indicated that NLR is an independent prognostic factor of the course of aEC.

Conclusions: NLR and PLR correlate significantly with OS and PFS in aEC. NLR is an independent prognostic factor in this group. It is possible to distinguish 3 risk groups, among aEC patients, based on NRL and PLR.

Key words: advanced endometrial cancer; NLR; PLR; adjuvant treatment

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INTRODUCTION

Endometrial cancer (EC) is the most frequently diagnosed gynaecological malignancy in the developed countries. There is an upturn in morbidity especially among older women, in which group the treatment is the most difficult. Even though most endometrial cancer patients are diagnosed at an early stage of the disease, in 2016 in Poland 19% of the reported cases were advanced endometrial cancer (aEC) [1–3]. Advanced endometrial cancer patients require an individual approach on every stage of treatment. Due to healthcare system setup in Poland many aEC patients begin their treatment in district hospitals and are referred to cancer centres after surgery. The amount of information available from before treatment is in most cases scarce. In this setting any data of reliable prognostic significance, that can be obtained while planning adjuvant treatment is very valuable.

The link between inflammation and carcinogenesis has been first described in the second half of 19th century. Currently two pathways connecting carcinogenesis with the immune system are distinguished: extrinsic, where chronic inflammation creates an environment favourable to carcinogenesis and intrinsic, where cancer cells induce immunologic response favouring further development of the tumour [4–7]. The exact mechanisms underlying the interaction between coagulation, inflammation and carcinogenesis remain unclear. Neutrophils inhibit the immune system by suppressing T-type lymphocytes, and through secretion of various cytokines, chemokines and growth factors they take part in the creation of tumour inducing microenvironment. It is said that

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glycoproteins such as platelet-derived growth factor (PlGF), transforming growth factor beta (TGF-β) or vasculo-epithelial growth factor (VEGF) secreted by platelets play a similar role. This effect is amplified by increased platelet production and aggregation associated with cancer [8–11].

Among other markers derived from complete blood count (CBC), the predictive value of neutrophil/lymphocyte ratio (NLR) and platelet/lymphocyte ratio (PLR) has been assessed for many types of tumours, such as breast, stomach, colon or lung cancer. There is paucity of data on its significance in endometrial cancer. [12–15]. At present there are no papers on their prognostic value in advanced endometrial cancer.

Objectives

The aim of this study was to assess the prognostic value of NLR and PLR calculated at the stage AT planning in aEC patients and the potential utility of these markers in clinical practice.

MATERIAL AND METHODS

Records of 266 patients treated in the Maria Sklodowska-Curie Memorial Cancer Centre and Institute of Oncology, Cracow Branch between year 2006 and 2018 were included in the analysis. Follow-up ranged from 1 to 138 months. Data collection was finished five years after the treatment of the last patient included in the study had ended. Detailed analysis of known EC prognostic factors, comorbidity, biochemical test results, type of surgery, its duration, extent and the hospital where it was performed, stage and grade of cancer, its histology and Bokhman type, the type of adjuvant treatment, and its outcome in RECIST criteria was performed.

Progression free survival (PFS) and overall survival (OS) have been set as endpoints and assessed in periods of 12, 36 and 60 months. The patients have not been differentiated by the cause of death due to insufficient data.

Qualitative data was analysed by counting the number and percentage of each value. Comparison of those variables was made using chi-squared test or Fisher detailed test in case of groups with low expected quantity. Kaplan-Meier curves were used to demonstrate the results of the analyses of qualitative features, and their comparison was made using log-rank test. Quantitative data was analysed by counting the mean value, standard deviation, the median, quartiles, the minimal value and the maximal value. Comparison of those variables was made using Mann-Whitney test. In cases of three or more groups the comparison was made using Kruskal-Wallis test. Features which showed statistically significant differences were analysed post-hoc with Dunn test. Cox proportional hazard ratio model was used to examine the influence of quantitative features on PFS and OS. The results have been shown using hazard ratio (HR) with 95% confidence interval. The cut-off values for tests based on quantitative data were determined using receiver operating characteristic (ROC) curves. Utility of a quantitative variable as a predictor was assessed using the area under the ROC curve (AUC). P value below 0.05 was set as the level of statistical significance. The analyses were made using R software.

RESULTS

The study group was comprised of 266 advanced endometrial cancer patients. The youngest patient was 34, while the oldest was 91 years old at the time of the beginning of treatment. The average age was 65.5, and its median was 66 years. 192 (72%) of patients had comorbidity, of which the most common was arterial hypertension (169 cases — 63.5%). Furthermore, there were cases of ischemic heart disease, arrhythmia, diabetes mellitus, hypo- and hyperthyroidism, asthma, chronic obturatory pulmonary disease, vascular lesions, thromboembolism and other. One hundred thirteen patients were obese and further 72 were overweight. FIGO stage IIIB accounted for 35% of cases, followed by IIIA — 28% and IIIC — 24%. Only 5% of patients were stage IV. There were 182 Bokhman type I EC cases, of which 152 were of pure endometrioid histology, and the others had mucinous and planoepithelial components. Bokhman type II EC cases accounted for 26% (n = 70) of the group and were comprised of histological types such as: serous (n = 17), clear cell (n = 10), carcinosarcoma (n = 13) and mixed (n = 30). The detailed data is shown in Table 1.

Five-year overall survival rate in the study group was 49,6%, and progression-free survival rate 45,4%. Median OS was 60 months, while half of the patients had progression after 50 months. Table 2 shows detailed data.

There was paucity of data on detailed CBC before treatment, because in most treatment centres the neutrophil count and the lymphocyte count were not assessed before surgery. The CBC data collected before adjuvant treatment was far more complete and of better quality because most of the results came from a single laboratory in COOK. Survival analysis in the context of variables such as: age at the moment of diagnosis, BMI before treatment, WBC before surgery, and before adjuvant treatment (AT), PLT before surgery and before AT, NLR and PLR before AT, comorbidity, in particular DM and its treatment with metformin, FIGO stage, histologic grade, Bokhman type, depth of myometrial invasion has been performed. Results of the analysis for the variables which correlated significantly with PFS and/or OS are given in Table 3 and 4.

Afterwards ROC curves have been drawn for NLR and PLR. Area under curve (AUC) values were 0.608 for NLR and 0,613 for PLR (Fig. 1). Optimal cut-off values for examined parameters have been assessed, equalling:

— NLR = 3.88 — sensitivity 80.6% and specificity 42.39%
— PLR = 231.3 — sensitivity 80.6% and specificity 42.39%.

Table 1. Demographic and clinical characteristic of the study group

Demographic and clinical characteristic of the study group			
Feature	Mean (SD)	Median (quartile)	
Age [years]	65.47 (9.75)	66 (59–73)	
		N	%
	22–44	5	1.9
	45–64	112	42.1
	65+	149	56
BMI	30.13 (5.93)	29.8 (25.98–33.85)	
	Underweight (< 18.5)	1	0.4
	Normal (18.5–25)	44	16.5
	Overweight (25–30)	72	27.1
	Obese (> 30)	113	42.5
	No data	36	13.5
Comorbidity	Total	192	72.18
	Hypertension	169	63.53
	Diabetes mellitus	58	21.8
Diabetic patients treated with metformin	Yes	33	56.90
	No	24	41.38
	No data	1	1.72
FIGO 2009 stage	IIIA	75	28.2
	IIIB	93	34.96
	IIIC	63	23.68
	IVA	5	1.88
	IVB	8	3.01
	No data	22	8.27
Bokhman type	Type I	182	68.42
	Type II	70	26.32
	No data	14	5.26
Histological Grade	G1	34	12.78
	G2	126	47.37
	G3	57	21.43
	No data	49	18.42

SD — standard deviation; BMI — body mass index

The results of a univariate analysis of the relation between dichotomised NLR and PLR values (high — above cut-off, low — below cut-off) and OS and PFS are given in Table 5, and on Figure 2 and 3 for NLR and PLR respectively. Due to the fact that both parameters presented statistically significant correlation with OS and PFS an attempt to distinguish three risk groups based on their value has been made: LL — both values „low", HH — both values „high", LH — one value „low" and the other one „high". The survival analysis in relation to subgroups has shown a significant correlation with both OS and PFS. Above-mentioned results are included in table 5 and presented on Figure 4.

A multivariate analysis of the prognostic value of NLR and PLR before AT was then conducted with inclusion of known significant prognostic factors such as age, histologic grade and Bokhman type. Due to similarity of NRL and PLR two separate analyses were done for each parameter alone. The results have shown that NRL was the only independent prognostic factor for both 5-year OS and PFS in the study group. Hazard ratios were similar for death and progression and equalled 2.6 in case of high NRL value. Detailed results of this analysis are presented in Table 6.

DISCUSSION

Neutrophils secrete an abundance of cytokines, growth factors and enzymes such as Il-6, Il-8, VEGF, HGF, metalproteinases and elastases, which take part in the creation of a tumour promoting microenvironment, by decomposition of the extracellular matrix, promotion of neoangiogenesis or inhibition of anti-cancer immune response — suppression of activated T-lymphocytes and natural killers. On the other hand, lymphocyte invasion into cancer tissue is frequently linked with better response to chemotherapy and thus better prognosis. NLR joins the neutrophil and the lymphocyte count into one clear parameter [16–19].

Table 2. Overall survival and progression-free survival in the study group

Number of patients	Number of events	Overall survival			
		12 months	36 months	60 months	Median [months]
266	106	87.23%	59.54%	49.59%	60
Number of patients	Number of events	Progression-free survival			
		12 months	36 months	60 months	Median [months]
266	122	71.02%	53.14%	45.42%	50

Post-treatment follow-up [months]							
N	Mean	SD	Median	Min	Max	Q1	Q3
266	36.94	31.63	25	1	138	11	61

SD — standard deviation

Table 3. Results of the analysis of selected variables in relation to overall survival

Results of the analysis of selected variables in relation to OS							
N	**Variable**		**Unit**	**HR**	**95%CI**		**p**
1	Age at the moment of diagnosis		years	1.035	1.013	1.056	0.001
2	PLT before surgery		$10^3/\mu L$	1.003	1	1.005	0.02
3	WBC before AT		$10^3/\mu L$	1.073	1.046	1.101	< 0.001
4	PLT before AT		$10^3/\mu L$	1.005	1.003	1.006	< 0.001
5	NLR			1.06	1.034	1.086	< 0.001
6	PLR			1.001	1	1.002	0.011
Variable		**Number of patients**	**Number of deaths**	**Overall survival**			**p**
				12 months	**36 months**	**60 months**	**Median [months]**	
7. Histologic grade								
	G1	34	8	93.21%	77.03%	64.19%	> max obs.	p < 0.001
	G2	127	40	92.22%	71.65%	63.24%	116	
	G3	57	30	81.03%	37.82%	24.82%	25	
8. Bokhman type								
	I	183	57	91.32%	69.08%	59.83%	116	p < 0.001
	II	71	42	75.24%	40.53%	28.43%	25	

OS — overall survival; HR — hazard ratio; CI — confidence interval; PLT — total platelet count; WBC — white blood count; AT — adjuvant therapy; NLR — neutrophil/lymphocyte ratio; PLR — platelet/lymphocyte ratio

Table 4. Results of the analysis of selected variables in relation to progression free survival

Results of the analysis of selected variables in relation to PFS							
N	**Variable**		**Unit**	**HR**	**95%CI**		**p**
1	Age at the moment of diagnosis		[years]	1.026	1.006	1.046	0.009
2	PLT before surgery		$10^3/\mu L$	1.003	1	1.005	0.027
3	LEU before AT		$10^3/\mu L$	1.064	1.043	1.085	< 0.001
4	PLT before AT		$10^3/\mu L$	1.004	1.003	1.005	< 0.001
5	NLR			1.054	1.03	1.078	< 0.001
6	PLR			1.001	1	1.002	0.036
Variable		**Number of patients**	**Number of events**	**Overall survival**			**p**
				12 months	**36 months**	**60 months**	**Median [months]**	
7. Histologic grade								
	G1	34	10	80.40%	73.09%	63.34%	> max obs.	p < 0.001
	G2	127	47	82.92%	65.18%	57.61%	93	
	G3I	57	34	52.86%	27.11%	23.24%	15	
8. Bokhman type								
	I	183	68	80.24%	62.69%	55.13%	93	p < 0.001
	II	71	46	48.74%	32.63%	24.16%	12	
9. Depth of myometrial invasion								
	< 1/2	39	10	88.89%	75.00%	71.43%	> max obs.	p = 0.018
	> 1/2	163	69	80.54%	58.59%	47.84%	58	

PFS — progression free survival; HR — hazard ratio; CI — confidence interval; PLT — total platelet count; WBC — white blood count; AT — adjuvant therapy; NLR — neutrophil/lymphocyte ratio; PLR — platelet/lymphocyte ratio

A meta-analysis conducted by Templeton gives an overview of the results of 100 papers, which include 40,559 patients with solid tumours, to assess the prognostic value of NLR [20]. Diseases such as breast, colon, ovarian, cervical cancer or mesothelioma were included, among others. There were no cases of endometrial cancer in the analysis. Cut-off

Table 5. Prognostic value analysis of neutrophil/lymphocyte ratio and platelet/lymphocyte ratio as qualitative variables in relation to overall survival and progression free survival

Prognostic value analysis of NLR and PLR as qualitative variables in relation to OS (1–3) and PFS (4–6)							
Variable	**Number of patients**	**Number of deaths or events**	**Overall survival**				**p**
			12 months	**36 months**	**60 months**	**Median [months]**	
1. NLR low (L) / high (H) — OS							
L	155	58	89.53%	64.98%	56.67%	116	p = 0.005
H	83	39	83.04%	48.29%	36.35%	35	
2. PLR low (L)/high (H) — OS							
L	158	57	89.66%	65.96%	57.37%	116	p = 0.001
H	80	40	82.67%	46.12%	35.37%	28	
3. Groups NLR + PLR — OS							
LL	135	48	90.39%	67.46%	58.87%	116	p = 0.002
LH/HL	43	19	84.44%	52.06%	44.86%	42	
HH	60	30	82.26%	45.55%	32.57%	26	
4. NLR low (L)/high (H) — PFS							
L	155	69	76.93%	58.58%	50.16%	63	p = 0.008
H	83	44	54.06%	41.26%	36.25%	18	
5. PLR low (L) / high (H) — PFS							
L	158	69	74.63%	60.40%	50.90%	63	p = 0.006
H	80	44	58.17%	35.90%	33.66%	21	
6. Groups NLR + PLR — PFS							
LL	135	58	77.41%	61.67%	51.93%	93	p = 0.008
LH/HL	43	22	65.29%	45.42%	41.93%	26	
HH	60	33	52.29%	36.02%	32.42%	16	

OS — overall survival; PFS — progression free survival; NLR — neutrophil/lymphocyte ratio; PLR — platelet/lymphocyte ratio

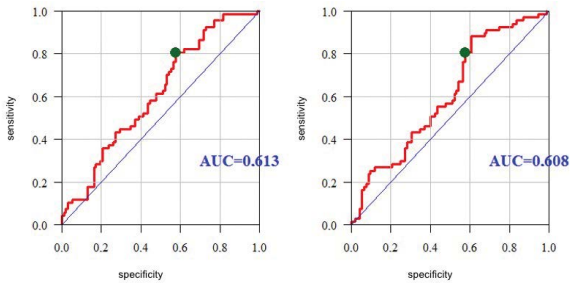

Figure 1. Kapplan-Meier overall survival and progression free survival curves for neutrophil/lymphocyte ratio (NLR)

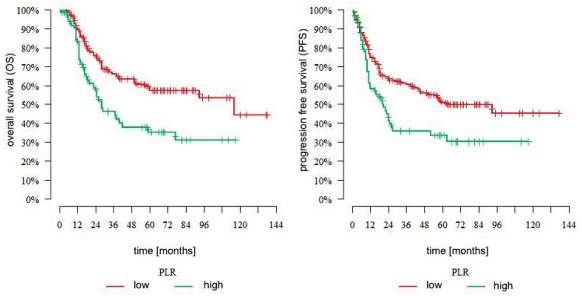

Figure 3. Kapplan-Meier overall survival and progression free survival curves for platelet/lymphocyte ratio (PLR)

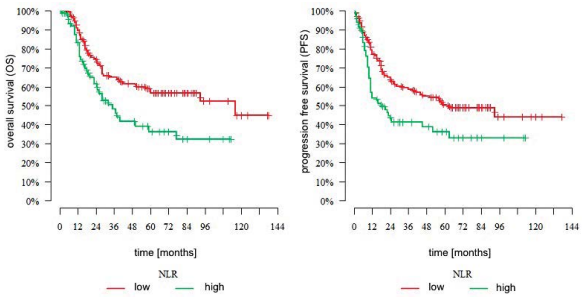

Figure 2. Receiver operating characteristic curves for neutrophil/ /lymphocyte ratio (NLR) (left) and platelet/lymphocyte ratio (PLR) (right); AUC — area under curve

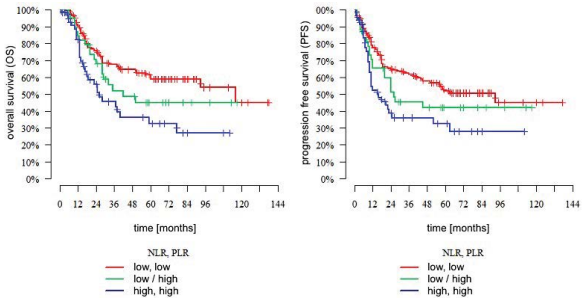

Figure 4. Kapplan-Meier overall survival and progression free survival curves for neutrophil/lymphocyte ratio (NLR)/platelet/lymphocyte ratio (PLR) — L/H.

Table 6. Multivariate analysis results — neutrophil/lymphocyte ratio

Multivariate analysis including NLR					
Feature		**HR**	**95%CI**		**p**
OS					
Age	[years]	1.03	0.998	1.062	0.064
Grade	G1	1	ref.		
	G2	1.012	0.364	2.815	0.982
	G3	1.634	0.544	4.912	0.382
Bokhman type	I	1	ref.		
	II	1.523	0.693	3.347	0.295
NLR	Low	1	ref.		
	High	2.589	1.281	5.235	0.008
PFS					
Age	[years]	1.026	0.997	1.057	0.084
Grade	GI	1	ref.		
	GII	1.291	0.524	3.183	0.578
	GIII	2.224	0.798	6.202	0.127
Bokhman type	I	1	ref.		
	II	1.661	0.796	3.467	0.177
NLR	Low	1	ref.		
	High	2.597	1.389	4.852	0.003

OS — overall survival; PFS — progression free survival; NLR — neutrophil/lymphocyte ratio

values for NLR ranged from 3.0 to 5.0, the latter one being the most common (33%). A marginally significant relation between cut-off values and hazard ratios was observed. There was a statistically significant correlation between NRL value and overall survival (HR = 1.81), which was also observed in relation to cancer specific survival (CSS), progression-free survival and disease-free survival (DFS). The strength of the correlation was bigger in cases of metastatic disease than in those confined to the primary tumour site. HR for metastatic cancer equalled 1.8 (1.63–1.99), and 1.57 (1.36–1.82) when there were no metastases. The authors explain that effect with bigger tumour burden or longer-lasting cancer-related inflammation in advanced cases [25].

The amount of papers on NLR in endometrial cancer is scarce. A meta-analysis conducted by Ethier on the prognostic value of NRL in gynaecological cancers includes only five studies concerning EC, three of which assessed only OS, and two where PFS was also taken into account. It has been noticed that in studies where five year survival was lower the NLR cut-offs tended to be set higher. No relation between most known clinic-pathologic prognostic factors and NLR was found, with the exception of histologic grade — G3. In cases of G3 endometrial cancer the correlation was stronger [21]. Haruma and al. made a retrospective analysis of 320 cases of EC. The study group was comprised of 253 FIGO stage I–II patients and 67 FIGO stage III-IV patients. There were 276 cases of Bokhman type I EC (of which 40 were G3), and 46 type II. NLR and PLR measurements were taken in the month preceding surgery. NLR was found to be dependent on stage (FIGO I-II vs III-IV), histology (G1–2 vs G3 + type II EC) and myometrial invasion. Cut-off values were set as 2.7 for OS and 2.41 for DFS. In multivariate analysis only NLR and "histology" were determined to be independent prognostic factors [26]. Currently the biggest study concerning NRL in endometrial cancer was conducted by Cummings. It is a retrospective analysis of 733 EC patients in all stages, of which 78% were FIGO I–II. The authors examined the prognostic value of NLR, PLR and monocyte-lymphocyte ratio (MLR) measured before operative treatment. The optimal cut-off value for NLR was set to 2.4 in this study. A statistically significant correlation between NLR and OS as well as CSS was found in univariate analysis. In the multivariate analysis including variables such as age, stage, grade, Bokhman type and LVSI invasion, NLR was determined to be an independent prognostic factor [15].

As opposed to the above-mentioned papers, this study is focused solely on the advanced EC patients — FIGO stages III–IV, and the NRL and PLR values have not been measured before surgery but at the stage of adjuvant treatment planning. The results of the univariate analysis indicate a statistically significant correlation between the value of NLR and 5-year OS — HR = 1.06 ($p < 0.001$) and PFS — HR = 1.054 ($p < 0.001$). The mean NLR value in the study group was 4.2 [standard deviation (SD) 6.43], and its median 3.13. An optimal cut-off value of 3.88 has been set using the ROC curve analysis. Five year overall survival was 57% and 36% for low and high NLR accordingly. No relation between NLR and Bokhman type, histologic grade or surgical radicality was found. The results of a multivariate analysis including age, histologic grade and Bokhman type have shown that NLR is the only independent prognostic factor of OS (HR = 2.6), as well as of PFS (HR = 2.6) in this study group. Hazard ratio values obtained in the univariate analysis are lower than in the cited papers which may be due to a smaller tumour burden after surgery, that may implicate a weaker cancer-related immune response. Such an explanation was suggested in the Templeton meta-analysis. It is important to notice that the set NLR cut-off value (3.88) was considerably different than those in Cummings and Haruma studies (2.4, 2.7), and were closer to those observed by Templeton in cases of advanced or metastatic cancer (4–5).

Platelets take part in the tumour promoting inflammatory response. One of the essential elements of the process is Il-6 which promotes megakaryocyte differentiation into platelets by stimulating the production of thrombopoietin. High level of Il-6 was proven to be an independent prognos-

tic factor of bad outcome in ovarian cancer. Its reflection in CBC might be high platelet count. PLR is a parameter derived from CBC, which takes into account the platelet count as well as the lymphocyte count [5, 22, 23].

One of the most comprehensive studies on the prognostic value of PLR in solid tumours is a 2014 meta-analysis conducted by Templeton. It includes 12,890 patients from 22 different studies, who were diagnosed with such malignancies as mesothelioma, pancreatic, breast or ovarian cancer among others. It does not include any studies concerning endometrial cancer. The authors point out that a significant prognostic value of PLR is observed especially with advanced cancer. In studies where the disease was confined to the primary site the effect was rarely seen or marginal. The determined optimal cut-off values ranged from 150 to 300 depending on the type of cancer and its stage, and in most cases were higher in the metastatic disease. The authors conclude that the prognostic value of PLR is strongly dependent on the stage of cancer, and it tends to be higher in more advanced stages [24].

The number of papers regarding PLR in EC is scant. The Haruma study quoted before is one of the two major studies relating to PLR in endometrial cancer. The results indicate that similarly to NLR also PLR was influenced by stage, „histology" and depth of myometrial invasion. The prognostic value of PLR was proven to be statistically significant in terms of OS and DFS only in the univariate analysis. The determined cut-off value was 175. The authors conclude that PLR is a weaker prognostic factor than NLR [26]. The second of the major studies, by Cummings, was also referred to previously in the context of NLR. The cut-off value set by the authors for PLR was 240. The results of the univariate analysis have shown a significant correlation between PRL and OS as well as CSS. The outcome of multivariate analysis, which included age, stage, histologic grade, Bokhman type, and LVSI status indicated PLR as an independent prognostic factor. It was also shown that the value of PRL is related significantly to age, stage, nodal involvement and LVSI status. The authors have distinguished three prognostic groups based on the PLR and NLR values, which differed in OS and CSS in a statistically significant way [15].

The results of Cox proportional hazard analysis in our group of aEC patients indicate that the correlation between PLR and 5-year OS (HR = 1.001; p = 0.011) and PFS (HR = 1.001; p = 0.011) is statistically significant in the univariate analysis. The hazard ratio value is low because of the small unitary value of the parameter — the mean value was 237, and the standard deviation was 178 in the study group. The determined optimal cut-off value was 231.3 (sensitivity 80.6%; specificity 42.4%). When dichotomised, the parameter allowed the formation of two groups differing significantly in terms of 5-year OS (L — 57.4%; H —35.4%) and PFS (L — 50.9%; H — 33.6%). Similarly to NLR there was no significant relation between PLR and histologic type, grade and surgical radicality. The outcome of a multivariate analysis indicated that PLR is not an independent prognostic factor of neither OS nor PFS in aEC. The cut-off values which were defined as optimal in our analysis were similar to those in the paper by Cummings et al.

What has to be pointed out is that due to the low specificity of the dichotomised NLR and PLR some patients might be misclassified, so the cut-off values should be reassessed in a better designed, preferably prospective study.

The outcome of stratification of our group of aEC patients to three risk groups, based on the NLR and PLR status met our expectations. The 5-year OS in the low-risk group was 59% in comparison to 33% in the high-risk group. The differences were statistically significant. The proposed division may provide an additional argument in the decision-making process while planning individual adjuvant treatment for advanced endometrial cancer patients.

CONCLUSIONS

Both NLR and PLR measured before adjuvant treatment were found to have significant prognostic value in relation to OS and PFS among advanced endometrial cancer patients, while in the multivariate analysis NLR was found to be an independent prognostic factor of OS as well as PFS. Taking into account the fact that the determination of those parameters is cost neutral, they may be easily taken into consideration in the decision-making process while planning individualised adjuvant treatment for aEC patients. Further prospective studies should be carried out for better determination of their prognostic value and optimal cut-off points in aEC.

Conflict of interest

The authors declare no conflict of interest.

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Risk factors for unsuccessful vaginal birth after caesarean at full dilatation

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ABSTRACT

Objectives: The purpose of this study was to determine the risk factors for caesarean sections in the second stage of labour after a previous caesarean section among women who underwent trial of labour (TOL).

Material and methods: From a total of 639 women who experienced one caesarean section, 456 women were qualified for TOL. From this group, 105 women were subjected to a caesarean section in the first stage of labour and another 351 women reached the second stage of labour. From the latter group, 309 women delivered naturally and 42 were subjected to a caesarean section.

Results: Risk factors for the necessity of performing a caesarean section in the second stage of labour after a previous caesarean section was the weight gain during pregnancy (OR = 1.07), the height of fundus uteri (OR = 1.25) before delivery, and the estimated foetal weight (OR = 1.01), a past delivery of a child with a birth weight exceeding 4.000 g (OR = 2.14), the presence of pre-gestational diabetes (OR = 15.4) and gestational diabetes (OR = 2.22), necessity of applying a delivery induction (OR = 2.52), stimulation of uterine activity during delivery (OR = 2.43) and application of epidural analgesia (OR = 4.04). A factor reducing the risk of a caesarean section in the second stage was a vaginal delivery in a woman's history (OR = 0.21).

Conclusions: Women should be encouraged to deliver naturally after a previous caesarean section, especially when their history includes a vaginal delivery and if there is no need for labour induction.

Key words: caesarean section; repeat; trial of labour; vaginal birth after caesarean

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INTRODUCTION

For the last few decades, the number of caesarean sections has been growing consistently, up to 32.7% in the USA, 22.0% in Great Britain, 37.4% in Italy, and 41.3% in Brazil in 2013 [1, 2]. In Poland, over 1/3 of deliveries result in a caesarean section [3].

A reason for this seems to be a liberalization of indications for a caesarean section, along with the gradually decreasing risk of complications during such a surgery. A rule that has been valid since the 1970s, "caesarean section once, caesarean section always", is no longer enforced. However, it should be accepted that managing a vaginal delivery after a caesarean section requires considerable experience from an obstetrician, and an appropriate qualification for a natural delivery is the key to success [4].

The percentage of women qualified for a trial of labour (TOL), for whom there is a necessity of performing another caesarean section in the second stage of delivery is relatively high. Caesarean sections performed at full dilatation are technically difficult procedures and trigger an increased risk of complications for a mother and foetus [5, 6].

Objectives

The purpose of this study was to determine the risk factors for caesarean sections in the second stage of labour after a previous caesarean section among women who underwent a trial of vaginal delivery.

MATERIAL AND METHODS

Analyses were performed among women delivering in the 2nd Department of Obstetrics and Gynaecology of the Medical University of Warsaw over a three-year period. Risk factors were searched within a group of patients who had already undergone one caesarean section, qualified for a natural delivery and reached full cervical dilation.

Within this period, 742 women with a single pregnancy, who experienced at least one caesarean section, were admitted for delivery. Out of them, 103 (13.9%) experienced

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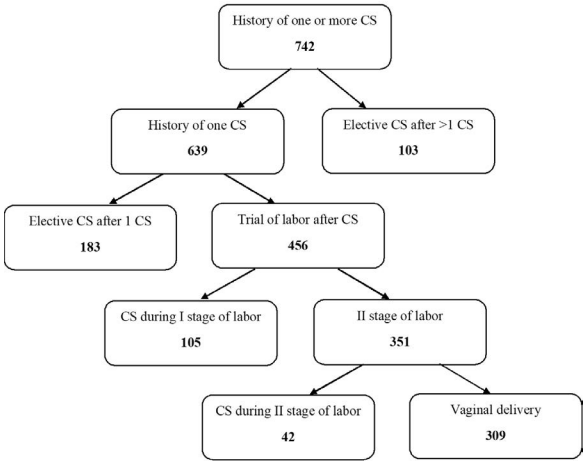

Figure 1. Study population

more than one caesarean section and were excluded from the analyses. Out of 639 women, who experienced one caesarean section, 183 (28.6%) were qualified for a repeated caesarean delivery (excluded from the analyses), and 456 were qualified for TOL. Out of 456 women qualified for TOL, 105 had caesarean section performed in the first stage of labour and 351 reached the second stage of labour. From the latter group 309 women delivered naturally and 42 were qualified for a caesarean section (Fig. 1).

The following potential risk factors for a caesarean section in the second stage of labour among patients after one caesarean delivery who underwent TOL were assessed: maternal age and gestational age at delivery, maternal anthropometric indices (pre-pregnancy weight, height and body mass index (BMI), gestational weight gain, pre-partum bodyweight, abdominal circumference and height of fundus uteri before delivery), reproductive history (the number and methods of previous deliveries, miscarriages and ectopic pregnancies, the history of the delivery large babies with a birth weight exceeding 4.000 g), the course of pregnancy (smoking tobacco, presence of gestational and pre-gestational diabetes, pre-gestational and pregnancy-induced hypertension, intrahepatic cholestasis of pregnancy, thyroid diseases, uterine fibroids, symptoms of threatened premature birth, preterm premature rupture of membranes, antenatal steroid therapy, presence of anaemia based on the mother's haemoglobin concentration prior to delivery), the course of delivery (delivery induction, stimulation of uterine activity, presence of fever > 38°C, application of epidural analgesia). An estimated foetal weight (EFW) evaluated in ultrasound up to seven days prior to delivery was also considered a potential risk factor.

Mean values and standard deviations or medians and maximum and minimum values of quantitative factors were determined, and a percentage distribution of qualitative factors within an analysed group of women was calculated. An odds ratio (OR) and 95% confidence interval were determined for each of the analysed risk factor. A value of $p < 0.05$ was assumed to be statistically significant. Statistical analysis was executed with using the SAS program [7, 8]. The study was approved by local Ethical Board.

RESULTS

Indications for a previous caesarean section within a group of 309 women who delivered naturally and 42 women who delivered by caesarean section during the second stage of labour are included in Table 1.

Repeated caesarean sections in the second stage of labour were performed based on the following indications: lack of delivery progress, 24 women (57.1%); foetal distress,

Table 1. Indications for the previous caesarean section

Indication	Vaginal delivery after caesarean (n = 309) n (%)	Caesarean section in the second stage TOL (n = 42) n (%)
Foetal asphyxia in the first stage of labour	100 (32.4%)	11 (26.2%)
Non-vertex foetal presentation	67 (21.7%)	2 (4.8%)
Prolonged first stage of labour	50 (16.2%)	11 (26.2%)
Prolonged second stage of labour	26 (8.4%)	8 (19.0%)
Vaginal bleeding in the first stage of labour	20 (6.6%)	3 (7.1%)
Maternal disease	14 (4.5%)	0
Placenta previa	9 (2.9%)	0
Cephalopelvic disproportion	8 (2.6%)	3 (7.1%)
Foetal asphyxia in the second stage of labour	4 (1.3%)	1 (2.4%)
Foetal disease	4 (1.3%)	0
Intrauterine infection	2 (0.6%)	0
Vaginal bleeding in the second stage of labour	0	1 (2.4%)
Others	5 (1.6%)	2 (4.8%0

16 women (38.1%); vaginal bleeding, 2 women (4.8%). Among women who delivered vaginally, 24 had an operative vaginal delivery with obstetric vacuum extractor. Indications for a vaginal intervention delivery were the following: foetal distress, 17 women (70.8%); lack of delivery progress, 6 women (25.0%); and maternal heart disease, 1 woman (4.2%).

The following risk factors influencing the necessity of performing a caesarean section in the second period of delivery during TOL were found: gestational weight gain (OR = 1.07), the height of fundus uteri before delivery (OR = 1.25), an ectopic pregnancy in a woman's history (OR = 7.67), a past delivery of a child with a birth weight exceeding 4.000 g (OR = 2.14), the presence of pre-gestational diabetes (OR = 15.4) or gestational diabetes (OR = 2.22), the delivery induction (OR = 2.52), and stimulation of uterine activity (OR = 2.43), the presence of fever during delivery (OR = 10.3), the application of epidural analgesia (OR = 4.04), and EFW (OR = 1.01).

A considerable non-linear dependency between the necessity of performing a caesarean section in the second period of labour and the gestational age was found. This risk was five times higher if a delivery occurred prior to a completed 32nd pregnancy week (OR = 5.04) and over two times higher if a delivery occurred after the 36th pregnancy week (OR = 2.62) in comparison with a delivery within a period between the 32nd and 36th weeks of pregnancy.

The factor reducing the risk of a caesarean section in the second stage of labour was a vaginal delivery in a woman's history (OR = 0.21). The results are presented in Table 2.

DISCUSSION

The number of caesarean sections performed in the second stage of labour increases along with the growing percentage of caesarean sections overall [9]. It reaches 6% according to a report of the Royal College of Obstetricians and Gynaecologists [10]. Various factors seem to determine such a situation. A lack of sufficient experience of an obstetrician in managing operative vaginal deliveries along with growing concerns related to an increased risk of complications among mothers and infants and resulting claims are issues that can significantly impact the number of caesarean sections performed in the second stage of delivery [11].

It should be emphasized that an additional factor increasing the risk of delivery with intervention is a history of previous caesarean section. Fifty-one point six percent of women delivering after one caesarean section had a second caesarean section, of which 55.5% had an elective one and 44.5% during a natural delivery, including 31.8% in the first and 12.7% in the second stage of delivery.

Lewkowitz et al. [12] determined that nearly half of women after caesarean sections due to the delivery arrest in the first or second stages have a chance for a natural delivery in the next pregnancy. Our results agree with this finding. The authors did not find any differences concerning the chances for a vaginal delivery depending on the lack of progress in the first versus second stage of labour. In our data, among women who delivered vaginally, 16.2% had a previous caesarean section due to delivery arrest in the first stage of labour and 8.4% in the second stage. These percentages equalled 25.0% and 19.0%, respectively, in women who had a caesarean section in the second stage. According to Davis et al. [9], the most common indication for a caesarean section in the second stage is delivery arrest, which also agrees with our results.

In our research, 5.0% of women after a caesarean section qualified for a TOL, were delivered with the use of an obstetric vacuum extractor due to foetal distress or prolonged second stage. According to the most recent data, a delivery with a such intervention in women after a caesarean section during TOL at a foetal station of at least + 2 is a safe procedure [13].

Our analyses did not show that the mother's age, height, weight and BMI prior to pregnancy have any influence on the risk of a caesarean section in the second stage during TOL. Bujold et al. found that the mother's age equal to or exceeding 35 years reduces her chances for natural delivery after a caesarean section not only in women who did not have a natural delivery in their history [OR = 0.73, 95% confidence interval (CI): 0.56–0.94] but also in women who had a natural delivery (OR = 0.47, 95% CI: 0.29–0.74) [14]. According to scientists from the other centre in our country, such parameters as maternal age, BMI and gestational weight gain did not change the percentage of women who delivered vaginally after one caesarean section during TOL [15].

Our data showed that gestational weight gain, maternal abdominal circumference prior to delivery and height of fundus uteri influenced the risk of a caesarean section during TOL. According to American authors, both excessive bodyweight growth during pregnancy and classification as overweight and obesity reduce the chances for a natural delivery after caesarean section [16]. Durnwald et al. [17] also found that women who were obese prior to pregnancy had a lower chance of delivering naturally after a caesarean section.

A history of ectopic pregnancy increased the risk of caesarean section in the second stage during TOL by over seven times. In the case of a previous delivery of the large baby the risk increased by twice. Unfortunately, there are no data in the literature concerning these issues. It seems that in such cases an obstetrician decides more easily to perform a caesarean section in the second stage of the delivery.

We found that occurrence of pre-gestational diabetes increased the risk of caesarean section in the second period of delivery by more than 15 times and that gestational

Table 2. Perinatal risk factors for caesarean section in the second stage of labour in women after previous caesarean

	mean ± SD (min–max) or n (%)	OR (95% CI)	p_{lin}	$p_{non\ lin}$
Quantitative: Maternal and fetal data: Age [years]	31.5 ± 4.3 (17–45)	1.20 (0.95–1.10)	NS	NS
Gestational age [weeks]	38.3 ± 2.7 (24–42)	0.70 (0.87–1.09)	NS	0.015
Pre-pregnancy weight [kg]	63.4 ± 13.2 (40–153)	1.02 (0.99–1.04)	NS	NS
Height [cm]	164.8 ± 6.0 (146–181)	0.97 (0.91–1.02)	NS	NS
Pre-pregnancy BMI [kg/m2]	23.3 ± 4.5 (16.0–55.5)	1.03 (0.99–1.04)	NS	NS
Gestational weight gain [kg]	13.5 ± 4.8 (0–28)	1.07 (0.99–1.15)	0.046	NS
Pre-partum weight [kg]	76.9 ± 13.2 (55–159)	1.02 (0.99–1.04)	NS	NS
Abdominal circumference [cm]	103.5 ± 8.4 (84–142)	1.07 (1.03–1.11)	0,001	NS
Fundal height [cm]	35.9 ± 3.8 (24–48)	1.25 (1.13–1.38)	0.001	NS
Estimated fetal weight [g]	3199.8 ± 590.0 (660–4244)	1.01 (0.99–1.01)	0.040	NS
Pre-partum hemoglobin level [g/L]	12.4 ± 1.0 (8.5–15.3)	1.34 (0.96–1.85)	NS	NS
Qualitative: Previous vaginal delivery	75 (21.4%)	0.21 (0.05–0.81)	0.024	
History of spontaneus abortion	82 (23.4%)	1.03 (0.64–1.65)	NS	
History of ectopic pregnancy	4 (1.1%)	7.67 (1.05–56.0)	0.045	
Previous LGA baby	55 (15.7%)	2.14 (1.01–4.58)	0.049	
GDM in current pregnancy	65 (18.5%)	2.22 (1.08–4.55)	0.03	
Pre-gestational diabetes	3 (0.9%)	15.40 (1.37–173.68)	0.027	
PIH in current pregnancy	18 (5.1%)	1.51 (0.42–5.44)	NS	
Pre–pregnancy hypertension	15 (4.3%)	1.14 (0.25–5.23)	NS	
Cholestasis in current pregnancy	17 (4.8%)	0.45 (0.06–3.46)	NS	
Thyroid disorders	29 (8.3%)	0.52 (0.12–2.28)	NS	
Threatened preterm birth in current pregnancy	25 (7.1%)	0.62 (0.14–2.74)	NS	
PPROM in current pregnancy	94 (26.8%)	0.42 (0.17–1.03)	NS	
Antenatal steroid therapy in current pregnancy	36 (10.3%)	0.64 (0.19–2.20)	NS	
Myomas	4 (1.1%)	2.49 (0.25–24.48)	NS	
Smoking status during pregnancy	57 (16.2%)	1.78 (0.78–4.04)	NS	
Labor induction	102 (29.1%)	2.52 (1.31–4.85)	0.006	
Augmentation of labor	177 (50.4%)	2.43 (1.22–4.84)	0.012	
Fever in labor	9 (2.6%)	10.30 (2.65–40.06)	0.001	
Epidural analgesia	154 (45.0%)	4.04 (1.83–8.91)	0.001	

BMI — body mass index; LGA — large for gestational age; GDM — gestational diabetes mellitus; PIH — pregnancy induced hypertension; PPROM — preterm premature rupture of membranes

diabetes increased this risk by more than twice. Blackwell et al. [18] already found that a mother with diabetes has reduced chances for a natural delivery after a caesarean section. American authors who analysed the chances of having a natural delivery after a caesarean section among women with diabetes in accordance with White's classification determined that 68.5% of women in class A1 delivered vaginally after a caesarean section, 55% in class A2, 70.0% in class B, 47.6% in class C, and 12.5% in class D/F/R [19].

According to our results, when qualifying a woman after a caesarean delivery for a natural delivery, higher EFW in USG should be considered as a factor reducing the chances for success in the second period of delivery. According to American authors, the frequency of natural deliveries among women after a caesarean section was the same among women who delivered children with a bodyweight equal or greater than 4.000 g (73.0%) in comparison with women who delivered smaller children (76.0%) [20]. However, Zelop et al. claimed that the bodyweight of an infant being equal to or greater than 4.000 g increases the risk of another caesarean section by 1.7 times (95% CI: 1.3–2.2) [21]. Phelan et al. [22] analysed the TOL among women after a caesarean section who delivered infants with bodyweights equal to or greater than 4.000 g. The percentage

of natural deliveries within this group equalled 67.0%, and a factor that decreased the chances for a successful natural delivery was an indication for a previous caesarean section due to a cephalopelvic disproportion. This was also confirmed by Elkousy et al. and Kalok et al. [23, 24]. Based on the results above, it could be claimed that the awareness that a woman undergoing a trial of natural delivery after a caesarean section may have a heavy child forces an obstetrician to repeat a caesarean section even during the second period of delivery.

It should also be mentioned that among women after a caesarean section, delivery ending with a caesarean section in the second period occurred more often prior to completing the 32nd week of pregnancy and after completing the 36th week of pregnancy. Hammoud et al. [25], analysed three groups of women qualified for TOL after a caesarean section: 24–36 weeks and 6 days, 37–40 weeks and 6 days and ≥ 41 weeks of pregnancy. The authors determined that advanced gestational age was related to decreased chances for a vaginal delivery (OR = 0.68, 95% CI: 0.51–0.89) and increased risk of uterine rupture (OR = 2.85, 95% CI: 1.27–6.42) in comparison to 37–40 weeks and 6 days gestational age.

We found that a risk of caesarean section in the second period of delivery among women after a caesarean section was increased by delivery induction, stimulation of uterine activity with oxytocin and epidural analgesia. Sakala et al. [26] evaluated the use of oxytocin to induce delivery or stimulate uterine activity among patients after a caesarean section and obtained results similar to ours: 68.0% of women treated with oxytocin delivered naturally in comparison to 89.0% of women who were not given oxytocin. This result has also been confirmed in other studies [22]. Antonakou et al. [27] analysed the influence of an epidural analgesia throughout the course of delivery among women who experienced delivery induction. They found that the application of an epidural analgesia did not increase the risk of caesarean section; however, it increased the risk of operative vaginal delivery (adjusted OR = 3.63; 95% CI: 2.51–5.24; $p < 0.001$) and extended the first and second periods of delivery. Other authors also did not find any relationship between the application of an epidural analgesia and an increased risk of caesarean section, whereas some scientific studies have suggested that epidural analgesia may extend the second period of delivery [26, 28, 29].

Davis et al. found that a caesarean section in the second period of delivery was usually performed in women who had a delivery for the first time [9]. We found that a factor that decreased the risk of caesarean section by 79.0% after previous caesarean section was a vaginal delivery in a woman's history. Hendler and Bujold stated that history of a vaginal delivery, especially after a caesarean section, increased chances for a natural delivery after a caesarean section [14, 30].

CONCLUSIONS

To conclude, it should be emphasized that women should be encouraged to try to deliver naturally after a previous caesarean section, especially when their history includes a vaginal delivery and if there is no need for labour induction. However, women with high weight gain during pregnancy, suspicion of macrosomia in an ultrasound scan, a previous large baby, women with diabetes or those requiring labour induction should be qualified very carefully for a natural delivery after a previous caesarean section because their risk of caesarean section in the second stage of labour is higher.

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The influence of hepatitis B virus (HBV) or hepatitis C virus (HCV) infections on the pregnancy course

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ABSTRACT

Objectives: The incidence of HBV infections among the pregnant in Europe falls within the range of 1–7%, whereas it is 1.7–4.3% for HCV.
The aim was to assess the course of pregnancy among women infected with HBV or HCV, and the condition of neonates in the fifth minute after the birth.

Material and methods: The study included 157 pregnant individuals infected with HBV, 53 infected with HCV, and 330 healthy pregnant women. None of the women infected with HBV and HCV as well as from the control group were infected with HIV, and none of them took intoxicants.

Results: Weight of neonates delivered by healthy women was higher as compared with children born by women infected with HBV or HCV (3.517 vs 3.347 and 3.366). The Apgar score of neonates delivered by women with HBV and HCV infections was lower as compared with the children born by healthy women (9.4 vs 9.3 vs 9.7; $p < 0.05$). Premature births occurred more often in HBV and HCV-infected women than in the control group (14.6% and 24.5% vs 6.96%; $p < 0.05$). Miscarriages were significantly more common among the patients with HCV infections as compared with the patients who were healthy (9.4% vs 1.8%; $p < 0.05$). In comparison with the healthy individuals, this group of patients experienced pruritus (10.5% vs 4.2%; $p < 0.05$), oedemas (9.4% vs 2.4%; $p < 0.05$), and hypertension (9.4% vs 1.5%; $p < 0.05$) more often.
An increase in HBV loads was observed between the 6th and 28th–32nd week of pregnancy among the infected with HBV, and then, a decrease was observed in the 6th months after the delivery.

Conclusions: The women infected with HBV without HBsAg (–) and the infected with HCV are subject to common incidence of premature births. Women infected with HCV often experience oedemas, hypertension, and pruritus.

Key words: HBV or HCV infection in pregnancy; childbirth

Ginekologia Polska 2021; 92, 1: 30–34

INTRODUCTION

The incidence of hepatitis B virus (HBV) infections in the pregnant women throughout Europe ranges from 1% to 7% [1]. Pregnant women are usually aware of the HBV infections; less often they learn about the infection upon examination performed during initial stages of the pregnancy. Neonates delivered by women infected with HBV become infected in less than 1% of cases in Europe [2]. The likelihood of a neonate becoming infected in a perinatal or postnatal way does not exceed 10% due to widely applied active and passive prophylaxis of children delivered by HBV-infected women [a vaccine and a hepatitis B immunoglobulin (HBIG) specific serum administered within 12 hours after the delivery] [3, 4]. It is possible for a child to become infected via an intrauterine way. Also, a child may become infected by an HBV-infected woman who has high HBV viraemia (> 200,000 IU/mL) or high surface antigen of the hepatitis B virus (HBsAg) concentration (> 4–4.5 Log_{10} IU/mL) [3]. The risk of such an infection regards most often the women with HBV viraemia above 6 Log_{10} IU/mL and *hepatitis B envelope antygen* (HBeAg*)* (+) presence. The likelihood of an infection with the virus increases proportionally to the viraemia increase [4, 5]. The devised guidelines present the ways of dealing with women infected with HBV that want to become pregnant (Tab. 1).

Antiviral drugs used in the pregnant infected with HBV decrease the risk of infecting the foetus, however, none of the currently used nucleoside/nucleotide analogues (NAs) are listed as category A according to Food and Drug Administration (FDA*)*, and thus, their use in pregnant women should be done cautiously. European [European Association for the Study of the Liver (EASL)] and American [American Association for the Study of Liver Diseases (AASLD)] guidelines allow for administering Tenofovir Disoproxil Fumarate (TDF) between the 24th and 32nd week of pregnancy

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Table 1. Guidelines regarding the ways of dealing with pregnant women infected with HBV [3, 6]

1st trimester of the pregnancy — a test for HBsAg presence is recommended; in case of HBsAg (+) — viraemia assessment
There is no indication to start the therapy for women without advanced fibrosis
Women with advanced fibrosis or cirrhosis — TDF therapy is recommended
The pregnant with high DNA HBV concentration (> 200,000 IU/mL) or HBsAg (> 4 $\log_{10}$ IU/mL) should received TDF in 24th–28th week of the pregnancy. It is recommended to discontinue the drug 12 weeks after the delivery
Pregnant women that are treated with NA should continue the TDF therapy; in case of ETV or another NA treatment, the drug should be changed to TDF
Breastfeeding is not contraindicated for women infected with HBV that are not and are treated with TDF

HBsAG — surface antigen of the hepatitis B virus; HBeAG — hepatitis B envelope antygen; TDF — Tenofovir Disoproxil Fumarate; HBV — hepatitis B virus; ETV — Entecavir; NA — Nucleoside/Nucleotide Analogues

in special cases. The drug is used in order to decrease the risk of infecting the foetus.

The probability of a newborn being infected by an hepatitis C virus (HCV)-infected mother ranges from 1.7% to 4.3%. It is the highest among the women that are infected with HCV/ Human immunodeficiency viruses (HIV) (19.4%) and among individuals that take intravenous intoxicants (and who are not HIV-infected; 8.6%) [7]. The risk of infecting a neonate and a negative influence on the clinical pregnancy course of patients infected with HCV were the basis for EASL and AASLD guidelines for antiviral treatment for all women at procreative age "in the first place" (especially the ones who wanted to become pregnant) [8]. Limited studies on DAA efficacy and adverse reactions among the HCV-infected patients indicate a decreased likelihood of infecting a neonate among the patients that take such antiviral drugs. Although these drugs have not been approved to be used in pregnant women yet, about 60% of women infected with HCV and pregnant declare that they are eager to use them in order to avoid infecting the child [9].

Despite specified procedures that concern dealing with the patients infected with HBV and HCV, observations regarding the influence of these viruses on the course of pregnancy are ambiguous.

Aim of the work

The aim of the work was to perform a clinical assessment of the pregnancy course among women infected with HBV or HCV. The following was determined: type of delivery, neonates' condition in the fifth minute after the delivery, weight at birth, and sex. All patients had their biological parameters of liver function monitored. The patients infected with HBV had viraemia monitored throughout the course of pregnancy and after the delivery. HCV-infected patients had the virus genotype and initial viraemia assessed.

MATERIAL AND METHODS

The study included 157 pregnant women infected with HBV aged from 21 to 42 (mean age: 29 y/o), and 53 pregnant women infected with HCV aged from 19 to 46 (mean age: 28 y/o). Three hundred and thirty healthy pregnant women aged from 18 to 40 (mean age: 28 y/o), who lived in the same region as the infected women, constituted a control group.

None of the women infected with HBV and HCV as well as from the control group was HIV-infected and none of them took intoxicants.

Qualification criteria for HBV-infected women included no HBeAg and exclusion of cirrhosis. None of the women infected with HBV had been qualified for the treatment earlier nor had been treated with antiviral drugs. The following was monitored among the HBV-infected women: viraemia, ALT activity, serum ALP within the first six weeks of pregnancy, between the 28th and 32nd week of pregnancy and six months after the delivery. In the group of the pregnant infected with HCV, viraemia and virus genotype were determined in the fifth week of pregnancy, whereas ALP and ALT activity was determined in the first six weeks of pregnancy, between 28th and 32nd week of pregnancy, and six months after the delivery.

Neonates had their clinical condition assessed in the fifth month of life by means of Apgar score.

All patients had serum HBsAg, HBeAg, anti-HBe, and anti-HCV antibodies assessed once by means of MEIA (microparticle enzyme immunoassay) and using Abbott tests (Germany).

HBV-DNA quantity was determined by RT-PCR using sets of COBAS AmpliPre/COBAS TagMan HBV Test, version 2.0 produced by ROCHE. The sensitivity amounted to 9 IU/mL, whereas linearity was 20 IU/mL.

Among women with positive anti-HCV, quantitative assessment and genotype were determined by RT-PCR method and using sets of COBAS HCV Test, version 2.0 produced by ROCHE (Germany).

The patients provided their informed consent to participate in the study according to the protocol accepted by the Bioethical Committee of Medical University in Bialystok (R-I-002/134/2019).

Statistical analysis of data was conducted by using STATISTICA.PL produced by StatSoft for Windows 10 operating system. The study used Mann-Whitney U test, Spearman's rho, student's t-test, and chi-squared test ($\chi 2$). The level of significance was set at $p < 0.05$.

RESULTS

Mean pregnancy duration in HBV- and HCV-infected as well as among the healthy patients was similar and amounted to 38–39 weeks. The frequency of spontaneous labour was comparable and amounted to 52% for HBV patients, 42% for HCV patients, and 58% in the control group.

Weight of children delivered by healthy women was higher as compared with children delivered by HBV- or HCV-infected females (3.517 vs 3.347 vs 3.366). In case of HBV-infected women, the weight was significantly lower as compared with the healthy women (Fig. 1).

Having assessed the Apgar score at the fifth minute of life, neonates of HBV- and HCV-infected women showed lower scores as compared with children born to healthy females (9.4 vs. 9.3 vs 9.7; $p < 0.05$), (Fig. 2).

Premature births occurred significantly more often in the HBV- and HCV-infected as compared with the control group (6.96% vs 14.6% and 24.5%; $p < 0.05$). In the group of HCV patients, miscarriages were significantly more common as compared with the healthy patients (9.4% vs 1.8%; $p < 0.05$). Among the HBV-patients, miscarriages were more frequent than in the control group, however, it was not statistically significant (Tab. 2).

Nausea was the most observed adverse reaction in all the pregnant women. HCV-patients significantly more often experienced pruritus (10.5% vs 4.2%; $p < 0.05$), oedemas (9.4% vs 2.4%; $p < 0.05$), and arterial hypertension (9.4% vs 1.5%; $p < 0.05$) as compared with the healthy patients (Tab. 3).

Among the HBV-patients, an increase in viraemia between the 6th and 28th–32nd week of pregnancy was confirmed in 46% of patients, a decrease in 15% of patients, and in 39% of cases there were no changes. In 90% of patients without detectable viraemia, in the sixth week of pregnancy, its increase was not confirmed between the 28th and 32nd week of pregnancy.

Among the HBV-patients, an increase in viraemia was observed between the 6th and 28th–32nd week of pregnancy.

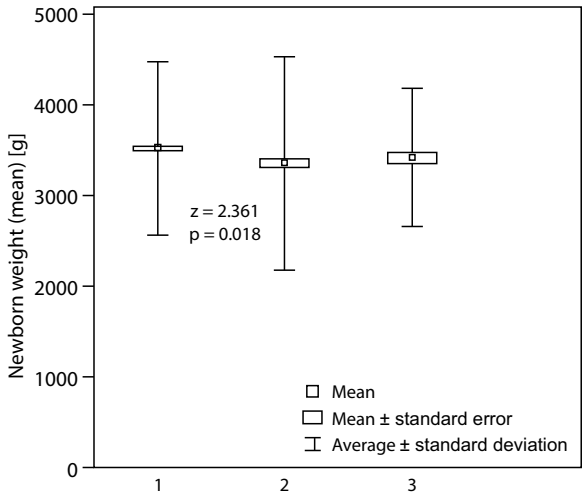

Figure 1. Neonatal weight (mean) among the examined patients and the control group; 1 — pregnant women healthy; 2 — pregnant women infected with hepatitis B virus (HBV); 3 — pregnant women infected with hepatitis C virus (HCV)

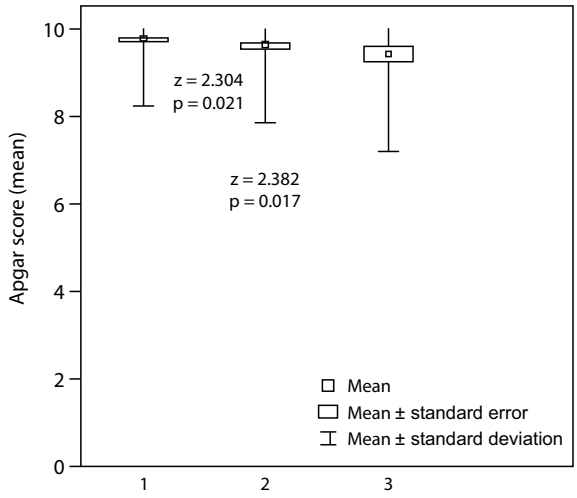

Figure 2. Neonatal scores (mean) on the APGAR scale (5 minutes) obtained in the examined groups of newborns; 1 — pregnant women healthy; 2 — pregnant women infected with hepatitis B virus (HBV); 3 — pregnant women infected with hepatitis C virus (HCV)

Table 2. Characteristics of pregnant women, pregnancy and basic data on newborns

	pregnant healthy	pregnant infected	
		HBV	HCV
n	330	157	53
Age, average in years (from ... to)	28; (18–41)	29; (21–42)	29; (20–46)
Date of delivery, week (from ... to)	39; (36–42)	38; (28–42)	38; (30–41)
Premature delivery, n (%)	23 (6.96%)[1,2]	20 (14.6%)[1]	13 (24.5%)[2]
Miscarriage	6 (1.8%)[1]	6 (3.8%)	5 (9.4%)[1]
Perinatal death	1	0	0
Childbirth through the ways of nature	194 (59%)	82 (52%)	22 (42%)
Child's sex ♀/♂	174/156; (53%/47%)	73/84; (46%/54%)	29/24; (55%/45%)
Birth weight of a child [g]	3517	3347	3366
Appgar scoring in 5 minutes	9.7	9.4	9.3

[1, 2] — statistically significant difference; HBV — hepatitis B virus; HCV — hepatitis C virus

Table 3. Symptoms that occurred in pregnant women during pregnancy

Symptoms	pregnant healthy	pregnant infected	
		HBV	HCV
n	330	157	53
Nausea, n (%)	20 (6.1%)	10 (6.4%)	2 (3.8%)
Edema, n (%)	8 (2.4%)*	8 (5.1%)	5 (9.4%)*
Hypertension, n (%)	5 (1.5%)*	6 (3.8%)	5 (9.4%)*
Diabetes, n (%)	4 (1.2%)	3 (1.9%)	2 (3.8%)
Urinary tract infection, n (%)	2 (0.6%)	6 (3.8%)	1 (1.9%)
Itchy skin, n (%)	14 (4.2%)*	11 (7.0%)	6 (10.5%)*
Anemia, n (%)	0	4 (2.5%)	0
HELLP syndrome, n (%)	0	0	1

* — statistically significant difference; HBV — hepatitis B virus; HCV — hepatitis C virus

The highest increase was confirmed among the pregnant with initial viraemia of HBV DNA ≤ 4 Log_{10} IU/mL in the 6th week of pregnancy.

In four HBV-patients, who experienced a miscarriage, HBV viraemia was at 4 Log_{10} IU/mL, whereas in two it was undetectable.

HCV infections were cased in 67% of patients by 1b genotype, in 20% — 3a, and in 13% — 4 genotype.

An influence of HCV RNA viraemia on possible clinical symptoms in the pregnant females was not observed.

In HBV- and HCV-patients, a mean ALT and ALP activity during the pregnancy did not change and remained within normal limits.

There were no cases of infecting a neonate both regarding HBV and HCV.

DISCUSSION

Patients with chronic HBV infections in Europe and the US are usually characterized by the lack of HBeAg. The situation is different in Asia, and it may exert a significant influence on the course of this infection among the pregnant.

HBV and HCV infections influence an increased activity of proinflammatory cytokines: IL-2, IL-6, IL-10, macrophage migration inhibitory factor (MIF), and TNF-α. In pregnant women they may cause an increase in the percentage of miscarriages, premature births, and a worse clinical condition of delivered neonates that is determined by the Apgar score [10]. Cui et al. [5] compared 513 pregnant women that suffered from chronic HBV infections with 20,491 pregnant women without this infection and showed a statistically more frequent occurrence of miscarriages in HBV patients that were pregnant. In the authors' studies, premature births were observed more often in HBV- and HCV patients. However, the frequency of miscarriages was statistically higher among HCV patients as compared with the healthy individuals.

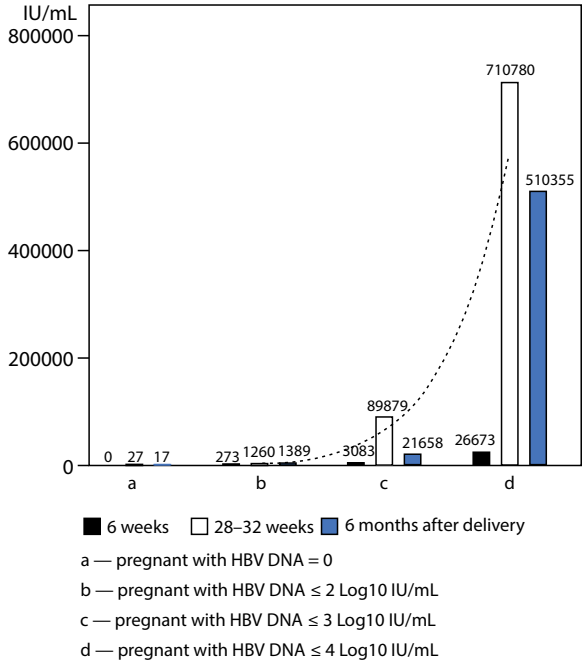

Figure 3. HBV load in serum at 6, 28–32 weeks of pregnancy and 6 months after delivery

Although miscarriages were often observed in HBV patients, there was no statistically significant difference as compared with the healthy females.

During pregnancy, high concentration of adrenal corticosteroids may influence the increase in HBV viraemia [11, 12]. In most pregnant women with HBV infections and absent HBeAg, viraemia is stable. However, in some patients an increase in HBV-DNA and ALT activity is observed during late pregnancy and in the postnatal period [13]. In the authors' studies, an increase in viraemia was observed at the turn of the 2nd and 3rd trimester, and then, a decrease was observed during the 6th month after the delivery. A significant increase with 2 Log_{10} was observed among the patients with HBV-DNA ≤ 4 Log_{10} IU/mL in the 6th week of pregnancy. In other pregnant females, a worrying increase in viraemia was not confirmed. Occasionally, during the perinatal period a significant HBV reactivation, and serious liver damage with encephalopathy and hepatic coma may occur [14]. Among such patients, an occurrence of disseminated intravascular coagulation (DIC), hepatorenal syndrome, brain oedema, and bile duct infections were observed. Interestingly, prophylactic administration of NA from the 2nd/3rd pregnancy trimester does not decrease the risk of liver failure, although it prevents a child from becoming infected [15]. Miscarriages were observed in six pregnant women infected with HBV. However, in none of them an HBV-DNA viraemia was confirmed to exceed 3 Log_{10} IU/mL.

Having assessed the incidence of adverse events, a more common occurrence of oedemas, hypertension and pruri-

tus was confirmed in HCV-patients as compared with the healthy ones. Dibba et al. [16] assessed the effects of HCV infections on the pregnant women and showed the role this infection played in occurrence of metabolic disorders of lipid and carbohydrate balance. It may have an influence on hepatic steatosis, appearance on insulin-resistant diabetes, and intensification of atherosclerotic processes. Seldom are clinical consequences of HCV infections regarding the course of pregnancy described. An influence of simultaneous HCV and HIV infections or patients addicted to intoxicants do not constitute a good comparative material. In the authors' studies, a frequent incidence of oedemas, hypertension, and pruritus was confirmed among the HCV patients. These observations are difficult to explain. A significant difference in the clinical course of the pregnancy between the healthy and HBV-infected women was not confirmed. Cai et al. [17] observed a more common incidence of cholestasis of pregnancy among the HBV-patients. Yet, their studies were conducted on a group of HBeAg (+) patients, what constitutes a significant difference as compared to the authors' studies.

None of the delivered babies was confirmed to have HBV or HCV infection, as well as congenital defects.

CONCLUSIONS

Pregnant women infected with HBV without HBsAg, and HCV-infected females are subject to frequent premature deliveries. An increase in viraemia during the pregnancy with its consequent decrease after the delivery is observed in the pregnant with HBV and without HBeAg. HBV infections do not exert an influence on the clinical pregnancy course, whereas HCV infections may lead to oedemas, arterial hypertension, and pruritus during the pregnancy course.

Conflict of Interest

The authors declare that there is no conflict of interest.

All authors have met the criteria for authorship and have participated sufficiently in the work to take responsibility for it.

The manuscript has been submitted with the full knowledge and approval of the institutions given as the affiliation of the authors.

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Determinants and coverage of seasonal influenza vaccination among women of childbearing age in Poland

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ABSTRACT

Objectives: Vaccination is the most effective method of controlling influenza in the human population, where pregnant women belong to a risk group that is especially vulnerable to influenza-related morbidity and mortality. The objectives of the survey were to report estimates of maternal vaccination coverage and assess reasons for the lack of influenza vaccination among Polish women of childbearing age.

Material and methods: The survey analysis included 564 pregnant women who had been surveyed in a self-reported questionnaire during the 2017–2018 influenza season in Warsaw, Poland.

Results: Over 95% of Polish women of childbearing age did not vaccinate against influenza due to the low perception of risk and a lack of providing evidence-based information on vaccine by physicians and midwives. General practitioners were most often indicated as healthcare workers who educated women about influenza risk factors and recommended influenza vaccine to them.

Conclusions: The results of the survey suggest that women of childbearing age did not vaccinate against influenza due to the low perception of risk and a lack of providing evidence-based information by healthcare workers (including obstetrician-gynaecologists and midwives), while their recommendations appear to be a powerful method of overcoming barriers to influenza vaccination among patients.

Key words: influenza; vaccine; women; pregnancy; coverage

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INTRODUCTION

Due to low influenza vaccination coverage (IVC), influenza constitutes one of the major health problems worldwide. While the main factor of low ICV in low and middle income countries is poverty, in high income countries it is related to poor knowledge of influenza complications and protective impact of vaccination for population health, along with high activity of anti-vaccination movements, resulting in the increase of vaccine hesitancy and refusals [1]. The influenza vaccine is one of the most important vaccines recommended in communicable disease prevention. This particularly concerns pregnant women, who are more prone to severe influenza, which is associated with hospitalization or death, increased risk of preterm births and low birth weight as well as an increased risk of hospitalization or death in the first six months of infant life [2, 3]. The World Health Organization (WHO) have classified pregnant women as the group of highest priority for seasonal influenza vaccination programs since 2012 [4]. Pregnancy might be an opportunity for healthcare providers (HCPs) to advocate for appropriate vaccination due to consistent contact with pregnant patients [5].

Objectives

The objectives of the analysis were to estimate maternal IVC and assess reasons for non-vaccination against influenza among Polish women of childbearing age.

MATERIAL AND METHODS

Setting and population

The survey was carried out in the 2nd Department of Obstetrics and Gynaecology, Medical University of Warsaw (MUW), a tertiary unit within the Polish National Health Insurance System. In 2017, the Department was one of 8 tertiary Obstetrics and Gynaecology units in Masovian voivodeship, providing public healthcare to the population of approximately 1 186 000 women of childbearing age (19–49 years) [6].

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Survey design

An original questionnaire was designed to establish main factors behind women of childbearing age getting vaccinated or not against influenza in the 2016–2017 (pre-pregnancy) and 2017–2018 (pregnancy) influenza seasons. The survey was anonymous and distributed during the 2017––2018 season. The responses were kept in secure data storage. Self-reported data included age, birth rate, noncommunicable diseases, gestational diabetes and vaccination status.

Inclusion criteria and recruitment

Women that were pregnant 9 weeks or more were eligible for inclusion. Information about the survey was distributed by obstetric providers among patients of the 2nd Department of Obstetrics and Gynaecology, MUW. Verbal invitation to participate in the study was issued by the obstetric providers, including the authors, within the context of a routine clinical care

Ethical approval

Ethical approval of the survey was granted by the MUW Ethics Committee (AKBE/160/17). Participants were provided a patient information form with the presentation of the aims of the study. It was emphasized that participation was voluntary and would have no implications for the antenatal care of the patients. The decision to participate or not was left to the patients in the absence of the authors of the survey.

Statistical analyses

Statistical analyses were performed using the statistical program Statistica 13. Quantitative variables had been checked for their data distribution before the analysis. The statistically significant results were at the $p < 0.05$. The Mann-Whitney's U-test and Pearson chi-square analysis were used to analyse the results. While assessing participants' knowledge, the answers "definitely yes" and "rather yes" were found to be correct, except questions about contraindications to vaccination, in which "definitely no" and "rather no" were correct answers.

RESULTS

Pregnant patients were asked about their opinions and practices related to influenza illness and vaccination.

The questionnaire was completed by 564 eligible women. Over 54% of participants were aged between 31––40 years (Fig. 1). Most patients declared having a higher education degree (64.9%) (Fig. 2). Similar percentage of women declared it was their first or second pregnancy (38.1% vs 36.2% respectively) (Fig. 3). Pregnancies were planned in 85.1%. Complications of pregnancy were reported by 75.4%

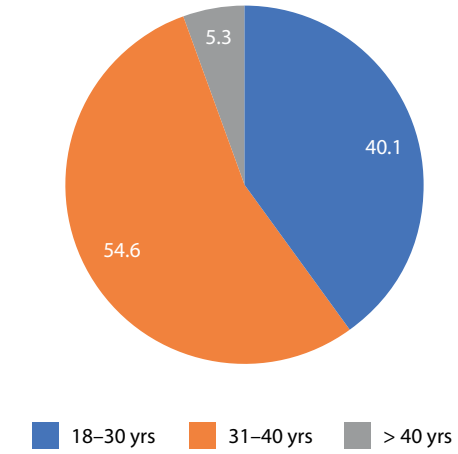

Figure 1. Percentage of participants by age (n = 564)

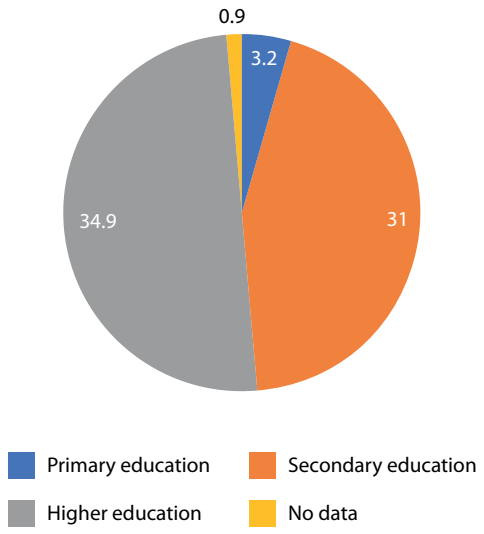

Figure 2. Percentage of participants by education level (n = 564)

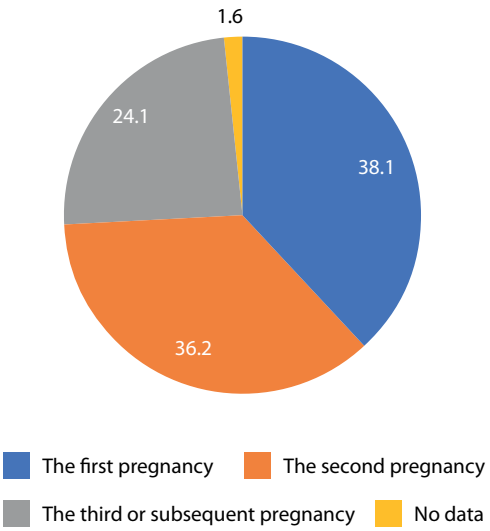

Figure 3. Percentage of women by the number of pregnancies (n = 564)

of patients, of which gestational diabetes was predominant (76.6%); whereas 17.7% women declared uncomplicated pregnancies, and no information about pregnancy status was indicated by 6.9% participants.

IVC declared in the 2016–2017 (pre-pregnancy) season was at the level of 2.8%, whereas 1.8% of participants did not remember their vaccination status in that season. Regular influenza vaccination was declared by the same percentage of women (2.8%). Occasional vaccination was declared by 16.9%. Only 3.5% of pregnant patients declared their willingness to be vaccinated against influenza in the upcoming 2017–2018 season, while 68.0% of them were strongly opposed to it, and 28.5% were hesitant. There was no statistically significant difference between women with uncomplicated and complicated pregnancies in the approach to influenza vaccination (p = 0.8340).

The analysis of patients' knowledge of influenza illness and vaccination showed that a low percentage of women of childbearing age had sufficient information on influenza risk factors and complications or influenza vaccines (Tab. 1, 2; Fig. 4). Only 0.5% of all women answered all questions correctly (Fig. 4).

To evaluate responses by age and education level, the participants were regrouped, as the number of women aged over 40 and those with the primary education were small (they were combined with women aged 31–40 and those with the secondary education, respectively).

A detailed analysis of data showed statistically significant differences in answers to 11 questions on the knowledge of influenza risk factors and vaccination in pregnant women with regard to their education level (p = 0.0059) (Tab. 3; Fig. 5); however, no differences were found with regard to the age of patients (Tab. 4).

Over 60% of participants reported the Internet as the main source of information on influenza and influenza vaccination, followed by general practitioners (GPs), media other than the Internet, family and friends as other sources of information (Fig. 6, 7). A detailed analysis by age and education level showed statistically significant differences in sources of information on influenza illness (Fig. 8, 9) and vaccination (Fig. 10, 11).

Table 1. Knowledge of the risk factors related to severe and complicated influenza among women of childbearing age (correct answer in bold type)

Question	Answer (%, N)				
	Definitely yes	Rather yes	I don't know	Rather no	Definitely no
1. Do you think that pregnancy and postpartum period are risk factors for severe and complicated flu? (n = 557)	**5.9% (33)**	**28.4% (158)**	32.0% (178)	29.3% (163)	4.5% (25)
2. Do you think that chronic pulmonary diseases are risk factors for severe and complicated flu? (n = 557)	**7.9% (44)**	**50.6% (282)**	22.4% (125)	17.2% (96)	1.8% (10)
3. Do you think that metabolic diseases, including diabetes, are risk factors for severe and complicated flu? (n = 557)	**4.9% (27)**	**21.3% (119)**	30.7% (171)	36.3% (202)	6.8% (38)
4. Do you think that overweight and obesity are risk factors for severe and complicated flu? (n = 557)	**3.8% (21)**	**18.7% (104)**	27.3% (152)	41.6% (232)	8.6% (48)
5. Do you think that the flu is a dangerous disease with the risk of complications for pregnant women and postpartum women? (n = 560)	**15.5% (87)**	**55.5% (311)**	18.4% (103)	7.9% (44)	2.7% (15)
6. Do you think that the flu is a dangerous disease with the risk of complications for the fetus and the newborn? (n = 560)	**18.0% (101)**	**55.5% (311)**	17.7% (99)	8.0% (45)	0.7% (4)

Table 2. Knowledge about influenza vaccination among women of childbearing age (correct answer in bold type)

Question	Answer {%, (N)}				
	Definitely yes	Rather yes	I don't know	Rather no	Definitely no
7. Do you think that flu vaccination is safe for pregnant women and postpartum women? (n = 561)	**1.4% (8)**	**9.4% (53)**	51.2% (287)	30.5% (171)	7.5% (42)
8. Do you think that flu vaccination is effective for pregnant women and postpartum women? (n = 560)	**1.1% (6)**	**12.0% (64)**	65.2% (348)	17.0% (91)	4.7% (25)
9. Do you think that flu vaccination is necessary for pregnant women and postpartum women? (n = 560)	**1.4% (8)**	**10.9% (61)**	56.1% (314)	24.6% (138)	7.0% (39)
10. Do you think that pregnancy and postpartum period are contraindications for flu vaccination? (n = 559)	7.3% (41)	28.1% (157)	47.9% (268)	**13.8% (77)**	**2.9% (16)**
11. Do you think that lactation is contraindication for flu vaccination? (n = 557)	5.4% (30)	23.3% (130)	52.2% (291)	**16.5% (92)**	**2.5% (14)**

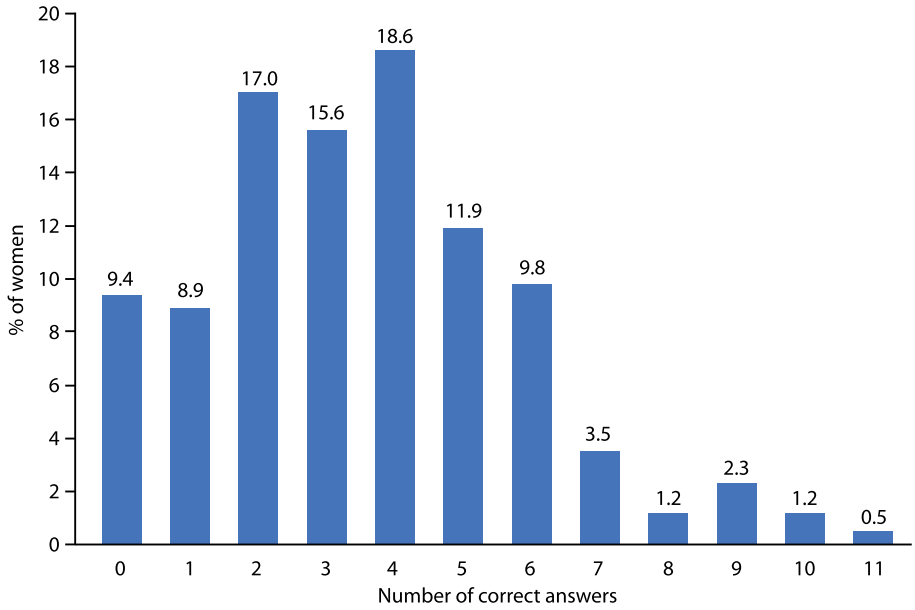

Figure 4. Percentage of answers given by women of childbearing age that were correct with regard to influenza risk factors and vaccination

Table 3. Correct answers to questions about influenza risk factors and vaccination with regard to education level

Correct answers	Education level						p value*
	Primary and secondary education		Higher education		Total		
	N	M (min–max)	N	M (min-max)	N	M (min–max)	
Number	194	3.00 (0.00–11.00)	365	4.00 (0.00–11.00)	559	3.00 (0.00–11.00)	0.0059
%	194	27.27 (0.00–100.00)	365	36.36 (0.00–100.00)	559	27.27 (0.00–100.00)	0.0059

M — median; *U Mann-Whitney test

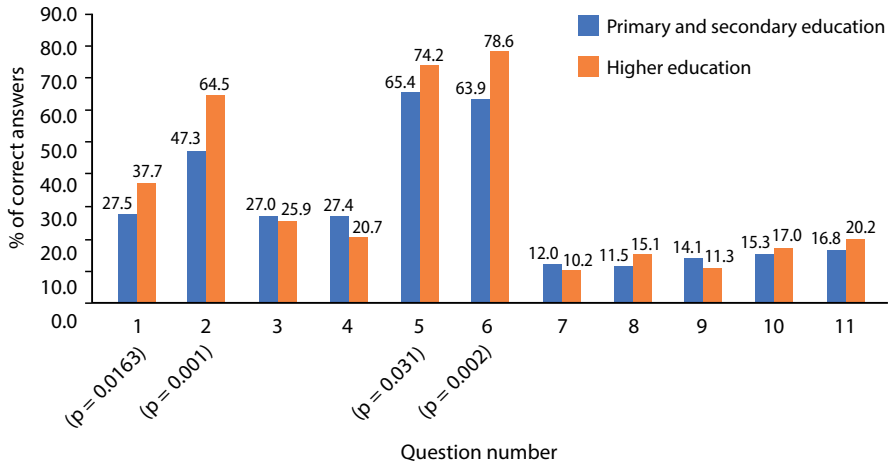

Figure 5. Percentage of correct answers to questions about influenza risk factors and vaccination with regard to education level

Table 4. Correct answers to questions on knowledge of influenza risk factors and vaccination with regard to age (n = 559)

Correct answers	Age						p value*
	18–30 years		> 30 years		Total		
	N	M (min–max)	N	M (min–max)	N	M (min–max)	
Number	225	4.00 (0.00–11.00)	338	3.00 (0.00–11.00)	559	3.00 (0.00–11.00)	0.5179
%	225	36.36 (0.00–100.00)	338	27.27 (0.00–100.00)	559	27.27 (0.00–100.00)	0.5179

M — median; *U Mann-Whitney test

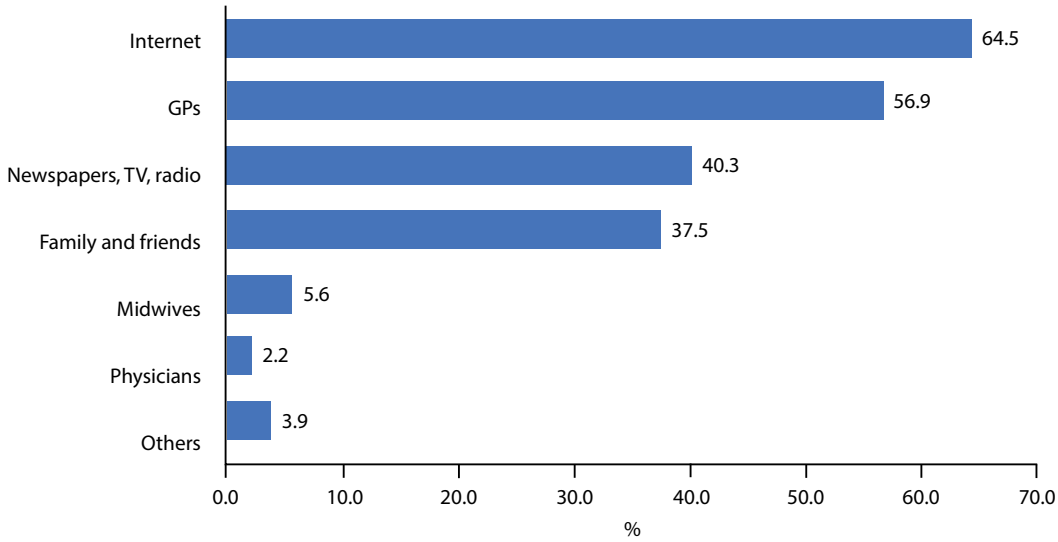

Figure 6. Sources of information on influenza illness (multiple-choice question) (n = 555)

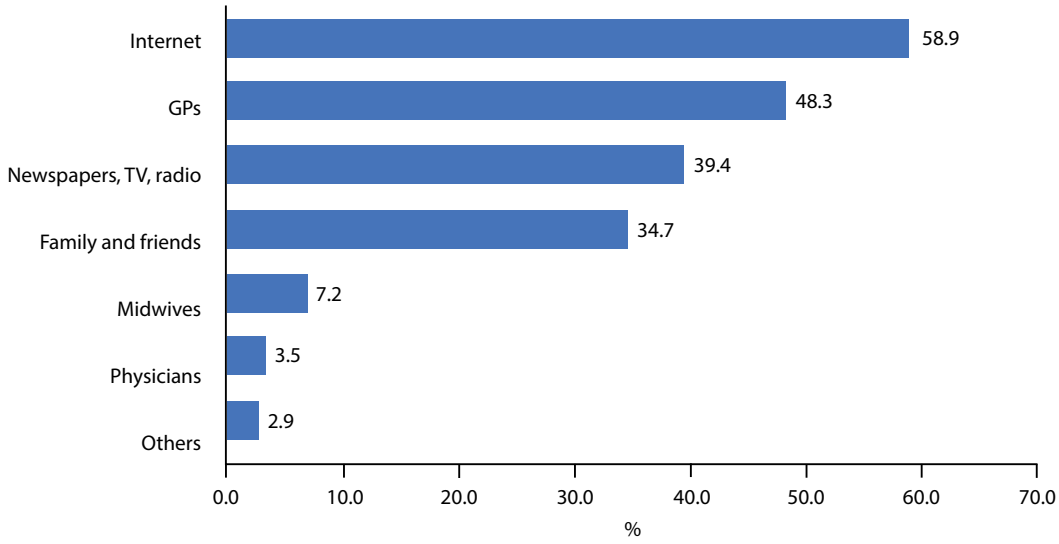

Figure 7. Sources of information on influenza vaccination (multiple-choice question) (n = 545)

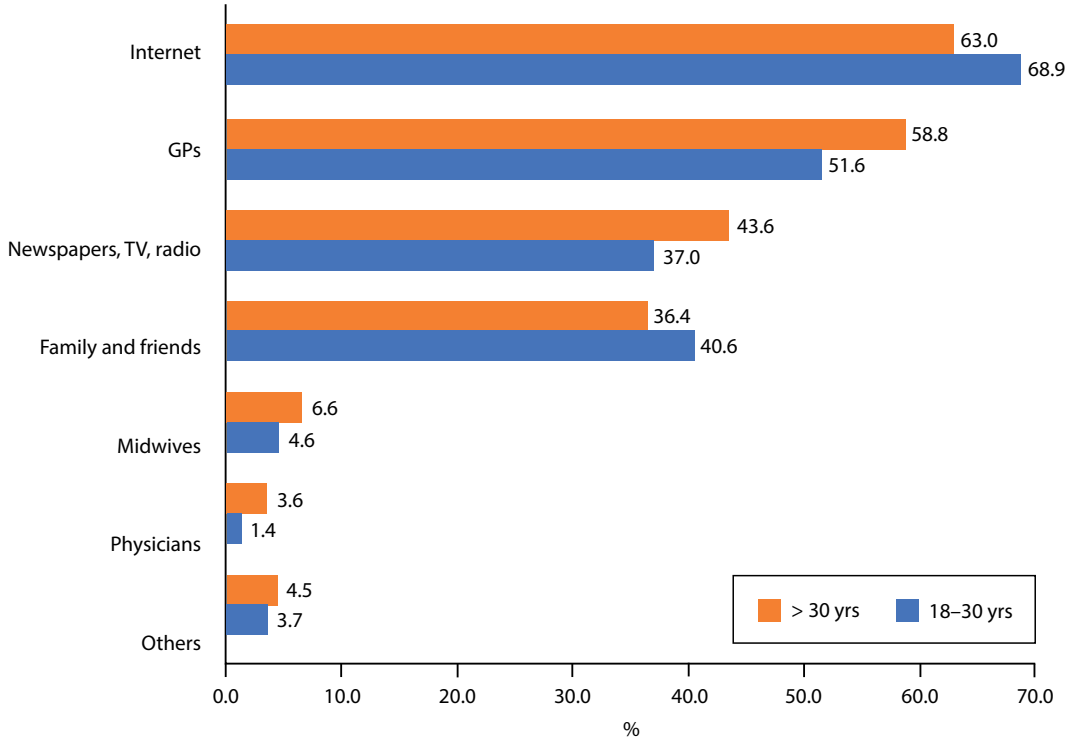

Figure 8. Sources of information on influenza illness by age group (multiple-choice question) (n = 554)

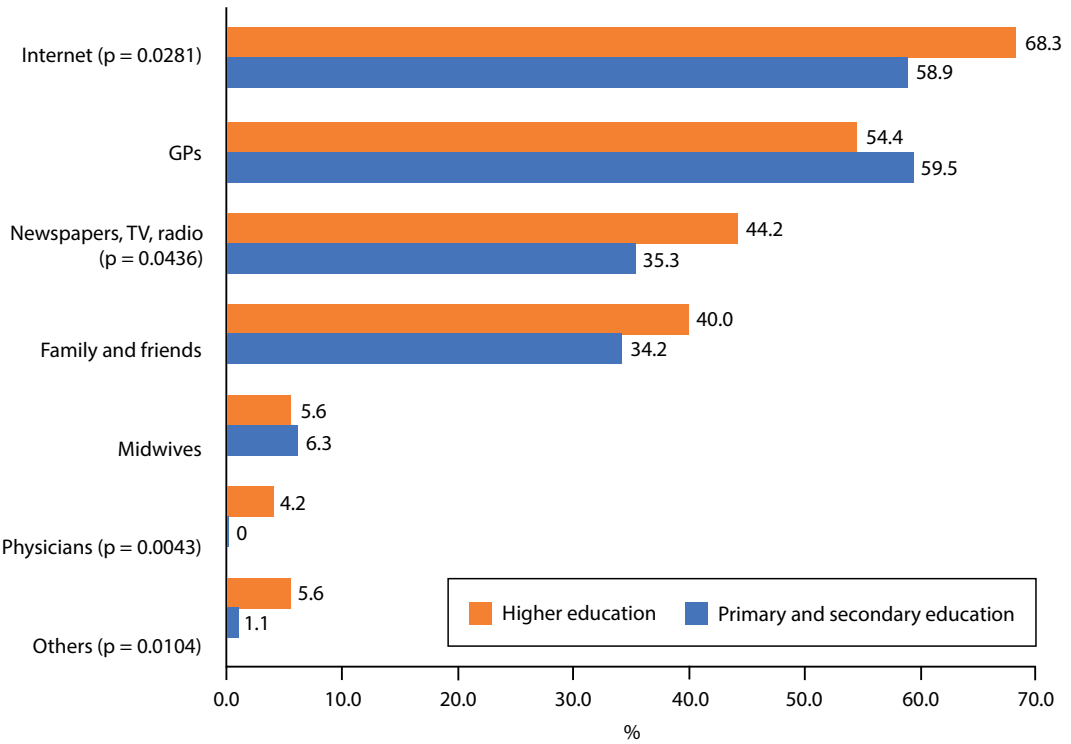

Figure 9. Sources of information on influenza illness by education group (multiple-choice question) (n = 550)

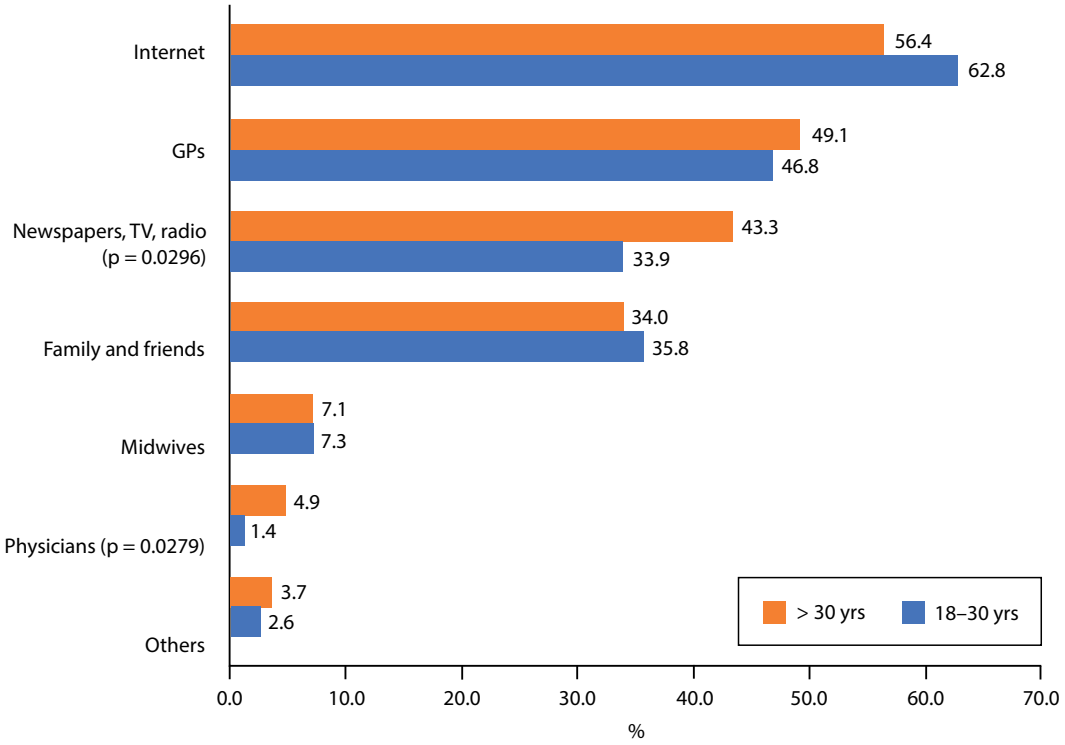

Figure 10. Sources of information on influenza vaccination by age group (multiple-choice question) (n = 544)

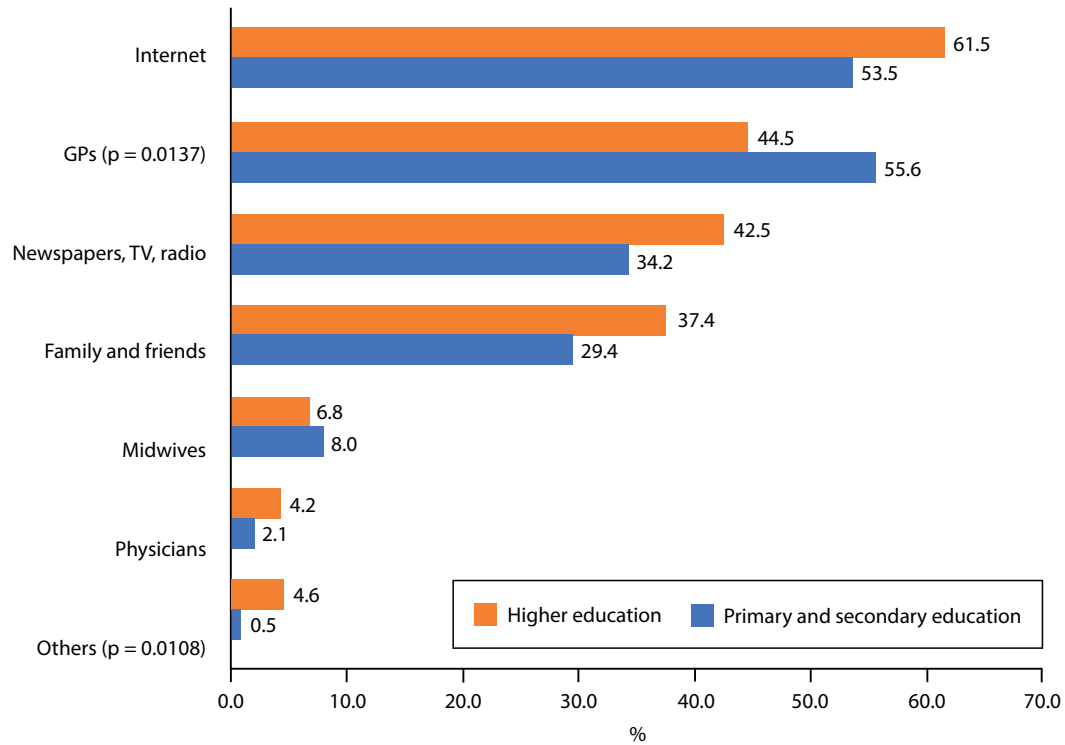

Figure 11. Sources of information on influenza vaccination by education group (multiple-choice question) (n = 540)

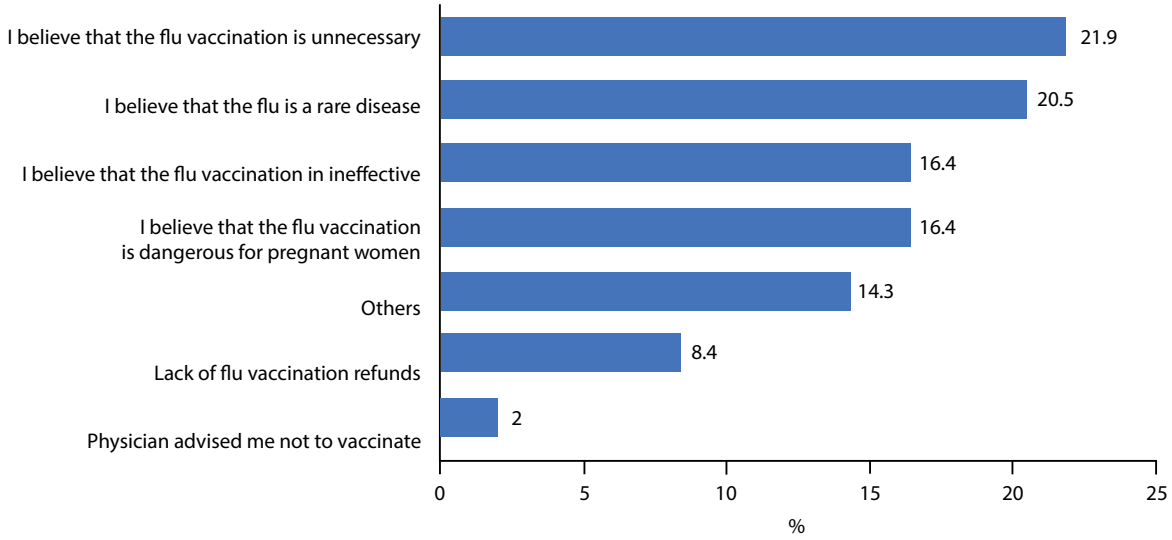

Figure 12. Reasons for vaccine refusal among pregnant women (n = 432)

Main reasons for refusing influenza vaccination were negative attitude towards vaccination (conviction that it is unnecessary, ineffective or dangerous for pregnant women), a belief that influenza was a rare disease and lack of vaccination refund (Fig. 12).

DISCUSSION

In the study, self-reported IVC rates were estimated and potential determinants of influenza vaccination uptake were examined (including sociodemographic factors, obstetric characteristics, maternal health beliefs and sources of information on influenza illness and vaccination) in the group of women of childbearing age in a single obstetric care centre in Warsaw, the capital of Poland.

Self-reported IVC in the survey was ca. 3%. A similar percentage of participants declared their willingness to get vaccinated against influenza during pregnancy in the upcoming influenza season; however, almost 70% of participants were strongly opposed to the vaccination. For many years, IVC in Poland has been very low and remained below 4% [7, 8]. IVC among the survey participants was comparable to the general population and much lower than that reported in other countries. In comparison to our survey, self-reported IVC rates among pregnant women in the previous and subsequent influenza seasons in other countries were as follows: 50–78% in the USA [9–13], ca. 50% in Australia [14], 45% in Belgium [15], 11–23% in Germany [16], less than 10% in France and Singapore [17, 18]. Regular influenza vaccination in previous years increased the probability of influenza immunization during pregnancy as much as 4 times [9] or at least it provided a similar level of IVC [12, 19], which has also been observed in our study: 3.5% of pregnant participants wanted to vaccinate in the upcoming 2017–2018 season, as compared with the observed 2.8% IVC in the 2016–2017 season.

Polish women of childbearing age had insufficient knowledge of influenza risk factors and vaccination, which has been identified as patient barriers to vaccination of the same importance as negative vaccination history, general mistrust towards the medical establishment, lack of established relationship with obstetrician-gynaecologists (OB/GYNs) as vaccine providers and no access to medical care [12]. Less than 5% of pregnant participants to the study gave correct answers to 8 or more out of 11 questions about influenza risk factors and vaccination; over 50% of patients provided less than 4 correct answers. Knowledge of influenza vaccination was poorer than that of the influenza risk factors. These results were worse than those observed by Kuchar E. et al. [7] for the general Polish population in 2018 and those obtained in the unvaccinated US pregnant female population [20]. Women with a higher level of education had a statistically significant better knowledge of risk factors, in particular, and according to some authors, higher level of education had a significant influence on the maternal IVC [15, 20, 21]. The majority of the surveyed women searched for the information on influenza illness and vaccination on the Internet (64.5% and 58.9% respectively), with a statistically significant difference with regard to the level of education: patients with higher education chose the Internet as the source of information on influenza illness and vaccination (68.3%), and they used TV, radio and newspapers as a source of information on influenza illness (44.2%) and vaccination (43.3%). A systematic review of the Internet use among pregnant women revealed that the Internet was recognized in many countries to be a reliable and useful source of information about pregnancy and birth: up to 75% of

childbearing women used it to deal with pregnancy-related doubts and decisions, whereby better educated women were three times more likely to seek advice online than those less educated [22]. Unfortunately, up to 70% of women did not discuss the information found online with their HCPs [20], which is why "HCPs may not be aware of potentially inaccurate information or mistaken beliefs about pregnancy, reported on the Internet", as Sayakhat et al. [22] aptly put it.

Influenza vaccination in pregnancy was included into the Polish National Immunisation Programme in 2014 as it was first recommended by the WHO in 2012 [4, 23]. The Programme is conducted by GPs in children and adults. This provides explanation why GPs were the second major source of information on influenza illness and vaccination (56.9% and 48.3% respectively) and why they were a statistically significant, more common source of information on influenza vaccination for the better educated participants ($p = 0.0137$). An exceptionally low percentage of pregnant women indicated midwives (< 10%) or physicians (< 5%) as the sources of information. A prospective observational hospital-based study performed in France in the 2014–2015 season on a group of 2045 pregnant women showed a similar percentage of vaccine recommendations by GPs (57.3%), but a significantly higher percentage of recommendations by midwives (40.1 to 54.3%) or physicians (48.1%). GPs administered 67.6% of vaccines among pregnant women in Belgium [15]. In our study, only 2 pregnant women indicated OB/GYNs as information providers. Almost 10% of Spanish pregnant women vaccinated against influenza recalled being informed about influenza vaccine by their GPs, whereas almost 90% declared midwives to be the source of information [19]. Bartolo et al. [24] reported that 50.7% of French OB/GYNs recommended influenza vaccine in the 2014–2015 season, which was similar to the data obtained in French reports since 2010 (56%) [17]. According to King JP et al. [20], in the 2016–2017 season ca. 80% of vaccinated or unvaccinated US pregnant women indicated that their obstetric providers (OB/GYNs and midwives) frequently recommended influenza vaccination. Over 90% of those women reported being recommended influenza vaccine by at least one HCP and none of them reported being advised against vaccination by their HCPs, while in our survey it was reported that 2% of Polish physicians advised their patients not to vaccinate during pregnancy. Gaps in HCPs' knowledge about influenza vaccine contributed to low IVC of patients, whereas lack of providing vaccination to pregnant women by the OB/GYNs resulted from the conviction that the influenza vaccine should be administered by GPs [12]. Vishram et al. [25] proved that HCPs were more likely to recommend influenza vaccination in pregnancy if they had been vaccinated as patients or healthcare workers. The observed IVC rates in the Polish HCPs ranged from 10% to 20% [26, 27], which may result in providing insufficient recommendations for influenza vaccination to pregnant women. Personal recommendation of HCPs to get vaccinated against influenza during pregnancy increased the odds ratio of accepting the vaccine from 1.45 to 7 times [9, 12, 18]. Pregnant women appeared highly motivated to improve their health in order to protect their children [12, 20]. If they were offered vaccination by HCPs, they were also more likely to have a positive attitude towards vaccine efficacy and safety [12, 21]. Statically, 50% of French mothers and 78% of Kenyan women reported their willingness to get vaccinated during their next pregnancy to protect their children or prevent a disease [17, 28].

It is worth noticing that good communication between HCPs and women of childbearing age, along with influenza vaccine recommendations, increased the IVC rates by 80% even among patients with a negative attitude towards influenza vaccination [12]. This is particularly crucial for the populations with extremely low IVC, such as Polish women of childbearing age. Over 95% of pregnant participants to the study did not get vaccinated in the 2016–2017 and 2017––2018 seasons. Between 15–22% of them believed vaccination was unnecessary, ineffective or dangerous for pregnant women and that influenza was a rare disease, which might be related to the observed ignorance of influenza risk factors and vaccination. Similar reasons for refusing vaccination were found in women in other countries. A comparable percentage of unvaccinated Spanish pregnant women underestimated the personal risk of contracting influenza (23%) or considered the vaccination as non-essential (16%) [19]. Up to 30% of US respondents who reported having received no influenza vaccine were concerned about vaccine effectiveness, and the risk of the mother or baby getting influenza after the vaccination [12, 20]. It should be stressed that during the pandemic of AH1N1pdm09 influenza, no harm to the fetus was found in the population of over 31,000 children exposed to influenza vaccine while in utero [29]. According to a retrospective observational matched-cohort study performed from 2004–2005 to 2008–2009 seasons on a group of over 57 000 women, maternal vaccination was not associated with an increased or decreased risk of preterm or small for gestational age birth [30]. Murthy NC et al. [13] observed that almost 65% of pregnant women did not know medical recommendations for seasonal influenza vaccination at the time of the study, and that IVC was higher among women who indicated correct maternal influenza vaccination recommendations (63.4%), as compared to those who did not know the correct recommendations (39.7%). The US study data also suggested that vaccination offers combined with HCP's recommendations were more likely to result in vaccination being performed than the vaccination recommendations alone; increasing IVC from 14.8% to 70.5% [11, 13],

whereby the IVC was limited by the cost of vaccine. Over 8% of Polish women of childbearing age indicated the lack of influenza vaccination refund as a reason for refusing influenza vaccination in pregnancy. If the vaccination cost was covered by the health insurance, IVC could be 2.3 times higher [18], therefore high IVC rates are observed in the countries where both the vaccine itself and vaccine administration are covered by the health insurance [8].

CONCLUSIONS

The results of our survey indicate that women of childbearing age did not vaccinate against influenza due to the low perception of risk and a lack of providing evidence-based information by HCPs (GPs, OB/GYNs and midwives). These findings highlight the need to improve the performance of influenza vaccination promotion activities among pregnant patients by HCPs, as their recommendations appear to be a powerful method of overcoming barriers to influenza vaccination among patients.

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Limitations

There are several limitations to our findings. Results are subject to reporting bias, since data were self-reported and not verified by review of medical records, including immunization information. Selection bias can result from pregnant women with higher prevalence of gestational diabetes or other complications being included into the study. Therefore, although influenza vaccine is recommended for all pregnant women, it is especially recommended for those with gestational diabetes, so IVC in population of pregnant women without complications might be even lower than the observed 2.8%.

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Conflict of interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Metformin administration during pregnancy — current insight

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ABSTRACT

The main mechanism of gestational diabetes mellitus (GDM) is insulin resistance, therefore using metformin as a medicine reducing insulin resistance appears to be promising.

Currently, the majority of medical associations do not recommend using metformin during pregnancy as the first-line of therapy when the diet regimen is insufficient for glycaemic control. However, they do allow its administration if there is no possibility of insulin treatment.

There is some evidence which suggests that using metformin during pregnancy is not related to an increased risk of obstetric complications during delivery and that its influence on the foetus can be beneficial.

Since metformin crosses the placenta, the major argument for cautious use of this drug are the potential long-term effects of the treatment for the child and its development in later life.

In this article, the authors attempt to discuss the use of metformin during pregnancy and the safety of the treatment in the light of current studies and recommendations.

Key words: metformin; pregnancy; diabetes mellitus; GDM

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INTRODUCTION

The main cause of gestational diabetes mellitus (GDM) is increasing insulin resistance caused by a rise in the level of gestational hormones (progesterone, leptin, placental lactogen, cortisol) which are insulin antagonists. In some women there is no sufficient increase in insulin secretion (impaired first phase secretion) by the pancreas and hyperglycaemia may develop. The main factor determining insulinemia and the insulin tissue sensitivity in pregnant and non-pregnant patients is the body mass index (BMI). The higher the body weight, the lower the insulin sensitivity index. Also, the genetic (familiar diabetes occurrence; HLA DR 2, 3,4 mutation) and environmental factors (obesity, lack of exercise, excessive food intake) appear to be significant [1].

Metformin has been present in the treatment of diabetes for over sixty years but its potential application and therapeutic effects are not yet fully known. The initial evidence regarding the use of metformin in pregnant women came from 1975 reports of Aberdeen International Colloquia on sulphonylureas, biguanides and insulin in pregnancy. In developing countries, due to its low cost, metformin is commonly used now including during pregnancy.

Over the last sixty years, the importance of metformin in medicine has been evolving.

THE MECHANISM OF ACTION OF METFORMIN

The main effect of metformin therapy is a reduction of insulin-resistance by lowering the conversion of glycogen to glucose in the liver and enhancement of peripheral insulin sensitivity, especially in the muscles. Metformin also restricts intestinal absorption of glucose and regulates lipolysis and lipogenesis processes in the fatty tissue by lowering the levels of free fatty acids. Due to the suppressing mechanism of mTOR signalization and the mechanism related to enhancing the activity of tyrosine kinase (AMPK), metformin lowers the levels of glucose, insulin and inflammatory proteins in the blood, lowers the blood pressure and rate of metabolism, as well as suppresses angiogenesis and cell multiplication.

In 2017, Romero at al. postulated a potential preventive effect of metformin in preeclampsia. Romero's research suggests that the potentially by better the placental blood flow the lower the risk of preeclampsia [2, 3].

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The main adverse effects of metformin include nausea, vomiting, abdominal pain and other gastrointestinal disorders. Metformin does not cause hypoglycaemia or weight gain [3].

Unfortunately, metformin crosses the placenta and its cord blood concentration is the same or even twice higher than that in the maternal blood. This gives rise to doubts concerning its use in everyday treatment during pregnancy [4].

EFFECTIVENESS AND ACCEPTANCE OF METFORMIN USE IN PREGNANCY

Metformin therapy seems to be attractive especially for the patients who wish to avoid insulin injections. Oral therapy is both simpler and more comfortable. A vast majority of pregnant women (about 77%) treated with metformin stated that they would like the same treatment during their next pregnancy while only 28% of patients treated with insulin prefer it to metformin [5].

It should be stressed that there is no evidence of any spectacular medical effect during metformin therapy. In addition, in over 40% of pregnant women metformin therapy is insufficient for appropriate everyday glycaemic control and the inclusion of insulin is necessary, especially in patients with a higher BMI at early stages of pregnancy (34 kg/m^2 vs 31 kg/m^2) and higher early blood glucose levels (6.1 mmol/L vs 5.3 mmol/L) [23]. Women diagnosed with GDM earlier, with higher BMI in early pregnancy and higher baseline glucose levels are more likely to require insulin and may be considered less suitable for oral medication [5].

Metformin is known for increasing the risk of lactic acidosis. In fact, concerns regarding the effects of another biguanide — phenformin — caused metformin to be withdrawn from the treatment of pregnant patients in many countries [6].

METFORMIN IN WOMEN WITH POLYCYSTIC OVARY SYNDROME (PCOS), INSULIN RESISTANCE AND DIABETES MELLITUS TYPE 2 DURING PREGNANCY

Nowadays, there seems to be a new epidemic not only of overweight and obesity, but also insulin resistance which may lead to a growing glucose intolerance and the resulting menstrual disorders and problems with becoming pregnant. As for the continuation of metformin therapy in women suffering from PCOS, insulin resistance, glucose intolerance or even diabetes type 2 who are at the beginning of pregnancy, there is still a limited number of studies regarding such patients. According to the ADA's 2016 recommendation metformin should be discontinued in those patients as soon as pregnancy is confirmed [6].

It should be also noted that hyperglycemia in early pregnancy, including women who suddenly discontinue metformin therapy, is teratogenic. Therefore, immediate insulin treatment should be introduced to ensure glycemia control. Moreover, metformin does not prevent GDM in women with PCOS [8].

Metformin therapy during pregnancy in women with pre-gestational diabetes mellitus type 2 is not well documented. It is likely that most women with type 2 diabetes before pregnancy will require treatment with insulin during their gestation to maintain glycaemic control.

In a retrospective study Hellmuth et al. [9] reported the use of metformin in 50 women, 19 of whom had type 2 diabetes. An increase in pre-eclampsia and perinatal mortality was noted.

In the group of pregnant women with diabetes mellitus type 2 or insulin-resistance present prior to pregnancy requiring greater insulin doses to ensure adequate glycemia control, the use of metformin as an insulin-saving therapy should be considered as potentially beneficial, although the issue warrants further research [5].

In the cohort from New Zealand, no increase in adverse pregnancy outcomes were observed in patients with type 2 diabetes mellitus [10].

Possibly, the safety of this therapy will be further determined pending the results of an ongoing randomized trial involving metformin treatment in diabetes type 2 during pregnancy [11].

METFORMIN AND THE FIRST TRIMESTER CONCERNS

There is no evidence of any potential teratogenic influence of the metformin resulting from its use during pregnancy [12].

The meta-analysis of studies in which 351 pregnant women with PCOS used metformin both before and during early pregnancy does not show an increased risk of serious congenital foetal defects [13].

In addition, there are some studies which confirm its higher efficacy in ovulation elicitation than clomiphene, which may prove significant given PCOS related fertility problems [14].

The observational study included 1250 women divided into two groups: metformin vs placebo. In the metformin group there were fewer lost pregnancies (8.8% vs 4.2%), fewer miscarriages (26% vs 62%), fewer cases of GDM (4% vs 26%), lower birth weight and lower incidence of pregnancy induced hypertension (PIH) [15].

METFORMIN AND OBSTETRIC RISK

There is some evidence that using metformin during pregnancy is unrelated with an increased risk of obstetric labour complications and that its influence on the foetus can be beneficial.

In 2008, in a randomized clinical trial entitled *Metformin in Gestational Diabetes* (MiG) the authors postulated the following conclusions: among pregnant women treated with metformin there were fewer large for gestational age (LGA) infants, fewer cases of severe (< 1.6 mmol/L) infant hypoglycaemia (reduction by about 60%), the time spent in the intensive care unit was significantly shorter. In addition, metformin was linked to a reduction in women's weight gain during the whole observation period (0.4 ± 2.9 kg vs 2.0 ± 3.3 kg; p < 0.001). It is particularly noteworthy since lower weight gain during pregnancy is an independent factor reducing LGA incidence. The occurrence of preterm deliveries in this group was greater (12.1% vs 7.6%, p = 0.04) which was, however, not statistically significant [16].

A comparative study involving 1832 women with GDM who used either metformin or insulin revealed a lower weight gain in mothers and fewer LGA infants in the metformin group patients. At the same time, insulin was linked to a significantly higher risk of hypoglycaemia and PIH in mothers. There were no differences in maternal glycaemic control or obstetric outcomes [15].

Prospective and retrospective studies on a group of 857 pregnant women, where the effects of oral anti-diabetic agents (metformin, glibenclamide, acarbose, glyburide) and insulin were compared, revealed a higher rate of preeclampsia and perinatal infant deaths in the metformin group. In the oral anti-diabetic agents group, lower maternal weight gain and fewer cases of infant hypoglycaemia were observed. In the insulin group, there were more preterm deliveries and infants requiring observation at the intensive care unit (ICU). There were no differences in maternal glycaemic control or labour complications [15].

In the Farrar et al. [17] meta-analysis, two groups were analysed: the first one included patients treated with metformin and insulin added when necessary, while the other one was comprised of women treated only with insulin. The potential risk of LGA, macrosomia, admission to ICU and hypoglycaemia in infants as well as PIH, preeclampsia and labour induction was lower in the metformin group. Instrumental birth and preterm birth were more frequent in the insulin group. Gestational age on delivery, birth weight and Apgar results did not differ between the groups.

METFORMIN AND LONG-TERM EFFECTS ON CHILDREN

After a 2-year observation of the infants born from mothers who took part in the 2008 MIG study, a follow-up project called *Metformin in gestational diabetes: the offspring follow-up* (MIG TOFU) was conducted. It showed that in the metformin group children had more subcutaneous fatty tissue but there was no difference in the amount of central fatty tissue, blood pressure or any other tested parameter in comparison to the children from the insulin group [18, 19].

In a follow-up study on the group of 7- to 9-year-old children of mothers involved in the MIG trial, the Adelaide Clinic subgroup (average age 7) showed no difference in body weight or structure (metformin vs insulin). By contrast, in the Auckland subgroup comprised of children whose average age was 9, the metformin patients showed higher body mass, waist-hip ratio (WHR), arm and hip circumference [20].

In the other study, children whose mothers had taken metformin during pregnancy were heavier at 12 months of age and both heavier and taller at 18 months (12.0 vs 11.3 kg). It should be underlined that only 96 children of mothers who suffered GDM were observed (31 treated with metformin only, 14 treated with metformin connected with insulin and 14 treated with insulin only) [21].

A systematic review and meta-analysis of Follow- up Studies of RCT's concerning long- term effects of oral antidiabetic drugs during pregnancy included 10 studies, with a maximal follow-up duration of 9 years, comprising 778 children of mothers with GDM or PCOS who were randomised to either metformin or insulin/placebo during pregnancy. Meta-analysis showed that children prenatally exposed to metformin were heavier compared to controls (standardised mean difference = 0.26, 95% CI 0.11–0.41), but not taller (SMD = 0.10, 95% CI 0.14–0.33). Additionally, offspring body mass index (BMI) z scores did not differ according to metformin exposure (mean difference = 0.30, 95% CI 0.01–0.61). Individual small studies reported that prenatal exposure to metformin was associated with greater mid-upper arm, head and waist circumferences, biceps skinfolds, waist-to-height ratio, more arm fat, higher fasting glucose, ferritin and lower LDL cholesterol in offspring [22].

The latest 5–10 — year follow-up on children from the PregMet study, a double-blind, randomised controlled trial comparing metformin with placebo in PCOS pregnancies, examines the cardiometabolic risk factors in these children. Of the 255 invited children from the PregMet study, 141 (55%) consented to participate. Maternal baseline characteristics in the first trimester were similar between the groups. Children in the metformin group had a higher BMI than those in the placebo group (mean difference = 0.41, 95% CI 0.03–0.78, p = 0.03). According to the authors an increased BMI in the metformin-exposed children might indicate a potential risk of inferior cardiometabolic health. Implications for adult health cannot be excluded [23].

Contrary to these facts, Butalia et al. [24] showed lower maternal weight gain, fewer LGA infants, fewer cases of pregnancy induced hypertension or events of intensive care unit infant hospitalization in the metformin group compared to the insulin alone group. There weres no difference in the incidence of preterm deliveries between the two groups. The

psychomotor development in children of mothers with GDM at 2 years of age showed no difference compared to the other group.

In Wouldes et al. study comparing the influence of metformin and insulin on child development, the neurodevelopmental outcomes at 2 years of age were similar between the children born from mothers who were treated with metformin compared to those treated with insulin for GDM. Lower score on the standardized measures of neurodevelopment were predominantly associated with parental self-identified ethnicity, smoking in the household and clinical outcomes at birth unrelated to the treatment [25].

In New Zealand, one of the latest cohort studies into the effects of metformin vs insulin treatment of GDM which included 211 children followed up at 2 years, 128 were from Auckland, New Zealand (64 metformin vs 64 insulin), and 83 from Adelaide, Australia (39 metformin vs 49 insulin). No differences in the weight, height and psychomotor development of the children was noted [26].

THE MEDICAL ASSOCIATIONS RECOMMENDATIONS

The American Food and Drug Administration (FDA) places metformin in category B of safety which means that animal reproduction studies did not demonstrate any risk to the foetus, however there are no corresponding well-documented studies on pregnant women [5].

According to the World Health Organisation (WHO) recommendation, metformin is acceptable but only as a second-line pharmacotherapy choice, after insulin. WHO currently recommends the use of metformin and glibenclamide in the resource limited areas where insulin administration involves logistic issues [27].

International Diabetes Federation (IDF) [2009] guidelines recommend the use of metformin in resource limited areas in patients who are least likely to comply with insulin. Metformin use is not recommended as the first-line of therapy when the diet is not efficient for glycaemic control before the 20 weeks of gestation and fasting glycemia exceeds 110 mg/dL or postprandial glycemia exceeds 140 mg/dL [28].

Both American College of Obstetricians and Gynecologists (ACOG) and American Diabetes Association (ADA) recommend insulin as the first-line medicine in gestational diabetes mellitus treatment when the diet regime is insufficient for glycaemic control. Metformin remains the second-line treatment [29].

Only the British National Institute for Health and Care Excellence (NICE) recommends metformin as a first-line therapy in women whose blood glucose levels do not stabilize after 1–2 weeks of diet and exercise regime. Insulin is recommended only in cases where metformin is contraindicated or unacceptable to the patient. At the same time, these recommendations indicate that the summary of product characteristics of metformin states that it should not be administered during pregnancy [30]. In the cases of prescribing metformin to treat GDM, the doctor is obliged to inform the pregnant women that the long-term effect of metformin on health or metabolism of the offspring during adulthood is still not known.

Conversely, the Society for Maternal-Fetal Medicine (SMFM) states that both insulin and metformin are safe and acceptable as the first-line treatment in GDM [31].

However, in 2018, Barbour LA et al. [32] published a cautionary response to the SMFM statement concerning pharmacological treatment of gestational diabetes. Even though the data on the short-term effects on mothers and foetuses appears to be promising, the potential long-term effects of metformin therapy — both beneficial and harmful — are still unknown. The authors emphasize the potential intrauterine programming and epigenetic aspects of the therapy. Metformin can suppress cell growth and mitochondrial respiration because in the later stages of pregnancy, when the number of mitochondrial transporters rises, metformin penetration into the mitochondria increases. In animal model research it has been demonstrated that metformin has negative effects on body weight and metabolism, which was pointed out in the 2018 publication.

International Federation of Gynaecology and Obstetrics (FIGO) recommends that insulin should be a first-line treatment also in developing countries in cases where one or more of the following occurs: diabetes mellitus is diagnosed before 20 weeks of gestation, diet regime is insufficient for glycaemic control during the period preceding 30 weeks of gestation, fasting blood glucose level exceeds 110 mg/dL, postprandial blood glucose exceeds 140 mg/dL and body weight gain is over 12 kg [33].

Both Polish Diabetological Association and Polish Society of Gynaecologists and Obstetricians do not recommend any oral anti-diabetic agents (including metformin) in GDM treatment as these substances cross the placenta and there is no research on their long-term effects on the offspring. In women who use metformin it is recommended to begin insulin therapy as soon as pregnancy is confirmed [34, 35].

CONCLUSIONS

Metformin during pregnancy can be an alternative to insulin only when the patient refuses the therapy with insulin and it is obligatory to inform her about its potential negative influence on the foetus and later on the child.

There is no evidence of an increased risk of miscarriage or congenital foetal anomalies when using metformin.

Metformin reduces the maternal weight gain during pregnancy and the incidence of severe hypoglycaemia in infants.

The major argument for cautious metformin administration are the still unknown or uncertain long-term effects of the treatment during pregnancy.

At present, the vast majority of medical associations does not recommend metformin during pregnancy as the first-line of therapy when the diet regimen is insufficient for glycaemic control and restrict its use to those cases in which there is no possibility of insulin treatment.

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Prenatal diagnosis of glutaric acidemia type 2 with the use of exome sequencing — an up-to-date review and new case report

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ABSTRACT

Introduction: Inborn errors of metabolism (IEM) also called metabolic diseases constitute a large and heterogenous group of disorders characterized by a failure of essential cellular functions. Antenatal manifestation of IEM is absent or nonspecific, which makes prenatal diagnosis challenging. Glutaric acidemia type 2 (GA2) is a rare metabolic disease clinically manifested in three different ways: neonatal-onset with congenital anomalies, neonatal-onset without congenital anomalies and late-onset. Neonatal forms are usually lethal. Congenital anomalies present on prenatal ultrasound as large, hyperechoic or cystic kidneys with reduced amniotic fluid volume.

Material and methods: We present a systematic literature review describing prenatal diagnosis of GA2 and a new prenatal case.

Results: Ten prenatally diagnosed cases of GA2 have been published to date, mainly based on biochemical methods. New case of GA2 was diagnosed using exome sequencing method.

Discussion: All prenatal cases from literature review had positive history of GA2 running in the family. In our study trio exome sequencing was performed in case of fetal hyperechoic kidneys without a history of GA2. Consequently, we were able to identify two novel pathogenic variants of the *ETFDH* gene and to indicate their parental origin.

Summary: Exome sequencing approach used in case of fetal hyperechoic kidneys allows to identify pathogenic variants without earlier knowledge of the precise genetic background of the disease. Hyperechoic, enlarged kidneys could be one of the clinical features of metabolic diseases. After exclusion of chromosomal abnormalities, urinary tract obstruction and intrauterine infections, glutaric acidemia type 2 and number of monogenic disorders should be consider.

Key words: inborn errors of metabolism; glutaric acidemia type 2; multiple acyl-coenzyme A dehydrogenase deficiency; fetal abnormalities; prenatal diagnosis; exome sequencing

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INTRODUCTION

Inborn errors of metabolism — overview

Inborn errors of metabolism (IEM) also called metabolic diseases constitute a large and heterogenous group of disorders characterized by a failure of essential cellular functions. In the vast majority of IEM single gene mutation causes production of defective enzyme and in consequence disruption of cellular metabolic pathways leading to a deficiency of vital metabolites, deficiency of energy or accumulation of toxic substrates [1]. However, depending on the type of the mutation and its position along the gene residual enzyme activity in affected fetus is possible [2, 3]. Moreover, during pregnancy gas exchange, nutrients supply and metabolic waste elimination occur mainly due to maternal metabolism [4]. For these reasons many of IEM are asymptomatic in the fetus. Clinical features of IEM like vomiting, impaired multiorgan function, encephalopathy, hypoglycemia, hyperammonemia or acidemia starts days, weeks, months or even years after birth and are often life-threatening. However, in some of IEM severe metabolic disorder disrupt fetal

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development and congenital anomalies occur. Antenatal manifestation of IEM is nonspecific and include nonimmune hydrops fetalis, intrauterine growth restriction, central nervous system anomalies, heart defects, hyperechoic kidneys or skeletal anomalies what makes prenatal diagnosis of IEM challenging [5].

Glutaric acidemia type 2 — basic facts

One of the IEM associated with fetal anomalies is glutaric acidemia type 2 (GA2; OMIM #231680). GA2 is a rare metabolic disease with a birth prevalence estimated at 1:250.000 [6]. Disease causing Multiple acyl-coenzyme A Dehydrogenase Deficiency (MADD) is clinically manifested in three different ways: neonatal-onset with congenital anomalies, neonatal-onset without congenital anomalies and late-onset. Both neonatal forms are usually lethal due to metabolic acidosis, hypoglycemia and multiorgan failure while late-onset form is highly variable and severe clinical deterioration or sudden death may occur at any age even without previous symptoms [3, 7]. In cases with prenatal manifestation congenital anomalies present on ultrasound as large, hyperechoic or cystic kidneys with reduced amniotic fluid volume [8]. Prenatal diagnosis of GA2 can be established based on dehydrogenase activity measurements, organic acids profile, acylcarnitine profile or genetic testing [9]. Pathogenic variants can be identified in one of the three genes (*ETFA, ETFB, ETFDH*) inherited in an autosomal recessive manner [10–12]. Differential diagnosis in cases with prenatally detected anomalies includes trisomy 13 or 18, autosomal recessive polycystic kidney disease (ARPKD), renal cysts and diabetes syndrome, nephronophthisis, Joubert syndrome, Bardet-Biedl syndrome, Meckel-Gruber syndrome, oral-facial-digital syndrome type 1 and other rare monogenic disorders, cytomegalovirus intrauterine infection or urinary tract obstruction with kidney dysplasia [13]. Herein we present a systematic literature review of all prenatally detected cases of GA2. We also report on a first prenatal diagnosis of GA2 established by exome sequencing (ES) as an example of a diagnostic pathway from nonspecific sonographic features to exact genetic diagnosis.

MATERIALS AND METHODS

Search strategy

The authors performed a systematic literature review for any study reporting prenatal diagnosis of GA2 published between first description of the disease in 1976 until December 2019. Review was conducted using Pubmed/MEDLINE and Web of Science databases. The search strategy with following formula was applied: (glutaric aciduria OR glutaric acidemia OR madd) AND (prenatal OR antenatal OR fetus OR fetal). There was no language restriction placed on the manuscript search. Additionally, the references of

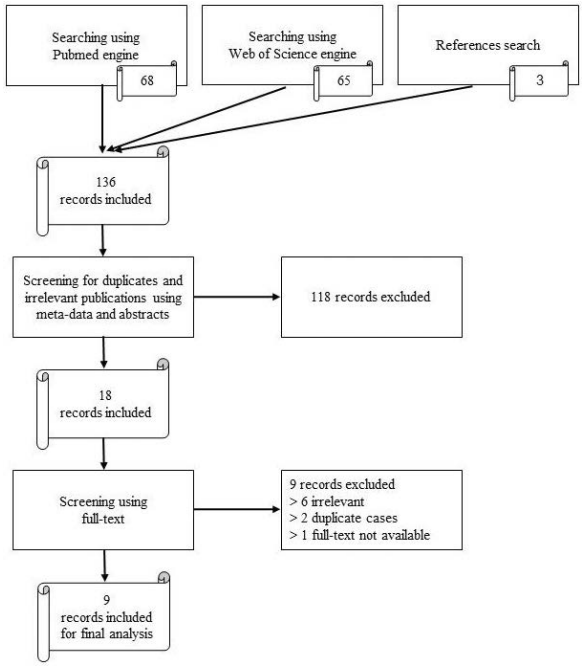

Figure 1. Flowchart for literature review

all selected manuscripts were screened for subsequent reports. Papers available in full text in which authors described methods used for prenatal diagnosis of GA2 in ongoing pregnancy not in stored material and in which diagnosis was positive were included. Papers not containing prenatal cases of GA2 or containing cases with negative diagnosis true or false were excluded. The systematic review flowchart and search strategy are summarized in Figure 1.

New case report

Clinical presentation

A 35-year-old patient presented in our ultrasound department for a detailed anomaly scan at 20 weeks of her third gestation due to history of complications in a previous pregnancies. Her first pregnancy ended in early miscarriage. Her second pregnancy was complicated by fetal anomalies — enlarged cystic kidneys, oligohydramnios and large cavum septi pellucidi (CSP). A full-term newborn delivered via cesarean section due to transverse presentation died 2 hours after birth. Prenatal karyotype was normal, and the patient was informed that a potential cause of fetal malformations was an autosomal recessive polycystic kidney disease (ARPKD) caused by *PKHD1* gene mutation. However, an autopsy was not performed, and only a buccal swab was taken from the newborn for molecular tests. Sequencing for the most frequent pathogenic variants in exons 32 and 36 of *PKHD1* gene gave negative result and ARPKD could not be confirmed nor excluded. The initial ultrasound scan at 20 weeks of patient's third pregnancy evaluated in our ultra-

sound department revealed large CSP, enlarged hyperechoic kidneys and normal amount of the amniotic fluid (Fig. 2A). After a detailed ultrasound scanning, fetal urinary tract obstruction was excluded. Routine screening tests for rubella, toxoplasmosis, cytomegalovirus, hepatitis-B, hepatitis-C, HIV and syphilis were negative. After genetic counsel, due to positive history and current fetal anomalies, the patient decided to continue the pregnancy aware of high risk of fetal or neonatal death. Amniocentesis was performed for cytogenetic and molecular tests as described in next sections. During the third trimester amniotic fluid volume decreased leading to a Potter sequence (flattened nose, retrognathia, low-set abnormal ears, pulmonary hypoplasia, club feet caused by small amount of amniotic fluid surrounding the fetus). The child was liveborn at 37 weeks of pregnancy via cesarean section due to breach presentation and died after 2 hours from metabolic and multiorgan failure. In the postmortem examination both kidneys were enlarged. In cross section no cyst has been found during the macroscopic examination (Fig. 2B). The lungs appeared hypoplastic. The liver seemed to be enlarged, but no pathologic findings on cross section were stated. No abnormalities were found in the heart, central nervous system, bile and pancreatic ducts. On microscopic examination both kidneys contained many round, simple cysts, which were lined by cuboidal or flattened epithelium. In the medulla they were surrounded by loose mature mesenchymal tissue (Fig. 2C–D). The liver presented features of adiposis and preserved extramedullary hematopoiesis. Some fibrosis around portal and central spaces of the lobe were detected.

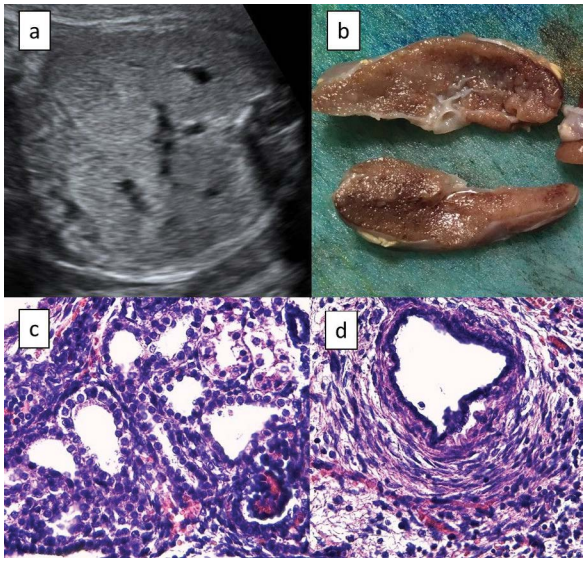

Figure 2. Kidneys in glutaric aciduria type 2; **A.** Ultrasound imaging at 24 weeks of gestation showing large hyperechoic kidneys; **B.** Cross section in postmortem examination of 37 weeks newborn — enlarged kidneys without macroscopic cysts; **C.** Microscopic examination with hematoxylin and eosin staining and magnification 400× — cortical cysts of the kidney; **D.** Microscopic examination with hematoxylin and eosin staining and magnification 400× — medullary cyst of the kidney

Cytogenetic testing

Fetal DNA isolated initially from uncultured amniotic fluid and then from cultured amniocytes was obtained. Array comparative hybridization (aCGH) was performed on DNA from uncultured amniotic fluid using CytoSure Constitutional v3 (8 × 60 k) array (Oxford Gene Technology). Karyotype was performed on cultured amniocytes. Karyotype and aCGH revealed normal results for both tests. Parental DNA was isolated from peripheral blood of each parent. Subsequently fetal DNA from cultured amniocytes and parental DNA were sent to the external laboratory for sequencing (CeGaT GmbH, Tübingen, Germany).

Exome sequencing

ES was performed simultaneously for the fetus, mother and father (trio). SureSelect Human All Exon enrichment kit v.6 (Agilent) was used for library preparation and capture. All laboratory preparations were done according to the manufacturers' protocols. The final products were sequenced on NovaSeq6000 (Illumina) with 100-bp paired-end reads generating raw sequence data stored in FASTQ format. Raw data were post-processed on site using the bcbio-nextgen pipeline [14]. DNA short reads were mapped against human genome reference sequence (GRCh38/hg38) using Burrows-Wheeler Alignment (BWA) and stored as binary Sequence Alignment Map (BAM) [15]. BAM files analysis using Genome Analysis Toolkit (GATK) and variant calling using GATKHaplotype Caller were performed [16, 17]. Next, ANNOVAR was used to annotate relevant information about gene names, predicted variant pathogenicity, reference allele frequencies and metadata from external resources and to add these data to the Variant Call Format (VCF) file [18]. Finally, we used HMZDelFinder algorithm to search for small deletions which were not detected by aCGH [19]. As a control we were able to use exome data from approximately 300 samples sequenced at the same platform and processed using the same pipeline. ES analysis revealed novel pathogenic variants on both alleles of *ETFDH* gene consistent with a diagnosis of GA2. Nonsense variant NM_001281738:c[1191C > A] was of maternal origin and frameshift variant NM_001281738:c[1560A>-] was of paternal origin (Fig. 3). Prenatal ultrasound, prenatal genetic tests and post-mortem examination support the diagnosis of GA2.

RESULTS

The literature search for prenatal glutaric acidemia yielded a total of 136 publications. Based on metadata and abstracts screening for duplicates and irrelevant publica-

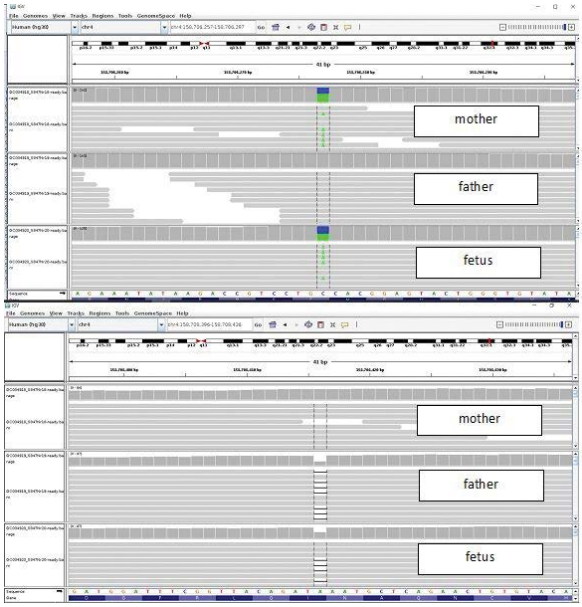

Figure 3. Exome sequencing of trio: nonsense pathogenic variant NM_001281738:c[1191C > A] of *ETFDH* gene in mother and fetus (upper image), frameshift pathogenic variant NM_001281738:c[1560A>-] of *ETFDH* gene in father and fetus (lower image). Fetus is compound heterozygote of two pathogenic variants

tions were performed and excluded 118 items (*e.g.* glutaric acidemia type 1). Then, based on full-text analysis nine further publications were excluded for irrelevant content, duplicate cases or no full-text availability (*e.g.* diagnosis of GA2 in stored material, negative diagnosis of GA2). Nine records were included for final analysis. Eight publications reported a single case and one publication reported two cases. The available data on prenatal diagnosis of GA2 concerning ten cases from literature review and one new case are summarized in Table 1 [20–28].

DISCUSSION

Prenatal diagnosis of glutaric acidemia 2 — current state of knowledge and clinical implications

Despite the continuous development of knowledge and technology in the field of genetics and ultrasound diagnostics, a large proportion of cases are still underdiagnosed or undiagnosed. This happens also in the case of GA2. Although prenatal diagnosis of GA2 is possible, only 10 prenatally diagnosed cases have been reported in over 40 years after first description of the disease [29]. In the ma-

Table 1. Literature review

Ref.	Family history of previously diagnosed GA 2	Prenatal presentation	Material	Diagnostic method	Outcome
20.	positive	N/A	cultured amniotic cells	enzyme activity (RA)	TOP
			amniotic fluid	organic acids profile (GC/MS)	
21.	positive	N/A	cultured amniotic cells	enzyme activity (RA)	TOP
			amniotic fluid	organic acids profile (GC/MS)	
22.	positive	no renal defects in US raised serum AFP	amniotic fluid	organic acids profile (GC/MS)	TOP
23.	positive	N/A	cultured amniotic cells	enzyme activity (RA)	live born - died after 4 months
24.	positive	N/A	cultured amniotic cells	enzyme activity (RA)	TOP
			amniotic fluid	organic acids profile (GC/MS)	
25.	positive	no defects in US	cultured amniotic cells	enzyme structure (IMA)	live born - doing well at 6 months
26. case 1	positive	N/A	amniotic fluid	organic acids profile (LC/MS)	TOP
			amniotic fluid	acylcarnitine profile (FAB/MS)	
			maternal urine	acylcarnitine profile (FAB/MS)	
26. case 2	positive	N/A	amniotic fluid	acylcarnitine profile (FAB/MS)	live born - no other data
			maternal urine	acylcarnitine profile (FAB/MS)	
27.	positive	large, hyperechoic kidneys normal amniotic fluid	–	US	TOP
28.	positive	large, hyperechoic kidneys raised serum and amniotic AFP	amniotic fluid	acylcarnitine profile (MS/MS)	TOP
			cultured amniotic cells	enzyme activity (SIA)	
present study	negative	large, hyperechoic kidneys oligohydramnios	cultured amniotic cells	DNA analysis (ES)	live born - died after 2 hours

US — ultrasound examination; AFP — alpha-fetoprotein; RA - radioisotope assays; GC/MS — gas chromatography/mass spectrometry; IMA — immunochemical assays; LC/MS — liquid chromatography/mass spectrometry; FAB/MS — fast atom bombardment/ mass spectrometry; MS/MS — tandem mass spectrometry; SIA — stable isotope assays; ES — exome sequencing; TOP — termination of pregnancy; N/A — not available

jority of cases prenatal diagnosis relied on enzyme activity measurement in cultured amniotic cells and/or glutaric acid measurement in the amniotic fluid while in other cases it was based on acylcarnitine profile in maternal urine and/or amniotic fluid, enzyme structure analysis or on ultrasound examination [20–28]. Measurement of enzyme activity is time-consuming, troublesome and available in a limited number of laboratories [30]. On the other hand glutaric acid measurement in the amniotic fluid by gas or liquid chromatography/mass spectrometry (GC/MS or LC/MS) is fast and simple, but it is prone to false negative diagnosis if the fetus does not excrete large amount of glutaric acid [26, 31]. Both tests are frequently used simultaneously to minimize the risk of misdiagnosis. Furthermore, acylcarnitine profile in the maternal urine may be unreliable as both abnormal as well as normal values have been reported in affected fetuses [26, 32]. DNA sequencing targeted for known pathogenic variants of *ETFA, ETFB* and *ETFDH* genes has already been performed in fetuses at risk of GA2. It demonstrated its potential usefulness as a diagnostic tool by giving negative results in unaffected fetuses [7]. Molecular analysis has also an advantage in cases with severe oligohydramnios as DNA can be isolated from fetal blood or trophoblast tissue not only from amniotic fluid [33]. However, it should be emphasized that all these methods were useful in cases with a positive history of GA2 running in the family. In all cases, history of death or severe illness of the previous child due to confirmed GA2 pointed out targeted prenatal diagnosis in the next pregnancy [20, 21, 23–26]. In three cases prenatal manifestation was observed in previous pregnancies as enlarged hyperechoic or cystic kidneys and elevated serum alfa fetoprotein (AFP) level but they were diagnosed as GA2 in postmortem examinations. In these three cases renal anomalies reoccur in the next pregnancy leading to the exact diagnosis [22, 27, 28]. In our study trio analysis was performed as it significantly improves the diagnostic yield compared with proband-only testing [34]. Consequently, we were able to identify two novel pathogenic variants of the *ETFDH* gene and to indicate their parental origin. These results allow the establishment of correct diagnosis in the affected fetus and calculate genetic risk in the family which meets expectations among Polish women regarding prenatal diagnosis [35]. Moreover, identification of novel variants enriches existing databases of single nucleotide polymorphism.

SUMMARY

Inborn errors of metabolism are rare disorders with unspecific manifestation in prenatal settings. Hyperechoic, enlarged kidneys could be one of the clinical features of metabolic diseases. After exclusion of chromosomal abnormalities, urinary tract obstruction and intrauterine infections, glutaric acidemia type 2 and number of monogenic disorders should be considered. Exome sequencing approach allows to identify pathogenic variants even without earlier knowledge of the precise genetic background. This strategy could help in early diagnosis, optimal perinatal care and family planning for affected individuals.

Conflict of interest

All authors declare no conflict of interest.

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COVID-19 impact on perinatal care: risk factors, clinical manifestation and prophylaxis. Polish experts' opinion for December 2020

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ABSTRACT

Rapid spread of severe acute respiratory syndrome coranovirus-2 virus (SARS-CoV-2) caused the pandemic of Coronavirus Disease 19 (COVID-19). Clinical course of the disease presents symptoms mainly from the respiratory system such as: cough, dyspnea and fever, and among some patients, can deteriorate even further to acute respiratory distress syndrome (ARDS), eventually leading to death. This outbreak, as well as previous ones (SARS, MERS) pose a significant challenge for health care managers, epidemiologists and physicians. Below we are presenting the clinical profile of the COVID-19 among special group of patients; pregnant women and newborns, who require special clinical management during hospitalization. In the summary of this manuscript, we present practical guidelines for managing pregnant women infected with SARS-CoV-2, labor and care of the newborn of a positive mother, as well as practical guidelines for COVID-19 vaccinations. It is important to stress, that this manuscript is based on information available as of December 2020.

Key words: COVID-19 infection; Sars-CoV-2 virus; maternal and neonatal outcome; coronavirus disease

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INTRODUCTION

SARS-CoV-2 belongs to a group of spherical enveloped RNA viruses, the beta subtype of coronaviruses. As of 2019, six viruses of this group were known to cause infections in humans. Four of them (229E, OC43, NL63, HKU1) are known to cause a mild infection in people. The remaining two have shown to be the cause life-threatening acute respiratory distress syndrome (ARDS): SARS (severe acute respiratory syndrome) caused by SARS-CoV and MERS (Middle East respiratory syndrome) caused by MERS-CoV [1–3]. COVID-19 is a disease caused by the Wuhan coronavirus (SARS-CoV-2). The name COVID-19 developed by the World Health Organization (WHO) stands for "CO" — corona, "VI" — virus, "D" — disease, and the number 19 indicates the year the virus appeared — 2019 (Corona-Virus-Disease-2019) [3]. By December 31, 2020, there were 85 899 563 confirmed cases and 1 858 412 deaths due to COVID-19. The rapid spread of the virus along with a severe clinical course of disease in most hospitalized patients raises questions about the risks of COVID-19 on people with an increased risk of infection. Based on this information, it is necessary to establish special procedures that will be used for the prevention, diagnosis and treatment of COVID-19, especially for pregnant women during labor and newborns who present to the hospital with symptoms of infection.

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CLINICAL MANIFESTATION OF COVID-19 INFECTION IN PREGNANCY

The results based on 28 studies and 11,432 patients selected for the systematic review found that from 7–14% of pregnant women presenting or admitted to the hospital tested positive for COVID-19; 85% of them had infection identified in third trimester. Of these positive women 75% were asymptomatic, severe COVID-19 was diagnosed in 13% of pregnant women, 4% was admitted to Intensive Care Unit (ICU) and 3% required invasive mechanical ventilation. Pregnant women with COVID-19 manifested fewer symptoms than general population while the predominant features of symptomatic COVID-19 in pregnant women were cough (33%) and fever (29%). Compared to non-pregnant women with COVID-19 pregnant women were less likely to report fever (OR = 0.48 CI: 0.22–0.85) and myalgia (OR = 0.48 CI: 0.45–0.51) [1, 2].

Among pregnant women with COVID-19 infection leukopenia (66.1%) and lymphopenia (48.3%) were the most common laboratory abnormality (66.1%) with other common abnormalities like elevated: CRP, D-dimer, lactate dehydrogenase (LDH) and IL-6. Combination of elevated D-dimer and IL-6 was associated with more severe disease and found in 60% of severely ill and in 80% of critically ill pregnant women, respectively.

Unilateral or bilateral ground-glass opacities were the most common imaging findings. Observed mortality rates for pregnant women with COVID-19 were 0.1-2.0% what is comparable to general population, but pregnant women were more likely to require mechanical ventilation and admission to an ICU; (OR = 1.62 CI: 1.33–1.96) [1]. As much as 40% of pregnant women who died from COVID-19 had obesity, diabetes or maternal age over 40 years.

CORONAVIRUSES AND THE OCCURRENCE OF FETAL MALFORMATIONS

There is currently insufficient evidence that coronavirus infection has a negative impact on the incidence of fetal defects. This applies to the "common cold" coronaviruses as well as SARS, MERS and SARS-CoV-2. The frequency of malformations in the offspring of infected women does not differ from the population average. This is possibly related to the low risk of vertical viral transmission due to short period of viremia and poor ACE-2 expression in the placenta. In the case of SARS-CoV-2, the estimated frequency of infection by this route may be 2.6% according to the CDC report. However, the negative impact of fever, one of the most common symptoms of COVID-19, on the occurrence of fetal malformations should not be underestimated. Among single congenital defects, the most common were heart defects, cleft lip palate, defects of the genitourinary system and chromosomal disorders. The use of anti-fever medications in the first trimester of pregnancy is very important. Paracetamol should be used as the first-line drug, while avoiding non-steroidal anti-inflammatory drugs, the use of which during this period increases the risk of such defects as gastroschisis, hypophysis, anencephaly, cleft lip/palate and spina bifida [3–5]. However, it should be noted that there are still too few reported cases of confirmed COVID-19 in early pregnancy, which makes it impossible to draw final conclusions supported by evidence-based medicine criteria.

THE IMPACT OF COVID-19 INFECTION ON PREGNANCY OUTCOMES

Knowledge regarding impact of COVID-19 on perinatal outcomes is limited due to small study population, different testing methods ranging from universal SARS-CoV-2 testing for all pregnant women to symptom-based testing, high heterogeneity of study population and lack of long-term follow-up. Some studies showed higher incidence of preterm birth in COVID-19 positive patients, but the rate of preterm birth was increased in COVID-19 mothers regardless of the severity of the disease. It is important to stress that caesarean sections account for nearly all preterm deliveries, which suggests the iatrogenic origin of preterm delivery. The PRIORITY study found no increased risk of preterm birth in COVID positive mothers with exception to mothers who tested positive 0-14 day before delivery. Similarly, meta-analysis published by Allotey et al. [1], indicated that overall rate of spontaneous preterm birth was not elevated –and reached only six percent. Overall, it seems that spontaneous preterm labour is not increased compared to general population. There are some data, although limited, indicating that miscarriage and stillbirth rates are not increased in COVID-19 positive pregnant women [1]. A retrospective study showed that miscarriage rate in pandemic period did not differ to that observed in pre-pandemic period (14.2% vs 12.8%; p = 0.76). Further data of maternal exposure including the preconception period is needed to determine the effects of COVID-19 on early pregnancy outcomes. McDonnell et al. [6], found that in a tertiary referral center in Dublin, there was no correlation between monthly number of COVID-19 deaths in general population and the number of perinatal deaths, preterm births, GDM or pregnancy induced hypertension including pre-eclampsia. There are mixed data indicating COVID-19 impact on the SGA rate from 5.7% in meta-analysis from USA to even 17.4% reported in Chinese population. Women diagnosed with COVID-19 did not have a significantly higher quantitative blood loss during delivery and did not present increased risk of obstetric hemorrhage as compared to those without confirmation of COVID-19. Pregnant patients after kidney transplant and under immunosuppression complicated by COVID-19 infection had higher rates of ICU admission

(30–57%) and higher mortality rates of 10–28% and should be treated as a high-risk group.

The results of cross-sectional survey conducted among pregnant women in antenatal clinics in Singapore based on validated Depression, Anxiety, and Stress Scales (DASS-21) showed that 35.8% of women screened positive for anxiety, 18.2% for depression and 11.1% for stress [7]. It seems that lack of timely and reliable information on the impact of COVID-19 on pregnancy and its outcome led to increased levels of depression, anxiety and stress. Evidenced-based information and psychological support should be provided for pregnant women by the healthcare providers.

THE MODE OF DELIVERY IN A PREGNANT WOMAN INFECTED WITH SARS COV-2

Rates of SARS-CoV-2 infection in neonates seem to be not affected by mode of delivery, feeding nor by direct contact with a mother suspected or being positive for SARS-CoV-2 infection [8]. The decision on caesarean delivery should be based on obstetric (fetal or maternal) indications or respiratory status instead of COVID-19 status alone. There is no evidence to favour one mode of birth over another in women with COVID-19. The final decision regarding the mode of delivery should be based on woman's preferences and any obstetric or fetal indications for the intervention [9]. In one systematic review, which included 666 neonates and 655 women, 28/666 (4%) neonates had confirmed COVID-19 infection postnatally. Infants born vaginally did not have higher risk for COVID infection; 8/292 (2.7%) compared with 20/374 (5.3%) born by Caesarean [10]. Gale et al. [11], in another publication included 82 infants of 116 positive mothers ,from which44% were delivered by Caesarean section and 56% vaginally, and none of the infants were positive for SARS-CoV-2 postnatally in follow-up at 14 of life days. The authors concluded that the decision on birth mode should be based on medical indications, the course of the COVID-19 infection as well as provision of safe working conditions for medical staff. In cases of pregnant women being positive for COVID-19, there are many issues to be considered, however, each medical case should be worked out individually.

ANTIVIRAL TREATMENT IN PREGNANT WOMEN WITH COVID-19

The vast majority of pregnant women with COVID-19 is only mildly symptomatic, however, cases of severe disease with pneumonia and respiratory failure have also been observed [12].

In general, the choice of treatment for COVID-19 in pregnancy should be based on the stage of the disease and recommendations for the general population. The course of COVID-19 can be divided into three clinical stages: viremic phase (day 1–7), pulmonary phase (day 5–10) and hyperimmune phase (after day 8) [13]. In patients with mild symptoms in the viremic phase (with normal oxygen saturation level, that is > 94%), only antipyretic drugs and home isolation are recommended. Hospitalization is required in all patients with oxygen saturation below 94%. In case of COVID-19 symptoms exacerbation, an intravenous of remdesivir should be administered for five days, but the treatment is effective if it is started within the first seven days from the onset of symptoms [13]. It is not contraindicated in pregnant women if the benefits of treatment outweight the possible risk of side effects. The drug is generally well tolerated, although its effect on the fetus remains unknown [14].

If the hyperimmunization phase begins (pneumonia with saturation drop < 94%), which occurs mostly after seven days of treatment, the use of tocilizumab, an anti-IL-6 monoclonal antibody, should be considered. In patients requiring hospitalisation, glucocorticosteroids (dexamethasone given in a dose of at least 6 mg/day), low-molecular-weight heparin in a prophylactic dose (prophylaxis of pulmonary embolism) and antibiotics (prophylaxis of superinfection with bacterial pneumonia) should be used simultaneously [13].

ORGANIZATION OF THE MATERNITY WARD IN PANDEMIC PERIOD OF COVID-19

The standard of the organization of the maternity ward was included in the regulation of the Polish Minister of Health of June 26, 2012 on detailed requirements to be met by the premises and equipment of the entity performing medical activities. The ordinance does not contain information about isolation rooms, strict supervision rooms and rooms with direct access to oxygen within the maternity ward. The Obstetrics ward is a highly specialized hospital unit with a very diverse medical staff (obstetricians, neonatologists, anaesthesiologists, midwives, nurses, instrumentalists). The reorganization of maternity wards is extremely important in the prevention and control of the COVID-19 pandemic not only among patients but also among staff. To effectively minimize nosocomial infections during the COVID- 19 pandemic period, preventive strategy should be applied including ward redesign and partition management.

1. Creation of the three zones fulfilling the need for triage: green, yellow and red. Patient with suspected COVID infection is managed in the yellow zone, whereas confirmed COVID cases are moved to zone red. In selected zones, there should be a carefully designated number of people who can stay at the same time with suspected/infected patient. Working time in a protective suit is limited up to four hours only. There is strict personal protective equipment defined: a barrier suit is obligatory protective gear for all medical workers in the red zone.

2. Patients stay in single or double rooms depending on their clinical condition. Medical visits take place twice a day and strict nursing supervision is of great importance, as patients with a severe course of COVID in the third trimester of pregnancy can worsen within a few hours.
3. There should be dedicated a separate operating room organized exclusively for caesarean sections of patients with COVID infection.
4. The most risky procedure for viral contamination is removing personal protective equipment after medical procedures on contagious patients, thus special training for this activity needs to be provided.
5. Appropriate protocols should be prepared regarding the order of entry, putting in and removing protective gear, moving patients, passing newborns after birth and providing postpartum care.
6. One-way traffic from entering the COVID zone to the exit should be implemented.

The only diagnostic test that guarantees highest quality of the presence of the SARS-CoV-2 is RT PCR test. However, due to the long waiting time for the result, new generation antigen test can be used instead.

Currently, every hospital with a maternity ward should be prepared to admit and temporarily hospitalize a patient with COVID infection. That is why it is so important to look for individual solutions suitable for a given place.

MASKS AND FAMILY ASSISTED BIRTHS

According to the orders of the Polish government and Ministry of Health, everybody should wear masks in public spaces and observe the rules of keeping an appropriate distance. The hospital should also be recognized as a form of public space. The principle of wearing masks applies to the staff, patients and those accompanying childbirth. Both sides can be a mutual source of infection. This applies to all departments, sick rooms, corridors and on-call duty rooms for both doctors and midwives. For obvious reasons, women in the active phase of labor should be exempt from the obligation to wear a mask.

Best protection is provided by type FFP2 or FFP3 masks. However, it is worth paying attention to the structure of the mask itself. If it has a forward-facing exhaust valve, although it protects the mask wearer, it poses a risk to everyone else. This type of mask should not be used at all and an additional surgical mask should be worn if it is on top.

FAMILY ASSISTED BIRTHS

In times of a pandemic, the presence of a loved one in childbirth is of great importance for a woman. However, for the safety of other patients and staff, the following rules must be followed:

a) completing the epidemiological questionnaire by the accompanying person during the delivery;
b) the accompanying person must wear a mask and gloves throughout the stay in the hospital;
c) the woman in labor and an accompanying person stay in a single, individual delivery room equipped with a separate sanitary facility;
d) the person accompanying the birthing child may be admitted at the beginning of the delivery and should leave the ward within two hours after the delivery;
e) persons in quarantine or in isolation may not participate in the delivery nor enter the hospital premises.

The final decision regarding family assisted births depends on the possibility of meeting the above-mentioned conditions and the decision of the head of the ward.

TRANSMISSION OF SARS-COV-2

SARS-CoV-2 is highly infective at 4°C which is decreasing in the temperature of 25°C, although is still present at 33°C, and even at 38°C. Infectiousness depends on the environmental temperature and humidity and can even last for 3-5 days. SARS-CoV-2 is very stable in the urine as well as stool and can be contagious for 96 and 72 hours respectively [15]. This indicates existing risks for fecal-oral infection route as well as potential risk for infection via fresh water [16].

SARS-CoV-2 is very sensitive for wide array of disinfection products and chemical inactivators [2]. Bilal et al. [15] tested hospital rooms and bathrooms in 15 different locations occupied by COVID-19 patients revealing 87% and 60% positive samples, respectively. After routine cleansing and disinfection procedures all samples were negative.

Walsh et al performed systematic review based on 113 publications from December 30, 2019 till May 12, 2020. Analysis showed that viral load in the upper airway peaks at first days of clinical signs and remains high through first few days of infection. Viral shedding is not present after 14 days from the beginning of infection. Viral load in the stool reaches highest values later and remains present for longer time than in the upper airways. Viral load in the upper airway depends on the severity of the diseases and can be even 60 times higher in patients with severe course of the disease. Viral transmission may occur two days before the first symptoms appear and lasts for seven days of clinical symptoms, which was shown in the early publications. The authors stressed that presence of viral RNA in the upper airways is not proof of infectiousness, which depends directly on viral load. There is no correlation between viral load and patient's age, which has been reported this same for children and adults [17].

ULTRASOUND EXAMINATION DURING COVID-19 PANDEMIC

Ultrasound diagnostics during ongoing pregnancy following the recommendations of the Ultrasound Section of the Polish Society of Gynecologists and Obstetricians must meet special requirements to minimize the risk of SARS-CoV-2 transmission. Naturally, the recommendations include triage — pre-selection of patients allowing ultrasound examinations only for asymptomatic patients with a negative history and when possible having recently made a negative SARS-CoV-2 test as a best option.

During COVID-19 infection in pregnancy, ultrasound examination of fetal growth, amniotic fluid and umbilical artery blood flow should be performed when clinically necessary.

In outpatient clinic, according to the Polish guidelines only the first, second and third trimester scans should be performed. As a precaution the number of vaginal scans should be minimized, when possible it is recommended to perform cervical length measurement by transabdominal examination [18].

NEONATAL CARE DURING COVID-19 PANDEMIC

COVID-19 pandemic forced health care providers to establish guidelines focused on care of the newborns born to mothers infected with SARS-CoV-2. In the beginning of the pandemic during its first wave, in March and April 2019 there were a series of the initial guidelines on this topic issued by The World Health Organization, American Academy of Pediatrics, American College of Obstetricians and Gynecologists, and European Academy of Pediatrics which were based on very limited knowledge of SARS-CoV-2 effect on newborns' health. There were very diverse approaches to neonatal care, from strict isolation of the newborn from mother with formula feeding to almost normal, unaffected care with skin-to-skin and rooming-in.

During the first wave of COVID-19 until the second wave of the pandemic more information on neonatal effect of maternal COVID-19 diseases has been gathered. Zhu and colleagues retrospectively analyzed the clinical course of 10 newborn babies of mothers with COVID-19 symptoms. This analysis showed that none of the women had been treated with antivirals prior to delivery despite the presence of clinical symptoms in two patients. The remaining pregnant women developed symptoms within a few days following delivery. Fetal life-threatening symptoms such as hypoxemia associated with respiratory failure occurred in six pregnant women. The studied cohort was eight male newborns and two female newborns of which six were born prematurely. The most observed clinical signs of respiratory failure in neonates were to be shallow breathing, fever and tachycardia. Disorders of the gastrointestinal tract such as reflux, regurgitation (spitting up), and bloody discharge from the stomach were observed in four newborns. Radiographic changes of the chest were observed in seven neonates: pneumonia (4), respiratory distress syndrome (2), pneumothorax (1) and none presented with SARS-CoV-2 in nasopharyngeal discharge. Two neonates, born at 34 weeks of gestation presented with very serious symptoms of respiratory failure, thrombocytopenia and liver failure. One of the newborns developed intravascular coagulation syndrome but despite the administration of plasma, platelets and red blood cells, the child died on the ninth day of life. Another severely ill newborn was treated with blood products, immunoglobulin, glucocorticosteroids and low molecular weight heparin and was cured on the 15th day of life [19].

One of the largest retrospectively analyzed cohort of newborns from SARS-CoV-2 infected mothers is study by Dumitriu et al. [20], from New York City. There were 101 newborns included in the study. Only one newborn was positive for the presence of SARS-CoV-2 but was asymptomatic. Out of all of them, 18 were admitted to neonatal intensive care unit (NICU) with non-COVID-19 related pathology. Newborns born to mothers with severe/critical COVID-19 (10%) were born one week earlier [37.9 (IQR) 37.1–38.4 vs 39.1 (IQR) 38.3–40.2, $p = 0.02$] and required more often phototherapy (30% vs 7%). None of the newborns presented any pathology in the follow-up. It is important to mention that direct breastfeeding after appropriate hygiene was encouraged in this study. Authors concluded that there was no clinical evidence of vertical transmission in 101 newborns of mothers positive for or with suspected SARS-CoV-2 infection, despite most newborns being cared for in rooming-in and directly breastfed.

Salvatore et al., analyzed cohort of pregnant women who were tested for COVID-19. Out of 1481 deliveries positive were eight percent, which accounted for 120 neonates. None of them were positive for SARS-CoV-2 on the first day of life, 83% were roomed in with mothers, and all were breastfed. Eight-two newborns had repeat PCR test at days 5–7 of life and all of them were also negative. Authors concluded that perinatal transmission of COVID-19 does not occur with optimal hygiene regime and rooming in with mothers is not increasing the risk for COVID-19 [21].

On the other hand, a less liberal approach for neonatal care is proposed by authors of the study by Farghaly et al. [22], in which their analysis showed significant association between symptoms and SARS-CoV-2 status regarding skin-to-skin contact ($p < 0.001$). Both studied groups showed significant differences regarding isolation patterns ($p < 0.001$). There was only one newborn with positive results for SARS-CoV-2 admitted to the neonatal

intensive care unit (NICU). It has been shown that newborns of SARS-CoV-2 positive mothers were three times as likely to have desaturations, four times more likely to have poor feeding and ten times more likely to be symptomatic at the 2nd week follow-up in comparison to newborns from negative mothers. This group concluded that neonates born to mothers with confirmed or suspected SARS-CoV-2 are most of the time asymptomatic. Nevertheless there is still possibility for COVID-19 infection among newborns, thus in some cases isolation precautions should be considered and studied. In addition, testing these newborns by nasopharyngeal swab at least at 24 hours after birth and monitoring them for the development of symptoms for 14 days after birth is needed.

So, one of the most important question from the neonatologist point of view is: What is the risk for intrauterine vertical COVID-19 infection? Recently, Kotlyar AK et al. [23], published results of quantitative analysis and revealed that out of 936 neonates from COVID-19 mothers, 27 neonates had SARS-CoV-2 viral RNA positive nasopharyngeal swab, indicating a pooled proportion of 3.2% for vertical transmission. SARS-CoV-2 viral RNA testing in neonatal cord blood was positive in 2.9% of samples, 7.7% of placenta samples, 0% samples of amniotic fluid and urine samples and 9.7% of fecal swabs. Neonatal serology was positive in 3.7% (based upon the presence of IgM). Although these results suggest possibility for vertical SARS-CoV-2 transmission more studies are needed to clinically proof for this route of infection.

Based on published retrospective analysis, observational studies and guidelines up to date of December 30th, 2020 the following procedures for neonatal care during the COVID-19 pandemic should be followed:

1. There is currently no clear evidence of intrauterine fetal infection with SARS-CoV-2. Although there is presence of viral genetic material in amniotic fluid, placenta and umbilical cord.
2. Every newborn baby of a COVID-19 positive mother should be tested for SARS-CoV-2 as soon as possible – to prevent contamination occurring after birth. Standard method is rt-PCR. Antigen test can be used to proof for end of viremia after infection,
3. After birth of a newborn from an infected COVID-19 mother, the newborn does not need to be isolated from mother and can be cared in "rooming-in". Mother and child should be hospitalized in special units dedicated to COVID-19 patients in separate rooms in order to avoid cross-infections with other women. There should be dedicated personnel appointed to care.
4. A newborn baby of a COVID-19 mother should be breastfed if mother's clinical status is stable or may receive mother's milk if the milk is pumped in accordance with all basic hygiene regulations. Up to date there is no evidence that mothers milk contains replicable RNA of SARS-CoV-2, contrary to the evidence for IgM antibody presence [24].
5. Newborns of mothers infected with SARS-CoV-2 should undergo all mandatory vaccinations. Newborns who have tested positive for SARS-CoV-2 and who have no clinical symptoms should receive vaccination for viral hepatitis B and tuberculosis preferably with consultation of a vaccinologist.
6. Lack of causal treatment for COVID-19 infection in newborns.
7. Discharge home as soon as possible, newborn should be picked by family member who is negative and not under quarantine.
8. Neonatal resuscitation:
   a) should be performed in designated room by trained personnel secured with protective clothing, N95 masks, goggles, and gloves;
   b) Resuscitation Equipment (based on NRP or ERC guidelines):
      - infant radiant warmer, dry linen sheets, plastic bag,
      - suction (pressure 80–100 mm Hg); preferred closed systems,
      - T-piece resuscitator or nasal CPAP (settings: PEEP = 6 cm H2O, PIP = 20–25 cm H2O, FiO2 according to gestational age, flow 6–10 L/min), masks with optimal size ranges, endotracheal tubes and laryngoscope of appropriate size, laryngeal mask if applicable, , self-inflating bag,
      - other equipment: Videolaryngoscope if available and used at site, drugs according to local list, stethoscope, pulse ox, ECG electrodes.
   c) transport incubator equipped with ventilator for neonatal transfer,
   d) d. delayed cord according to regular local guidelines.
9. Skin-to-skin contact possible based on the clinical and organizational conditions [25].

VACCINATION

At the end of December, the vaccinations against COVID-19 were initiated in Poland. There were various doubts and questions raised regarding the safety of the new mRNA vaccine. During perinatal care there are two major issues related to vaccination that may need further explanations:

1. Vaccinations of the pregnant women
   Since manufacturers of the vaccines did not include pregnant women in the phase III clinical trials, there is insufficient evidence to recommend **routine** use of COVID-19 vaccines during pregnancy. Joint Committee on Vaccination and Immunization (JCVI) advises that, for women who are offered vaccination, vaccination in pregnancy should be considered **only** where the risk of

development of Acute Respiratory Distress Syndrome (ARDS) is very high, or where the woman has underlying conditions that put them at very high risk of serious complications of COVID-19. In these circumstances, clinicians should discuss the risks and benefits of vaccination with the woman, who should be told about the absence of safety data for the vaccine during pregnancy [26, 27].

2. Vaccinations of the breastfeeding women

   Due to outweighed benefits of breastfeeding as well as lack of evidence of associated risks to non-live vaccines during breastfeeding, JCVI allow for vaccination against COVID-19 of breastfeeding women.. Nevertheless, absence of safety data for the vaccination procedure among breastfeeding women should be explained by medical personnel.

JCVI does not advise routine pregnancy testing before receipt of a COVID-19 vaccine. Those who are trying to become pregnant do not need to avoid pregnancy after vaccination. These recommendations are in sync with recommendations by The Royal College of Obstetricians and Gynecologists

In summary: Women should discuss the benefits and risks of having the vaccine with their healthcare professional and commonly seek decision [26, 27].

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VIA MEDICA

RECOMMENDATIONS

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Recommendations of the Group of Experts of the Polish Society of Gynecologists and Obstetricians regarding proceeding with victims of crimes against sexual freedom (01.01.2021)

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The recommendations present the current knowledge and procedures, which can be modified and changed in some cases, after careful analysis of a given clinical situation, which in the future may become the basis for their modification and updating.

A gynecologist in his professional practice often encounters victims of crimes against sexual freedom and victims of domestic violence. The list of crimes against sexual freedom is included in the Criminal Code in Chapter XXV and includes the crime of rape (Art. 197), abuse of dependence (Art. 199), sexual intercourse with minors under 15 (Art. 200), and forbidden contact with a minor (Art. 200a), incest (Art. 201) — to name only those crimes that the gynecologist can most clearly reveal. Domestic violence has its own legal definition and such violence is a one-time or repeated deliberate action or omission that violates the rights or personal rights of family members, in particular exposing these people to the risk of losing life, health, violating their dignity, bodily inviolability, freedom, including sexual, causing harm to their physical or mental health, as well as causing suffering and moral harm to people affected by violence. However, family members, also under the statutory definition, should be considered as a spouse, an ascendant, descendant, siblings, related in the same line or degree, a person in an adopted relationship and their spouse, as well as a person who is living together or managing (Art. 2 of the Act of 29 July 2005 on Counteracting Domestic Violence). A similar definition of the closest person is contained in Art. 115 §11 of the Criminal Code.

It will always be the doctor's duty to provide medical assistance in the first place, and he or she has the right to focus on this, although some of the medical activities, which will be emphasized each time in the recommendations, should be carried out taking into account the needs of the evidence proceedings in connection with the suspected crime.

Secondly, the doctor should consider whether he or she is under a legal or social obligation to report the suspected crime, and whether there is a basis for exempting him or her from medical confidentiality. According to Art. 304 §1 of the Code of Criminal Procedure, everyone having learned about the commission of an offense prosecuted ex officio has a social obligation to notify the prosecutor or the police about it.

In §2 it was decided that state and local government institutions that deal with cases of offenses prosecuted ex officio, are obliged to notify the prosecutor or the police about it and to take the necessary steps until the arrival of the person appointed to prosecute the crime.

THE ROLE OF A DOCTOR IN TAKING CARE OF A VICTIM OF SEXUAL VIOLENCE

In the first place, the doctor should provide medical care, which consists of:

- recognition and stabilization of emergencies,

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- resolving the issue of the need to aid other patients under his care,
- conducting and documenting a medical interview,
- physical and gynecological examination,
- assessment and treatment of physical injuries,
- collection of material for bacteriological tests,
- prevention of sexually transmitted infections,
- pregnancy prevention counseling,
- scheduling control visits,
- psychotherapeutic assistance,
- preparation of medical documentation, assistance in collecting evidence of a crime after establishing the expectations of law enforcement agencies in this regard (a doctor appointed as an expert),
- notifying the relevant authorities of suspected crime (depending on the specific case).

In case of suspicion of sexual abuse of a girl, the examination should be performed by an obstetrician-gynecologist; in the case of a boy — a pediatric surgeon in cooperation with an obstetrician-gynecologist. If it is suspected the presence of injuries to internal organs that may endanger the life of an injured minor, a consultative pediatric surgeon should be called.

1. Conducting and documenting a medical interview

Persons suspected of being victims of sexual abuse should be promptly admitted to the emergency room and placed in a separated room for privacy and intimacy. After the initial assessment of the basic vital functions of the patient (airway patency, cardiovascular capacity) and the exclusion of the presence of injuries of internal organs that may be life-threatening, a detailed medical history should be collected and documented, if possible, which should include the following issues:

- age and personal data of the victim and the alleged perpetrator (link to the victim),
- date, time, place and circumstances of the event,
- date and time of the examination,
- details of the sexual abuse (descriptions of the sexual acts committed, the occurrence of ejaculation, the use of physical violence, weapons, drugs, alcohol consumption, drug use by the victim or perpetrator before the event occurred),
- actions performed by the victim after the incident/attack (change of clothes, bathing, showering, urinating),
- gynecological and obstetric interview (date of the last menstruation, contraception used, current and past sexually transmitted infections (STI), the last voluntary sexual contact, previous operations, pregnancies, births and miscarriages).

2. General physical examination

General physical examination should begin with a thorough assessment of the general and emotional state of the victim, assessment of the entire body, with particular emphasis on the area of the lower abdomen, inner and outer surface of the thighs, buttocks and limbs, in order to look for signs related to violence (edema, ecchymosis, skin abrasions, bites, wounds, fractures). All injuries located outside the genitals should also be accurately described on the forensic examination card (character, injury location sketch).

The medico-forensic analysis should be performed within 72 hours of the sexual act; the earlier the examination and sampling takes place, the more likely it is to secure the evidence properly.

Physical examination may take place in the presence of an assistant - another doctor, midwife or nurse, only when it is necessary due to the type of service or with the consent of the patient and in the presence of a relative indicated by the victim (in the case of an adult victim's request), conditions ensuring comfort and intimacy.

Pursuant to Art. 3 sec. 1 point 2 of the Act on Patient Rights and the Patient's Rights Ombudsman, a close person means a spouse, relative or affinity up to the second degree in a straight line, a statutory representative, a person living together or a person indicated by the patient.

In the case of minors, the examination should be conducted in the presence of a statutory representative or a de facto guardian. Pursuant to the provisions of the Family and Guardianship Code, the legal representative is, in principle, the parent or legal guardian. According to Art. 3 sec. 1 point 1 of the Act on Patient's Rights and the Patient's Rights Ombudsman, actual guardian means a person who, without statutory obligation, takes permanent care of a patient who requires such care due to age, health or mental state.

A minor may ask for a gynecological examination in intimate conditions — without the presence of a statutory representative/actual guardian, which should be recorded in the medical documentation. If the statutory representative/actual guardian does not consent to the examination without his or her presence, this fact should be recorded in the medical documentation and the examination should be carried out in his or her presence.

However, it should be borne in mind that in the event of a suspicion that a minor is a victim of a crime against sexual freedom, the doctor may conduct an examination of this person, if there is neither a statutory representative nor a de facto guardian, or communication with these persons is impossible (e.g. intoxication, state after the use of narcotic drugs and psychotropic substances). The objection of the legal representative or de facto guardian, with the possibility of communicating with them, can be overcome with the consent of the guardianship court.

Legal regulations regarding obtaining the consent of a patient who is a victim of a crime against sexual freedom or domestic violence to provide health services and examination do not differ from the general principles expressed in art. 15–19 of the Act of November 6, 2006 on patient's rights and the Patient's Rights Ombudsman and in Art. 32–34 of the Act of December 5, 1996 on the professions of doctor and dentist:

- in the case of a minor patient, it is obligatory each time to obtain the consent of his or her statutory representative for the provision of health services to the patient, and if the patient is over 16 years of age — to obtain the consent of this patient. In a situation where such a patient uses his or her right to object to the provision of a health service, despite the consent of the statutory representative or actual guardian, the consent of the guardianship court is required;
- in the absence of a statutory representative, consent may be given by the actual guardian of a minor patient, but only regarding the examination themself;
- in a situation where the patient does not have a statutory representative or it is impossible to contact him, the consent of the guardianship court is required to provide health services;
- exceptions include situations where the patient requires immediate medical attention, and due to his health or age, he or she cannot give his consent and it is not possible to contact his or her legal representative or actual guardian. In this case, examination or providing the patient with another health service without his or her consent is permissible, but such a decision should be consulted with another doctor, if possible, and the circumstances should be noted in the patient's medical records. If the delay caused by the consent procedure would pose a threat to the patient's life, serious injury or serious health impairment, the doctor is obliged to consult another doctor, if possible, of the same specialty, if possible. The doctor immediately notifies the statutory representative, actual guardian or the guardianship court about the performed activities, informing them of the circumstances, and all these conditions must be met jointly - from the conditions determining the patient's situation to the fulfillment of formal conditions;
- consent or objection may be expressed orally or by such behavior of the entitled person, which clearly indicates the will to undergo the activities proposed by the doctor or the lack of such will, only in the case of a surgical procedure or the use of a treatment or diagnostic method that poses an increased risk for the patient , consent to provide health services must be received in writing;
- in each case, before giving consent, the person authorized to express consent has the right to obtain information on his or her health condition, diagnosis, proposed and possible diagnostic and treatment methods, foreseeable consequences of their use or omission, treatment results and prognosis;
- the doctor should take into consideration the minor's opinion and respect the position taken by him or her, considering the degree of his maturity, unless it is contrary to the regulation described above.

3. Gynecological examination

Gynecological examination should be the final stage of the physical examination of a minor or adult victim of sexual violence. All genital injuries should be carefully recorded on the victim's examination card (detailed description, sketch of the location). In gynecological examinations, carefully selected gynecological specula should be used, which in selected cases can only be moistened with 0.9% NaCl solution. A rectal examination should be performed if anal penetration is suspected or there is evidence of trauma to the area.

In girls, gynecological examination can be performed in the lithotomy position, "frog" position or knee-thoracic position - the most comfortable for the child and allowing the collection of the material. The most common injuries to female genital organs resulting from sexual violence against minor include abrasions to the posterior commissure, labia minora, hymen and the urethral fossa.

During the gynecological examination, a swab should be taken from the vaginal vestibule (girls), vagina and the external os of the cervix (adult patients and sexually active girls) using a properly prepared sterile swab — ensuring constant air access (provided by a forensic technician). Then take a swab around the anus in a similar way.

If vaginal penetration is suspected, collect vaginal discharge or, in its absence, vaginal lavage using a small volume of sterile 0.9% NaCl solution (set consisting of a plastic pipette and test tube) and collect a cytological smear from the cervix and cervical canal (set for cytology collection). Laboratory testing of such material can detect motile sperm, other sperm components (acid phosphatase, p30 protein, antigen specific for seminal vesicles) and ABO antigens. Detection of sperm in vaginal discharge confirms sexual contact within the previous few hours (motile sperm can survive up to 8 hours, immobile sperm up to 24 hours). In a cervical smear, mobile sperm can be detected for several days (2–3 days), and motionless sperm up to 17 days after vaginal intercourse.

In the case of sexual abuse against a boy, the male genitalia should be carefully assessed, and the existing injuries

should be accurately described in the boy's examination card. A swab should also be collected from the external urethra and the anal area using properly prepared sterile swabs with constant air access.

The collection of material evidence in the case of genital-oral contacts consists of taking a swab from the oral cavity (using a properly prepared sterile swab with constant air access) and oral rinses (using a 10% ethanol solution, which fixes DNA acid and prevents the growth of bacteria) into a sterile container (urine container). It should be emphasized that semen is quickly destroyed by the enzymes of saliva, so it is extremely difficult to determine whether ejaculation has occurred in the oral cavity.

4. Prevention of sexually transmitted infections

The risk of having a sexually transmitted infection (STI) as a result of forced sexual contact in the group of sexually active women in the last three months is approximately 14.4%, and among sexually inactive children and girls — approximately 4.3%. The frequency of different infections among victims of forced sexual contact varies as follows: 19.5% — *Gardnerella vaginalis*, 12.3% — *Trichomonas vaginalis*, 6–12% — *Neisseria gonorrhoeae*, 4–17% — *Chlamydia trachomatis*, 3% — *Treponema pallidum* and viral infections (HBV, HCV, HIV) — about 0.5%.

In rape victims, it is recommended to perform diagnostic microbiological tests for gonorrhea and chlamydiosis, if possible. The culture material should be collected from all contact sites (vagina, cervix, anus, pharynx). Additionally, it is recommended to perform diagnostic tests for syphilis and adequate treatment after obtaining the result.

In some adult women/underage girls — victims of sexual abuse, prophylactic antibiotic therapy is recommended, depending on individual indications:

- in the case of N. gonorrhoeae infection — ceftriaxone (250 mg i.m. in a single dose) or cefixime (400 mg in a single dose) or ciprofloxacin (500 mg in a single dose) or ofloxacin (400 mg in a single dose) or spectomycin (2 g in a single dose). single dose), in children — dosage depending on age and body weight;
- Ch. trachomatis — azithromycin (1 g p.o. in a single dose) or doxycycline (100 mg p.o. every 12 hours for 7 days) — contraindicated in pregnant women, in children — dosage depending on age and body weight;
- T. vaginalis or G. vaginalis — metronidazole (2 g p.o. in a single dose) — in pregnant women only after completing the first trimester, in children — dosing depending on age and weight;
- immunization against hepatitis B — if the victim has not been fully vaccinated before;
- prophylactic treatment of tetanus — unvaccinated women/girls.

Victims of sexual violence should be tested for HIV infection during the first examination and repeated six weeks after the incident. The WHO also recommends that all rape victims should receive prophylactic antiretroviral treatment within 72 hours of the act, including: Zidovudine (300 mg every 12 hours) and Lamivudine (150 mg every 12 hours) for 28 days; in children, the dosage depends on age and body weight.

5. Counseling in the field of pregnancy prevention

The overall risk of pregnancy following an act of sexual violence is around five percent. The routine procedure during the examination of the victim is to perform a pregnancy test, document the result and determine the date of the last menstruation. Rape victims should be allowed to use emergency contraception, according to individual indications.

6. Psychological help

The victims of sexual violence may have symptoms of the acute phase of post-traumatic stress disorder in the form of anger, fear, anxiety, increased tearfulness or lack of expression of emotions. The physician should provide psychological support to the victim of sexual abuse. The ideal solution is the availability and immediate intervention of a clinical psychologist. The tasks of the doctor also include informing the injured person about the possible long-term consequences of sexual abuse (*e.g.* sleep disorders, mood swings, depression) and indicating the place of psychotherapeutic help.

7. The issue of notifying the law enforcement agencies and the guardianship court about the suspected crime

There are regulations in the legal system which require cooperation with judicial authorities in certain situations.

The most important obligation results from Art. 240 of the Penal Code, as failure to comply with it is punishable by a criminal sanction. The obligation of immediate notification under the Act in situations that may be encountered by a doctor applies to the following prohibited acts: murder, unlawful deprivation of liberty, as well as any crime of a terrorist nature. At the same time, it should be emphasized what may be important in practice, that the obligation to notify also applies to the attempted offenses mentioned above and, equally important, also to situations in which, due to insanity or age, the perpetrator of the act will not be held criminally responsible. In such a situation, notification should be made "as soon as possible", which does not

mean"immediately", but only "without undue delay". Only in a situation where a doctor is already dealing with decease, in the case of a justified suspicion that the cause was a crime, the doctor, as well as other persons appointed to inspect the body, should immediately notify the prosecutor or the nearest police station (Art. 11 par. 8 of the Act of January 31, 1959 on cemeteries and burying the dead).

According to Art. 12 of the Act on Counteracting Domestic Violence in the version from 2010, persons who, in connection with the performance of their official or professional duties, suspect that an ex officio criminal offense involving domestic violence has been committed, shall immediately notify the Police or the prosecutor. In this way, the act clearly identifies the addressee of such notification. Therefore, this obligation currently has a wide subjective scope, as it covers persons practicing their profession even outside the employment relationship, and therefore also within the individual medical practices.

This obligation, however, only applies to offenses prosecuted ex officio, which from 27 January 2014 also include the crime of rape (also rape of an adult — Art. 197 of the Penal Code), so far prosecuted under absolute petition. Offenses of violation of bodily inviolability, including minor health detriment, and punishable threats prosecuted under the application procedure are still prosecuted under private prosecution, if these behaviors do not turn into a crime of abuse.

However, according to Art. 304 §1 of the Code of Criminal Procedure (CCP), everyone who learns about the commission of an offense prosecuted ex officio is obliged to notify the prosecutor or the Police about it. Therefore, this obligation is universal and, as it results directly from the act, it is a social obligation, and therefore it has not been sanctioned.

The legislator has shaped this obligation somewhat differently with regard to state and local government institutions which, pursuant to Art. 304 §2 of the Code of Criminal Procedure, provided that, in connection with their activity, they learn about the commission of an offense prosecuted ex officio, they are obliged to immediately notify the prosecutor or the Police about it. Moreover, in such a situation, these institutions have an additional obligation to take the necessary actions until the arrival of the authority appointed to prosecute crimes or until the authority issues an appropriate order to prevent the obliteration of traces and evidence of the crime. This obligation does not rest with every employee, but only with those persons who are authorized to act on behalf of the institution. A self-government institution is also a medical chamber as an institution of professional self-government.

The obligation to notify may be fulfilled by written or personal notification to any unit of the Police or the prosecutor's office, and it may be done even by telephone after making sure that the caller is identified. This fact should be noted in your notes due to the high probability of being a witness in a possible court case.

However, notification of the guardianship court is possible under Art. 572 of the Code of Civil Procedure. This provision stipulates that anyone who is aware of an event justifying the initiation of proceedings ex officio is obliged to notify the guardianship court about it. This obligation rests primarily with registry offices, courts, public prosecutors, notaries, bailiffs, local government and government administration departments, police departments, educational institutions, social welfare workers, and organizations and institutions dealing with the care of children or mentally ill people.

Pursuant to Art. 109 of the Family and Guardianship Code, if the child's welfare is at risk, the guardianship court will issue appropriate orders. The guardianship court may, in particular:

1. oblige the parents and the minor to specific proceedings, in particular to work with a family assistant, carry out other forms of work with the family, refer the minor to a day support facility, specified in the provisions on supporting the family and the foster care system, or refer parents to an institution or a specialist dealing with to family therapy, counseling or providing other appropriate help to the family, while indicating how to control the implementation of issued orders;
2. determine what activities may not be performed by the parents without the consent of the court;
3. submit the parental authority to the constant supervision of a probation officer;
4. refer the minor to an organization or institution established for apprenticeship or to another facility that takes partial custody of children;
5. order the minor to be placed in a foster family, family orphanage or in institutional foster care or temporarily entrust the performance of the function of a foster family to spouses or a person who does not meet the conditions for foster families, in terms of the necessary training, specified in the provisions on supporting the family and foster care system, or order the placement of the minor in a care and treatment institution, a nursing and care institution or a medical rehabilitation facility.

The appropriate court in this case will be the family division of the district court consistent with the child's place of residence.

It is aptly argued in the literature that the society's willingness to cooperate with law enforcement agencies depends on the level of awareness and legal culture of the society, the degree of the sense of the threat of crime and the public opinion on the efficiency of law enforcement

agencies, the way citizens are treated by these authorities and the role they play in society. The summing up conclusion is also indisputable that the more law enforcement agencies are perceived as acting for the benefit of the citizen and the less they are perceived as an apparatus of repression, the more they can count on citizens' readiness to cooperate.

8. The issue of the obligation to maintain doctor-patient confidentiality and the notification of a suspected crime

Each time, when considering notifying law enforcement authorities about a suspected crime, a doctor must first of all determine whether he or she is exempt from the obligation to keep confidential information related to the patient and obtained in connection with the performance of the profession. The doctor is also bound by the doctor-patient confidentiality after the patient's death.

According to Art. 40 sec. 2 of the Act on the Professions of Physician and Dentist **the prohibition of disclosing information covered by medical confidentiality shall not apply only when** this is provided for in another Acts, or when the medical examination was carried out at the request of authorized persons, on the basis of separate acts, departments and institutions, but then the doctor is obliged to inform only those authorities and institutions about the patient's health. This prohibition does not apply to the doctor also when keeping the secret may pose a threat to the life or health of the patient or other people, or the patient or his legal representative agrees to disclose the secret, after informing about the negative consequences of its disclosure for the patient. This prohibition also does not apply when there is a need to provide the necessary information about the patient to the forensic doctor or when there is a need to provide the necessary information about the patient related to the provision of health services to another doctor or authorized persons participating in the provision of these services.

Statutory regulations that impose an obligation on a physician to disclose, to a certain extent, information covered by medical confidentiality include, for example, Art. 27 of the Act of December 5, 2008 on preventing and combating infections and infectious diseases in humans. However, it is commonly accepted that the obligation to maintain medical secrecy is "stronger" than the obligation to denounce under Art. 304 §1 of the Code of Criminal Procedure due to the above-mentioned universal nature of this obligation. However, the nature of the regulation under Art. 12 of the Act on Counteracting Domestic Violence is debatable, but in this case, in the majority number of situations, the doctor will be released from the obligation of secrecy when he decides that his behavior may pose a threat to the life or health of the patient or other people. It is also argued in the literature that exemption from medical confidentiality may also take place on the basis of the patient's consent in a situation where such consent will only be presumed by the doctor, e.g. in the case of an unconscious rape victim, i.e. in a situation where the doctor believes that the conscious patient would give such consent.

To sum up, a gynecologist, having encountered victims of crimes against sexual freedom and victims of domestic violence in his professional practice, is, beyond all doubts, released from the obligation to keep confidential information related to the patient and obtained in connection with the performance of his profession in any of the following situations:

- specified in art. 240 of the Criminal Code
- when confidentiality may endanger the life or health of the patient or other people
- when the patient or his legal representative consents to the disclosure of the secret, having previously informed about the negative consequences of its disclosure for the patient.

It should be emphasized that in each of the situations described above, disclosure of a secret may only take place to the extent necessary, i.e. to initiate and conduct criminal proceedings.

Violation of medical confidentiality may be associated with professional liability in a medical court (Articles 25––29 of the Code of Medical Ethics), civil liability (infringement of the patient's personal rights), and the most far reaching consequence may be criminal liability (Art. 266 §1 of the Penal Code). Article 266 of the Penal Code provides that anyone who, contrary to the provisions of the Act discloses or uses information which he has become acquainted with in connection with his/her function, work, public, social, economic or scientific activity, is subject to a fine, penalty restriction of liberty or imprisonment for up to two years. The prosecution of this crime takes place at the request of victim.

On the other hand, a public official who discloses to an unauthorized person information classified as "restricted" or "confidential" or information obtained in connection with the performance of official activities, and the disclosure of which may endanger a legally protected interest, shall be subject to imprisonment for up to three years. This offense is prosecuted ex officio.

9. The issue of appointing a doctor as an *ad hoc* expert — examination of a patient at the request of law enforcement agencies

Procedural authorities, accepting a notification of an offense from the victim or gaining reasonable knowledge of a suspected crime, should immediately proceed to the implementation of procedural steps.

One of the procedural steps is visual inspection (Art. 207 §1 of the Code of Criminal Procedure), carried out only by a procedural authority who may summon an expert (Art. 198 §1 of the Code of Criminal Procedure) or a specialist (Art. 205 §1 of the Code of Criminal Procedure). This operation cannot be repeated at further stages of the criminal proceedings and therefore should be performed with particular care. The observations made during it will not only guide further proceedings, but above all will verify the preliminary findings.

In cases of rape and other sexual offenses, material evidence is of particular importance as material evidence provide objective knowledge about the facts. In the case of rape crime, the physical contact of the victim with the perpetrator usually leaves specific traces of interaction on their bodies and clothes, e.g. hair, fibers, biological traces (e.g. blood, skin, sperm, vaginal discharge). The victim may also be injured in some way. Their number and severity will depend on the degree of violence used by the attacker, as well as on how much resistance the victim himself or herself resists. It should be emphasized, however, that in a situation where the victim did not resist strongly, or the perpetrator underwent the desired sexual activities or intercourse out of fear of more painful behavior, bodily injuries may be minimal or imperceptible.

Pursuant to Art. 192 §1 of the Code of Criminal Procedure, the victim cannot object to body inspections and examinations when the punishment of the act depends on his or her health condition. Whereas Art. 192 §4 of the Code of Criminal Procedure stipulates that, for evidentiary purposes, every witness may be subjected to a body inspection and a medical or psychological examination, but only with his or her consent.

Due to the multiplicity and variety of events that violate the norms of criminal law, procedural authorities must use the assistance of experts. An expert opinion is requested when the circumstances significant for the resolution of the case requires special knowledge (Art. 193 §1 of the Code of Criminal Procedure). Therefore, an opinion is always needed if the determination of a given circumstance requires special knowledge and it does not matter whether the procedural body has such knowledge itself. The Supreme Court indicates that special knowledge should include all the knowledge and skills that go beyond the average and practical. Undoubtedly, the doctor participating in the body inspection is a person who has special information within the meaning of Art. 193 §1 of the CCP.

At the same time, the Act of 5 December 1996 on the professions of physician and dentist provides within physician's duties issuing medical reports (Art. 2). These judgments can be of different nature, form and purpose. A medical report should be understood as a written or oral statement by a doctor containing conclusions drawn from the stated facts and intended for non-medical institutions. In the legal sense, the submitted written or oral statement of a doctor appointed as an expert is called an expert doctor's opinion or a forensic medical opinion.

The expert is appointed ex officio or at the request of the parties, specifying the scope of his tasks. We can distinguish two types of experts:

- a court expert is a person entered on the list of court experts,
- an ad hoc expert is a person who is not a court expert but, due to his knowledge, is called to perform the activities of an expert.

Pursuant to Art. 195 of the Code of Criminal Procedure, not only an expert witness is obliged to act as an expert witness, but also any person known to have appropriate knowledge in a given field. There is no difference in the treatment and assessment of an expert opinion submitted by a court expert or by another expert appointed in a specific case by a procedural authority.

If activities are performed to the extent necessary (Art. 308 §1 of the Code of Criminal Procedure), it is permissible, if necessary, to conduct an inspection with the participation of an expert. These activities take place before the formal initiation of an investigation. In such a case, the appointment of an expert may also take place in a form dictated by the need to prevent the loss of evidence of the crime, their distortion or destruction. In urgent cases, the appointment of an expert may therefore take place in a form other than a written decision, even e.g. in a telephone conversation, although it must be confirmed in the appropriate form in the further course of the proceedings.

Pursuant to Art. 205 §1 of the Code of Criminal Procedure, when inspections, interrogations with the use of technical devices enabling this activity to be carried out at a distance, experiment, expertise, keeping things or searching, will require technical activities, in particular, such as: taking measurements, calculations, photos, recording traces, specialists may be called in to participate. A specialist is a person who has special knowledge necessary to perform technical activities (e.g. a forensic technician).

Therefore, if a doctor, acting as an expert, does not have the appropriate equipment to secure the traces of sexual abuse and to properly collect material evidence, he or she should call a forensic technician through the duty officer of the nearest Police unit.

The doctor appointed as an expert is obliged to provide the competent authorities with information about the patient's health, because art. 40 sec. 2 point 2 u.z.l.l.d. allows the disclosure of the secret when the examination was carried out at the request of authorized bodies and institutions.

The expert is entitled to obtain remuneration for the activities performed. In relation to expert doctors, detailed guidelines on the method of calculating remuneration can be found in Annex 1 to the Ordinance of the Minister of Justice of April 24, 2013 on determining the rates of expert remuneration, flat rates and the method of documenting expenses necessary for issuing an opinion in criminal proceedings issued on pursuant to Art. 618 f §5 of the CCP.

An expert serves as an auxiliary to a judicial authority and therefore is excluded from giving an opinion for the same reasons as a judge, i.e. when doubts as to his impartiality could arise. Persons closest to the parties to the proceedings, or persons who witnessed the act (Art. 196 §1 of the Code of Criminal Procedure) cannot be experts. If the reasons for excluding an expert are revealed, the opinion issued by him does not constitute evidence, and another expert is appointed in place of the excluded expert (Art. 196 §1 of the Code of Criminal Procedure).

The doctor appointed as an expert during the examination of the person should assist the law enforcement authorities in securing the traces of the crime.

A person who unjustifiably evades the performance of an expert's activity may be fined with an ordinal fine of up to PLN 10,000, and in the event of persistent and unjustified evasion, also order arrest (Art. 287 §1 and 2 of the CCP).

The role of the doctor as an expert is extremely important. It enriches the knowledge of the procedural authority about the subject of inspection by communicating the facts detected and revealed thanks to his or her special information. The information obtained from him or her indicates to the procedural authority the need to perform other activities related to the conducted proceedings.

ANNEX 1. DOCUMENTATION NECESSARY FOR FORENSIC EXAMINATION OF THE VICTIM OF SEXUAL ABUSE EXAMINATION OF AN ADULT VICTIM OF SEXUAL ABUSE

A sexual abuse victim examination and evidence collection kit should contain:

- properly prepared sterile swabs with constant access to air (6–8 pieces)
- plastic pipettes and test tubes (2 pieces)
- cytology collection kit
- basic slides (8–10 pieces)
- a sterile urine container (mouthwash)
- solutions: 100 mL of 0.9% NaCl and 100 mL of 10% ethanol

Each sample of the collected material for testing should contain information on the label regarding: the type of material, date and time of collection, identification data of the victim and the person who collected the material. The samples should be stored in a safe place, and when handing them over to the Police, obtain appropriate documentation (material evidence receipt protocol).

ANNEX 2. EXAMINATION CARD OF AN ADULT VICTIM OF SEXUAL CRIME

1. Identification of the victim and the allegedperpetrator

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2. Date and time of examination

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3. Date, time and place of an event

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4. Details of the sexual abuse (sexual acts, ejaculation, physical violence, drug, alcohol, drug consumption by the victim or perpetrator before the event)

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5. Actions performed by the victim after the incident (change of clothes, bathing, showering, urinating

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6. Gynecological and obstetric interview (last period, used contraception, current and past STI, last voluntary sexual contact, previous operations, pregnancies, births and miscarriages)

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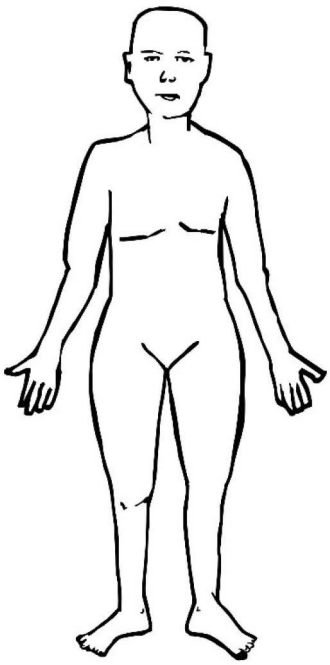
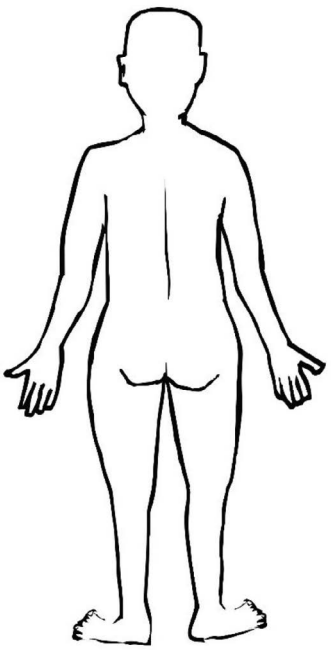
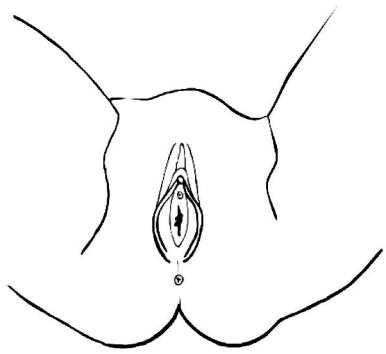
7. Physical examination - description of the general state, emotional, body injuries (injuries location sketch)





8. Gynecological examination - description of genital injuries (injury localization sketch)



9. Laboratory material collected during a physical and gynecological examination

10. Treatment used (antibiotics, contraceptives, painkillers, sedatives)

11. Medical recommendations (medications, contraceptives, hospitalization, specialist consultations)

I consent to the notification of the law enforcement authorities about the incident
Patient's signature

I consent to the examination and activities related to the collection of evidence
(including tissue breakdown) and treatment procedures
Patient's signature

I consent to the disclosure of medical documentation to law enforcement authorities
Patient's signature

I declare that I have been informed about the negative consequences of disclosing medical confidentiality
Patient's signature

Stamp and signature of the doctor who was examining and drawing up the test card

Stamp and signature of the assistant

ANNEX 3. EXAMINATION CARD OF A GIRL — MINOR VICTIM OF SEXUAL CRIME

1. Identification of the victim, statutory representative, and the alleged perpetrator

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2. Date and time of examination

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3. Date, time and place of an event

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4. Details of the sexual abuse (sexual acts, ejaculation, physical violence, drug, alcohol, drug consumption by the victim or perpetrator before the event)

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5. Actions performed by the victim after the incident (change of clothes, bathing, showering, urinating

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6. Gynecological and obstetric interview (last period, used contraception, current and past STI, last voluntary sexual contact, previous operations, pregnancies, births and miscarriages)

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7. Physical examination - description of the general state, emotional, body injuries (injuries location sketch)

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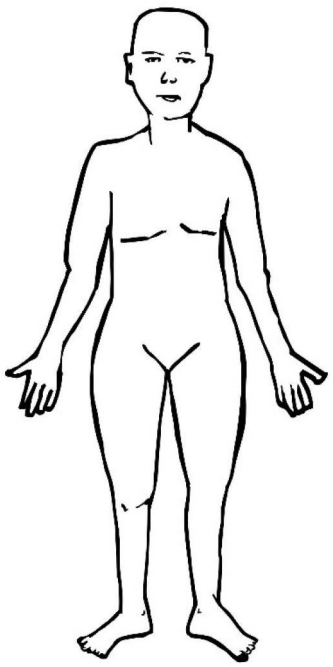
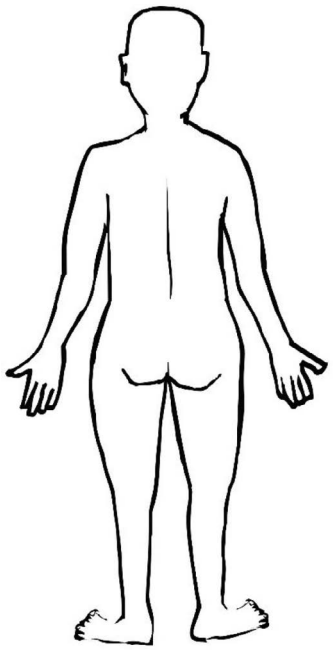
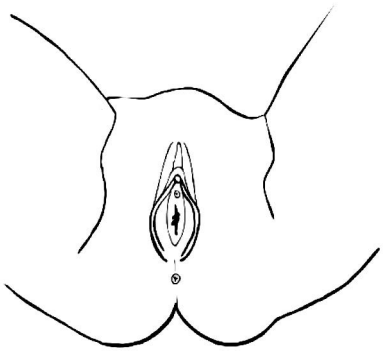




8. Gynecological examinationdescription of genital injuries (injury localization sketch)



9. Laboratory material collected during a physical and gynecological examination

10. Treatment used (antibiotics, contraceptives, painkillers, sedatives)

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11. Medical recommendations (medications, contraceptives, hospitalization, specialist consultations)

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I consent to the notification of the law enforcement authorities about the incident
Patient's signatureStatutory representative's signature

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I consent to the examination and activities related to the collection of evidence
(including tissue breakdown) and treatment procedures
Patient's signatureStatutory representative's signature

.....

I consent to the disclosure of medical documentation to law enforcement authorities

Patient's signature	Statutory representative's signature
.....	.....

I declare that I have been informed about the negative consequences of disclosing medical confidentiality

Patient's signature	Statutory representative's signature
.....	.....

Stamp and signature of the doctor who was examining and drawing up the test card	Stamp and signature of the assistant
.....	.....

ANNEX 4. EXAMINATION CARD OF A BOY-MINOR VICTIM OF SEXUAL CRIME

1. Identification of the victim, statutory representative, and the alleged perpetrator

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2. Date and time of examination

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3. Date, time and place of an event

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4. Details of the sexual abuse (sexual acts, ejaculation, physical violence, drug, alcohol, drug consumption by the victim or perpetrator before the event)

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5. Actions performed by the victim after the incident (change of clothes, bathing, showering, urinating

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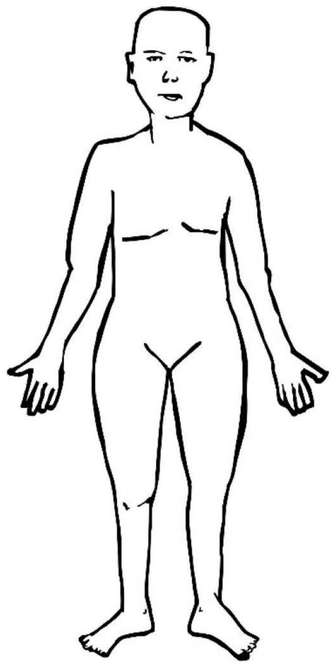
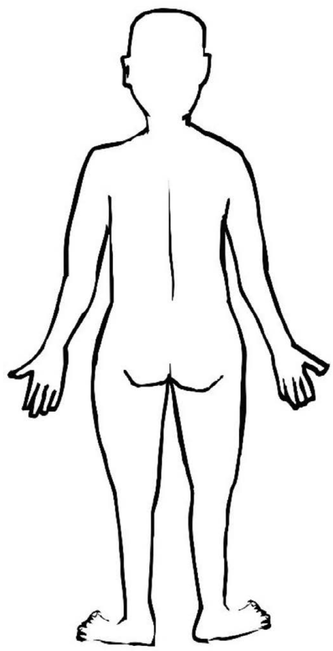
6. Gynecological and obstetric interview (current and past STI, last voluntary sexual contact, previousoperations)

7. Physical examination - description of the general state, emotional, body injuries (injuries location sketch)





8. Genital examination - description of the injury (sketch of the location of the injury)

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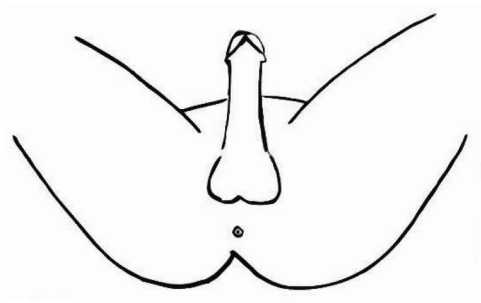

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9. Laboratory material collected during a physical and gynecological examination

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10. Treatment used (antibiotics, contraceptives, painkillers, sedatives)

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11. Medical recommendations (medications, contraceptives, hospitalization, specialist consultations)

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I consent to the notification of the law enforcement authorities about the incident

Patient's signature — Statutory representative's signature

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I consent to the examination and activities related to the collection of evidence (including tissue breakdown) and treatment procedures

Patient's signature — Statutory representative's signature

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I consent to the disclosure of medical documentation to law enforcement authorities

Patient's signature — Statutory representative's signature

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I declare that I have been informed about the negative consequences of disclosing medical confidentiality

Patient's signature — Statutory representative's signature

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Stamp and signature of the doctor who was examining and drawing up the test card — Stamp and signature of the assistant

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Successful perinatal management and pacemaker stimulation during the first hour of life in a 1.6 kg newborn with autoimmune congenital complete heart block diagnosed prenatally

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[2]*Department of Pediatric Cardiac Surgery, Jagiellonian University Medical College, Cracow, Poland*

[3]*Department of Obstetrics and Gynecology in Ruda Slaska, Medical University of Silesia, Ruda Slaska, Poland*

Key words: congenital heart block; Sjogren's syndrome; autoantibodies; pacemaker

Ginekologia Polska 2021; 92, 1: 80–81

Autoimmune congenital complete heart block (CCHB) occurs in 2–5% of pregnancies with anti-Ro/SSA (most common) and/or anti-La/SSB positive antibodies. The risk is higher in women with anti-Ro antiobodies in moderate (≥ 50 U/mL) and high (> 100 U/mL) titers, whereas an anti-La high titer is associated with non-cardiac features of neonatal lupus. After 16 weeks of gestation, antibodies cross the placenta and may destroy cardiomyocytes and conductive tissue in the atrio-ventricular node causing complete third degree heart block in more than 80% of cases. The highest risk of block development occurs up to 28 weeks of gestation. Current management of the condition includes: 1) decreasing inflammation through the administration of maternal fluorinated steroids and/or plasmapheresis; 2) increasing fetal cardiac output through beta-agonists administration; and 3) digoxin and/or lasix to treat hydrops and ventricular dysfunction. Direct fetal pacing was also tried but without success. Preliminary data suggest that a prophylactic treatment with hydroxychloroquine may be beneficial in preventing CCHB, but the safety of this drug should be evaluated. However, these therapies only have limited benefits and the mortality rate due to autoimmune CCHB is 16–30% of which 70% die in utero. Antibody-associated myocardial inflammation, dilated cardiomyopathy, ventricular rate < 55 bpm, impaired left ventricular function, fetal hydrops, diagnosis of CHB< 20 weeks, prematurity and low birth weight are the known risk factors of mortality. Therefore, pacemaker therapy should be considered in some cases after birth. However, there are only a few reports of pacemaker treatment for low birthweight infants with CCHB. Our report concerns a low birth infant with CCHB who underwent emergent pacemaker implantation in the first hour of life.

The 28-year old Polish Caucasian woman presented with Sjögren syndrome diagnosed 6 years earlier due to dry mouth and eyes, with Anti-SSA/Ro (151 RU/mL) and Anti-SSB/La (128 RU/mL) antiobdies, and was only on Plaquenil treatment. First trimester ultrasound screening showed normal anatomy and low risk of aneuploidy with a fetal heart rate (FHR) of 146 bpm (5th centile). Due to positive anti-Ro/La antibodies from the 16th week of pregnancy FHR was monitored weekly and at 18 weeks PR interval was 116 ms (Fig.1) whereas a week later a complete block was diagnosed by M-mode modality with an atrial rate of 134 bpm, a ventricular rate of 63 bpm (Fig. 2). Fetal echocardiogram demonstrated normal cardiac anatomy and CCHB with no signs of heart failure. After consultation with a prenatal cardiologist, dexamethason was prescribed. At 26 weeks of gestation, fibroelastosis (Fig. 3), cardiomegaly and a ventricular rate of 57 bpm were noticed, and salbutamol was introduced. After a week, the ventricular rate was 61 bpm. In the following weeks, a decrease in amniotic fluid, fetal growth retardation, and increased placental and uterine resistance were observed. At 36 weeks, because of anhydramnion, no weight gain, difficulties in fetal monitoring, decreased biophysical profile score to 7 and with cardiovascular profile of 7 (DV atrial reversal, holosystolic TR, heart size 0.45), it was decided to deliver the baby by cesarean section. The pediatric cardiovascular team set up an operating station in the delivery room. Physical examination after birth demonstrated a premature female infant in respiratory distress with a birth weight of 1600 g, Apgar scores 5/5/5, venous pH 7.198, and a ventricular rate of 45–50 bpm. The surfactant was administered, the child was intubated in moderate hypothermia (34.5 °C), and a limited median sternotomy was performed after umbilical arteriovenous vascular access. Two epicardial electrodes were fixed on the RV epicardial surface (apex and outflow tract) (Fig.4). Cardiac pacing with the external pacemaker was started at a rate of 110 bpm in VVI mode. After 2 months and the infant having reached 3.1 kg of body weight, the permanent pacemaker was implanted (Microny II SR+, St. Jude Medical) with stimulation in VVI mode. At the 2.5-year follow-up, the baby remains well without any complications.

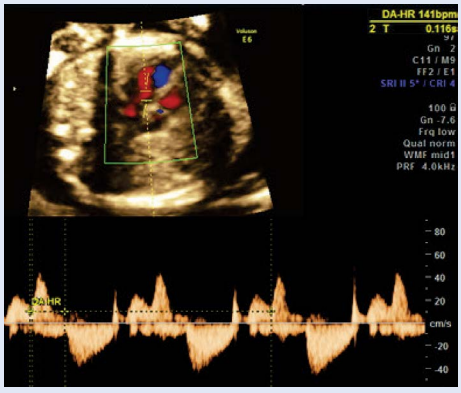

Figure 1. PR interval at 18weeks of gestation in a fetus with congenital complete heart block (CCHB)

To our knowledge, this is the first case of a pacemaker implantation due to autoimmune CCHB during the first hour of life, and with a long follow-up period, in Poland. This case report draws attention to the possibility of a sudden onset of the CCHB despite treatment with Plaquenil, difficulties in antenatal monitoring as Doppler parameters of umbilical artery, ductus venosus and extra-sinus slow FHR with no variation during fetal movements and uterine contractions

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phone: +48 600 243 156; e-mail: anna.3.wojtowicz@uj.edu.pl

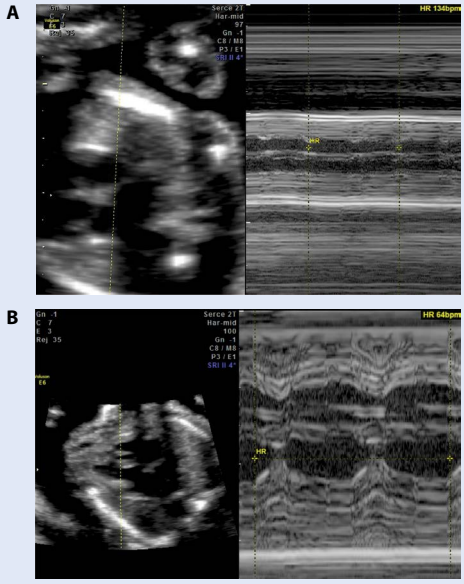

Figure 2. Atrial rate (**A**) and ventricular rate (**B**) at 19 weeks of gestation in a fetus with congenital complete heart block (CCHB)

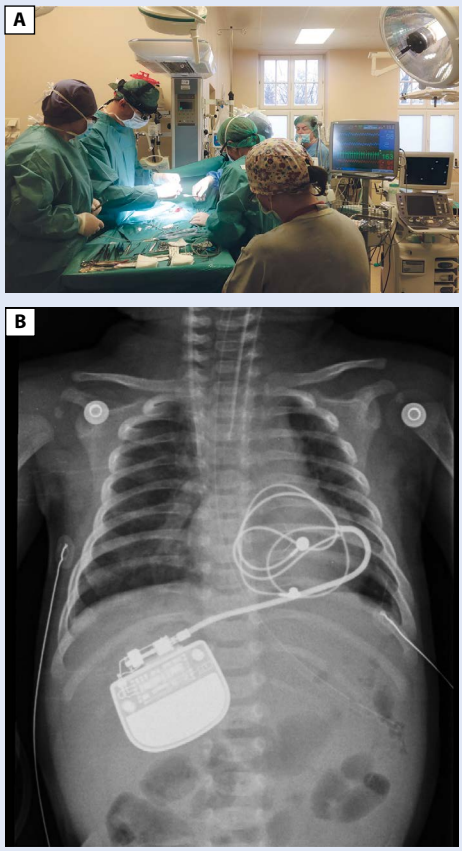

Figure 4. Pacemaker implantation in the delivery room in a newborn with congenital complete heart block (CCHB); **A.** Pediatric cardiac surgery team; **B.** Chest x-ray image of pacemaker implant

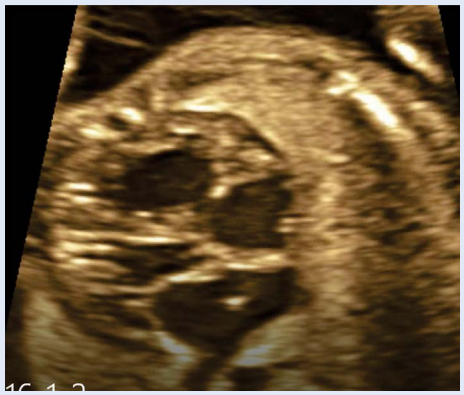

Figure 3. Four chamber view with endocardial fibroelastosis in a fetus with congenital complete heart block (CCHB)

are not useful. However planned delivery with a multidisciplinary team, followed by early pacemaker implantation may be an option for a severly affected newborns with CCHB. Temporary wires and external stimulation preceding the implantation of the permanent pacemaker seems to be the reasonable choice in newborns with low body weight.

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VIA MEDICA

CLINICAL VIGNETTE

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Long-term response to hormone therapy in a young woman with aggressive pelvic angiomyxoma

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[2]Department of Pathology National Cancer Institute, Warsaw, Poland
[3]Department of Oncology, Military Institute of Medicine, Warsaw, Poland

Key words: aggressive angiomyxoma; antiestrogen therapy; pelvic tumor

Ginekologia Polska 2021; 92, 1: 82–83

A 39-year-old woman initially presented in May 2014 after transrectal core needle biopsy of the pelvic tumor. Pathology examination showed a spindle shaped cells within a predominantly myxoid richly vascularized stroma, nuclear atypia and low mitotic activity. Another tumor fragment included some adipose tissue and some thick bundles of smooth muscle. The tumor was diagnosed as an aggressive angiomyxoma (AAM) based on the positive staining with desmin, CD34, estrogen receptor and some convincing positive nuclear staining for HMGA2, especially in the more myxoid component. A diagnostic magnetic resonance imaging (MRI showed a huge mass in the retroperitoneal space (size 113 × 65 × 130 mm; volume 300 cm^3) with tissue adhesion to the anal muscle levator on the right side and to the vaginal vestibule wall (with possible infiltration) (Fig. 1A). The tissue filled the space behind the right part of the pubic symphysis and shaped the urinary bladder. The case was presented at sarcoma tumor board and was deemed to be unresectable. Based on literature review, the patient was administered subcutaneous gonadotropin-releasing hormone agonist (LHRH) in a dose of 3.6 mg every month. After 3 months of LHRH therapy, MRI showed a marked partial tumor regression, although the lesion still adhered and connected to the right leg of the clitoris, the vaginal wall and anal muscle levator on the right side (size 47 × 30 × 50 mm; volume 40 cm^3) (Fig. 1B). After another 3 months the tumor has doubled compared to the best response (size 90 × 40 × 85 mm; volume 115 cm^3). The pressure on adjacent structures increased and there was greater displacement of the rectum to the left. Additionally, there was more pronounced adhesion to the right muscle of the internal veil and filling of the space behind the shaft of the right pubic bone. The decision was made to continue with an off-label combination of LHRH and tamoxifen (20 mg daily). After 2 months, the control MRI showed partial regression (size 70 × 37 × 55 mm; volume 50 cm^3) (Fig. 1C). She has been continuing therapy for 6 years with good tolerance and response. AAM is a rare locally infiltrative mesenchymal tumor affecting young women and less frequently men [1, 2]. AAM usually develops in the perineal and pelvic regions. Most of AAMs show estrogen and progesterone receptor positivity and are likely to be hormone-dependent, although clinical data on sequential hormone therapy are scarce and mostly obtained from case reports [2–5]. The majority of cases concerned LHRH therapy before or after surgery, and demonstrated improving disease control with this approach [2–4, 6–14]. In a few cases, anti-estrogen therapy with tamoxifen, raloxifene or an aromatase inhibitor with LHRH showed activity in first or second-line treatment [11, 15–17].

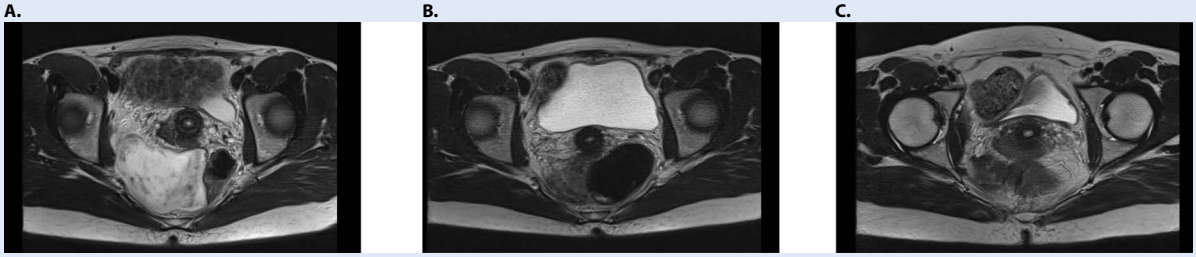

Figure 1. MRI of the pelvis, imaging sequences after administration of Gadovist 5 mL Siemens Magnetom Avanto 1.5 T contrast; **A.** At the diagnosis; **B.** After 3 months LHRH therapy; **C.** After 2 months LHRH and tamoxifen therapy

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In conclusion, off-label drug use is an opportunity for patients for whom formally approved therapy options have been exhausted or do not exist. Our study highlights the importance of sequential anti-estrogen hormone therapy, which may prove as an effective therapy in patients with hormone receptor positive AAMs. Lifetime follow-up to monitor for progression is mandatory.

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