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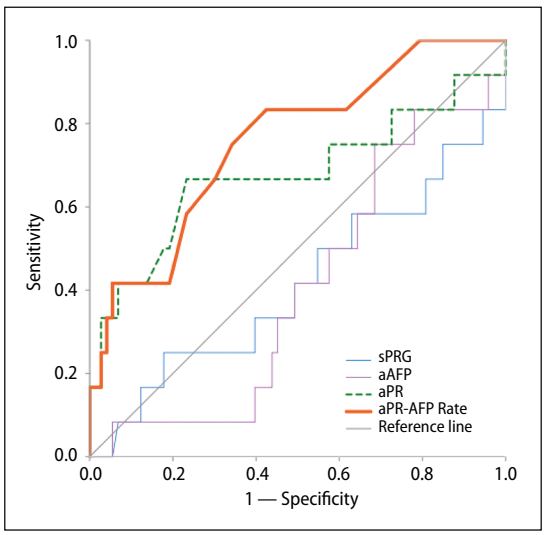

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EDITORIAL

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Aspects of gynaecological care for individuals with a transmasculine identity

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In recent decades, there has been a notable increase in professional acceptance of transgender individuals and their hormonal and surgical treatments. In the latest scientific reports, researchers are placing significant emphasis on the terminology used to describe this concept, as it undergoes continual redefinition. Earlier works may refer to this topic under the heading "transsexualism," which is gradually giving way to more inclusive and less pathologizing terminology such as "transsexuality" and "transgenderism." The eleventh revision of International Classification of Diseases (ICD-11) also has a non-pathologizing tone compared to the classification system for the diagnosis of mental disorders (DSM). In the ICD-11, transsexuality is defined as gender non-conformity. It has been relocated from the section of the classification related to mental disorders to a distinct category focusing on sexual health conditions. Gender non-conformity is defined as a persistent, marked incongruence between an individual's experienced gender and assigned gender. Currently, medicine has not developed uniform standards of treatment for potentially transsexual people. Detailed principles of diagnosis, treatment and therapy of patients suffering from persistent gender identity disorder differ in individual countries. The World Professional Association for Transgender Health (WPATH) has made an attempt to establish standards of conduct for individuals affected by permanent gender identity disorder and in September 2022 issued the eighth edition of the Standards of Care for the Health of Transsexual, Transgender, and Gender Non-conforming People (SOC) [1, 2].

The existing literature on this subject highlights the underrepresentation and marginalization of discussions concerning the reproductive health of transgender individuals. Hormone therapy restricts reproductive choices, underscoring the importance of patients making informed decisions regarding fertility before commencing hormonal and surgical treatments. The attending physician should discuss with the patient the importance and options for preserving their fertility prior to initiating treatment. These discussions should take place, even if patients are not currently prioritizing these concerns, which may be particularly relevant for younger individuals. Modern reproductive medicine allows for the preservation of fertility in people who, as a result of the disease or its treatment, may expect a significant reduction in fertility or even infertility — the patient should be informed that these techniques are not available everywhere and may be very expensive. Hormonal medications taken as part of gender reassignment therapy are not recommended or approved as contraceptives. Obstetrician-gynaecologists should ensure that transgender patients under their care are informed that testosterone treatments are not a suitable means of contraception for preventing pregnancy. Additionally, they should offer tailored contraception guidance to transgender patients engaging in sexual activity that may lead to pregnancy, irrespective of their testosterone use or pregnancy intentions. The use of testosterone preparations does not preclude the safe use of any hormonal or non-hormonal contraception, emergency contraception, or abortifacient drugs [2, 3].

In Poland, recent research indicates that every transgender patient consulting a specialist undergoes an individual interdisciplinary evaluation for gender identity concerns. This evaluation plays a key role in determining the duration of the diagnostic process and addressing subsequent steps related to this process.

In the research report titled "Transgenderism and Healthcare in Poland," published by the Trans-Fuzja Foundation, it is noted that there continues to be a scarcity of healthcare professionals with expertise in the field of gender identity in Poland. The diagnostic process itself is difficult and requires extensive knowledge and experience from specialists. The report highlights that the subject of transgenderism in master's programs within psychology and

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medicine is occasionally minimized, with its inclusion limited to optional courses. Transgender people benefit from medical and psychological support throughout their lives, it does not end with the diagnostic process. These people usually take hormonal drugs for the rest of their lives, which can cause many side effects. Therefore, transsexual people turn to public and private institutions for help and have difficulties accessing services due to the lack of knowledge of specialists who not only refuse to help, but also are unable to indicate another person who can provide a given service. This document draws attention to the lack of educational materials for doctors and psychologists, which results in systemic discrimination — transsexual people are looking for solutions to their problems in the field of injection supply on their own, as well as foreign centres that provide such individuals with comprehensive care, which, of course, involves huge financial outlay [2–6].

Cancer prevention is a crucial component of gynaecological care for transgender individuals, with special focus on transgender men who possess a uterus and cervix. Like cisgender women, these individuals should undergo cervical cancer screenings. When performing a cytological test in transsexual men, the patient should be informed that due to the testosterone preparation he is taking, there may be a risk of screening failure and the need for a follow-up test. In general, as in cisgender women, if the Pap test fails, it should be repeated within the next 2–4 months. In the case of transsexual men who require repeated cytological examination, as in the case of postmenopausal women, initial treatment with an oestrogen preparation administered vaginally for a period of five days should be performed - which may reduce the percentage of unsatisfactory test results in the presence of atrophic changes [1–7].

In summary, providing care for transgender patients is a highly significant and pertinent topic for medical professionals. It should not only be considered that a transgender person may be heterosexual, homosexual or bisexual, but also attention should be paid to specific health problems related to the process of gender change. Any medical examination must be performed in accordance with the patient's sexual organs, not the presumed gender. An example of neglect in the field of proper medical care is the small number of trans men covered by breast cancer prevention and trans women examined for prostate cancer. The process of surgical gender reassignment is associated with specific health issues of a given group of patients. A common complication in trans men after phalloplasty surgery is problems with micturition. In trans women, strictures and fistulas of the urogenital system are most often observed after transition. In addition to surgical intervention, a transsexual patient should be under constant care of an endocrinologist. In case of increased exogenous supply of oestrogens, the risk of thrombosis, hypertension and diabetes increases. During testosterone therapy, attention should be paid to the increased risk of stroke or myocardial infarction and severe liver damage. Therefore, an interdisciplinary approach to a transgender patient is necessary, ensuring his physical and mental well-being [7, 8].

Article information and declarations

Conflict of interest

All authors declare no conflict of interest.

REFERENCES

1. Tishelman A, Rider G. Assessment of Gender Diverse Children. Child and Adolescent Psychiatric Clinics of North America. 2023; 32(4): 719–730, doi: 10.1016/j.chc.2023.05.008.
2. Smaś-Myszczyszyn M, Ryziński R. Podsumowanie najważniejszych zmian w obrębie zaburzeń seksualnych i zdrowia seksualnego, które wprowadza najnowsza rewizja Międzynarodowej Statystycznej Klasyfikacji Chorób i Problemów Zdrowotnych ICD-11. Przegląd Psychologiczny. 2022; 65(2): 9–27, doi: 10.31648/przegldpsychologiczny.7678.
3. Milionis C, Ilias I, Koukkou E. Progesterone in gender-affirming therapy of trans women. World Journal of Biological Chemistry. 2022; 13(3): 66–71, doi: 10.4331/wjbc.v13.i3.66.
4. Nowakowski A, Jach R, Szenborn L, et al. Recommendations of the Polish Society of Gynaecologists and Obstetricians, Polish Paediatric Society, Polish Society of Family Medicine, Polish Society of Vaccinology, Polish Society of Oncological Gynaecology and Polish Society of Colposcopy and Pathophysiology of the Uterine Cervix on prophylactic vaccinations against infections with human papillomaviruses in Poland. Ginekol Pol. 2022 [Epub ahead of print], doi: 10.5603/GP.a2022.0101, indexed in Pubmed: 36134760.
5. Sobczyk K, Woźniak-Holecka J, Holecki T, et al. The organization and financing of cervical cancer prevention carried out by midwives in primary health care. Ginekol Pol. 2016; 87(12): 798–804, doi: 10.5603/GP.2016.0091, indexed in Pubmed: 28098929.
6. Connolly D, Hughes X, Berner A. Barriers and facilitators to cervical cancer screening among transgender men and non-binary people with a cervix: A systematic narrative review. Prev Med. 2020; 135: 106071, doi: 10.1016/j.ypmed.2020.106071, indexed in Pubmed: 32243938.
7. Jach R, Mazurec M, Trzeszcz M, et al. Cervical cancer screening in Poland in current SARS-CoV-2 pandemic: Interim guidelines of the Polish Society of Gynecologists and Obstetricians and the Polish Society of Colposcopy and Cervical Pathophysiology - a summary January 2021. Ginekol Pol. 2021; 92(2): 165–173, doi: 10.5603/GP.2021.0043, indexed in Pubmed: 33751524.
8. Wojcik M, Plagens-Rotman K, Merks P, et al. Visceral therapy in disorders of the female reproductive organs. Ginekol Pol. 2022; 93(6): 511–518, doi: 10.5603/GP.a2022.0021, indexed in Pubmed: 35766196.

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Comparison of the efficacy of pharmacological and nonpharmacological treatments in women with primary dysmenorrhea: randomized controlled parallel-group study

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ABSTRACT

Objectives: To compare the effectiveness of pharmacological (PT) and nonpharmacological treatments (NPT) in women with primary dysmenorrhea (PD) and determine the most effective treatment method.

Material and methods: We enrolled 85 PD participants with PD who were randomly classified into five groups: pharmacological groups; naproxen sodium (NS) and micronized purified flavanoid fraction (MPFF), nonpharmacological groups; motor imagery focused pelvic floor exercise (MOPEXE) and acupressure, and no treatment group; control. Initial assessment was conducted in all groups on the first day of the menstrual cycle. After the end of the third menstrual cycle, the specialist physiotherapist and the obstetrician conducted a final evaluation. Intensity and nature of pain were evaluated with the Short-Form McGill Pain Questionnaire (SF-MPQ), and menstrual attitudes and behaviors were evaluated using the Menstruation Attitude Questionnaire (MAQ).

Results: In the total pain dimension scores, which are the sum of the affective dimension of pain and sensory dimension scores, the pre–post treatment difference was the highest in the mean of the total pain dimension. The highest was for MOPEXE (15.12 ± 4.44), followed by MPFF (7.53 ± 6.8); acupressure (7.47 ± 5.28) and NS (4.47 ± 4.91) showed more significant change than the control group ($p = 0.001$). The mean difference in visual analog scale (VAS) scores was highest in MOPEXE (4.53 ± 1.5), followed by acupressure (2.35 ± 1.66); MPFF (1.88 ± 1.73) and NS (1.65 ± 1.84) scores were more significant than the control group ($p = 0.001$). Regarding total pain intensity, the highest was MOPEXE (2.59 ± 0.94), followed by MPFF (1.18 ± 0.88); acupressure (1.06 ± 0.83) and NS (0.82 ± 1.01) scores were more significant compared to the control group (p = 0.001). There was no significant change in the pre–post difference values in the MAQ subparameters: menstruation as deliberate event, menstruating as bothersome event, menstruation as natural event, anticipation and prediction of the onset of menstruation, and denial of any effects of menstruation; menstruation as a natural event resulted in insignificant changes in parameters (p = 0.579, p = 0.074, p = 0.892, p = 0.056, p = 0. 377).

Conclusions: PT and NPT methods in the study were effective in coping with PD-associated pain. MPFF was more effective than the NS group in terms of relieving pain. In terms of pain, MOPEXE and acupressure groups were as effective as PT. The most effective of these treatment methods was the MOPEXE group created by the researcher.

Keywords: acupressure; drug therapy; dysmenorrhea; exercise

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INTRODUCTION

Dysmenorrhea is a menstrual disorder that occurs in women of reproductive age. Dysmenorrhea symptoms can be seen in many ways such as pain in the lower abdomen and back during menstruation, nausea, vomiting, and headache [1]. The two types of dysmenorrhea are as follows: primary dysmenorrhea (PD) and secondary dysmenorrhea. The type of dysmenorrhea is diagnosed by evaluating the

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medical history and ultrasonography. Dysmenorrhea without an underlying organic problem is called PD. Primary dysmenorrhea etiology includes vasospasm in the myometrium along with an increase in prostaglandin production in the endometrium during the menstrual cycle and uterine hypercontraction with ischemia. Secondary dysmenorrhea is a type of dysmenorrhea that occurs in pathological conditions with anatomical and physiological differences [2].

The incidence of dysmenorrhea in different societies ranges from 16% to 90% [1]. Examination of the treatment options for dysmenorrhea in the literature revealed that nonsteroidal anti-inflammatory drugs (NSAID), one of the pharmacological approaches, was the most commonly used treatment option [3]. There are many different drugs used to treat PD. One of these drugs is micronized purified flavonoid fraction (MPFF) [4], which has rarely been used in treating dysmenorrhea in the literature. Therefore, we compared the effectiveness of naproxen sodium (NS) and MPFF treatment in the present study.

Nonpharmacological PD treatments have been increasingly preferred in recent years because nonpharmacological treatments do not have side effects or which are very rare. In the literature, several nonpharmacological treatments currently exist for PD [5]. These nonpharmacological treatments can be summarized as lifestyle changes (reducing alcohol, smoking, and caffeine consumption; regular sleep; reducing daily salt and animal fat consumption; avoiding very hot and very cold foods and drinks; increasing plant-based nutrition, and so on) [6], vitamin-mineral supplements (zinc, vitamins E and B1, and so on) [7], herbal products (ginger, rose tea, fennel, valerian, honey, and so on) [7], and acupressure and acupuncture, which are traditional, complementary, and physiotherapy treatments (massage, electrotherapy, exercise, kinesio taping, and manipulation techniques) [8].

In systematic reviews, acupressure is one of the nonpharmacological treatments. Moreover, studies showing that acupressure therapy is as effective as pharmacological treatments in reducing dysmenorrhea symptoms were noted [9, 10].

Another NPT is exercise. Studies investigating the effects of exercise have shown that regular exercise can reduce pain and other symptoms and improve quality of life [11]. Several exercise types, including yoga, jogging, aerobic exercises, pilates, isometric exercises, stretching exercises, dance, breathing exercises, relaxation exercises and kegel exercises, have been used to treat PD [8].

In line with this information, there are many PT and NPT modalities applied to individuals with PD.

Objectives

This study aimed to identify the most effective treatment by comparing the efficacy of pharmacological approaches with exercise approaches and acupressure treatment, which is one of the traditional complementary therapies.

MATERIAL AND METHODS

This study was conducted on women with dysmenorrhea who applied to an obstetrician in Istanbul Medipol University Midwifery Practice Laboratory between February 2020 and January 2021. The study was approved by the Istanbul Medipol University Non-Invasive Clinical Research Ethics Committee with the decision number 10840098-604.01.01.-E.66761 dated December 25, 2019. The study was conducted as a randomized controlled parallel-group study, following the principles of human experimentation set in the Declaration of Helsinki and obtaining the approval of the ethics committee. The participants provided an informed consent form. The clinical trial number for this study is NCT0468785.

We recruited 120 participants to be considered for inclusion by a specialist physician. The study was completed with 85 participants. Figure 1 depicts the flow of participants through the study.

The inclusion criteria of this study were being between 18 and 30 years old, having an active menstrual cycle, and having a positive PD diagnosis using ultrasonographic evaluation by an obstetrician. In this study, the participants were evaluated by an obstetrician using pelvic ultrasonography. In the supine position with full bladder, participants with dysmenorrhea were assessed using pelvic ultrasonography. Obstetrician examination was performed as described in the literature [12].

Study exclusion criteria were hormonal therapy (*e.g.*, patients using progesterone for premenstrual syndrome or dopamine for galactorrhea), psychiatric treatment, intrauterine contraception, use of birth control pills, diagnosed secondary dysmenorrhea, neurological disorders, gastric ulcer, history of gastrointestinal bleeding, history of drug allergy, presence of asthma, presence of disease-causing bleeding disorders, and presence of vascular disease. Moreover, patients with kidney and liver disease were excluded from the study.

Additionally, during the treatment period, participants who received any pharmacological or nonpharmacological treatment other than the treatment type determined in all groups and who were prescribed regular MPFF and NS treatment for any disease other than the menstrual period were excluded from the study.

Participants were randomly divided into five groups (NS, MPFF, acupressure, MOPEXE [created for the first time by the researcher], and the control).

Participants who met the inclusion criteria for randomization were given enrollment numbers by the physician. The enrollment numbers were randomly selected and grouped by the researchers and groups were recorded.

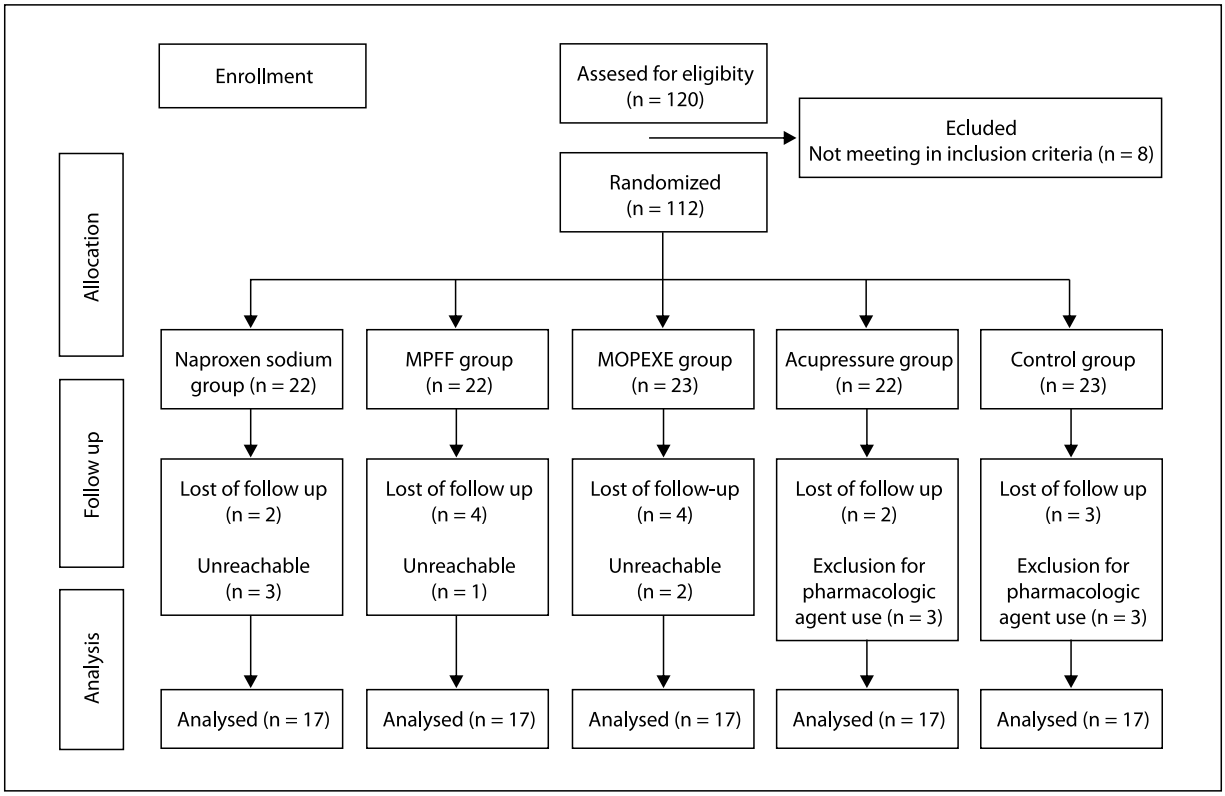

Figure 1. Consort flowchart. MOPEXE — motor imagery focused pelvic floor exercise group; MPFF — micronized purified flavanoid fraction group

Following the physician's examination, an initial assessment was conducted in all groups on the first day of the menstrual cycle. The specialist physiotherapist and the obstetrician conducted the final evaluation after the end of the third menstrual cycle.

Treatment groups

Naproxen sodium group

Naproxen sodium is a pharmacological agent of the NSAID class that has analgesic, antipyretic, and anti-inflammatory effects. It is widely used in dysmenorrhea [13]. Naproxen sodium reduces symptoms of dysmenorrhea by inhibiting cyclooxygenase (COX-1 and COX-2) enzymes and preventing prostaglandin formation [3]. Participants began NS therapy in the first menstrual cycle following the assessment. NS treatment was administered as 550 mg tablets twice a day at most. The treatment was applied only in the menstrual cycle during the 12-week period.

Micronized purified flavanoid fraction group

Micronized purified flavanoid fraction group is a U.S. Food and Drug Administration approved medication used in our country. Micronized purified flavanoid fraction group contains 90% diosmin and 10% hesperidin. Micronized purified flavanoid fraction group acts on the venous system and reduces venous distension and stasis [14]. Micronized purified flavanoid fraction group treatment in dysmenorrhea suppresses prostaglandins E2, F2a, thromboxane A2, and prostacyclin; reduces capillary hyperfragility, and increases lymphatic drainage [15]. In the present study, MPFF was used as 90% diosmin and 10% hesperidin in women with PD. Participants began MPFF therapy in the first menstrual cycle following assessment. MPFF treatment was administered in the form of 500 mg tablets twice a day at most. The treatment was applied only in the menstrual cycle during the 12-week period.

Motor imagery focused pelvic floor exercise group

Motor imagery focused pelvic floor exercise group is an exercise model created by the researcher for the first time, combining Pilates-based exercises with the motor imagery technique accepted in the literature.

The steps to be followed for 60 minutes in the MOPEXE include the following: meditation therapy for five minutes, accelerated progressive relaxation exercises (Bernstein–Borkovec) for 10 min, breathing exercises (diaphragmatic & pursed lip) for five minutes, MOPEXEs for 35 minutes (pelvic stretching, core, and pelvic floor exercises), and meditation therapy for five minutes. Motor imagery focused pelvic floor exercise group consists of Pilates-based exercises. Motor imagery focused pelvic floor exercise group was applied to the participants for 60 minutes twice a week for

12 weeks. The first three sessions were held face-to-face so that the participants could learn the exercises. Subsequent sessions were continued as telerehabilitation. Owing to the COVID-19 pandemic, the participants were followed up with the telerehabilitation method. Telerehabilitation was performed in groups and online via computer or smartphone.

As motor imagery, the participants were instructed to imagine that they had a ping pong ball in their vagina, and they were asked to squeeze their pelvic floor muscles to keep this imaginary ball in their vagina for 10 seconds. Later, they were asked to relax their pelvic floor muscles for 6 seconds. The intensity of the exercises was increased every 2 weeks and the exercise was performed for both type 1–2 muscle fibers. Motor imagery focused pelvic floor exercise group exercises were uploaded to www.mopexe.com, thereby allowing participants to continue the exercises after the treatment. Photos of exercises performed in the MOPEXE group (pelvic stretching, core, and pelvic floor exercises) are available at www.mopexe.com.

Acupressure group

Acupressure therapy, which is a noninvasive method applied in Chinese medicine, is a technique performed by applying pressure to the acupoints of the meridians in our body, causing mild pain [16].

In the literature review, CV-6 and CV-4 were acupressure points and LI-4 and SP-6 were bilateral administration [17, 18]. Acupressure was applied to these points for 10 min, twice a day, 10 times (60 s), with 5 s pressure applied to these points and 1 s rest. Acupressure application was taught to the participants by an expert physiotherapist who was trained in acupressure.

Acupressure points were determined by an expert physiotherapist who was trained on this subject. The participants were taught how to apply acupressure on the acupressure points on their own. The first three sessions were held face-to-face. Participants were asked to apply 10 minutes of acupuncture to the determined acupuncture points twice a day, in the morning and evening, for 12 weeks. Reminder notifications for acupressure applications were sent by text message during the day. Participants' feedback was recorded. Therefore, the participants were encouraged to do the exercises regularly.

Control group

In this study, the women included in the control group were asked to stay away from all treatments for 12 weeks. They were informed via daily text messages to refrain from taking any treatment. Feedback was recorded. As a result of this feedback, participants who received pharmacological and nonpharmacological treatment were excluded from the study. After the study ended, the participants were presented with treatment options. Treatment was initiated in selected groups.

Outcome measures

In the present study, changes in dysmenorrhea symptoms between groups and before and after treatment were evaluated using the Short-Form McGill Pain Questionnaire (SF-MPQ) and Menstruation Attitude Questionnaire (MAQ). The demographic characteristics of the participants were recorded.

SF-MPQ

The quality and severity of the pain felt by the participants during menstruation were evaluated with the SF-MAQ. Yakut et al. [19] conducted the Turkish validity and reliability study. It evaluates the sensory dimension of pain and the affective dimension of pain. Affective and sensory dimension scores of pain are measured using a Likert-type scale (0 — no pain, 3 — severe pain). Pain severity was assessed using the visual analog scale (VAS) in the Mcgill Pain Questionnaire. The total pain dimension subparameter is the sum of the sensory dimension and the affective dimension of the pain. Total pain intensity is measured with a 6-point Likert-type scale (0 — no pain, 5 — unbearable pain). A high score indicates a high level of pain [19].

Menstruation Attitude Questionnaire

Menstruation Attitude Questionnaire is applied to determine the attitudes and behaviors of the participants during menstruation. Furthermore, Kulakaç et al. [20] conducted the Turkish validity and reliability study. Evaluated subdimensions include menstruation as a deliberate event, menstruating as a bothersome event, menstruation as a natural event, anticipation and prediction of the onset of menstruation, and denial of any effects of menstruation. The scale is evaluated using a 5-point Likert-type." A high mean score indicates a "positive" attitude toward menstruation [20].

Statistical analysis

Data analysis was performed using SPSS (IBM SPSS, Chicago, IL, USA) 22.0 package program. Shapiro–Wilk test was used as a normality test. Between groups comparisons were made using the one-way ANOVA, Brown–Forsythe, or Kruskal–Wallis tests following the normality test results.

Tukey and Tamhane tests were used as post hoc tests. Pre and posttreatment comparisons were made with Paired Samples t-test and Wilcoxon signed rank test. The Chi-square test was used in the analysis of categorical variables. Statistical significance was indicated by $p < 0.05$ in all analyses.

The sample size was calculated as 85 individuals in G*Power 3.1.9.4 program for five groups and two time points, with 80% power, 5% type I error, and a minimum

Table 1. Demographic characteristics of the participants (n = 85)

Variables		NS mean ± SD/n (%)	MPFF mean ± SD/n (%)	MO mean ± SD/n (%)	Ac mean ± SD/n (%)	C mean ± SD/n (%)	Total mean ± SD/n (%)	p value
Age [years]		20.47 ± 1.12	19.82 ± 1.13	19.76 ± 1.14	20.17 ± 0.95	20.91 ± 1.87	20.23 ± 1.39	0.061*
BMI [kg/m^2]		22.15 ± 3.68	21.58 ± 2.80	21.91 ± 2.97	22.23 ± 3.75	21.61 ± 3.37	22.09 ± 3.31	0.641*
Age of menarche	10–14 years	17 (100)	15 (88.2)	15 (88.2)	13 (76.5)	14 (82.4)	74 (87.1)	
	15–18 years	0 (0.0)	2 (11.8)	1 (5.9)	4 (23.5)	3 (17.6)	10 (11.8)	
	18 years over	0 (0.0)	0 (0 0)	1 (5.9)	0 (0.0)	0 (0.0)	1 (1.1)	**0.295**
Menstrual period	1–3 days	0 (0.0)	1 (5.9)	0 (0.0)	1 (5.9)	1 (5.9)	3 (3.5)	
	4–5 days	5 (29.4)	4 (23.5)	6 (35.3)	6 (35.3)	4 (23.5)	25 (29.4)	
	6–7 days	9 (52.9)	9 (52.9)	9 (52.9)	6 (35.3)	8 (47.1)	41 (48.2)	
	8–10 days	3 (17.6)	3 (17.6)	2 (11.8)	4 (23.5)	4 (23.5)	16 (18.8)	**0.973**
Menstrual cycle length	< 10 days	1 (5.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.2)	
	10–15 days	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.9)	1 (1.2)	
	16–20 days	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.9)	2 (11.8)	3 (3.5)	
	20–25 days	3 (17.6)	5 (29.4)	1 (5.9)	5 (29.4)	2 (11.8)	16 (18.8)	0.270
	26–30 days	10 (58.8)	10 (58.8)	13 (76.5)	9 (52.9)	9 (52.9)	51 (60.0)	
	30–40 days	3 (17.6)	1 (5.9)	0 (0.0)	0 (0.0)	2 (11.8)	6 (7.1)	
	Irregular	0 (0.0)	1 (5.9)	3 (17.6)	2 (11.8)	1 (5.9)	7 (8.2)	
Family history of dysmenorrhea	No	6 (35.3)	8 (47.1)	3 (17.6)	6 (35.3)	3 (17.6)	26 (30.6)	
	Yes, mother	4 (23.5)	5 (29.4)	6 (35.3)	4 (23.5)	4 (23.5)	23 (27.1)	
	Yes, sisters	2 (11.8)	1 (5.9)	3 (17.6)	3 (17.6)	4 (23.5)	13 (15.3)	0.782
	Yes, mother's relatives	1 (5.9)	1 (5.9)	1 (5.9)	3 (17.6)	1 (5.9)	7 (8.2)	
	Yes, father's relatives	1 (5.9)	1 (5.9)	1 (5.9)	0 (0.0)	0 (0.0)	3 (3.5)	

p*: One-Way ANOVA; p: Chi-square test. p < 0.05 was considered significant; Ac — acupressure group; BMI — body mass index; C — control group; MO — motor imagery focused pelvic floor exercise group (MOPEXE) group; MPFF — micronized purified flavanoid fraction group; n — number of participants; NS — naproxen sodium group; SD — standard deviation

0.20-correlation between variables and 25% effect size. The G* power analysis of the study was reached.

RESULTS

A total of 85 women with PD participated in this study. Table 1 shows the demographic characteristics of the participants. Furthermore, there is no significant difference in demographic characteristics across the groups (p > 0.05), as shown in Table 1.

The nondrug coping methods of the participants with dysmenorrhea symptoms are shown in Table 2. There was no significant difference between the groups with nondrug coping methods with dysmenorrhea symptoms 3 months before (p = 0.421).

When the SF-MPQ scores of the treatment groups were compared before the treatment, there were no significant intergroup differences, except for the total pain intensity (p > 0.05). Table 3 lists the pre and posttreatment values of SF-MPQ scores and the differences between the groups.

The difference between the groups in total pain intensity before treatment was between NS and Acupressure groups (p < 0.05). Significant changes were observed between the groups and after treatment in all subdimensions including sensory dimension, affective dimension, total pain dimension, VAS, and total pain intensity (p < 0.001). The greatest change within a specific group was observed in the MOPEXE group. Relative changes in SF-MPQ are shown in Figure 2.

Table 4 shows the pre and posttreatment values of MAQ scores and the differences between the groups. In the pretreatment evaluation of the MAQ, a significant difference was observed between the groups before treatment in the subparameters of "Menstruation as a deliberating event," "Menstruation as a natural event," and "Denial of any effects of menstruation" (p < 0.05). This difference was between the control group and the other groups. There was no significant difference between the groups after the treatment (p > 0.05). Figure 3 depicts the changes in MAQ pre and posttreatment and relative changes between groups.

DISCUSSION

There are different treatments for PD [9]. However, the number of studies examining the superiority of the treatments

Table 2. Nondrug coping methods with dysmenorrhea symptoms 3 months ago (n = 85)

Nondrug coping methods with dysmenorrhea symptoms 3 months before	NS n (%)	MPFF n (%)	MO n (%)	Ac n (%)	C n (%)	TOTAL n (%)	p value
Exercise	0 (0.0)	1 (5.9)	1 (5.9)	0 (0.0)	1 (5.9)	3 (3.5)	0.421
Hot application	3 (17.6)	4 (23.5)	4 (23.5)	1 (5.9)	4 (23.5)	16 (18.8)	
Acupressure	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.9)	1 (5.9)	2 (2.4)	
Lying prone and assuming the fetal position	3 (17.6)	1 (5.9)	1 (5.9)	0 (0.0)	1 (5.9)	6 (7.1)	
Exercise, hot application, herbal tea	1 (5.9)	2 (11.8)	3 (17.6)	2 (11.8)	5 (29.4)	13 (15.3)	
Hot application, herbal tea, lying in prone position, and assuming fetal position	10 (58.8)	8 (47.1)	8 (47.1)	9 (52.9)	4 (23.5)	39 (45.9)	
Acupressure, herbal tea, meditative approaches	0 (0.0)	0 (0.0)	0 (0.0)	2 (11.8)	0 (0.0)	2 (2.4)	
All	0 (0.0)	1 (5.9)	0 (0.0)	2 (11.8)	1 (5.9)	4 (4.7)	

p: Chi-square test; p < 0.05 was considered significant; Ac — acupressure group; C — control group; MO — motor imagery focused pelvic floor exercise group (MOPEXE) group; MPFF — micronized purified flavanoid fraction group; n — number of participants; NS — naproxen sodium group

used in the treatment of dysmenorrhea is insufficient [5]. Therefore, the present study compared the effectiveness of different treatments used in dysmenorrhea. In the present study, while the change in SF-MPQ scores was significant in all PT and NPT groups, no significant change was found in the MAQ scores in which menstrual attitudes and behaviors were evaluated.

Primary dysmenorrhea is a gynecological problem that commonly occurs between the ages of 17–24 years [1]. In terms of body mass, PD is also seen in women with normal body mass index [1]. The present study is consistent with the literature.

In the literature, NSAIDs are the first treatment option in PD [3, 13]. Many studies investigating the effects of NSAID showed improved symptoms of dysmenorrhea [13]. In a study, the pain change of acetaminophen and NS within 12 hours in PD was investigated. Pain changes were evaluated using "*Total Pain*" Relief and Sum of Pain Intensity Difference. As a result of the evaluations, NS was found to be more effective than acetaminophen [21]. Ortiz et al. [22], the effect of naproxen-paracetamol-pamabrom versus pyrilamine-paracetamol-pamabrom treatment on pain change was compared, and it was observed that both treatments reduced PD symptoms according to VAS, but had no superiority over each other. Similar to these studies, the intensity and nature of pain were evaluated with the SF-MPQ in the present study. In this study, the change in SF-MPQ scores was significant in all groups.

Another pharmacological agent used in our study was MPFF. Mukherjee et al. [4], the efficacy of MPFF in women with abnormal uterine bleeding was investigated during three menstrual cycles. In the study, pain change was evaluated using the VAS. MPFF treatment was shown to be effective in reducing pain for treating dysmenorrhea.

Similar to the present study, treatment continued for three menstrual cycles. Pain change was evaluated with SF-MPQ. Micronized purified flavanoid fraction group treatment was found to be an effective pharmacological treatment in reducing pain from dysmenorrhea symptoms. Although MPFF treatment is effective on dysmenorrhea, it is rarely used in the literature. More detailed evaluations are needed in the future to disseminate the use of MPFF treatment.

In recent years, many alternative treatment and exercise approaches, which are preferred in the treatment of dysmenorrhea owing to mild or nonexistent side effects, have been discussed in the literature [9, 10]. In some studies, the effects of alternative therapies and exercise approaches were found to be similar to the effects of NSAID therapy [23, 24].

Motahari-Tabari et al. [23], the effects of stretching exercises and mefenamic acid treatment were compared. Pain changes and intensity were evaluated using the VAS. The study lasted two menstrual cycles. Based on the results of this study, it was found that stretching exercises were as effective as mefenamic acid in coping with pain.

In another study [24], the effects of ginger tablets and mefenamic acid treatment on pain in dysmenorrhea were compared. The study lasted two menstrual cycles. Pain changes and pain intensity were evaluated using the VAS. The effect of ginger is similar to ibuprofen and mefenamic acid as determined on the basis of the results of the current study.

The assessments of the current study are similar to the literature. Moreover, the treatment in the current study

Table 3. Results of McGill-Melzack Pain Form (SF-MPQ) subparameters pre-treatment-post-treatment scores and intergroup differences

SF-MPQ	Groups	Pretreatment X ± SD	Posttreatment X ± SD	Difference	
				X ± SD	p_{time}
Sensory dimension of pain	NS	19.59 ± 2.62	16.29 ± 4.38	3.29 ± 3.72	0.002
	MPFF	19.94 ± 3.54	14.12 ± 5.18	5.82 ± 5.21	< 0.001
	MOPEXE	18.24 ± 3.67	7.18 ± 1.85	11.06 ± 2.59	< 0.001
	Acupressure	18.47 ± 2.92	12.76 ± 3.72	5.71 ± 4.31	< 0.001
	Control	18.29 ± 4.97	16.43 ± 4.29	1.75 ± 1.6	< 0.001
p_{group}		0.517	< 0.001	< 0.001*	
Affective dimension of pain	NS	5.59 ± 1.37	4.41 ± 1.84	1.18 ± 1.47	0.011**
	MPFF	5.76 ± 1.82	4.06 ± 2.01	1.71 ± 1.72	0.001*
	MOPEXE	6.18 ± 2.51	2.12 ± 0.93	4.06 ± 2.16	< 0.001**
	Acupressure	5.47 ± 1.33	3.71 ± 1.83	1.76 ± 1.2	0.001*
	Control	6.59 ± 2.06	6.08 ± 1.93	0.51 ± 0.7	0.009*
p_{group}		0.410	< 0.001	< 0.001	
Total pain dimension	NS	25.18 ± 3.61	20.71 ± 5.8	4.47 ± 4.91	0.002
	MPFF	25.71 ± 4.96	18.18 ± 6.87	7.53 ± 6.8	< 0.001
	MOPEXE	24.41 ± 5.62	9.29 ± 2.11	15.12 ± 4.4	< 0.001
	Acupressure	23.94 ± 3.21	16.47 ± 5.29	7.47 ± 5.28	< 0.001
	Control	24.88 ± 6.79	22.51 ± 5.84	2.25 ± 1.72	< 0.001
p_{group}		0.868	< 0.001	< 0.001*	
Visual Analog Scale (VAS)	NS	7.65 ± 1.41	6 ± 2.03	1.65 ± 1.84	0.002*
	MPFF	7.47 ± 2.12	5.59 ± 2.58	1.88 ± 1.73	0.002**
	MOPEXE	7.47 ± 1.23	2.94 ± 1.2	4.53 ± 1.5	< 0.001*
	Acupressure	7.06 ± 1.09	4.71 ± 1.79	2.35 ± 1.66	0.001**
	Control	6.29 ± 1.83	5.7 ± 1.5	0.59 ± 1.36	0.086**
p_{group}		0.144*	< 0.001	< 0.001	
Total Pain Intensity	NS	4.35 ± 0.7	3.53 ± 1.07	0.82 ± 1.01	0.006**
	MPFF	3.71 ± 0.92	2.53 ± 1.33	1.18 ± 0.88	0.001**
	MOPEXE	3.82 ± 0.73	1.24 ± 0.44	2.59 ± 0.94	< 0.001**
	Acupressure	3.24 ± 0.56	2.18 ± 1.01	1.06 ± 0.83	0.002**
	Control	3.82 ± 0.81	3.74 ± 1.01	0.08 ± 0.43	0.336**
p_{group}		0.002*	< 0.001*	< 0.001	

p_{group}: Brown–Forsythe, *Kruskal–Wallis Test, p_{time}: Paired Sample T-Test, **Wilcoxon Signed Rank Test; Ac — acupressure group; C — control group; MOPEXE — motor imagery focused pelvic floor exercise group; MPFF — micronized purified flavanoid fraction group; n — number of participants; NS — naproxen sodium group; SD — standard deviation; X — mean

lasted three menstrual cycles. The study strength is that the treatment duration was longer than in other studies**.**

When the studies on acupressure treatment, which is one of the nonpharmacological approaches, are examined, it is seen that different acupuncture points are investigated in the literature. Yu et al. [17], it was noted that the most commonly used acupuncture points in the treatment of dysmenorrhea were SP-6, SP-8 CV-3, CV-4, CV-6, and BL-32. Blödt et al. [25] also evaluated the effect of the self-acupressure application on LR-3, LI-4, and SP-6 points on PD symptoms using the Numeric Rating Scale. Self-acupressure is effective in reducing pain from dysmenorrhea symptoms. The study was conducted over the phone during six menstrual cycles and reported that the acupressure effectiveness would be demonstrated with at least three menstrual cycles.

In the current study, similar to the literature, self-acupressure was applied to CV-6, CV-4, LI-4, and SP-6 points during three menstrual cycles. Moreover, the pain was evaluated with the MPQ in the current study. Furthermore, acupressure points similar to the literature were used. In this respect, the current study is similar to the literature.

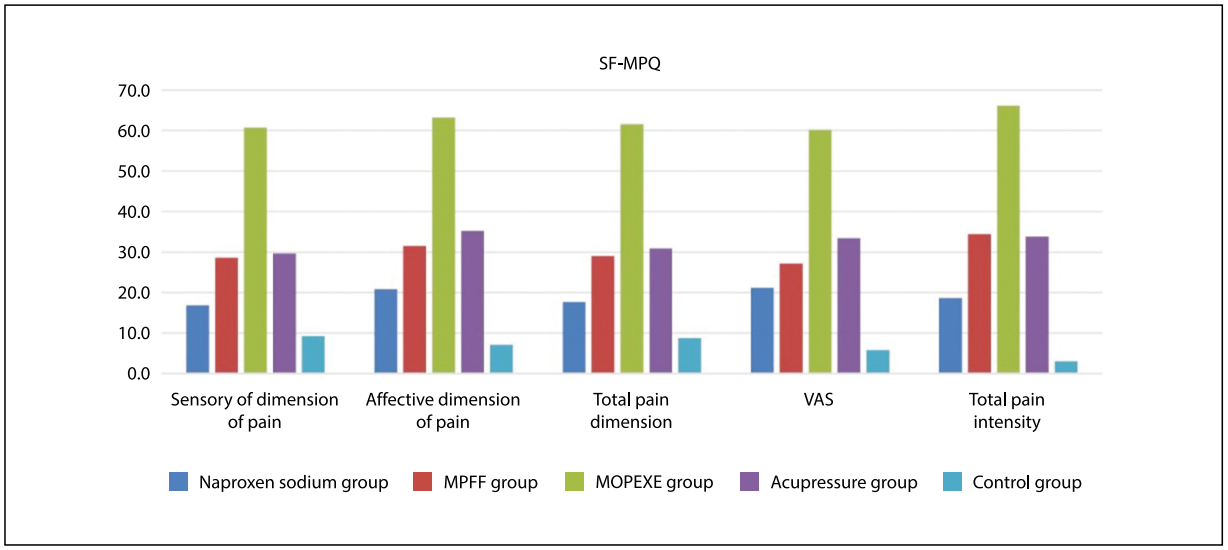

Figure 2. Relative percentage change of Short-Form McGill Pain Questionnaire (SF-MPQ) subparameters on pretreatment, posttreatment, and between groups (n = 85); MOPEXE — motor imagery focused pelvic floor exercise group; MPFF — micronized purified flavanoid fraction group; VAS — visual analog scale

There are many recent studies investigating the effects of exercise types on dysmenorrhea [11]. In parallel with this information, the MOPEXE exercise model, which includes many different exercise types, was created by the researcher. In the MOPEXE, the exercises were performed in line with the motor imagery technique. Guillot et al. [26] and Fusco et al. [27] showed that the performance was higher in the dynamic imagery group in which movement and motor imagery techniques were performed simultaneously. Moawed et al. [28], on pelvic floor exercises, it was observed that pelvic floor strength increased more in the motor imagery group. Additionally, it was stated that motor imagery approaches added to conventional training would increase the effectiveness of treatment. When the literature is examined, for this purpose MOPEXE can be seen as an approach for motor imagery exercises to make the patient aware of the pelvic floor muscles and to understand the pelvic floor movement.

Systematic reviews stated that acupressure and different exercise types are as effective as pharmacological approaches in reducing PD symptoms [8, 29–31]. Armour et al. [31] showed that the exercise duration in PD when applied for 45–60 min, thrice a week for 8–12 weeks, reduced pain. Another review stated that effective exercises for pain severity and duration in dysmenorrhea should be performed for 8 weeks and should include stretching exercises [11].

In this study, in parallel with systematic reviews, MOPEXE exercises, including different exercise types, were performed for 12 weeks (twice a week for 60 min). Pain changes were also evaluated with the SF-MPQ in parallel with the reviews.

Although studies in which self-acupressure applications reduce pain severity were noted when systematic reviews examining the effect of acupressure treatment in PD are examined, the effect could not be fully determined due to low-quality studies in the literature. In systematic reviews, pain assessment of acupressure therapy was evaluated using the MPQ and VAS in parallel with the current study [32, 33].

In this study, in parallel with the literature, self-acupressure therapy was as effective as pharmacological agents in reducing dysmenorrhea symptoms when applied twice a day for 12 weeks.

The limitation of this study is that it does not measure pelvic floor muscle strength although MOPEXE focuses on the pelvic floor and it has some participants because it was conducted during the COVID-19 pandemic.

CONCLUSIONS

In this study comparing PT and NPT groups in women with PD, it was observed that pain associated with dysmenorrhea decreased in all groups. There was no significant change in menstrual attitude in all groups. MPFF treatment was more effective in reducing pain than NS treatment. Acupressure treatment was also as effective as the drug groups in reducing pain. The change in pain scores was higher in the treatment groups than in the control group. There was no significant change in menstrual attitude scores between the treatment groups and the control group. The greatest change in nature and intensity of pain among all treatment groups was in the MOPEXE group. There is a need for future studies in which pharmacological and nonpharmacological treatments are used together.

Table 4. Results of Menstruation Attitude Questionnaire (MAQ) subparameters pre-treatment-post-treatment scores and intergroup differences

MAQ	Groups	Pretreatment X ± SD	Posttreatment X ± SD	Difference	
				X ± SD	p_{time}
Menstruation as a deliberating event	NS	19.35 ± 1.73	19.76 ± 2.7	–0.41 ± 2.81	0.554
	MPFF	19.71 ± 2.42	19.82 ± 2.01	–0.12 ± 3.06	0.876
	MOPEXE	19.47 ± 1.23	20.29 ± 2.23	–0.82 ± 2.65	0.219
	Acupressure	19.47 ± 2.21	19.88 ± 2.2	–0.41 ± 3.26	0.610
	Control	21.65 ± 1.73	21.86 ± 1.8	0.14 ± 1.64	0.604
p_{group}		0.003	0.036	0.579	
Menstruating as a bothersome event	NS	15.71 ± 2.78	15.12 ± 2.45	0.59 ± 1.58	0.145
	MPFF	15.18 ± 2.07	15.29 ± 2.08	–0.12 ± 1.36	0.727
	MOPEXE	15 ± 2.32	15.71 ± 2.59	–0.71 ± 1.1	0.018
	Acupressure	15.12 ± 1.62	15.88 ± 2.57	–0.76 ± 1.68	0.079
	Control	14.59 ± 2.72	15.1 ± 3.16	0.43 ± 2.05	0.310
p_{group}		0.736	0.866	0.074*	
Menstruation as a natural event	NS	11.94 ± 1.56	12.65 ± 2.15	–0.24 ± 1.86	0.157
	MPFF	13.29 ± 2.39	13.12 ± 1.87	–0.71 ± 1.96	0.719**
	MOPEXE	13.18 ± 1.78	13.41 ± 2.35	0.43 ± 2.05	0.608
	Acupressure	14.06 ± 1.52	14.35 ± 1.87	0.18 ± 1.7	0.569
	Control	19.76 ± 2.25	20.27 ± 2.04	–0.29 ± 2.08	0.289
p_{group}		< 0.001*	< 0.001	0.892*	
Anticipation and prediction of the onset of menstruation	NS	27 ± 2.37	27.29 ± 3.12	–0.29 ± 1.83	0.477**
	MPFF	25.76 ± 2.41	25.88 ± 2.87	–0.12 ± 2.52	0.850*
	MOPEXE	26.71 ± 2.23	25.24 ± 2.99	1.47 ± 2.29	0.018*
	Acupressure	26.47 ± 2	26.41 ± 1.91	0.06 ± 1.39	0.768**
	Control	27.82 ± 3.57	27.36 ± 4.08	–0.36 ± 1.89	0.338**
p_{group}		0.354*	0.070*	0.056*	
Denial of effects of menstruation	NS	19 ± 1.84	18.88 ± 1.93	0.12 ± 2.57	0.800**
	MPFF	19.53 ± 1.59	18.76 ± 1.86	0.76 ± 2.11	0.171**
	MOPEXE	19.76 ± 1.82	19.12 ± 1.8	0.65 ± 2.5	0.081**
	Acupressure	20.12 ± 1.05	20.24 ± 1.03	–0.12 ± 1.27	0.707*
	Control	13 ± 3.95	13.84 ± 3.94	0.69 ± 1.62	0.039*
p_{group}		< 0.001*	< 0.001*	0.377*	

p_{group}: One-Way Analysis of Variance, *Kruskal–Wallis Test, p_{time}: Paired Samples T-Test, **Wilcoxon Signed Rank Test; Ac — acupressure group; C — control group; MO — MOPEXE group; MPFF — micronized purified flavanoid fraction group; n — number of participants; NS — naproxen sodium group; SD — standard deviation; X — mean

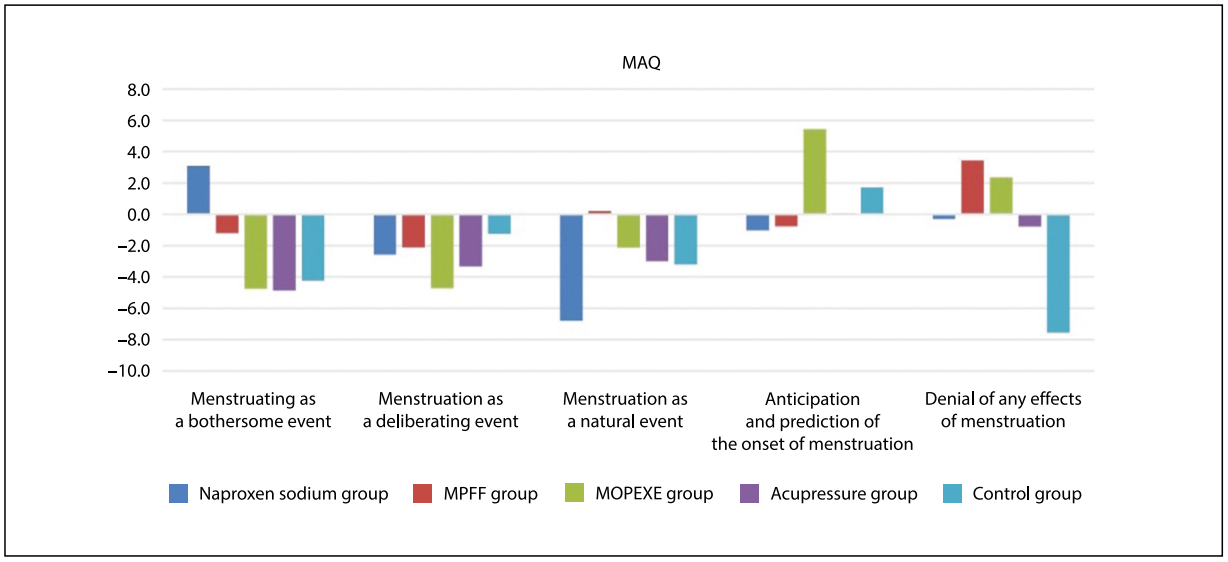

Figure 3. Relative percentage change of Menstruation Attitude Questionnaire (MAQ) subparameters on pretreatment, posttreatment, and between groups (n = 85); MOPEXE — motor imagery focused pelvic floor exercise group; MPFF — micronized purified flavanoid fraction group

Article information and declarations

Authorship contributions

Initial conception: GE, NA, EA; design: GE, NA; data collection or processing: GE, NA; analysis or interpretation of data: GE, NA, EA; literature search: GE, NA; writing and revision of paper: GE, NA, EA.

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Conflict of interest

The authors declare that they have no conflict of interest.

REFERENCES

1. Ju H, Jones M, Mishra G. The prevalence and risk factors of dysmenorrhea. Epidemiol Rev. 2014; 36: 104–113, doi: 10.1093/epirev/mxt009, indexed in Pubmed: 24284871.
2. Latthe PM, Champaneria R. Dysmenorrhoea. BMJ Clin Evid. 2014: 813, indexed in Pubmed: 25338194.
3. Oladosu FA, Tu FF, Hellman KM. Nonsteroidal antiinflammatory drug resistance in dysmenorrhea: epidemiology, causes, and treatment. Am J Obstet Gynecol. 2018; 218(4): 390–400, doi: 10.1016/j.ajog.2017.08.108, indexed in Pubmed: 28888592.
4. Mukherjee GG, Gajaraj AJ, Mathias J, et al. Treatment of abnormal uterine bleeding with micronized flavonoids. Int J Gynaecol Obstet. 2005; 89(2): 156–157, doi: 10.1016/j.ijgo.2004.11.032, indexed in Pubmed: 15847886.
5. Aboualsoltani F, Bastani P, Khodaie L, et al. Non-pharmacological treatments of primary dysmenorrhea: a systematic review. Arch Pharma Pract. 2020; 11(S1): 136–142.
6. Bavil DA, Dolatian M, Mahmoodi Z, et al. Comparison of lifestyles of young women with and without primary dysmenorrhea. Electron Physician. 2016; 8(3): 2107–2114, doi: 10.19082/2107, indexed in Pubmed: 27123219.
7. Pattanittum P, Kunyanone N, Brown J, et al. Dietary supplements for dysmenorrhoea. Cochrane Database Syst Rev. 2016; 3: CD002124, doi: 10.1002/14651858.CD002124.pub2, indexed in Pubmed: 27000311.
8. López-Liria R, Torres-Álamo L, Vega-Ramírez FA, et al. Efficacy of physiotherapy treatment in primary dysmenorrhea: a systematic review and meta-analysis. Int J Environ Res Public Health. 2021; 18(15): 7832, doi: 10.3390/ijerph18157832, indexed in Pubmed: 34360122.
9. Ferries-Rowe E, Corey E, Archer JS. Primary dysmenorrhea: diagnosis and therapy. Obstet Gynecol. 2020; 136(5): 1047–1058, doi: 10.1097/AOG.0000000000004096, indexed in Pubmed: 33030880.
10. Sharghi M, Mansurkhani SM, Larky DA, et al. An update and systematic review on the treatment of primary dysmenorrhea. JBRA Assist Reprod. 2019; 23(1): 51–57, doi: 10.5935/1518-0557.20180083, indexed in Pubmed: 30521155.
11. Carroquino-Garcia P, Jiménez-Rejano JJ, Medrano-Sanchez E, et al. Therapeutic exercise in the treatment of primary dysmenorrhea: a systematic review and meta-analysis. Phys Ther. 2019; 99(10): 1371–1380, doi: 10.1093/ptj/pzz101, indexed in Pubmed: 31665789.
12. Beuscher-Willems B. Female genital tract. In: Schmidt G. ed. Differential diagnosis in ultrasound imaging: A teaching atlas. Thieme Medical Publishers, New York 2006: 389–404.
13. Marjoribanks J, Ayeleke RO, Farquhar C, et al. Nonsteroidal anti-inflammatory drugs for dysmenorrhoea. Cochrane Database Syst Rev. 2015(7): CD001751, doi: 10.1002/14651858.CD001751.pub3, indexed in Pubmed: 26224322.
14. Pascarella L. Essentials of daflon 500 mg: from early valve protection to long-term benefits in the management of chronic venous disease. Curr Pharm Des. 2007; 13(4): 431–444, doi: 10.2174/138161207780162953.
15. Lyseng-Williamson KA, Perry CM. Micronised purified flavonoid fraction: a review of its use in chronic venous insufficiency, venous ulcers and haemorrhoids. Drugs. 2003; 63(1): 71–100, doi: 10.2165/00003495-200363010-00005, indexed in Pubmed: 12487623.
16. Mehta P, Dhapte V, Kadam S, et al. Contemporary acupressure therapy: adroit cure for painless recovery of therapeutic ailments. J Tradit Complement Med. 2017; 7(2): 251–263, doi: 10.1016/j.jtcme.2016.06.004, indexed in Pubmed: 28417094.
17. Yu S, Yang J, Yang M, et al. Application of acupoints and meridians for the treatment of primary dysmenorrhea: a data mining-based literature study. Evid Based Complement Alternat Med. 2015; 2015: 752194, doi: 10.1155/2015/752194, indexed in Pubmed: 25802545.

18. Bazarganipour F, Taghavi SA, Allan H, et al. A randomized controlled clinical trial evaluating quality of life when using a simple acupressure protocol in women with primary dysmenorrhea. Complement Ther Med. 2017; 34: 10–15, doi: 10.1016/j.ctim.2017.07.004, indexed in Pubmed: 28917360.
19. Yakut Y, Yakut E, Bayar K, et al. Reliability and validity of the Turkish version short-form McGill pain questionnaire in patients with rheumatoid arthritis. Clin Rheumatol. 2007; 26(7): 1083–1087, doi: 10.1007/s10067-006-0452-6, indexed in Pubmed: 17106618.
20. Kulakaç Ö, Oncel S, Firat MZ, et al. Menstrual attitude questionnaire: validity and reliability study. Turkiye Klinikleri J Gynecol Obst. 2008; 18(6): 347–356.
21. Daniels SE, Paredes-Diaz A, An R, et al. Significant, long-lasting pain relief in primary dysmenorrhea with low-dose naproxen sodium compared with acetaminophen: a double-blind, randomized, single-dose, crossover study. Curr Med Res Opin. 2019; 35(12): 2139–2147, doi: 10.1080/03007995.2019.1654987, indexed in Pubmed: 31397597.
22. Ortiz MI, Murguía-Cánovas G, Vargas-López LC, et al. Naproxen, paracetamol and pamabrom versus paracetamol, pyrilamine and pamabrom in primary dysmenorrhea: a randomized, double-blind clinical trial. Medwave. 2016; 16(9): e6587, doi: 10.5867/medwave.2016.09.6587, indexed in Pubmed: 27813503.
23. Motahari-Tabari N, Shirvani MA, Alipour A. Comparison of the effect of stretching exercises and mefenamic acid on the reduction of pain and menstruation characteristics in primary dysmenorrhea: a randomized clinical trial. Oman Med J. 2017; 32(1): 47–53, doi: 10.5001/omj.2017.09, indexed in Pubmed: 28042403.
24. Shirvani MA, Motahari-Tabari N, Alipour A. The effect of mefenamic acid and ginger on pain relief in primary dysmenorrhea: a randomized clinical trial. Arch Gynecol Obstet. 2015; 291(6): 1277–1281, doi: 10.1007/s00404-014-3548-2, indexed in Pubmed: 25399316.
25. Blödt S, Pach D, Eisenhart-Rothe Sv, et al. Effectiveness of app-based self-acupressure for women with menstrual pain compared to usual care: a randomized pragmatic trial. Am J Obstet Gynecol. 2018; 218(2): 227.e1–227.e9, doi: 10.1016/j.ajog.2017.11.570, indexed in Pubmed: 29155036.
26. Guillot A, Moschberger K, Collet C. Coupling movement with imagery as a new perspective for motor imagery practice. Behav Brain Funct. 2013; 9: 8, doi: 10.1186/1744-9081-9-8, indexed in Pubmed: 23425312.
27. Fusco A, Iosa M, Gallotta MC, et al. Different performances in static and dynamic imagery and real locomotion. An exploratory trial. Front Hum Neurosci. 2014; 8: 760, doi: 10.3389/fnhum.2014.00760, indexed in Pubmed: 25324758.
28. Moawed MA, Salem NA, Elbalawy YM. Effect of motor imagery training on urinary incontinence in patients with incomplete spinal cord injury. Med J Cairo Univ. 2020; 88(3): 869–873, doi: 10.21608/mjcu.2020.104900.
29. Kannan P, Claydon LS. Some physiotherapy treatments may relieve menstrual pain in women with primary dysmenorrhea: a systematic review. J Physiother. 2014; 60(1): 13–21, doi: 10.1016/j.jphys.2013.12.003, indexed in Pubmed: 24856936.
30. Corral-Moreno V, Munuera-Jiménez FJ, Cascos-Vicente L, et al. Tratamiento fisioterapéutico para la dismenorrea primaria: una revisión sistemática. Fisioterapia. 2022; 44(1): 43–50, doi: 10.1016/j.ft.2021.02.005.
31. Armour M, Parry K, Manohar N, et al. The prevalence and academic impact of dysmenorrhea in 21,573 young women: a systematic review and meta-analysis. J Womens Health (Larchmt). 2019; 28(8): 1161–1171, doi: 10.1089/jwh.2018.7615, indexed in Pubmed: 31170024.
32. Selçuk A, Yanikkerem E. Effect of acupressure on primary dysmenorrhea: review of experimental studies. J Acupunct Meridian Stud. 2021; 14(2): 33–49, doi: 10.51507/j.jams.2021.14.2.33.
33. Jiang HR, Ni S, Li JL, et al. Systematic review of randomized clinical trials of acupressure therapy for primary dysmenorrhea. Evid Based Complement Alternat Med. 2013; 2013: 169692, doi: 10.1155/2013/169692, indexed in Pubmed: 24023570.

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Modified segmental bowel resection technique in deep infiltrating endometriosis. Is it a suitable method to reduce the risk of bowel leakage after an extensive complex surgery?

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ABSTRACT

Objectives: To evaluate the novel modified laparoscopic technique of the bowel resection for deep infiltrating endometriosis (DIE) of the bowel versus the classical technique of bowel segmental resection in terms of anastomosis leakage.

Material and methods: Patients (n = 138) treated with segmental bowel resections due to DIE were included; 30 patients had the classic, while 108 patients had the modified laparoscopic bowel segmental resection with indocyanine green (ICG) vascular visualization and fibrin sealant use.

Results: The modified technique was used more often in complex operations (65.7% vs 46.6%). More anastomotic leakages occurred in patients undergoing the classic technique than the modified technique (10% vs 2.8%; p = 0.117). No leakage in modified versus 12% in classic technique was observed in simple segmental bowel resections (p = 0.05); 2.5% of cases with leakage in modified versus 7.1% in classic technique were observed in bowel resections with hysterectomy. In complex cases operated with the modified technique, the frequency of anastomotic leakage was 4.2%, which were even less than leakage in simple cases in classic technique group (10%). Although the low location of the lesions increases the risk of leakage, the modified technique was associated with a small percentage of leakages (25% vs 6.3%). The laparotomy conversion rate was similar in both groups (3.4% for classic and 2.7% for modified).

Conclusions: In DIE, the modified technique of segmental bowel resection showed superiority over the classic technique in terms of the risk of anastomotic leakage. This risk was lower regardless of the complexity of the surgery and lesion location.

Keywords: deep infiltrating endometriosis; laparoscopy; modified technique; anastomotic leakage

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INTRODUCTION

Endometriosis is a chronic inflammatory disease characterized by the presence of endometrial tissue outside of a normal location, *e.g.*, in the ovaries, peritoneum, bowels, bladder, and even lungs. It is commonly diagnosed in women of reproductive age, but the time of diagnosis can vary because symptoms and signs can be mistaken for other diseases [1]. A patient with endometriosis can present many symptoms, including dysmenorrhea, pain during ovulation, dyspareunia, abnormal bleeding, chronic pelvic pain, dyschezia, constipation, and infertility [2]. Bowel endometriosis is the presence of endometriotic tissue infiltrating the intestinal wall into different depths, but mostly to the muscular layer. Endometriotic nodules can cause significant stenosis of the intestinal lumen and obstruction [3]. They can be present anywhere along the lower gastrointestinal tract, but the main location is the distal colon-rectum and sigmoid.

Bowel endometriotic nodules can be treated using different surgical techniques such as shaving, discoid excision, and segmental resection. The shaving method is used when

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the lesions are superficial and of a small diameter, mostly limited to serosa. Discoid excision is used for a full-thickness resection of small nodules of the intestinal wall. Many authors recommend it for lesions up to 3 cm in diameter and lower location such as the rectum and distal part of the sigmoid colon, and an anterior part of the bowel wall. However, it is not recommended for multifocal bowel lesions. Segmental resection is the removal of the bowel segment with subsequent anastomosis. It has been the most common technique for treating intestinal endometriosis. It is performed for larger, obstructive nodules and multiple endometriotic nodules (multifocal disease) [4], with no limitation on the involvement in the bowel wall. One of the most dangerous complications after this surgery is anastomosis leakage, a major cause of postoperative mortality and morbidity. The prevalence of anastomosis leakage varies from 1% to 19% depending on an anatomical site, as well as other preoperative, intraoperative, and postoperative factors [5]. Several surgical techniques and prevention methods have been developed in the last few decades to reduce the risk of anastomosis leakage.

Objectives

The goal of our study was to evaluate the laparoscopic technique of bowel resection for deep infiltrating bowel endometriosis. We compared our modified technique with the classic bowel segmental resection technique, taking into account the occurrence of leakage from anastomosis.

MATERIAL AND METHODS

In total, 138 patients who had segmental bowel resection were included in the study. Each patient was operated on due to deep infiltrating bowel endometriosis between June 2018 and November 2021. The qualification for surgery was done based on the complex examination of the patients. Patient's history, physical examination, bimanual gynecological examination, per rectum examination, pelvic expert magnetic resonance imaging for endometriosis, and expert gynecological ultrasound were analyzed. The patients were included in the study according to the specified inclusion and exclusion criteria. The primary inclusion criterion was a diagnosis of deep infiltrating endometriosis qualified to segmental bowel resection based on the measurement of changes, localization or the number of foci. Patients who had confirmed COVID-19 infection, endometriotic nodules qualified for shaving procedures, and absolute contraindications to surgery were excluded.

Patients

The patients were divided into two groups:

Group A (n = 30) had the classic laparoscopic bowel resection without indocyanine green (ICG) control. This group was further divided into group A1 (n = 16) treated with only bowel resection and group A2 (n = 14) undergoing bowel resection with hysterectomy.

Group B (n = 108) had the modified laparoscopic bowel segmental resection with ICG vascular visualization and fibrin sealant use. This group was also divided into group B1 (n = 37) treated with bowel resection only, group B2 (n = 39) treated with bowel resection and hysterectomy, B3 (n = 6) treated with bowel resection with urinary tract surgery, B4 (n = 20) treated with bowel resection with a hysterectomy and urinary tract surgery, and B5 (n = 6) undergoing multiple bowel resections with hysterectomy. All resections in this group were done close to the wall of the bowel with preserving the vascularity and nerves.

Surgical techniques

Classic laparoscopic technique

The classic laparoscopic technique of segmental bowel resection for bowel endometriosis was described in 1990 by Redwine and Sharpe [6].

Below we present the classical technique in detail done by our team:

1. The procedure starts with lysis of adhesions and bilateral dissection of the ureters, opening of pararectal spaces, mobilization of the ureters, uterosacral ligament and hypogastric nerve.
2. A bowel endometriotic nodule is detached from surrounding structures (vagina, uterosacral ligament, ovaries, vagina, etc.).
3. Resection of the intestine is done by clipping and cutting the vessel(s) that corresponded to the vascularity of the bowel segment planned to remove.
4. Resection is performed with a part of adequate mesentery that belongs to the segment of the bowel. The bowel is sectioned with a healthy intestinal margin of 1–2 cm using a linear laparoscopic stapling device, but according to an avascularized segment of the bowel.
5. Later, an end-to-end anastomosis with a circular stapler or side-to-side anastomosis with the use of linear stapler is done if needed.
6. The anvil is inserted by minilaparotomy, Fishing technique, or by vagina [vaginal NOTES (*Natural Orifice Transluminal Endoscopic Surgery*) technique] when removal of the uterus is performed. The bowel segment is extracted through a suprapubic minilaparotomy.
7. When two organs are operated at the same time, the flap technique for the suture separation is performed.

Modified laparoscopic technique

The modified laparoscopic technique is changed in some respects compared to the classic technique. The differences are as follows:

Table 1. Occurrence of anastomotic leakages per group

	A1	A2	B1	B2	B3	B4	B5
Number of cases	16	14	37	39	6	20	6
Number of leakages	2	1	0	1	1	1	0
Percentage of leakages	12.5%	7.1%	0%	2.5%	16.6%	5%	0%
Total A1–A2; B1–B5	10%		2.8%				
Total B2–B5				4.2%			

1. Bowel resection is performed tailored at the border of the bowel wall with endometriotic nodule and with a few millimeters of healthy margin.
2. Vascularity is checked by injecting ICG into the vein just before bowel resection (first dose of ICG) and just after anastomosis (second dose of ICG).
3. The bowel planned to be resected is extracted using a surgisleeve technique or Fishing technique, which is a preferred method that can reduce the need for mobilization of the intestine compared to the vaginal NOTES technique. It also gives an opportunity to check once again all bowel segments planned to be resected if there are any undetected endometriotic nodules located close to the first one by palpation, which is not rare.
4. The anastomosis is later secured by sealing materials such as fibrin sponge or fibrin glue and separated from other organs (bladder or vagina) by an omental flap.

Statistical analysis

The number and percentage of anastomotic leakage were presented and compared between the groups of patients operated with the presented techniques. To determine the statistical significance of differences between groups, the chi-squared or Fisher's exact test was used. Statistical analyses were performed using R version 3.4.4 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Overall, anastomotic leakage occurred in 10% of patients operated with the classic technique (group A) and 2.8% of patients operated with the modified technique (group B), which is 4 times less. Considering patients who had isolated resection of an affected segment of the intestine, using the classic technique (group A1) led to the development of anastomotic leakage in 12.5% of patients, while no such complications were observed in 37 patients operated with the modified technique (group B1). The difference was statistically significant ($p = 0.05$). Considering patients who had bowel resections and the uterus removed with the classical technique, the leakage rate was 7.1% (group A2), while for the modified technique, it was only 2.5% (group B2). Taking into account all complex cases operated with the modified technique in which, in addition to an intestine resection, a reproductive organ, bladder, or additional segments of the bowel were removed, or the uterus was re-transplanted, the leakage rate was 4.2%. Detailed data are presented in Table 1.

In both groups A and B, the same total number of leakages (3 in each) were observed, but group B was three times bigger. Most patients who underwent modified technique resection had much more complex operations (65.7% in group B vs 46.6% in group A). Only in group B, there were surgeries on the 3 or 4 organs (24% of cases). The conversion rate to laparotomy was similar in both groups (3.4% in group A vs 2.7% in group B). Significantly more surgeries were performed by a surgeon in group A than in group B (83% vs 16.7%; $p < 0.001$). In the rest of the cases, 83.3% were performed by a team of gynecological oncologists and gynecologists. Protective stomas were used only in group B due to the most comprehensive treatments employed in this group, which were not performed in group A. Table 2 describes the characteristics of the groups by the complexity of the procedures.

Analysis of various factors that influence the incidence of leakage considered cooccurring intraoperative complications. More complications were associated with anastomotic leakages in group B (2 of 3 cases). Leakages were not related to intraoperative complications in group A and even more of them were seen in the group with only bowel segmental resection (2/3) than in a group with bowel resection and hysterectomy. All leakages in group A were related to the quality of the anastomosis. Leakages without previous intraoperative complications occurred in 33% of the cases in group B (1/3). However, considering the entire number of patients in group A, the percentage of leakage without prior complications was 10% (3/30), while in group B, it was only 0.9% (1/108) of all patients. Exclusion of intraoperative complications was associated with a very significant reduction in the risk of leakage. Similar numbers of low anastomosis were performed in both groups A and B. The final and total number of leakages in group B was 4 times smaller than in group A. The characteristics of the groups by the location of the anastomosis and complications are presented in Table 3.

Table 2. Characteristics of the groups by complexity of the procedure

	Group A	Group B	p value
Number of cases	30	108	
Number of leakages	3 (10%)	3 (2.8%)	0.117
Complex cases (at least 2 organs)	14 (46.6%)	71 (65.7%)	0.057
Complex cases (at least 3 organs)	0 (0%)	26 (24.1%)	0.001
Conversion to laparotomy	1 (3.4%)	3 (2.8%)	0.999
Procedures done with surgeon	25 (83.3%)	18 (16.7%)	< 0.001
Protective stomas	0 (0%)	4 (3.7%) B4 i B5	0.577

Table 3. Characteristics of the groups by localization of the anastomosis and complications

	Group A	Group B	p value
Number of cases	30	108	–
Number of leakages	3 (10%)	3 (2.8%)	0.117
Low localization of anastomosis < 60 mm Leakage in this group	4 (13.3%) 1/4 (25%)	16 (14.8%) 1/16 (6.3%)	0.999 –
Intraoperative complications prior to leakage	0	2/3 (66.6%)	–
Leakage without any prior complications	3/3 (100%)	1/3 (33.3%)	–
Leakage without prior complications in all groups	3 (10%)	1 (0.9%)	0.032

The intraoperative complications in group B were the unnoticed microperforation above the anastomosis associated with the method of introducing an anvil into the intestine - the fishing technique. We had to use the colonoscope to regain the anvil that escaped us to the proximal part of the bowel. The second complication was the leakage of urine from the sutured and stented ureter after thermal damage. Both bowel leakages occurred after the operation due to the complications mentioned. In each of these cases, the double leakage test performed intraoperatively with blue, and water and gas did not reveal a lack of continuity of the intestine.

DISCUSSION

The main goal of laparoscopic or laparotomic surgeries in patients with deep infiltrating endometriosis is to remove all endometrial lesions. We compared two laparoscopic approaches to evaluate their safety. Our study showed differences between the classic and modified techniques in favor of the modified technique. The modified technique of bowel resection based on the use of ICG, the tailored technique, and the sealant materials considerably reduced the risk of anastomotic leakage from 10% to 2.8% ($p = 0.117$). The complexity of surgery increased the risk of anastomotic leakage; however, based on our observations, the use of the modified technique in such cases reduced this risk from 7.2% to 4.2% ($p = 0.462$). The low location of the lesions tends to increase the risk of leakage, but the use of the modified technique of bowel resection reduced this risk from 25% to 6.3%.

Surgery for deep infiltrating endometriosis requires a multidisciplinary approach and skilled teams to perform it [7]; however, our study showed that the experienced team of gynecological oncologists performs equally well as multidisciplinary teams. As shown in our study, the number of bowel leakages in more complex surgeries performed only by the team of gynecological oncologists was even lower than by the team with the surgeon involved. However, the comparison was not adjusted for the complexity of the surgery that was the reason for using the modified technique due to its superiority in such cases.

The number of conversions to laparotomy in the literature ranges from 3.2% to 7.8% [3, 4]. The conversion rate in group A was 3.4% and 2.7% in group B. In total in groups A and B (138 patients), conversions were carried out in four cases (2.8%), demonstrating the experience of the team and the possession of appropriate qualifications for laparoscopic procedures. It should be noted that all cases of endometriosis admitted to our hospital were qualified for laparoscopy independently of the number of previous abdominal surgical procedures. This group was heterogeneous and included cases with a history of 10 abdominal surgeries in the past, as well as those without any surgery at all, although they were in the minority. In our study, previous abdominal surgeries were not considered the exclusion criterion for laparoscopy.

The rate of anastomotic leakage in severe cases is around 1–6% [8], 1–19% [9], 1.8–19% [10]. In our group B treated with the modified technique, in more complex surgeries with two or more resected organs, the risk of anastomotic leakage was 2.8% for the entire group. Excluding patients with coexisting intraoperative complications, the leakage rate was 0.9%. The difference is in favor of our modified technique. We are convinced that one of the important advantages of this method is the use of ICG, as determined by Chan et al. as well [11]. In a systematic evaluation of 5,498 patients from 20 studies, including two randomized controlled trials conducted to assess the use of ICG fluorescence imaging in patients undergoing colon surgery, it was shown that ICG can considerably reduce the likelihood of an anastomotic leak. The number of studies reporting benefits of ICG in patients with endometriosis is lower, but the results are consistent [12, 13]. The use of ICG plays as crucial role as a tailored surgery in deep infiltrating bowel endometriosis compared with the classic technique used in traditional colon surgery. The tailored surgery in deep infiltrating bowel endometriosis is strongly recommended by most specialists experienced in surgery conducted in endometriosis [14, 15].

Some centers recommend and perform protective stoma for all low rectum resections [16, 17], while others recommend them for patients who have other intraoperative risk factors for leakage [18]. In our group, protective stoma was performed only in a few very complex cases and one case of a very low resection that led to the rate of 2.9% in the entire segmental bowel resection group (138 patients). We observed only one leakage in the low rectum resection group treated with the modified technique (1/16; 5.4%) and one in the classical technique (1/4; 25%). For a more adequate conclusion in this category, we would need a larger group of low resections. However, in our observation, the low resection of the rectum is an important risk factor for leakage. Even in this group, it is worth using the modified technique and deciding on a case-by-case basis whether to do or not to do the protective stoma. From our point of view, the crucial issues are to be prudent about hemostasis, about the vascularity of the saved bowel and the tension of the tissue, which many other authors have also pointed out [19–21]. As we observed, the extent of excised tissues (*e.g.*, levator ani and other muscles, as well as other layers of low pelvic muscles) increases the risk of the leakage, and it should be a decision-making factor for the need for protective stoma [22]. In summary, what makes our modified technique more unique and very suitable is not only tailored surgery and detection of vascularity with the ICG but also a coherent use of fibrin sealant, which was used before by other surgeons [23, 24], but not in combination with all other agents, decreasing, in our opinion, the risk of leakage.

Our study is not without limitations. The study group is relatively small, with an uneven distribution of cases among the techniques studied. We observed a low number of complications/leakages and a low number of patients who were operated with the classical technique due to ethical reasons. After obtaining preliminary results, we could not qualify more patients for that less effective method.

CONCLUSIONS

In deep infiltrating endometriosis, the modified technique of segmental bowel resection showed superiority over the classic technique of segmental bowel resection in terms of the risk of anastomotic leakage. This risk was lower regardless of the complexity of the surgery and the location of lesions. Our study showed that the modified technique is safer than the classic technique; however, further research is needed on larger populations of patients, including patients at high risk of complications.

Article information and declarations

Conflict of interest

All authors declare no conflict of interest.

REFERENCES

1. Giudice L, Kao L. Endometriosis. The Lancet. 2004; 364(9447): 1789–1799, doi: 10.1016/s0140-6736(04)17403-5.
2. Simoens S, Dunselman G, Dirksen C, et al. The burden of endometriosis: costs and quality of life of women with endometriosis and treated in referral centres. Hum Reprod. 2012; 27(5): 1292–1299, doi: 10.1093/humrep/des073, indexed in Pubmed: 22422778.
3. Yong PJ, Bedaiwy MA, Alotaibi F, et al. Pathogenesis of bowel endometriosis. Best Pract Res Clin Obstet Gynaecol. 2021; 71: 2–13, doi: 10.1016/j.bpobgyn.2020.05.009, indexed in Pubmed: 32646752.
4. Ferrero S, Stabilini C, Barra F, et al. Bowel resection for intestinal endometriosis. Best Pract Res Clin Obstet Gynaecol. 2021; 71: 114–128, doi: 10.1016/j.bpobgyn.2020.05.008, indexed in Pubmed: 32665125.
5. McDermott FD, Heeney A, Kelly ME, et al. Systematic review of preoperative, intraoperative and postoperative risk factors for colorectal anastomotic leaks. Br J Surg. 2015; 102(5): 462–479, doi: 10.1002/bjs.9697, indexed in Pubmed: 25703524.
6. Redwine DB, Koning M, Sharpe DR, et al. Laparoscopic segmental resection of the sigmoid colon for endometriosis. J Laparoendosc Surg. 1991; 1(4): 217–220, doi: 10.1089/lps.1991.1.217, indexed in Pubmed: 1834272.
7. Keckstein J, Wiesinger H. Deep endometriosis, including intestinal involvement--the interdisciplinary approach. Minim Invasive Ther Allied Technol. 2005; 14(3): 160–166, doi: 10.1080/14017430510035916, indexed in Pubmed: 16754158.
8. Vigueras SA, Sumak R, Cabrera R, et al. Bowel anastomosis leakage following endometriosis surgery: an evidence based analysis of risk factors and prevention techniques. Facts Views Vis Obgyn. 2020; 12(3): 207–225, indexed in Pubmed: 33123696.
9. Vasiliu EC, Zarnescu NO, Costea R, et al. Review of Risk Factors for Anastomotic Leakage in Colorectal Surgery. Chirurgia (Bucur). 2015; 110(4): 319–326, indexed in Pubmed: 26305194.
10. Iversen H, Ahlberg M, Lindqvist M, et al. Changes in Clinical Practice Reduce the Rate of Anastomotic Leakage After Colorectal Resections. World J Surg. 2018; 42(7): 2234–2241, doi: 10.1007/s00268-017-4423-7, indexed in Pubmed: 29282510.
11. Chan DK, Lee SK, Ang JJ. Indocyanine green fluorescence angiography decreases the risk of colorectal anastomotic leakage: Systematic review and meta-analysis. Surgery. 2020; 168(6): 1128–1137, doi: 10.1016/j.surg.2020.08.024, indexed in Pubmed: 33010938.

12. Raimondo D, Mastronardi M, Mabrouk M, et al. Rectosigmoid Endometriosis Vascular Patterns at Intraoperative Indocyanine Green Angiography and their Correlation with Clinicopathological Data. Surg Innov. 2020; 27(5): 474–480, doi: 10.1177/1553350620930147, indexed in Pubmed: 32501181.
13. Raimondo D, Maletta M, Borghese G, et al. Indocyanine Green Fluorescence Angiography after Full-thickness Bowel Resection for Rectosigmoid Endometriosis-A Feasibility Study. J Minim Invasive Gynecol. 2021; 28(6): 1225–1230, doi: 10.1016/j.jmig.2020.12.017, indexed in Pubmed: 33352315.
14. Afors K, Centini G, Fernandes R, et al. Segmental and Discoid Resection are Preferential to Bowel Shaving for Medium-Term Symptomatic Relief in Patients With Bowel Endometriosis. J Minim Invasive Gynecol. 2016; 23(7): 1123–1129, doi: 10.1016/j.jmig.2016.08.813, indexed in Pubmed: 27544881.
15. Minelli L, Fanfani F, Fagotti A, et al. Laparoscopic colorectal resection for bowel endometriosis: feasibility, complications, and clinical outcome. Arch Surg. 2009; 144(3): 234–9; discussion 239, doi: 10.1001/archsurg.2008.555, indexed in Pubmed: 19289662.
16. Räsänen M, Renkonen-Sinisalo L, Carpelan-Holmström M, et al. Low anterior resection combined with a covering stoma in the treatment of rectal cancer reduces the risk of permanent anastomotic failure. Int J Colorectal Dis. 2015; 30(10): 1323–1328, doi: 10.1007/s00384-015-2291-x, indexed in Pubmed: 26111635.
17. Wu SW, Ma CC, Yang Yu. Role of protective stoma in low anterior resection for rectal cancer: a meta-analysis. World J Gastroenterol. 2014; 20(47): 18031–18037, doi: 10.3748/wjg.v20.i47.18031, indexed in Pubmed: 25548503.
18. Ledu N, Rubod C, Piessen G, et al. Management of deep infiltrating endometriosis of the rectum: Is a systematic temporary stoma relevant? J Gynecol Obstet Hum Reprod. 2018; 47(1): 1–7, doi: 10.1016/j.jogoh.2017.10.005, indexed in Pubmed: 29097291.
19. Oliveira MA, Pereira TR, Gilbert A, et al. Bowel complications in endometriosis surgery. Best Pract Res Clin Obstet Gynaecol. 2016; 35: 51–62, doi: 10.1016/j.bpobgyn.2015.11.002, indexed in Pubmed: 26694586.
20. Madiedo A, Hall J. Minimally Invasive Management of Diverticular Disease. Clin Colon Rectal Surg. 2021; 34(2): 113–120, doi: 10.1055/s-0040-1716703, indexed in Pubmed: 33642951.
21. Kryzauskas M, Poskus E, Dulskas A, et al. The problem of colorectal anastomosis safety. Medicine (Baltimore). 2020; 99(2): e18560, doi: 10.1097/MD.0000000000018560, indexed in Pubmed: 31914032.
22. Akladios C, Messori P, Faller E, et al. Is ileostomy always necessary following rectal resection for deep infiltrating endometriosis? J Minim Invasive Gynecol. 2015; 22(1): 103–109, doi: 10.1016/j.jmig.2014.08.001, indexed in Pubmed: 25109779.
23. Bonanomi G, Prince JM, McSteen F, et al. Sealing effect of fibrin glue on the healing of gastrointestinal anastomoses: implications for the endoscopic treatment of leaks. Surg Endosc. 2004; 18(11): 1620–1624, doi: 10.1007/s00464-004-8803-3, indexed in Pubmed: 15931477.
24. Huh JW, Kim HR, Kim YJ. Anastomotic leakage after laparoscopic resection of rectal cancer: the impact of fibrin glue. Am J Surg. 2010; 199(4): 435–441, doi: 10.1016/j.amjsurg.2009.01.018, indexed in Pubmed: 19481197.

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Does asymptomatic/uncomplicated SARS-CoV-2 infection during pregnancy increase the risk of spontaneous preterm birth?

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ABSTRACT

Objectives: The aim of this study was to analyze the perinatal outcomes of asymptomatic/uncomplicated SARS-CoV-2 infection during pregnancy and the relationship between gestational age at the time of infection and spontaneous preterm birth (PTB).

Material and methods: This was a retrospective cohort study. The study population included pregnant women who were 19–45 years old and who had been admitted to a Research and Training Hospital for singleton birth delivery. Women who had contracted SARS-CoV-2 during their pregnancy (n = 102) were compared to those who were not infected (n = 378) for the development of spontaneous PTB and other perinatal outcomes. The factors associated with spontaneous PTB were analyzed through univariate and multivariate methods.

Results: Spontaneous PTB developed in 22.5% of the pregnant women with a history of SARS-CoV-2 infection and in 5.3% without a history of the infection ($p < 0.001$). The multivariate model determined that compared to the non-infected women, the OR of spontaneous PTB among those who had contracted the virus in the first, second, and the third trimesters were 9.13 ($p < 0.001$), 1.85 ($p = 0.292$) and 7.09 ($p < 0.001$), respectively. Pregnancy cholestasis (3.9% vs 0.5%; $p = 0.020$) and placental abruption (3.9% vs 0.5%; $p = 0.040$) were significantly higher in cases with a history of SARS-CoV-2 infection compared to the non-infected women.

Conclusions: Asymptomatic or uncomplicated SARS-CoV-2 infection during pregnancy increases the risk of spontaneous PTB. This risk is higher particularly among pregnant women who develop the infection in the first and the third trimesters.

Keywords: SARS-CoV-2; COVID-19 pandemic; pregnancy; preterm birth; perinatal outcome

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INTRODUCTION

The 2019 Coronavirus Disease (COVID-19) pandemic is an ongoing major global health crisis in our time. To date, close to 233 million cases infected with SARS-CoV-2 have been confirmed, and 4.8 million deaths have been reported [1]. A multicenter prospective study from Spain, one of the countries most affected by the pandemic, reported that SARS-CoV-2 screening of 16,308 pregnant women who were admitted for delivery and had no suspected infection or symptoms showed a 2.07% positivity rate [2]. Indeed, the current literature highlights the prevalence of asymptomatic infections and recommends that all pregnant women be routinely screened for SARS-CoV-2 infection during their hospital stay [3].

According to the data of centers in London and New York that routinely order SARS-CoV-2 testing for patients admitted to the labor floor, 88% of infected women remain asymptomatic [4]. It has been determined that SARS-CoV-2

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infection causes changes in systemic immune response and an increase in the pro-immune inflammatory response in pregnancy, as well as in non-pregnant women. In addition, histopathological examinations have shown that the virus causes pathologic changes of the placenta [5]. The World Association of Perinatal Medicine (WAPM) has reported that COVID-19 infection may increase the risk of hypoxemia in pregnant women, thereby increasing maternal morbidity and mortality compared to the general population [6]. Recent studies have shown that pregnant women infected with SARS-CoV-2 are more at risk of adverse perinatal outcomes such as maternal death, need for maternal intensive care, preterm birth (PTB), premature rupture of membranes (PROM), venous thrombosis, and neonatal intensive care need compared to the general population [7, 8].

However, most of the studies conducted so far have reported maternal and neonatal outcomes of pregnant women who had complicated SARS-CoV-2 infection during pregnancy or were infected with SARS-CoV-2 peripartum. The effect of COVID-19 on pregnancy outcomes in women who had asymptomatic or uncomplicated SARS-CoV-2 infection during pregnancy has not been adequately demonstrated. In addition, the relationship between gestational age at SARS-CoV-2 infection and pregnancy outcomes remains unclear.

Objectives

The aim of this study is to analyze the perinatal outcomes of asymptomatic/uncomplicated SARS-CoV-2 infection during pregnancy and the relationship between gestational age at the time of infection and spontaneous PTB.

MATERIAL AND METHODS

Setting and study participants

Designed as a retrospective cohort study, this study was carried out between March 2021 and June 2021 in Zeynep Kamil Women and Children's Diseases Training and Research Hospital. The study population is women admitted for delivery and followed up during the postpartum period in clinic.

Pregnant women aged between 19–45 years, between 22 and 42 weeks of gestation, and who had a negative SARS-CoV-2 polymerase chain reaction (PCR) test at admission to the delivery room were included in the study. SARS-CoV-2 PCR test includes real-time PCR (qPCR)(RT-qPCR) that targets the RdRp gene fragment. All pregnant women who presented to our hospital for delivery, regardless of the presence of symptoms, underwent screening for SARS-CoV-2. The laboratory has been authorized by the Republic of Turkiye Ministry of Health, General Directorate of Public Health, Microbiology Reference Laboratory. For PCR analysis, swab samples from the oropharynx and nasopharynx were used. Women who gave birth at ≤ 22 weeks of gestation, stillbirths and termination of pregnancy cases, multiple pregnancies, and positive SARS-CoV-2 PCR test at the time of admission were excluded from the study.

Sample size calculation

The sample size was calculated using OpenEpi (Version 3). The primary outcome was PTB rate, which was reported to be approximately 23% in women with COVID-19 in a systematic review by Capobianco et al. [9]. In Turkiye, among the general population without a history of COVID-19, the PTB rate is approximately 10%. Considering the relatively limited number of people with COVID-19, we thought that it was appropriate to include a positive history of COVID-19 and non-exposed group in a 1:3 ratio; therefore, we planned to include at least 79 postpartum women in the positive history of SARS-CoV-2 group and at least 235 postpartum women in the negative history of SARS-CoV-2 group for a 5% alpha error and 80% power.

Definition of the variables

Outcome variable: In the study, the primary outcome was spontaneous PTB, which was defined as spontaneous (spontaneous rupture of membranes or spontaneous onset of contractions and onset of labor) or iatrogenic [planned cesarean section or induction of labor due to maternal (severe preeclampsia, abruptio placentae) or fetal (FGR and fetal distress) reasons] delivery before 37 weeks of gestation. Exposure variable: The exposure group consisted of women who were diagnosed with COVID-19 by PCR test at any time during pregnancy. Some of the women were tested due to symptoms, while others were tested because they had been in contact with a COVID-19 patient. PCR results were obtained from electronic patient records, and the time of infection was recorded to determine the trimester of the exposure. Clinical symptoms of the disease (fever, shortness of breath, air hunger, weakness, cough, headache, inability to taste and smell), the need for hospitalization due to COVID-19, and the need for medication or intensive care were questioned.

The COVID-19 clinical disease spectrum of the participants was determined according to the criteria of the NIH and the Turkish Ministry of Health. According to this spectrum, all cases were asymptomatic or met the criteria for mild disease [10]. Two out of 104 women with a positive history of COVID-19 infection were excluded because they did not meet the inclusion criteria, and 102 women were included in the study. The non-exposure group consisted of pregnant women who were not diagnosed with COVID-19 by PCR test during their pregnancy. Considering that there may be those without a positive PCR test even though they had COVID-19, symptoms of upper and lower

respiratory tract diseases during pregnancy were questioned, and those with possible suspected COVID-19 were excluded from the study.

Cases without exposure were determined by the systematic sampling method. The 3rd, 6th, 9th, and 12th women, starting from the 3rd woman in the registry on the day of admission to the postpartum service of the participant included in the exposure group, constituted the non-exposure group. Three hundred seventy-eight pregnant women were included in the group without exposure. The participants' sociodemographic characteristics, medical history, obstetric history [spontaneous PTB, preeclampsia, gestational diabetes mellitus (GDM), intrahepatic cholestasis of pregnancy], and current obstetric characteristics (antenatal period, birth, and neonatal period information) were evaluated. The definitions of perinatal outcomes (GDM, preeclampsia, small for gestational age (SGA), low birth weight (LBW), and intrahepatic cholestasis of pregnancy) were determined according to international criteria [11–15].

Data collection tools

Gestational age was calculated by using the first day of the last menstrual period and was confirmed by first trimester crown-rump length (CRL). Socio-demographic, personal health, antenatal period, birth, and postnatal characteristics of the participants and clinical characteristics of COVID-19 were obtained from the electronic database of our institution. Missing data were obtained by phone interviews with patients.

Ethical approval

The study was approved by the local ethics committee (decision number 65, dated 03/2021). All procedures in our study were carried out per the 1964 Declaration of Helsinki and subsequent amendments.

Data analysis

The conformity of the variables to the normal distribution was examined using visual (histogram and probability graphs) and analytical methods (Kolmogorov-Smirnov). Descriptive statistics are presented as median [interquartile ranges (IQR)] for the numerical variables and as ratios for the categorical variables. The median differences between groups were compared using the Mann-Whitney U test. The Kruskal-Wallis test was used to compare the quantitative data of three groups that did not show normal distribution. In the comparison of qualitative data, Chi-Square test or Fisher's Exact Chi-Square test was used when test conditions could not be met. For multivariate analyses, logistic regression backward stepwise method was used. Variables with $p < 0.1$ and those found to be associated in the literature were included in the multivariate model. The strength of the relationship was defined by the OR (95% confidence interval). $p < 0.05$ was evaluated as statistically significant.

RESULTS

Between March and June 2021, a total of 1387 pregnant women gave birth at Zeynep Kamil Women and Children's Diseases Training and Research Hospital. All patients were screened for SARS-CoV-2 infection at the time of admission to the maternity ward, and 15 (1.08%) women were excluded due to SARS-CoV-2 PCR positivity. The study population is shown in the flowchart (Fig. 1).

The demographic characteristics of the participants are presented in Table 1. Univariate analysis evaluating the relationship between perinatal and neonatal outcomes of the participants with SARS-CoV-2 infection history are presented in Table 2. Spontaneous PTB was detected in 22.5% of cases with a history of SARS-CoV-2 infection and 5.3% of cases without a history of infection; the difference was statistically significant ($p < 0.001$). In our study, iatrogenic preterm birth rates were found to be statistically similar in the group with and without a history of COVID-19 ($p = 0.058$). In the group with a history of COVID-19, pregnant women had iatrogenic preterm deliveries due to severe preeclampsia (n = 4, 3.9%) and abruptio placentae (n = 4, 3.9%). Among the pregnant women without a history of COVID-19, pregnant women had iatrogenic preterm deliveries due severe preeclampsia (n = 34, 9%), abruptio placentae (n = 3, 0.8%), and FGR and fetal distress (n = 20, 5.3%).

The relationship between the gestational week of COVID-19 exposure and fetal anomaly was examined and no statistically significant difference was found ($p = 0.9$). However, fetal CNS anomalies were detected in three (10.3%) out of 29 women with a history of COVID-19 in the first trimester, and all these patients were symptomatic (all of them had fever, respiratory distress, headache, and malaise) (Tab. 3). The median (IQR) gestational week at which the participants were infected with SARS-CoV-2 was 22.0 weeks (13.0–29.0); 29 (28.4%) were infected in the first trimester, 41 (40.2%) were infected in the second trimester, and 32 (31.4%) were infected in the third trimester. When the groups were compared according to the trimester of infection, no significant differences were found in terms of maternal age, BMI, and mode of delivery ($p > 0.05$). However, the gestational age at birth of the pregnant women who were infected in the first trimester was lower than in pregnant women who were infected in the second and third trimesters ($p = 0.005$). Birth weight was also found to be lower if the infection was contracted in the first trimester compared to the second trimester ($p = 0.018$). The rates of spontaneous PTB were found to be higher in pregnant women who were infected in the first (34.5%) and third (28.1%) trimesters than in pregnant

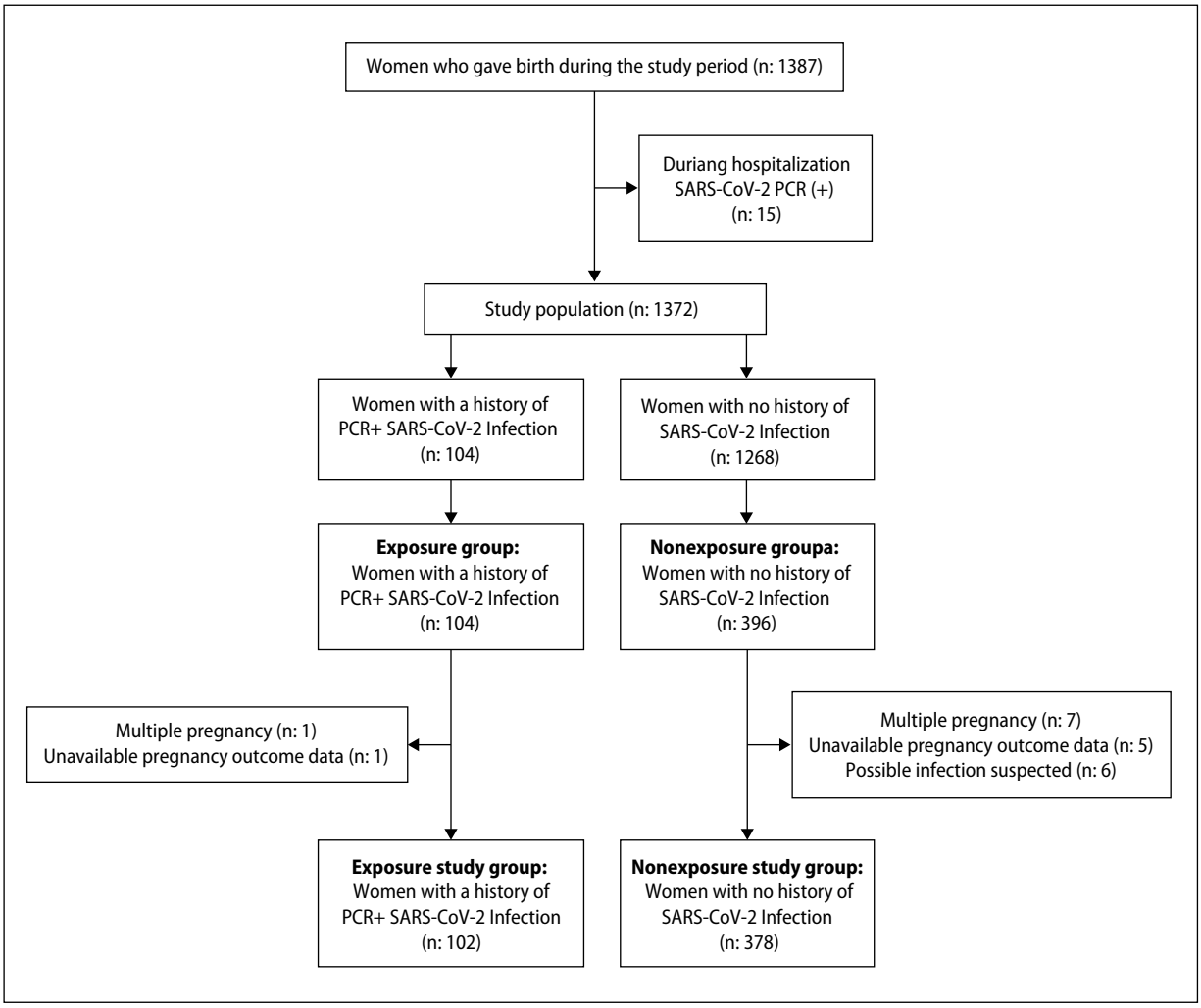

Figure 1. Flow chart of the study population; aCases without exposure were determined by the systematic sampling method; PCR — polymerase chain reaction

women who were infected in the second trimester (9.8%) ($p = 0.034$).

All cases diagnosed with intrahepatic cholestasis of pregnancy were women who had the infection in the third trimester. Although not statistically significant, placental abruption was detected in 10.3% of the cases infected with SARS-CoV-2 in the first trimester ($p = 0.086$). Birth weight of < 2500 g was more common among those who had the infection during the first and third trimesters, but this result was not statistically significant ($p = 0.060$). Neonatal complications did not differ between groups ($p > 0.05$) (Tab. 3).

Models were created using multivariate logistic regression (Backward LR) analysis to evaluate the independent effects of variables associated with spontaneous PTB. The model included maternal age groups, BMI, smoking, mode of conception (spontaneous/in vitro fertilization), fetal sex, and history of COVID-19 during pregnancy.

In multivariate logistic regression analysis, when the status of not having COVID-19 infection during pregnancy is taken as a reference, we calculated that the risk of spontaneous PTB was 9.13 times higher (95% CI 3.68–22.66; $p < 0.001$) in those who were infected in the first trimester, and 7.09 times higher (95% CI 2.85–17.62; $p < 0.001$) in those infected in the third trimester. If the infection occurred in the second trimester, the risk of spontaneous PTB birth was 1.85 times higher (95% CI 0.59–5.79; $p = 0.292$); this result was not statistically significant (Tab. 4).

DISCUSSION

It is known that various viral infections increase the risk of fetal anomalies, fetal growth restriction (FGR), and PTB by negatively affecting fetal health [16]. When the first data on COVID-19 and pregnancy began to emerge, it was reported that almost all PTB were iatrogenic, due to deteriorating maternal status of COVID-19 or because of obstetric

Table 1. Socio-demographic and health characteristics of participants (n: 480)

		Exposure group[a] n: 102	Nonexposure group[b] n: 378	p value
Maternal Characteristics and Maternal Comorbidities				
BMI [kg/m^2], median (IQR)		31.2 (27.3–34.1)	30.4 (27.3–33.3)	0.352
		n (%)	n (%)	
Age Range [years]	19–24	14 (13.7)	67 (17.7)	0.462
	25–34	66 (64.7)	220 (58.2)	
	35–45	22 (21.6)	91 (24.1)	
Educational status	Primary school	26 (25.2)	80 (21.2)	0.215
	Secondary school	19 (18.6)	101 (26.7)	
	High school	30 (29.4)	121 (32.0)	
	University	27 (26.5)	76 (20.1)	
Family income	Low	17 (16.7)	56 (14.8)	0.896
	Medium	76 (74.5)	287 (75.9)	
	High	9 (8.8)	35 (9.3)	
Employed		27 (26.5)	76 (20.1)	0.165
Social security		86 (84.3)	317 (83.9)	0.912
Nulliparous		31 (30.4)	110 (29.1)	0.799
In vitro fertilization		5 (4.9)	3 (0.8)	0.013*
History of smoking[c]		22 (21.6)	73 (19.3)	0.612
Husband's history of smoking		54 (52.9)	225 (59.5)	0.232
Chronic diseases		30 (29.4)	108 (29.1)	0.953

[a]Women with a history of PCR + SARS-CoV-2 Infection; [b]Women with no history of SARS-CoV-2 Infection; [c]current smoker or ex-smoker; IQR — interquartile range; BMI — body mass index; *Statistically significant difference

complications not related to COVID-19 [17]. Recent studies have reported that SARS-CoV-2 infection leads to an increased risk of PTB and LBW [9, 18–21].

Two systematic reviews from studies conducted in the early period of the pandemic reported an increased incidence of PTB, LBW, cesarean section, and Neonatal İntensive Care Unit (NICU) admissions in pregnant women infected with SARS-CoV-2 [18, 22]. Most of these studies were laboratory-confirmed, admitted to the intensive care unit, and nearly all had positive findings on thoracic computed tomography (CT) scans. Therefore, these studies have undeniable limitations such as that most of the cases were in critical condition, sample sizes were small, and there was a lack of information about pre-pregnancy medical conditions. SARS-CoV-2–positive pregnant women with comorbidities are more likely to develop complications [23]. From this point of view, we analyzed the perinatal outcomes of asymptomatic and uncomplicated women and, by this, to reveal what kind of damage COVID-19 actually causes in pregnancy. The reason why we have chosen asymptomatic/uncomplicated pregnant women as the study population is that the most common form of COVID-19 is mild and moderate disease, and the literature data on this subject is limited.

The WAPM COVID-19 Working Group retrospectively analyzed the data of 266 women who had a singleton pregnancy, had laboratory-confirmed SARS-CoV-2 infection, and gave birth between February and April 2020. It was reported that 94.4% of women had a live birth, 26.3% had PTB before 37 weeks of gestation, 27.5% of newborns were admitted to the NICU, and 2.0% neonatal deaths were reported. What draws our attention is that approximately 70% of the pregnant women included in the study were in the third trimester [6]. In the meta-analysis by Capobianco et al. [9], consisting of 13 publications and 114 cases, the authors reported a high rate of maternal and neonatal complications in infected individuals. Elshafeey et al. [24] analyzed the results of 385 SARS-CoV-2–positive pregnant women. In that study, 95.6% of the cases were mild infections, similar to the case group we selected in our study. However, in the study of Elshafeey et al., SARS-CoV-2–positive pregnant women were not compared to uninfected pregnant women. The authors reported PTB (< 37 weeks of gestation) in 39 pregnant women, LBW (< 2500 g) in 20 newborns, fetal distress in 20, and need for NICU admission in 8 newborns. In our study, 23 cases had spontaneous PTB (< 37 weeks of gestation), 15 cases had LBW (< 2500 g), and 31 newborns required NICU admission in the asymptomatic or uncomplicated

Table 2. Pregnancy, birth, postpartum period, and neonatal outcomes of the participants (n: 480)

			Exposure group[a] n: 102	Nonexposure group[b] n: 378	p value
Obstetric Outcomes of the Participants					
Gestational age at delivery median [weeks] (IQR)			38 (37–39)	39 (37–39)	0.271
			n (%)	n (%)	
Mode of birth	C/S		68 (66.7)	241 (63.8)	0.586
	Vaginal delivery		34 (33.3)	137 (36.2)	
Spontan. preterm delivery (< 37 weeks)			23 (22.5)	20 (5.3)	< 0.001*
Iatrogenic preterm labor (< 37 weeks)			8 (7.8)	57 (15.1)	0.058
Spontan. early preterm delivery (< 34 weeks)			6 (5.9)	16 (4.2)	0.435
Spontaneous PPROM			6 (5.9)	15 (4.0)	0.415
Hypertensive disease			12 (11.8)	43 (11.4)	0.913
Type of hypertensive disease	Chronic HT		–	1 (0.3)	0.663
	Gestational HT		4 (3.9)	8 (2.1)	
	Preeclampsia/Eclampsia		8 (7.8)	30 (7.9)	
	Superimposed Preeclampsia		-	4 (1.1)	
	No hypertensive disease		90 (88.2)	335 (88.6)	
GDM			24 (23.5)	61 (16.1)	0.083
Cholestasis			4 (3.9)	2 (0.5)	0.020*
Abruptio Placenta			4 (3.9)	3 (0.8)	0.040*
Neonatal Outcomes					
Newborn birth weight [grams], median (IQR)			3305.0 (2740–3580.0)	3230.0 (2880.0–3580.0)	0.999
			n (%)	n (%)	
Fetal gender Male		Female	43 (42.2)	201 (53.2)	0.048*
		59 (57.8)	177 (46.8)		
Admitted in NICU			31 (30.4)	95 (25.1)	0.284
Apgar 5 score < 7			5 (4.9)	6 (1.6)	0.061
SGA			10 (9.8)	35 (9.3)	0.867
LGA			19 (18.6)	81 (21.4)	0.536
Birthweight < 2500 gm			15 (14.7)	50 (13.2)	0.699
Birthweight > 4000 gm			5 (4.9)	18 (4.8)	1.0
Neonatal Death			1 (1.0)	4 (1.1)	1.0
Fetal anomaly			9 (8.8)	21 (5.6)	0.226
Cardiac anomaly			2 (2.0)	4 (1.1)	0.612
CNS anomaly			4 (3.9)	4 (1.1)	0.067

[a]Women with a history of PCR + SARS-CoV-2 Infection; [b]Women with no history of SARS-CoV-2 Infection; IQR — interquartile range; C/S — Cesarean section; PPROM — Preterm premature rupture of membranes; GDM — Gestational diabetes mellitus; HT — Hypertension; NICU — Neonatal İntensive Care Unit; SGA — Small for gestational age (Intergrowth 21); LGA — large-for-gestational-age; CNS — Central nervous system; *Statistically significant difference

SARS-CoV-2 infection group. The rate of spontaneous PTB in pregnant women with a history of COVID-19 was significantly higher than in pregnant women without exposure to COVID-19.

Maternal SARS CoV-2 infection causes maternal immune activation resulting in pro-inflammatory cytokine release. This leads to the disturbance of placental perfusion and ultimately to placental dysfunction. Vascular malperfusion, fetal vascular thrombosis, infection with widespread inflammation, fibrin deposition, and intervillous thrombosis have been demonstrated in placenta samples of pregnant women infected with SARS-CoV-2 [5]. Smithgall et al. [25] collected placenta samples from 51 women with SARS-CoV-2 positive at delivery, and pathological examination was performed. Interestingly, it was reported that the frequency of placental histopathological findings was independent of the clinical

Table 3. The relationship between trimester during SARS-CoV-2 infection and maternal, current obstetric, postpartum, and neonatal period characteristics (n: 102)

		Infection in 1st trimester n: 29	Infection in 2nd trimester n: 41	Infection in 3rd trimester n: 32	p value
Maternal and Current Obstetric Outcomes of the Participants					
BMI [kg/m^2], median (IQR)		31.2 (27.6–34.0)	31.6 (29.6–34.9)	30.2 (26.5–33.6)	0.408
Gestational age at delivery [weeks], median (IQR)		37.0 (36.0–39.0)	39.0 (38.0–39.0)	38.0 (37.0–39.5)	0.005*
Newborn birth weight [grams], median (IQR)		2940.0 (2490.0–3440.0)	3400.0 (3210.0–3600.0)	3125.0 (2650.0–3595.0)	0.018*
		N (%)	N (%)	N (%)	
Age Range [years] 25–34 35–45	19-24	4 (13.8)	4 (9.8)	6 (18.8)	0.752
	19 (65.8)	29 (70.7)	18 (56.2)		
	6 (20.7)	8 (19.5)	8 (25.0)		
Symptomatic SARS-CoV-2		22 (75.9)	17 (41.5)	21 (65.6)	0.010*
Mode of birth Vaginal delivery	C/S	20 (69.0)	29 (70.7)	19 (59.4)	0.566
	9 (31.0)	12 (29.3)	13 (40.6)		
Spontan. preterm delivery (< 37 weeks)		10 (34.5)	4 (9.8)	9 (28.1)	0.034*
İatrogenic preterm labor (< 37 weeks)		6 (20.7)	1 (2.4)	1 (3.1)	0.010*
Spontaneous PPROM		4 (13.8)	1 (2.4)	1 (3.1)	0.100
Hypertensive disease		6 (20.7)	4 (9.8)	2 (6.2)	0.190
Type of hypertensive disease	Chronic HT	–	–	–	0.469
	Gestational HT	2 (6.9)	1 (2.4)	1 (3.1)	
	Preeclampsia/Eclampsia	4 (13.8)	3 (7.3)	1 (3.1)	
	Superimposed Preeclampsia	–	–	–	
	No hypertensive disease	23 (79.3)	38 (90.5)	30 (93.8)	
GDM		6 (20.7)	10 (24.4)	8 (25.0)	0.912
Cholestasis		–	–	4 (12.5)	0.011*
Abruptio placenta		3 (10.3)	–	1 (3.1)	0.086
Neonatal Outcomes					
Admitted to NICU		10 (34.5)	10 (24.4)	11 (34.4)	0.558
Apgar 5 score < 7		1 (3.4)	2 (4.9)	2 (6.2)	0.880
SGA		4 (13.8)	4 (9.8)	2 (6.2)	0.613
LGA		4 (13.8)	9 (22.0)	6 (18.8)	0.689
Birthweight < 2500 gr		7 (24.1)	2 (4.9)	6 (18.8)	0.060
Birthweight > 4000 gr		1 (3.4)	1 (2.4)	3 (9.4)	0.361
Fetal anomaly		3 (10.3)	3 (7.3)	3 (9.4)	0.900
Neonatal death		1 (3.4)	–	–	0.281

BMI — body Mass Index; IQR — interquartile range; C/S — cesarean section; PPROM — preterm premature rupture of membranes; GDM — gestational diabetes mellitus; HT — hypertension; NICU — neonatal Intensive Care Unit; SGA — small for gestational age (Intergrowth 21); LGA — large-for-gestational-age; CNS — central nervous system; *Statistically significant difference

status, and there was no difference between symptomatic and asymptomatic cases in terms of histopathological findings. This information suggests that asymptomatic or uncomplicated COVID-19 may also increase the risk of obstetric complications such as PTB, FGR, and LBW.

Another important issue that remains unknown is whether perinatal outcomes change according to the timing of infection (in which trimester). Although the WAPM COVID-19 Working Group reports that the incidence of combined adverse fetal outcomes increases significantly if infection occurs in the first trimester, we observed that spontaneous PTB occurred 9.13 and 7.09 times more often in women who were infected during the first and third trimesters, respectively, independent of other risk factors. Although we found that second trimester infection did not independently affect the risk of spontaneous PTB, we think

Table 4. Characteristics associated with spontaneous preterm birth, univariate and multivariate analyses

Spontaneous preterm delivery					
OR (95% CI)		Univariate analysis (OR)		Multivariate analysis (aOR)	
		p value	aOR (95% CI)	p value	
SARS–CoV–2 positive status in pregnancy	SARS–CoV–2 negative	1.0	–	1.0	–
	1st Trimester	9.42 (3.88–22.90)	< 0.001*	**9.13** (3.68–22.66)	< 0.001*
	2nd Trimester	1.94 (0.63–5.96)	0.250	1.85 (0.59–5.79)	0.292
	3rd Trimester	7.00 (2.87–17.10)	< 0.001*	**7.09** (2.85–17.62)	< 0.001*
Age [years]	19–24	1.0	–	–	–
	25–34	1.78 (0.67–4.75)	0.249	–	–
	34–45	1.16 (0.37–3.68)	0.803	–	–
BMI [kg/m^2]		0.95 (0.89–1.01)	0.117	0.94 (0.88–1.01)	0.096
Educational status	Primary school	0.52 (0.17–1.60)	0.252	–	
	Secondary school	1.38 (0.57–3.33)	0.475	–	
	High school	1.15 (0.48–2.74)	0.749	–	
	University	1.0	–	–	
Income of family	Low	0.56 (0.18–1.72)	0.312	–	
	Medium	0.46 (0.19–1.12))	0.087	–	
	High	1.0		–	
Working Status	Yes	0.90 (0.73–2.98)	0.168	–	
	No	1.0		–	
Fetal gender	Female	1.0	0.014*	1.0	0.023*
	Male	2.30 (1.18–4.48)		**2.25** (1.12–4.53)	
IVF pregnancy	No	1.0	0.013*	–	–
	Yes	6.48 (1.49–28.11)		–	
Smoking habit[a]	No	1.0	0.165	–	–
	Yes	1.65(0.81–3.35)		–	
Chronic diseases	No	1.0	0.587	–	–
	Yes	0.82 (0.40–1.68)		–	
Hypertensive diseases during pregnancy	No	1.0	0.340	–	–
	Yes	0.56 (0.17–1.86)		–	

BMI — Body Mass Index; IVF — In vitro fertilization; [a]current smoker or ex–smoker; OR — Odds ratio; CI — confidence interval; Adjusted odds ratio (aOR) — multiple imputation model adjusted for age groups, BMI, smoking habit, IVF pregnancy and SARS-CoV-2 positive status in pregnancy; 1.0 = as a reference; *Statistically significant difference

that a possible type 2 error should not be ignored, and this issue should be re-examined with prospective studies in larger samples.

Preterm birth is an important public health problem that may adversely affect the health of the newborn and has short- and long-term effects [26]. The global prevalence of PTB has been reported as 10.6% [27]. As information from studies cumulates, countries may need to reconsider their healthcare policies regarding COVID-19. Determining vaccination strategies in pregnant women will be important in preventing COVID-19 and associated obstetric complications, especially PTB.

In our study, with its retrospective cohort design, SARS-CoV-2 infection during pregnancy was confirmed by PCR test positivity, and the gestational age at the time of the infection was correctly determined; these are the strengths of our research. Until now, most studies have evaluated PTB cases without distinguishing them as spontaneous and iatrogenic. However, in our study, we evaluated iatrogenic PTB cases of obstetric or maternal origin separately from spontaneous PTB cases. Therefore, our findings will help to explain the relationship between spontaneous PTB and COVID-19, for which there is not yet enough information in the literature.

Our study has some limitations. A significant number of COVID-19 infected individuals survive the disease without any symptoms or are not diagnosed by PCR. The diagnostic value of the PCR test is limited to 50-60%, and it may result in missed diagnosis. This may cause misclassification bias between the groups that had and did not have the

infection. Since our research was conducted in a single center, the generalizability of the results to the general population is limited.

CONCLUSIONS

In conclusion, asymptomatic or uncomplicated pregnant women infected with SARS CoV-2 during the first and third trimesters should be followed up carefully and closely for spontaneous PTB, at least as much as pregnant women with complicated disease. In addition, one should keep in mind placental abruption and intrahepatic cholestasis of pregnancy during the course of follow-up. The fact that SARS CoV-2 infection has been associated with the risk of PTB in all spectrums, regardless of the severity of the disease, may reveal the importance of the COVID-19 vaccine in pregnancy, although data on its safety are limited. In this context, it seems reasonable to offer the vaccine option to pregnant women after proper counseling.

Article information and declarations

Author contribution

P Kumru: Project development, data collection, data analysis
S Hıdıroğlu: Project development, methodology, editing, supervision
E Cogendez: Manuscript writing / editing
H Ayvacı: Data collection
B Yılmazer: Data collection
H Erol: Data collection
O Demirci: Supervison
P Ay: Project development, methodology, supervision

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Conflict of interest

All authors declare no conflict of interest.

REFERENCES

1. https://www.who.int/publications/m/item/weekly-epidemiological-update-on-covid-19---13-october-2021.
2. Encinas Pardilla MB, Caño Aguilar A, Puig BM, et al. [Spanish registry of Covid-19 screening in asymptomatic pregnants] . Rev Esp Salud Publica. 2020; 94: e202009092, indexed in Pubmed: 32945290.
3. Ortiz Molina E, Hernandez Pailos R, Pola Guillen M, et al. COVID-19 infection in symptomatic pregnant women at the midpoint of the pandemic in Spain: a retrospective analysis. Ginekol Pol. 2020; 91(12): 755–763, doi: 10.5603/GP.a2020.0130, indexed in Pubmed: 33447995.
4. Khalil A, Hill R, Ladhani S, et al. Severe acute respiratory syndrome coronavirus 2 in pregnancy: symptomatic pregnant women are only the tip of the iceberg. Am J Obstet Gynecol. 2020; 223(2): 296–297, doi: 10.1016/j.ajog.2020.05.005, indexed in Pubmed: 32387327.
5. Cavalcante MB, Cavalcante CT, Sarno M, et al. Maternal immune responses and obstetrical outcomes of pregnant women with COVID-19 and possible health risks of offspring. J Reprod Immunol. 2021; 143: 103250, doi: 10.1016/j.jri.2020.103250, indexed in Pubmed: 33249335.
6. WAPM (World Association of Perinatal Medicine) Working Group on COVID-19. Maternal and perinatal outcomes of pregnant women with SARS-CoV-2 infection. Ultrasound Obstet Gynecol. 2021; 57(2): 232–241, doi: 10.1002/uog.23107, indexed in Pubmed: 32926494.
7. Cruz Melguizo S, de la Cruz Conty ML, Carmona Payán P, et al. Pregnancy Outcomes and SARS-CoV-2 Infection: The Spanish Obstetric Emergency Group Study. Viruses. 2021; 13(5), doi: 10.3390/v13050853, indexed in Pubmed: 34067086.
8. Martinez-Perez O, Prats Rodriguez P, Muner Hernandez M, et al. Spanish Obstetric Emergency Group. The association between SARS-CoV-2 infection and preterm delivery: a prospective study with a multivariable analysis. BMC Pregnancy Childbirth. 2021; 21(1): 273, doi: 10.1186/s12884-021-03742-4, indexed in Pubmed: 33794829.
9. Capobianco G, Saderi L, Aliberti S, et al. COVID-19 in pregnant women: A systematic review and meta-analysis. Eur J Obstet Gynecol Reprod Biol. 2020; 252: 543–558, doi: 10.1016/j.ejogrb.2020.07.006, indexed in Pubmed: 32713730.
10. COVID-19 Treatment Guidelines Panel. Coronavirus Disease 2019 (COVID-19) Treatment Guidelines. National Institutes of Health. https://www.covid19treatmentguidelines.nih.gov/ (25.01.2021).
11. Coustan DR, Carpenter MW, Carpenter MW, et al. Criteria for screening tests for gestational diabetes. Am J Obstet Gynecol. 1982; 144(7): 768–773, doi: 10.1016/0002-9378(82)90349-0, indexed in Pubmed: 7148898.
12. Hypertension in pregnancy. Report of the American College of Obstetricians and Gynecologists' Task Force on Hypertension in Pregnancy. Obstet Gynecol. 2013; 122(5): 1122–1131, doi: 10.1097/01.AOG.0000437382.03963.88, indexed in Pubmed: 24150027.
13. Hadlock FP, Harrist RB, Sharman RS, et al. Estimation of fetal weight with the use of head, body, and femur measurements--a prospective study. Am J Obstet Gynecol. 1985; 151(3): 333–337, doi: 10.1016/0002-9378(85)90298-4, indexed in Pubmed: 3881966.
14. https://www.rcog.org.uk/globalassets/documents/guidelines/gtg_43.pdf.
15. Villar J, Ismail L, Victora C, et al. International standards for newborn weight, length, and head circumference by gestational age and sex: the Newborn Cross-Sectional Study of the INTERGROWTH-21st Project. Lancet. 2014; 384(9946): 857–868, doi: 10.1016/s0140-6736(14)60932-6.
16. Racicot K, Mor G, Silasi M, et al. Viral infections during pregnancy. Am J Reprod Immunol. 2015; 73(3): 199–213, doi: 10.1111/aji.12355, indexed in Pubmed: 25582523.
17. Wastnedge EAN, Reynolds RM, van Boeckel SR, et al. Pregnancy and COVID-19. Physiol Rev. 2021; 101(1): 303–318, doi: 10.1152/physrev.00024.2020, indexed in Pubmed: 32969772.
18. Smith V, Seo D, Warty R, et al. Maternal and neonatal outcomes associated with COVID-19 infection: A systematic review. PLoS One. 2020; 15(6): e0234187, doi: 10.1371/journal.pone.0234187, indexed in Pubmed: 32497090.
19. Huntley BJF, Huntley ES, Di Mascio D, et al. Rates of Maternal and Perinatal Mortality and Vertical Transmission in Pregnancies Complicated by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-Co-V-2) Infection: A Systematic Review. Obstet Gynecol. 2020; 136(2): 303–312, doi: 10.1097/AOG.0000000000004010, indexed in Pubmed: 32516273.
20. Knight M, Bunch K, Vousden N, et al. UK Obstetric Surveillance System SARS-CoV-2 Infection in Pregnancy Collaborative Group. Characteristics and outcomes of pregnant women admitted to hospital with confirmed SARS-CoV-2 infection in UK: national population based cohort study. BMJ. 2020; 369: m2107, doi: 10.1136/bmj.m2107, indexed in Pubmed: 32513659.
21. Trocado V, Silvestre-Machado J, Azevedo L, et al. Pregnancy and COVID-19: a systematic review of maternal, obstetric and neonatal outcomes. J Matern Fetal Neonatal Med. 2022; 35(12): 2362–2374, doi: 10.1080/14767058.2020.1781809, indexed in Pubmed: 32635775.
22. Juan J, Gil MM, Rong Z, et al. Effect of coronavirus disease 2019 (COVID-19) on maternal, perinatal and neonatal outcome: systematic review. Ultrasound Obstet Gynecol. 2020; 56(1): 15–27, doi: 10.1002/uog.22088, indexed in Pubmed: 32430957.

23. Hessami K, Homayoon N, Hashemi A, et al. COVID-19 and maternal, fetal and neonatal mortality: a systematic review. J Matern Fetal Neonatal Med. 2022; 35(15): 2936–2941, doi: 10.1080/14767058.2020.1806817, indexed in Pubmed: 32799712.
24. Elshafeey F, Magdi R, Hindi N, et al. A systematic scoping review of COVID-19 during pregnancy and childbirth. Int J Gynaecol Obstet. 2020; 150(1): 47–52, doi: 10.1002/ijgo.13182, indexed in Pubmed: 32330287.
25. Smithgall MC, Liu-Jarin X, Hamele-Bena D, et al. Third-trimester placentas of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)-positive women: histomorphology, including viral immunohistochemistry and in-situ hybridization. Histopathology. 2020; 77(6): 994–999, doi: 10.1111/his.14215, indexed in Pubmed: 32692408.
26. Kuint J, Lerner-Geva L, Chodick G, et al. Israel Neonatal Network. Re-hospitalization Through Childhood and Adolescence: Association with Neonatal Morbidities in Infants of Very Low Birth Weight. J Pediatr. 2017; 188: 135–141.e2, doi: 10.1016/j.jpeds.2017.05.078, indexed in Pubmed: 28662947.
27. Martin JA, Hamilton BE, Osterman MJK, et al. Births: Final Data for 2018. Natl Vital Stat Rep. 2019; 68(13): 1–47.

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Increased risk of low infant birth weight in pregnant women with low PAPP-A values measured in the first trimester

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ABSTRACT

Objectives: Testing pregnant women as early as in the first trimester has multiple advantages. Firstly, the first trimester screening combining ultrasound and serum marker testing (PAPP-A and free β-hCG) offers the highest currently possible — except for expensive tests using cell-free DNA biomarkers from the mother's blood (ccf DNA) — detectability of aneuploid fetuses. Secondly, nuchal translucency (NT) measurement helps determine the risk of numerous abnormalities other than aneuoploidies. Lastly, nearly complete ultrasound assessment of fetal anatomy can be performed as early as in the first trimester of pregnancy.

Material and methods: This study is based on prospective analysis. Study subjects were 236 pregnant women. One hundred thirty-one patients with a single pregnancy were qualified into the study group and had a combined ultrasound and biochemical screening for Down's syndrome performed between 11 + 0 and 13 + 6 weeks of gestation, with the measured PAPP-A value at ≤ 0.50 MoM (multiples of the median). The control group comprised 105 pregnant women with PAPP-A value at a similar stage of pregnancy at > 0.5 MoM.

Results: The average observed value of the PAPP-A in the study group was 0.35 MoM while in the control group 1.29 MoM. Moreover, combined observation of infant birth weights in both groups compared to the PAPP-A MoM values has shown a significant relationship between those characteristics (r = 0.15, p = 0.0184).

Conclusions: The results showed that pregnant women with low PAPP-A MoM value measured during the first trimester have a higher risk of giving birth to a low-birth-weight infant (which is the value below 2500 g), than the pregnant women whose PAPP-A MoM value in the first trimester did not meet this criterion.

Keywords: small-for-gestational-age infants; PAPP-A protein; β-hCG; ultrasound scan

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INTRODUCTION

Small-for-gestational-age (SGA) infants are at a higher risk of perinatal mortality and both short-term and long-term morbidity; this risk can, however, be reduced if the condition is diagnosed prior to delivery permitting strict supervision, appropriate delivery date, and immediate post-natal care [1]. Testing pregnant women as early as in the first trimester has multiple advantages. Firstly, the first trimester screening combining ultrasound and serum marker testing (PAPP-A and free ß-hCG) offers the highest currently possible — except for expensive tests using cell-free DNA biomarkers from the mother's blood (ccf DNA) — detectability of aneuploid fetuses [2]. Secondly, nuchal translucency (NT) measurement helps determine the risk of numerous abnormalities other than aneuploidies [2–4]. Lastly, nearly complete ultrasound assessment of fetal anatomy can be performed as early as in the first trimester of pregnancy [2, 3]; moreover, the first trimester ultrasound assessment includes measurement of crown-rump length which is the most reliable method of estimating the actual gestational age. It can be assumed with a high degree of probability that a correctly determined gestational age is one of key pieces of information required to manage normal and high-risk pregnancies [2]. Pregnancy-associated plasma protein A was first identified in 1974 [5]. It is currently used in most screening programs oriented at early detection

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of the Down syndrome as its low serum concentration in maternal blood has been found to be associated with trisomies 21, 18, and 13 [6, 7]. Circulating pregnancy-associated protein A is mainly derived from syncytiotrophoblast [8], and PAPP-A gene is located on human 9q33.1 chromosome. Moreover PAPP-A increases bioavailability of insulin-like growth factors (IGF I and IGF II) by fragmenting their binding proteins (IGFBP-4, -5). IGF is believed to have mitogenic and antiapoptotic effect and to be vital for cellular growth in most human tissues [9]. PAPP-A, involved in control of the insulin-like growth factor system in the first trimester of pregnancy, at low levels, seems to result in a significantly reduced activity of IGF-I and IGF-II, showing an affinity with the early placentation process and, consequently, placental growth and function [10].

PAPP-A concentration in maternal blood serum is detectable shortly following implantation, with its level growing with gestational age, doubling every 3–4 days during the first trimester. PAPP-A concentration reaches its maximum level at the final stage of pregnancy [11]. Average half-life of pregnancy-associated plasma protein A following a spontaneous childbirth is 53 ± 26 hours [12]. In addition to gestational age, PAPP-A concentration on maternal blood serum is affected by maternal and pregnancy-related characteristics [13]. Some of them, like multiparosity and smoking, are probably associated with the trophoblastic tissue mass since PAPP-A concentration increases with placental volume measured by ultrasound [13]. Other factors, such as the mother's body weight prior to pregnancy, have been correlated with distribution volume, while its association with the fetus' sex, number of previous pregnancies, ethnicity, and assisted reproduction has not found any biological explanation to date. The best documented clinical application of PAPP-A are first trimester screening programs aimed at detecting chromosomal abnormalities characterized by low PAPP-A levels. These programs are aimed at identifying pregnant women who should be offered testing cell-free DNA biomarkers from maternal blood, the so-called non-invasive prenatal test (NIPT), chorionic villus sampling (CVS), or amniocentesis. Since maternal PAPP-A level indirectly reflects placental volume and, probably, trophoblastic tissue mass, it would seem logical that low PAPP-A values are associated with reduced biometric fetal values in the first and the second trimester of pregnancy, as well as adverse pregnancy outcomes, such as IUGR and — consequently — low birth weight, spontaneous abortion, stillbirth, preeclampsia, or premature birth [3]. Clinical utility of the above-mentioned relationships has not been fully explained, however, since detection rates of adverse pregnancy outcomes are, regrettably, relatively low (8–16%) [3].

Definitions of an SGA fetus and severe SGA vary. For the purposes of this paper, we assumed that SGA would refer to a fetus with estimated weight (EFW) or abdominal circumference (AC) values below 10th percentile, while severe SGA would refer to cases with EFW or AC values under 3rd percentile [14]. IUGR indicates that the prenatally presenting pathognomic factor reduced the genetic potential of fetal growth, and fetal growth rate did not reflect gestational age. IUGR is not synonymous to SGA. Some fetuses/infants with IUGR features have low biometric measurement values compared to gestational age, while 50–70% of SGA fetuses are constitutionally smaller because their growth rate depends on the mother's body proportions and ethnicity [15]. Structurally normal SGA fetuses have a higher risk of perinatal complications and deaths, but the most adverse health outcomes apply to IUGR-burdened fetuses with adverse implications for further mental and physical development of such infants [1]. Methods used to assess the risk of SGA fetus development in the first and second trimesters of pregnancy include: general medical and obstetrical history, obstetrical examination, screening for the first trimester Down syndrome markers in maternal blood, and evaluation of uterine arterial flow, and the risk of preeclampsia. SGA detection methods in the second and third trimester of pregnancy allowing an accurate diagnosis include serial ultrasound measurements of fetal AC and assessment of estimated fetal weight using individualized percentile norms performed every 2–3 weeks. The published average AC and EFW growth rates after 30 weeks of gestation are 10mm over 14 days and 200 g over 14 days for EFW likewise, although when the values are lower there is also a greater diversity [reflecting various methods of calculating standard deviation (SD)] [16]. It was also shown that AC value change by less than 5mm over 14 days was indicative of IUGR [17]. There is evidence that statistically best prognoses for SGA are achieved with universal ultrasound biometric screening of fetuses in the third trimester, especially around 36 weeks of gestation [18]. This is related to the fact that 85% of SGA infants with birth weight < 10 percentile are born after 37 weeks of gestation [1]. The most sensitive single biometric measurement in SGA prediction is abdominal circumference of the fetus, reflecting liver size and — thus — the stored glycogen and degree of nutrition. A systemic review of 45 studies describing a total of 70 models for EFW in various combinations of measurements of fetal head circumference (HC), biparietal diameter, femoral length (FL), and abdominal circumference (AC) [19] has showed the model devised by Hadlock et al. [20] to be the most accurate, including measurements of HC, AC, and FL; EFW measured within two days of birth was within 10% of birth weight in 80% of cases.

A lower volume of amniotic fluid may be another one of first signs of IUGR in ultrasound scans. Clinically significant oligohydramnios (*i.e.*, AFI < 5 cm or the largest single fluid

pocket < 2 cm) has a positive predictive value of 86% for IUGR. Bottom threshold values of AFI (5–10cm) were shown to be correlated with a 4-fold increased incidence of fetal growth restriction [21].

Objectives

This study aimed to evaluate the risk of placental dysfunction expressed with intrauterine fetal growth inhibition and low birth weight of the infant related to low PAPP-A levels found in a double test from maternal blood.

MATERIAL AND METHODS

General characteristics

This study is based on prospective analysis which was approved by the Ethics Committee — Medical University of Warsaw (Number AKBE/89/13). Ultrasound scans were performed by physicians holding Certificates of Competence issued by the Fetal Medicine Foundation (FMF) for testing between 11 and 13 + 6 weeks of gestation. Procedures used during this study were performed in accordance with the criteria defined by the Fetal Medicine Foundation (FMF).

Study group

All the patients consented in writing to being included in the study. Pregnant women who did not consent and/or had an abnormal fetal karyotype diagnosed were excluded from the study. Information on gestational week of delivery and birth weight were obtained during phone call interviews with the mothers.

The study included 236 pregnant women who in the years 2010–2012 were under perinatal care at NZOZ ARS Medical Specialist Medical Services Centre in Poznan or at the Division of Gynecological Surgery at Poznan University of Medical Sciences. In this research project, data from combined ultrasound and biochemical screening for Down syndrome in the first trimester of pregnancy were used. Abnormal fetal karyotype was an exclusion criterion for the study. In continuation of the research process, the patients were divided into two groups: study group and control group. One hundred thirty-one patients with a single pregnancy were qualified into the study group, and had a combined ultrasound and biochemical screening for Down's syndrome performed between 11 + 0 and 13 + 6 weeks of gestation, with the measured PAPP-A value at ≤ 0.50 MoM (multiples of the median). The control group comprised 105 pregnant women with PAPP-A value measured between 11 + 0 and 13 + 6 weeks of gestation at > 0.5 MoM. In continuation of the research process, descriptive statistics of the study material analyzed gestational week of delivery and infant birth weight. Then, the relationship between maternal serum PAPP-A values measured and the above-mentioned characteristics was evaluated. To evaluate the effect of low PAPP-A values on intrauterine fetal growth and infant birth weight, the population of the study and control groups infants born were divided into two groups: low birth weight (LBW) < 2500 g and birth weight of > 2500 g.

Testing PAPP-A and β-hcg serum levels

Blood for measurement of PAPP-A and β-hCG serum levels in the first trimester of pregnancy was sampled from the patients' antecubital veins. The next step involved measurement of the levels of the analyzed biochemical parameters using DELFIA® Xpress system with PAPP-A and β-hCG measurement kits. The kit has been approved and recommended by the Fetal Medicine Foundation. The measured PAPP-A concentration values were archived in an electronic database created for the purposes of this research project. PAPP-A levels in maternal blood serum were expressed as multiples of the median (MoM) for gestational age, as is conventional for biochemical variables varying depending on gestational week [22]. Individual risk of giving birth to an infant with a chromosomal aberration was calculated using ASTRAIA calculating program, having considered the initial risk associated with the mother's age and gestational age calculated using the date of last menstruation and corrected using crown-rump length (CRL), nuchal translucency (NT), PAPP-A MoM, and β-hCG MoM values.

Statistical analysis

Data from the interval scale were analyzed using Student's t-test. Distribution normality evaluation was performed using the Kolmogorov-Smirnov normality test, and the hypothesis of homogenous variance was validated using Fisher-Snedecor test. Should the data distribution be other than normal or when the data derived from the ordinal scale, they would be analyzed using the Mann-Whitney non-parametric test. Comparisons of more groups at the same time were made using the Kruskal-Wallis test. Where significant differences had been found, the Dunn post-hoc tests were used to identify homogenous groups. The relationship between the parameters was analyzed using Spearman's correlation coefficient. Data from the nominal scale were analyzed using the chi-square test. Statistica 10 PL (StatSoft) software was used to perform statistical analysis. The tests were considered statistically significant at $p < 0.05$.

RESULTS

Descriptive statistics for the PAPP-A parameter

Analysis of the PAPP-A values measured and expressed in MoM values in the study and control groups has shown that the average values of this parameter in both groups are respectively 0.35 MoM, and 1.29 MoM (Tab. 1, Fig. 1).

Table 1. Descriptive statistics of the PAPP-A parameter in prospective analysis

Variable	N valid	Mean	SD
Study group			
PAPP-A [MoM]	131	0.352911	0.103403
Control group			
PAPP-A [MoM]	105	1.285000	1.282284

SD — standard deviation

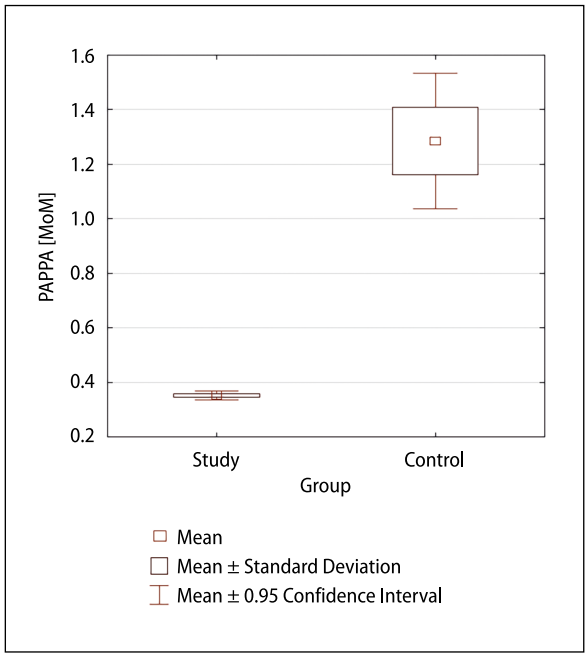

Figure 1. Average and 95% confidence intervals for PAPP-A values in the study and control groups

Relationship between infant birth weight and PAPP-A values measured in blood serum of pregnant women

The correlation between infant birth weights in the study and control groups combined and the measured PAPP-A MoM values were observed ($r = 0.15$, $p = 0.0184$) (Fig. 2).

To evaluate the effect of low PAPP-A values on intrauterine fetal growth and infant birth weight, the population of the study and control groups infants born were divided into two groups: low birth weight (LBW) < 2500 g and birth weight of > 2500 g. There were 10 infants with low birth weight in the study group, while only two such cases were observed in the control group (Fig. 2). Analysis of the correlation between the study groups and the birth weight (< 2500g and ≥ 2500g) has shown that in the group of pregnant women with low PAPP-A values (PAPP-A < 0.5 MoM), a statistically significant increase in the incidence of low infant birth weight was observed — 7.6% vs. 1.9% ($p = 0.0465$) (Fig. 2).

It was found that pregnant women with a low level of PAPP-A MoM value measured between weeks 11 and 13 + 6 have a statistically significantly higher risk of giving birth to a low birth weight infant than the pregnant women whose PAPP-A MoM value measured in that period did not meet this criterion (Fig. 3).

DISCUSSION

Low birth weight is a major cause of infant morbidity and mortality, and intrauterine growth restriction (IUGR) may be a late manifestation of early placental growth disorders [23]. This study has shown that low PAPP-A levels found in an integrated double test have a predictive value for identifying fetuses at risk of intrauterine fetal growth inhibition expressed as an increased risk of low-birth-weight infant. The first references indicating the relationship between low levels of proteins produced by the placenta and pregnancy abnormalities in the form of disturbed fetal growth were published in 1984 by Westergaard et al. [24] and Pledger et al. [25].

Evaluation of material in prospective analysis comprising 236 observations (study group n = 131, control group n = 105) has shown a statistically significant correlation between infant birth weights the measured PAPP-A values ($r = 0.15$, $p = 0.0184$) (Fig. 2). Lower PAPP-A value was correlated with lower infant birth weight value. PAPP-A value < 0.5 MoM in maternal serum was the study group inclusion criterion. Average value of this parameter in the study group was 0.35 MoM, and 1.29 MoM in the control group (Tab. 1, Fig. 1). Division of infants into those with birth weight < 2500 g and those with birth weight ≥ 2500g has shown that low PAPP-A levels found in an integrated double test have a predictive value for identifying fetuses at risk. There were 10 cases of infants with low birth weight in the study group, while in the control group, there were only two such cases (Fig. 3). Relationship analysis has shown that in the group of pregnant women with low PAPP-A level values, 7.6% of infants were born with birth weight > 2500 g, compared to only 1.9% in the control group ($p = 0.0465$) (Fig. 3)

The relationship presented above is analogous to other studies and observations [26]. The quoted experiment involved a prospective clinical trial with 8347 pregnant female subjects. It evaluated the relationship between pregnancy-associated plasma protein A (PAPP-A) in maternal serum in the first trimester of pregnancy and an increased risk of intrauterine growth restriction measured using biometric parameters assessed in ultrasound scan between the first and the second trimester of pregnancy. In addition to this, Salvig et al. [26] found PAPP-A values under 0.30 MoM to be associated with a nearly two times greater risk of reduced fetal growth rate below the 10th percentile than higher PAPP-A values. This study also found that extremely low PAPP-A levels are not only associated with low birth weight but also with a slower

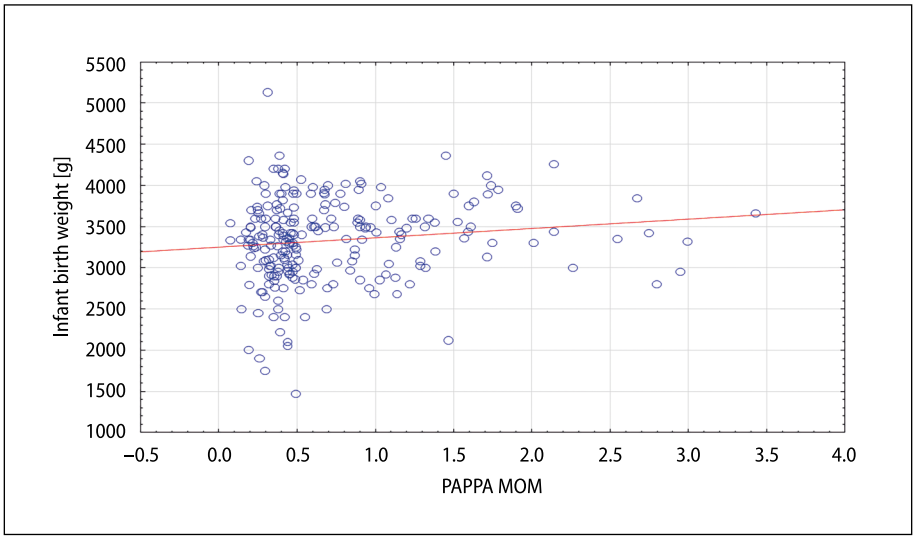

Figure 2. Relationship between infant birth weight in the study and control groups combined and the PAPP-A MoM values measured (p = 0.0184)

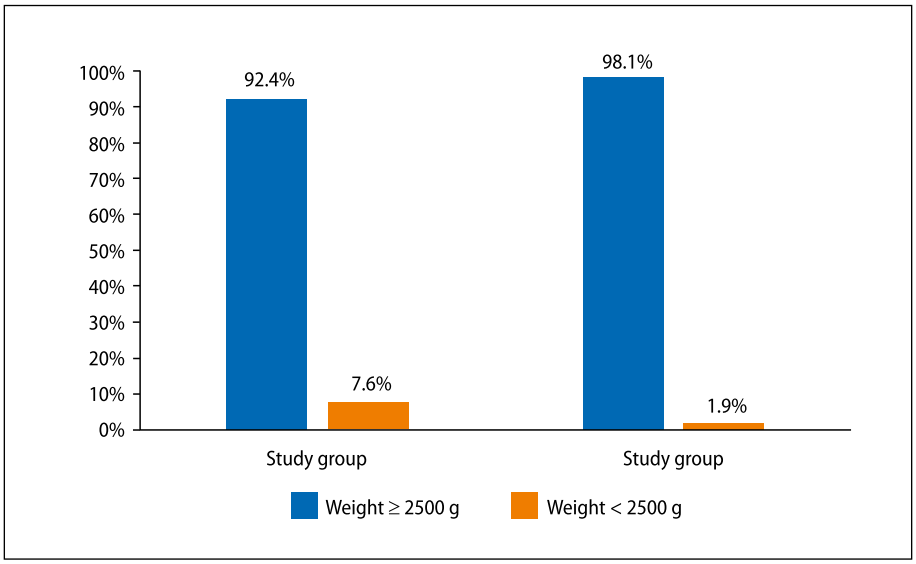

Figure 3. Incidence of low infant birth weight in the study and control groups (p = 0.0465)

fetal growth rate prior to 20 weeks of gestation. Moreover, these researchers found high PAPP-A values (≥ 3.0 MoM) to be associated with fetal growth rate above the 90th percentile. Other available references indicate that taking into consideration both the results of fetal size assessment at 18–20 weeks of gestation or its growth between 11–14 and 18–20 weeks of gestation, as well as the results of testing for first trimester placental function markers in maternal serum improves prognostic value for small-for-gestational age (SGA) fetuses [27]. Another study of a series of cases involving a large number (49,801) women in 11 + 0 to 13 + 6 weeks of gestation found that low PAPP-A values also showed a reversely proportional association with the risk of SGA fetal growth. [28]. Other authors have also shown low PAPP-A levels to be associated with low birth weight or SGA [27–29]. According to Smith GC et al. [30], checks of insulin-like growth factor (IGF) system, directly affected by PAPP-A in the first and early in the second trimester of pregnancy, may have a vital role in determination of further course of the pregnancy. In the analysis by Scott et al. [31], the risk of fetal growth disorders with PAPP-A MoM values < 0.2 was twice as high as in the general population. According to Krantz et al. [32], PAPP-A MoM value below the 1st percentile was associated with a 24.1% incidence of SGA infants, while values below the 5th percentile with 14.1% incidence of SGA infants in that group. Peterson et al. [33] in 2008 published their study results presenting a positive correlation between PAPP-A values and infant birth weight. PAPP-A values < the 10th, 5th, and 1st percentile increased the

probability of infant being SGA by 2.0, 2.4, and 9.3 times, respectively, while PAPP-A values > the 90th percentile increased the probability of the infant having birth weight > 4500 g by 2.9 times [33]. Similar conclusions were also reached in the paper by Canini et al. [34]. PAPP-A values in the group of women who had SGA infants were significantly statistically lower, while in the group of women who had LGA infants PAPP-A values were significantly statistically higher. Interesting conclusions were put forward following data analysis by Barret et al. [35]. The risk of having a low-birth-weight infant increased by 4.1 times if PAPP-A MoM values were < 0.3, the risk of premature birth by 2.9 times, and the risk of losing the pregnancy — 5 times. These results corroborate with those previously presented by Kabili et al. [36] in 2004. Fox et al. [27] have shown in their study that PAPP-A concentration is a reliable marker of intrauterine fetal growth inhibition in the second trimester of pregnancy. They presented results of tests on 1098 pregnant women diagnosed with intrauterine growth inhibition in the second trimester of pregnancy. PAPP-A value below the 15th percentile was correlated with an increased incidence of SGA in the second trimester and a lower birth rate, premature birth, and intrauterine death of the fetus. The association between PAPP-A and early fetal growth rate is logical considering PAPP-A's biological function. Pregnancy-associated plasma protein A is of trophoblastic origin and was identified as a protease specific to insulin-like growth factor binding proteins (IGFBPs), specifically IGFBP-4 [37] and IGFBP-5 [38]. These proteins bind IGF-I and IGF-II, thus inhibiting their interaction with cell surface receptors [9]. Low concentration of PAPP-A is associated with a low concentration of bioactive insulin-like growth factors. IGF-I and IGF-II are believed to play a key role in early implantation and regulation of intrauterine fetal growth [10]. According to the available knowledge, the present paper is one of the first of such scientific reports in Poland to have found that placental biomarkers, such as PAPP-A, may affect intrauterine fetal growth rate evaluated between the first trimester of pregnancy (confirmed crown-rump length measurement) and giving birth and, subsequently, evaluation of infant birth weight. In the conducted experiment, the first trimester was confirmed using a precise measurement of crown-rump length compliant with FMF criteria which is a separate and objectively measurable parameter, thus excluding the effect of a potential late ovulation or uncertainty in estimating the date of last menstruation on the results obtained. Pregnant women were selected for the program randomly, and the adopted clinical experiment schema proved to be a reliable and universal tool for population-based studies. One of its possible limitations is that there are fetuses with retarded intrauterine growth prior to the first trimester ultrasound scan, and normal intrauterine growth afterwards. Such retardation of intrauterine growth prior to 12 weeks of gestation is, however, rare and was not an object of focus in this paper [26]. Another potential factor which might adversely affect the quality of study results presented herein is tobacco smoking by pregnant mothers. It has been proven that smoking adversely affects intrauterine fetal growth during pregnancy and contributes to low birth weight [39], and that PAPP-A in the first trimester of pregnancy is lower in smokers than in non-smokers [40]. According to other authors, however, there is a small statistically significant relationship between smoking and fetal growth rate [26]. Relationship between pregnant mother's smoking and fetal growth rate was not included in the scope of this paper and this aspect has not been studied herein.

CONCLUSIONS

This paper has proven that low PAPP-A levels found in a double test have a predictive value for identifying intrauterine fetal growth inhibition of the fetuses and associated low birth weight. Clinical utility of the presented association between low PAPP-A values measured in maternal serum in the first trimester of pregnancy and an increased risk of pregnancy complications expressed as intrauterine growth inhibition and, subsequently, an increased risk of low infant birth weight requires further research. Owing to the better understanding of the biological role of pregnancy-associated plasma protein A, this paper contributes important answers to the detailed questions about the status of the network of interactions between proteins, including PAPP-A, and its importance for the pregnant mother and the fetus. Additional studies may in the future improve our understanding of PAPP-A's function in early pregnancy as well as perinatal care programs for pregnant women.

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REFERENCES

1. Ciobanu A, Formuso C, Syngelaki A, et al. Prediction of small-for-gestational-age neonates at 35-37 weeks' gestation: contribution of maternal factors and growth velocity between 20 and 36 weeks. Ultrasound Obstet Gynecol. 2019; 53(4): 488–495, doi: 10.1002/uog.20243, indexed in Pubmed: 30779239.
2. Sonek J, Nicolaides K. Additional first-trimester ultrasound markers. Clin Lab Med. 2010; 30(3): 573–592, doi: 10.1016/j.cll.2010.04.004, indexed in Pubmed: 20638573.

3. Souka AP, Von Kaisenberg CS, Hyett JA, et al. Increased nuchal translucency with normal karyotype. Am J Obstet Gynecol. 2005; 192(4): 1005–1021, doi: 10.1016/j.ajog.2004.12.093, indexed in Pubmed: 15846173.
4. Czuba B, Borowski D, Węgrzyn P, et al. Influence of first trimester biochemistry methodology on detection rate in screening for trisomy 21. Ginekol Pol. 2017; 88(9): 492–496, doi: 10.5603/GP.a2017.0090, indexed in Pubmed: 29057435.
5. Lin TM, Galbert SP, Kiefer D, et al. Characterization of four human pregnancy-associated plasma proteins. Am J Obstet Gynecol. 1974; 118(2): 223–236, doi: 10.1016/0002-9378(74)90553-5, indexed in Pubmed: 4129188.
6. Spencer K, Ong C, Skentou H, et al. Screening for trisomy 13 by fetal nuchal translucency and maternal serum free beta-hCG and PAPP-A at 10-14 weeks of gestation. Prenat Diagn. 2000; 20(5): 411–416, indexed in Pubmed: 10820411.
7. Ziolkowska K, Dydowicz P, Sobkowski M, et al. The clinical usefulness of biochemical (free β-hCg, PaPP-a) and ultrasound (nuchal translucency) parameters in prenatal screening of trisomy 21 in the first trimester of pregnancy. Ginekol Pol. 2019; 90(3): 161–166, doi: 10.5603/GP.2019.0029, indexed in Pubmed: 30950006.
8. Bonno M, Oxvig C, Kephart GM, et al. Localization of pregnancy-associated plasma protein-A and colocalization of pregnancy-associated plasma protein-A messenger ribonucleic acid and eosinophil granule major basic protein messenger ribonucleic acid in placenta. Lab Invest. 1994; 71(4): 560–566, indexed in Pubmed: 7526035.
9. Clemmons DR, Busby W, Clarke JB, et al. Insulin-like growth factor binding proteins and their role in controlling IGF actions. Cytokine Growth Factor Rev. 1997; 8(1): 45–62, doi: 10.1016/s1359-6101(96)00053-6, indexed in Pubmed: 9174662.
10. Conover CA, Bale LK, Overgaard MT, et al. Metalloproteinase pregnancy-associated plasma protein A is a critical growth regulatory factor during fetal development. Development. 2004; 131(5): 1187–1194, doi: 10.1242/dev.00997, indexed in Pubmed: 14973274.
11. Bischof P, DuBerg S, Herrmann W, et al. Pregnancy-associated plasma protein-A (PAPP-A) and hCG in early pregnancy. Br J Obstet Gynaecol. 1981; 88(10): 973–975, doi: 10.1111/j.1471-0528.1981.tb01683.x, indexed in Pubmed: 6169364.
12. Bischof P, Amandruz M, Weil-Franck C, et al. The disappearance rate of pregnancy-associated plasma protein-A (PAPP-A) after the end of normal and abnormal pregnancies. Arch Gynecol. 1984; 236(2): 93–98, doi: 10.1007/BF02134005, indexed in Pubmed: 6084476.
13. Kirkegaard I, Uldbjerg N, Oxvig C. Biology of pregnancy-associated plasma protein-A in relation to prenatal diagnostics: an overview. Acta Obstet Gynecol Scand. 2010; 89(9): 1118–1125, doi: 10.3109/00016349.2010.505639, indexed in Pubmed: 20804336.
14. Chang TC, Robson SC, Boys RJ, et al. Prediction of the small for gestational age infant: which ultrasonic measurement is best? Obstet Gynecol. 1992; 80(6): 1030–1038, indexed in Pubmed: 1448248.
15. Alberry M, Soothill P. Management of fetal growth restriction. Arch Dis Child Fetal Neonatal Ed. 2007; 92(1): F62–F67, doi: 10.1136/adc.2005.082297, indexed in Pubmed: 17185432.
16. Robson SC, Chang TC. Intrauterine growth retardation. In: Reed G, Claireaux AC, Cockburn F. ed. Diseases of the Fetus and the Newborn. 2nd ed. Chapman and Hall, London 1994: 277–286.
17. Owen P, Donnet ML, Ogston SA, et al. Standards for ultrasound fetal growth velocity. Br J Obstet Gynaecol. 1996; 103(1): 60–69, doi: 10.1111/j.1471-0528.1996.tb09516.x, indexed in Pubmed: 8608100.
18. Sovio U, White IR, Dacey A, et al. Screening for fetal growth restriction with universal third trimester ultrasonography in nulliparous women in the Pregnancy Outcome Prediction (POP) study: a prospective cohort study. Lancet. 2015; 386(10008): 2089–2097, doi: 10.1016/S0140-6736(15)00131-2, indexed in Pubmed: 26360240.
19. Hammami A, Mazer Zumaeta A, Syngelaki A, et al. Ultrasonographic estimation of fetal weight: development of new model and assessment of performance of previous models. Ultrasound Obstet Gynecol. 2018; 52(1): 35–43, doi: 10.1002/uog.19066, indexed in Pubmed: 29611251.
20. Hadlock FP, Harrist RB, Sharman RS, et al. Estimation of fetal weight with the use of head, body, and femur measurements--a prospective study. Am J Obstet Gynecol. 1985; 151(3): 333–337, doi: 10.1016/0002-9378(85)90298-4, indexed in Pubmed: 3881966.
21. Ropacka-Lesiak M, Breborowicz G. [Management of pregnancy complicated by intrauterine fetal growth restriction]. Ginekol Pol. 2012; 83(5): 373–376, indexed in Pubmed: 22708336.
22. Spencer K, Crossley JA, Aitken DA, et al. Temporal changes in maternal serum biochemical markers of trisomy 21 across the first and second trimester of pregnancy. Ann Clin Biochem. 2002; 39(Pt 6): 567–576, doi: 10.1177/000456320203900604, indexed in Pubmed: 12564838.
23. Karim JN, Sau A. Low pregnancy associated plasma protein-A in the 1st trimester: is it a predictor of poor perinatal outcome? J Obstet Gynaecol. 2013; 33(4): 351–354, doi: 10.3109/01443615.2013.773294, indexed in Pubmed: 23654313.
24. Westergaard JG, Teisner B, Hau J, et al. Placental protein measurements in complicated pregnancies. I. Intrauterine growth retardation. Br J Obstet Gynaecol. 1984; 91(12): 1216–1223, doi: 10.1111/j.1471-0528.1984.tb04740.x, indexed in Pubmed: 6083800.
25. Pledger DR, Belfield A, Calder AA, et al. The predictive value of three pregnancy-associated proteins in the detection of the light-for-dates baby. Br J Obstet Gynaecol. 1984; 91(9): 870–874, doi: 10.1111/j.1471-0528.1984.tb03699.x, indexed in Pubmed: 6206887.
26. Salvig JD, Kirkegaard I, Winding TN, et al. Low PAPP-A in the first trimester is associated with reduced fetal growth rate prior to gestational week 20. Prenat Diagn. 2010; 30(6): 503–508, doi: 10.1002/pd.2487, indexed in Pubmed: 20509148.
27. Fox NS, Shalom D, Chasen ST. Second-trimester fetal growth as a predictor of poor obstetric and neonatal outcome in patients with low first-trimester serum pregnancy-associated plasma protein-A and a euploid fetus. Ultrasound Obstet Gynecol. 2009; 33(1): 34–38, doi: 10.1002/uog.6274, indexed in Pubmed: 19115230.
28. Spencer K, Cowans NJ, Nicolaides KH. Low levels of maternal serum PAPP-A in the first trimester and the risk of pre-eclampsia. Prenat Diagn. 2008; 28(1): 7–10, doi: 10.1002/pd.1890, indexed in Pubmed: 18000943.
29. Ziolkowska K, Tobola-Wrobel K, Dydowicz P, et al. The significance of maternal blood pregnancy-associated plasma protein A (PAPP-A) and free beta-subunit of human chorionic gonadotropin (β-hCG) levels for the risk assessment of fetal trisomy 18 during the first prenatal testing between 11 and 13+6 weeks of pregnancy. Ginekol Pol. 2020; 91(12): 748–754, doi: 10.5603/GP.a2020.0126, indexed in Pubmed: 33447994.
30. Smith GCS, Stenhouse EJ, Crossley JA, et al. Early pregnancy levels of pregnancy-associated plasma protein a and the risk of intrauterine growth restriction, premature birth, preeclampsia, and stillbirth. J Clin Endocrinol Metab. 2002; 87(4): 1762–1767, doi: 10.1210/jcem.87.4.8430, indexed in Pubmed: 11932314.
31. Scott F, Coates A, McLennan A. Pregnancy outcome in the setting of extremely low first trimester PAPP-A levels. Aust N Z J Obstet Gynaecol. 2009; 49(3): 258–262, doi: 10.1111/j.1479-828X.2009.01001.x, indexed in Pubmed: 19566556.
32. Krantz D, Goetzl L, Simpson JL, et al. First Trimester Maternal Serum Biochemistry and Fetal Nuchal Translucency Screening (BUN) Study Group. Association of extreme first-trimester free human chorionic gonadotropin-beta, pregnancy-associated plasma protein A, and nuchal translucency with intrauterine growth restriction and other adverse pregnancy outcomes. Am J Obstet Gynecol. 2004; 191(4): 1452–1458, doi: 10.1016/j.ajog.2004.05.068, indexed in Pubmed: 15507982.
33. Peterson SE, Simhan HN. First-trimester pregnancy-associated plasma protein A and subsequent abnormalities of fetal growth. Am J Obstet Gynecol. 2008; 198(5): e43–e45, doi: 10.1016/j.ajog.2007.12.026, indexed in Pubmed: 18295168.
34. Canini S, Prefumo F, Pastorino D, et al. Association between birth weight and first-trimester free beta-human chorionic gonadotropin and pregnancy-associated plasma protein A. Fertil Steril. 2008; 89(1): 174–178, doi: 10.1016/j.fertnstert.2007.02.024, indexed in Pubmed: 17509577.
35. Barrett SL, Bower C, Hadlow NC. Use of the combined first-trimester screen result and low PAPP-A to predict risk of adverse fetal outcomes. Prenat Diagn. 2008; 28(1): 28–35, doi: 10.1002/pd.1898, indexed in Pubmed: 18186146.
36. Kabili G, Stricker R, Stricker R, et al. First trimester screening for trisomy 21; Do the parameters used detect more pathologies than just Down syndrome? Eur J Obstet Gynecol Reprod Biol. 2004; 114(1): 35–38, doi: 10.1016/j.ejogrb.2003.09.044, indexed in Pubmed: 15099868.
37. Lawrence JB, Oxvig C, Overgaard MT, et al. The insulin-like growth factor (IGF)-dependent IGF binding protein-4 protease secreted by human fibroblasts is pregnancy-associated plasma protein-A. Proc Natl Acad Sci U S A. 1999; 96(6): 3149–3153, doi: 10.1073/pnas.96.6.3149, indexed in Pubmed: 10077652.
38. Laursen LS, Overgaard MT, Søe R, et al. Pregnancy-associated plasma protein-A (PAPP-A) cleaves insulin-like growth factor binding protein (IGFBP)-5 independent of IGF: implications for the mechanism of IGFBP-4 proteolysis by PAPP-A. FEBS Lett. 2001; 504(1-2): 36–40, doi: 10.1016/s0014-5793(01)02760-0, indexed in Pubmed: 11522292.
39. Kramer MS. Intrauterine growth and gestational duration determinants. Pediatrics. 1987; 80(4): 502–511, indexed in Pubmed: 3658568.
40. Spencer K, Bindra R, Cacho AM, et al. The impact of correcting for smoking status when screening for chromosomal anomalies using maternal serum biochemistry and fetal nuchal translucency thickness in the first trimester of pregnancy. Prenat Diagn. 2004; 24(3): 169–173, doi: 10.1002/pd.819, indexed in Pubmed: 15057947.

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Retrospective evaluation of outcomes of vaginal birth after caesarean section in a tertiary center: a single-center study from Türkiye

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ABSTRACT

Objectives: The aim of this study was to evaluate the trial of labor after caesarean (TOLAC) outcomes and determine its reliability by comparing it with elective repeat caesarean delivery (ERCD) and vaginal delivery.

Material and methods: For this purpose, the outcomes of patients aged 18–40 years who had 57 TOLACs, 72 vaginal deliveries, and 60 elective caesarean sections in Ankara Koru Hospital between January 1, 2019, and January 1, 2022 were compared.

Results: Gestational age was lower in the normal vaginal delivery (NVD) group than in the elective caesarean section and vaginal birth after caesarean delivery (VBAC) groups ($p < 0.0005$). The birth weight was statistically significantly lower in the NVD group than in the elective caesarean section and VBAC groups ($p < 0.0002$). No statistically significant correlation was found between the BMI values in all three groups ($p < 0.586$). There was no statistically significant difference between the groups in terms of pre- and post-natal haemoglobin and APGAR scores ($p < 0.575$) ($p < 0.690$) ($p < 0.747$). The rate of epidural and oxytocin use was higher in the NVD group than in the VBAC group ($p < 0.001$) ($p < 0.037$). There was no statistically significant correlation between the birth weights of the infants in the TOLAC group and failed VBAC ($p < 0.078$). No statistically significant correlation was observed between the use of oxytocin for induction and failed VBAC ($p < 0.842$). There was no statistically significant correlation between epidural anaesthesia and failed VBAC ($p < 0.586$). A statistically significant correlation was found between gestational age and caesarean section as a result of a failed VBAC ($p < 0.020$).

Conclusions: The main reason for not preferring TOLAC continues to be uterine rupture. It can be recommended to eligible patients in tertiary centers. Because even when the factors increasing the success of VBAC were excluded, the rate of successful VBAC remained high.

Keywords: TOLAC; VBAC; vaginal birth after caesarean delivery; caesarean section

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INTRODUCTION

The World Health Organization (WHO) has determined the ideal rate for caesarean sections to be between 10–15%. However, in the past 40 years, caesarean section rates have increased all over the world, as well as in Türkiye. The positive attitude toward vaginal birth after caesarean delivery (VBAC) has become widespread since 1995, with the bulletin published by the American College of Obstetrics and Gynecology (ACOG) stating that it can be recommended to patients who are eligible and have no contraindications [1]. Recently, VBAC rates have increased all over the world. Between 1990 and 2009, VBAC rates in the USA ranged from 38.5% to 69.8% [2]. Vaginal birth after caesarean delivery rates in Germany are 36.0–49.8% [3], while we could not find any clear data on VBAC rates in Türkiye. The data on VBAC rates is mostly reported by studies with small sample sizes. Studies have found that VBAC is primarily recommended and performed by private practice physicians [4], and although VBAC is an alternative to an elective repeat caesarean section, obstetricians who still abstain from this due to uterine rupture, which is the most mortal maternal and neonatal risk, recommend an elective repeat caesarean

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section to patients. The probability of uterine rupture (single CD 0.72%; double CD 1.59%) increases as the number of caesarean sections increases [5]. Many studies have found that the most important predictive factor for successful VBAC is spontaneous labor [6–7]. International guidelines indicate very low complication rates in patients who have a cephalic presentation, who have a lower segment incision at the previous caesarean section, and who are eligible for VBAC [8–11]. Studies have found higher maternal mortality (0.013 vs 0.004%) in elective caesarean sections and higher neonatal mortality in VBAC (0.13 vs 0.05% for elective caesarean section) [12]. While the rate of unscarred uterine rupture is 0.003% [13], this rate is 0.30% in a previously operated uterus [12]. The incidence of uterine rupture for a patient scheduled for an elective caesarean section is 0.03%, while this rate is 0.47–5.6% for VBAC [12, 14]. In their nomogram for successful VBAC, Grobman et al. [15] first listed the factors that determine VBAC success and should be considered at the first visit. They found that maternal age, BMI, ethnic group, previous vaginal delivery, vaginal birth after caesarean section, and recurrence of the previous caesarean indication had predictive values [15]. Then, models, which include the admission Bishop score and are believed to provide a better prediction, were created [16]. In addition, factors such as prostaglandin use [17], a fetal weight of 4000 g and above [18], a short inter-delivery interval (12 months or less time from the previous caesarean delivery) [14], a lower uterine segment measurement of 0.6 mm thinner in the third trimester [19] have been reported to pose a risk for trial of labor after caesarean (TOLAC).

Here, it is necessary to define two different conditions, TOLAC and VBAC. Vaginal birth after caesarean delivery may occur as a result of the TOLAC. Not every TOLAC may result in VBAC. Elective repeat caesarean delivery (ERCD) is elective performed before onset uterine contractions.

This study was conducted in Ankara Koru Hospital, where an average of 4800 deliveries occur annually. Without using any model, the VBAC decision was made based on the patient's request, pelvic examination, and Bishop score. The aim of this study was to examine the outcomes of patients admitted to the delivery room upon the request of VBAC, to analyze the VBAC success rate and uterine rupture rates in the group without previous successful VBAC or vaginal delivery, and to compare the outcomes with those of patients who had elective C/S and primigravida vaginal delivery.

MATERIAL AND METHODS

This retrospective study included three groups of patients, aged 18–40, who were admitted to the delivery room for a trial of labor after caesarean (TOLAC), elective repeat caesarean delivery (ERCD), and primigravid patients who delivered vaginally in Ankara Koru Hospital between January 1, 2019, and January 1, 2022. Group 1 included TOLAC patients; Group 2 included patients who had ERCD with only one previous caesarean section; and Group 3 included primigravid pregnant women who had a spontaneous vaginal delivery (SVD). Those with a history of myomectomy, classical vertical incision, cardiovascular disease, cerebrovascular disease, hematologic disease, history of pelvic trauma, estimated fetal weight of 4500 g and above, placenta previa or placental invasion anomaly, non-cephalic presentation, fetal malformation, termination, intrauterine still fetuses, vaginal delivery between previous deliveries, high-risk pregnant women (IUGR, preeclampsia, etc.), and patients with a history of delivery < 37 weeks gestation and above were excluded from the study. Since having a history of a previous vaginal delivery increases the probability of a successful VBAC, this was not included in the study as it would affect the results, causing bias. Patient data were obtained from patient files. Parameters such as patient age, gestational age, total number of deliveries, number of caesarean or vaginal deliveries, previous caesarean section, initiation of induction, pharmacological drugs used, maternal complications of rupture, infant's birth weight, and newborn well-being were examined.

Spontaneous labor was expected for all patients who had a vaginal delivery. Patients who were scheduled for an elective caesarean section after 39–40 weeks of gestation and had a caesarean section were included. Patients with a request for VBAC were referred to an experienced team. All the deliveries were carried out by a team of three obstetricians and three midwives who were experienced in TOLAC. Patients were informed in detail about all possible risks, and their consent was obtained. The onset of spontaneous labor was waited up to 42 weeks of gestation. Patients who presented with amniotic fluid discharge or with a complaint of pain were transferred to the delivery room, where fetal non-stress testing and tocodynamometer (toco) monitoring were performed. The labor process was monitored using a partograph. Patients with a Bishop score of < 4 and below were initiated on prostaglandin E2 for cervical ripening. In addition, amniotomy with oxytocin or for augmentation was performed on patients with a cervical dilatation of < 1.2 cm/hour or less than three contractions in 10 minutes of toco monitoring.

RESULTS

Between January 1, 2019, and January 1, 2022, a total of 13,755 deliveries occurred in Ankara Koru Hospital, of which 7703 (56%) were vaginal. A total of 467 patients had a vaginal birth after caesarean delivery, but only 57 of them were included in the study. One hundred and eighty-seven patients whose pregnancy was terminated between 20–24 weeks of gestation due to a major fetal anomaly, 36 patients with stillbirths, 93 pregnant women with a history of previous

Table 1. Comparison of the groups

	NVD	ERCD	TOLAC	p
N	72	60	57	
Maternal age [years]	Mean: 29.4 SD: ± 2.99 Median: 30 Range: 19–37	Mean: 32.05 SD: ± 3.6 Median: 32 Range: 24–40	Mean: 30.6 SD: ± 4.3 Median: 31 Range: 20–40	**0.0002***
GW	Mean: 38 + 6 SD: ± 8.4 Median: 39 Range: 36–41	Mean: 39+3 SD: ± 3.5 Median: 39–40 Range: 39–40	Mean: 39 + 5 SD: ± 8.4 Median: 40 Range: 37–42	0.0005*
Birth weight [gr]	Mean: 3193.5 SD: ± 365.6 Median: 3190–3200 Range: 2170–4200	Mean: 3404.3 SD: ± 362.4 Median:3340–3360 Range: 2820–4650	Mean: 3460.7 SD: ± 425.1 Median: 3490 Range: 2500–4260	**0.0002***
Uterine rupture	0	0	0	
Apgar 5. min	Mean: 9 SD: ± 1 Median: 9 Range: 4–10	Mean: 9.5 SD: ± 0.2 Median: 9 Range: 7.5–9.5	Mean: 8.5 SD: ± 0.6 Median: 9 Range: 6–10	0.747*
HGB before birth [gr/dL]	Mean: 11.5 SD: ± 1.3 Median: 11.6 Range: 6.8–14.3	Mean: 12.05 SD: ± 1.06 Median: 12.1–12.2 Range: 9.6–14	Mean: 11.5 SD: ± 2.3 Median: 11.6 Range: 6.8–14.3	0.575*
Postpartum HGB [gr/dL]	Mean: 10.6 SD: ± 1.3 Median: 10.5 Range: 5.5–13.5	Mean: 10.9 SD: ±1.23 Median: 11 Range: 7.8–13.2	Mean: 10.5 SD: ± 1.35 Median: 10.5 Range: 5.5–13.5	0.690*
HGB difference before and after birth [gr/dL]	Mean: 0.9 SD: ± 0.9 Median:0.9 Range: (–1.3)–3.9	Mean: 1.2 SD: ± 0.9 Median:1.2 Range: (–1.5)–4.1	Mean: 0.9 SD: ± 0.8 Median:1 Range: (–1.3)–3.9	0.782*

*One-way ANOVA; NVD — normal vaginal delivery; ERCD — elective repeat caesarean delivery; TOLAC — trial of labor after caesarean; SD — standard deviation; GW — gestation week; HGB — hemoglobin

vaginal delivery, and 94 patients with deliveries below 37 weeks of gestation were excluded from the study.

Maternal age was statistically significantly lower in the normal vaginal delivery (NVD) group than in the ERCD group ($p < 0.0002$). There was no significant difference between the NVD and VBAC groups, as well as between the ERCD and VBAC groups.

Gestational age was lower in the NVD group than in the ERCD and VBAC groups ($p < 0.0005$). Birth weight was statistically significantly lower in the NVD group than in the ERCD and VBAC groups ($p < 0.0002$). No statistically significant correlation was found between the BMI values in all three groups ($p < 0.586$). There was no statistically significant difference between the groups in terms of pre- and post-natal hemoglobin and APGAR scores. In addition, no uterine rupture was observed in all three groups (Tab. 1).

The comparison of the DVD and VBAC groups revealed no statistically significant difference between the groups in terms of time to delivery, prostaglandin use rate, and pre- and post-natal haemoglobin levels. The rate of epidural and oxytocin use was higher in the NVD group than in the VBAC group (Tab. 2).

In the TOLAC subgroup analysis, the reasons for previous caesarean sections were non-progressed labor in 27 (47%) patients, acute fetal distress in 7 (12%) patients, fetal macrosomia in 5 (8.7%) patients, cephalo-pelvic disproportion in 15 (26.3%), and non-vertex presentation in 3 patients (5.2%). Of the patients, 44 (77.1%) had a history of a caesarean section once, 11 (19.3%) had a cesarean section twice, and 2 (3.4%) had a cesarean section three times. Nine (15.7%) of these 57 patients had to undergo a cesarean section. Eighty-eight percent (n = 8) of patients who had a repeat caesarean section after TOLAC had a history of only one caesarean, and 12% (n = 1) had a history of two previous caesarean sections. Of the patients with unsuccessful VBAC, 55.5% (n = 5) had a repeat caesarean section due to labor dystocia, 33.3% (n = 3) due to acute fetal distress, and 11.1% (n = 1) due to cephalo-pelvic disproportion.

No statistically significant correlation ($p < 0.078$) was found between unsuccessful VBAC and birth weight in the

Table 2. Comparison of normal vaginal delivery (NVD) and vaginal birth after caesarean delivery (VBAC)

	NVD	VBAC	p
Time until birth [hour]	Mean: 6.4 SD: ± 3.7 Median: 6 Range: 0–15	Mean: 6.9 SD: ± 5.1 Median: 6.1–6.4 Range: 0–22.5	0.059[t]
Epidural use [n/%]	42/58.3%	16/29%	**0.001[c]**
Oxytocin use [n/%]	53/73.6%	32/56%	**0.037[c]**
Prostaglandin use [n/%]	2/2.8%	2/3.5%	0.811[c]

[t]t-test; [c]Chi-Square test

TOLAC group. In the VBAC group, 2 (3.5%) patients were initiated on prostaglandin for induction, 32 (56%) patients were initiated on oxytocin, and the number of patients who underwent an amniotomy was 7 (12%). On the other hand, 16 patients were followed up spontaneously.

In the TOLAC group, 3 (21.4%) of the 16 patients who received epidural anaesthesia had a caesarean section, and 9 had a successful VBAC. In addition, 2 patients in the TOLAC group received prostaglandin. In the TOLAC group, 7 (24%) of the 32 patients who received oxytocin had a caesarean section, and 22 (76%) had VBAC.

In the TOLAC group, patients had a repeat caesarean section at a maximum of 40 weeks (n = 8, 88%) as a result of failure. No statistically significant correlation ($p < 0.842$) was found between the use of oxytocin for induction and failed VBAC. A total of 16 (29%) patients received epidural analgesia. No statistical correlation ($p < 0.586$) was found between epidural anaesthesia and caesarean section. There was a statistically significant correlation ($p < 0.020$) between gestational age and caesarean section as a result of unsuccessful VBAC. Patients had a caesarean section at a maximum of 40 weeks (n = 8, 80%).

DISCUSSION

Our study can be described as one of the few studies in Turkish clinics. Although caesarean rates are known to be 52% in Türkiye [20], VBAC rates are not known exactly, but successful VBAC rates have been reported as 55–84% in studies conducted with a small number of patients [21–24]. The most important non-medical factor for the low preference for VBAC may be the fear of medico-legal problems. As a matter of fact, in countries where malpractice cases are less frequent, obstetricians recommend and perform VBAC at higher rates [25]. Moreover, studies have shown that senior and more experienced obstetricians recommend vaginal birth after caesarean sections much more than less experienced physicians [26, 27]. In our study, maternal age was statistically significantly lower in the NVD group than in the ERCD group because the NVD group consisted of primigravid patients. Patients in the ERCD group had a history of caesarean section, and patients in the TOLAC group also had a history of birth. Therefore, it is normal for the NVD group to have a lower mean age.

A similar retrospective study by Sahin et al. [24] evaluated the outcomes of a total of 474 patients scheduled for VBAC, resulting in 216 (45.6%) successful deliveries while 258 (54.4 %) patients had to have a repeat caesarean section. Unlike our study, 98 (20.6%) patients included in this study had a vaginal birth before a caesarean section. In addition, 29 (6.2%) patients had a history of vaginal birth after caesarean section. In total, 27.1% of the patients included in the study had a history of vaginal delivery. This leads to a significant reduction in the rate of failed VBAC [24]. In contrast, we only included patients who did not have a history of vaginal delivery or successful VBAC in their previous pregnancies. Patients with a history of vaginal delivery or a history of VBAC were excluded from the study. Of the patients admitted for TOLAC, 84.2% (n = 48) had successful VBAC. The difference between our study and other studies was the exclusion of patients with a history of previous vaginal deliveries, which increased the success factors.

Lazarou et al. [28] also found a successful VBAC rate of 85% in their study, which supports the results of our study.

Different studies have reported uterine rupture rates in VBAC to be approximately 0.3–0.7% [29, 30]. We are of the opinion that a zero rate of uterine rupture in all three groups in our study is related to the number of patients. However, we believe that the main reason obstetricians do not prefer TOLAC is the complication of uterine rupture. Therefore, larger prospective studies are needed to predict and minimize this complication.

Medical induction of labour with prostaglandin E2 (dinoprostone) is not recommended by some scientific societies, such as ACOG or SOGC, in patients with a previous cesarean section and should not be used except in rare circumstances after appropriate counselling [31, 32]. Some studies that have evaluated cervical ripening with prostaglandin E2 (PGE2) have shown conflicting results [33, 34]. Due to the lack of conclusive results, many countries continue to use PGE2.

Rare circumstances after appropriate counselling. Chiemsi et al. [35] investigated the effect of oxytocin and prostaglandin E2 use on VBAC success in VBAC patients and found no statistically significant relationship. Our study also showed no statistical relationship between VBAC success and oxytocin, in line with this study. Sakala et al. [36] showed in their study that epidural anaesthesia did not increase the success rate of VBAC. Our study also supports the results of this study.

Birth weight was significantly higher in the ERCD and TOLAC groups than in the SVD group. This is related to the fact that the gestational week of the SVD group was lower than that of the other two groups in our study. The TOLAC subgroup analysis revealed no correlation between birth weight and having a caesarean section ($p < 0.078$). There are also studies supporting our results (28) and, conversely, supporting that birth weight is directly related to failed VBAC [37, 38].

Although uterine rupture was not observed in our TOLAC trials in patients with a history of two or more caesarean sections, studies have shown high maternal morbidity rates in TOLAC trials after two or more caesarean sections [39]. Women who request TOLAC trial after two or more caesarean sections, considering the available evidence, they should have the option of a carefully monitored vaginal delivery.

Our study showed no significant difference in the minute 5 Apgar score of infants between all three groups. In their study, Guise et al. [40] found that the well-being of infants born in the TOLAC group was statistically significantly better than that of those in the ERCD group. Moreover, our study revealed no statistically significant difference in decreased postnatal haemoglobin between all three groups. In their study, Takeya et al. [41] did not find a significant difference in pre- and post-operative haemoglobin difference between the patient group with an elective caesarean section after caesarean section and the TOLAC group.

The limitations of our study are its retrospective design and small sample size. The strength of the study is that all patients in the TOLAC group were selected from candidates who will have their first vaginal delivery and compared with primigravida NVD patients, excluding patients with characteristics that increase VBAC success. Furthermore, patients who had ERCD, which is considered a reliable method of delivery for those who previously had a caesarean section, were also compared with patients in the TOLAC group.

CONCLUSIONS

According to the results of our study, VBAC may be a safe option for eligible patients in tertiary centers under the supervision of an obstetrician experienced in TOLAC and a midwife, considering that the caesarean section rates in Türkiye are much higher than the limits recommended by the World Health Organization.

Article information and declarations

Author's contribution

All authors have read and approved the submission of the manuscript. The manuscript has not been published and is not considered for publication elsewhere in whole or in part in any language.

Ethics

This study was completed in accordance with the principles of the Declaration of Helsinki. The approval for the study was obtained from the Ethics Committee of Gazi University under the number E.537062.

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Conflict of interest

There is no conflict of interest to declare.

REFERENCES

1. Vaginal delivery after previous cesarean birth. Int J Gynaecol Obstet. 2004; 52(1): 90–98, doi: 10.1016/s0020-7292(96)90009-0.
2. Uddin SFG, Simon AE. Rates and success rates of trial of labor after cesarean delivery in the United States, 1990–2009. Matern Child Health J. 2013; 17: 1309–1314.
3. Gross MM, Matterne A, Berlage S, et al. Interinstitutional variations in mode of birth after a previous caesarean section: a cross-sectional study in six German hospitals. J Perinat Med. 2015; 43(2): 177–184, doi: 10.1515/jpm-2014-0108, indexed in Pubmed: 25395596.
4. Wells CE. Vaginal birth after cesarean delivery: views from the private practitioner. Semin Perinatol. 2010; 34(5): 345–350, doi: 10.1053/j.semperi.2010.05.008, indexed in Pubmed: 20869551.
5. Tanos V, Toney ZA. Uterine scar rupture - Prediction, prevention, diagnosis, and management. Best Pract Res Clin Obstet Gynaecol. 2019; 59: 115–131, doi: 10.1016/j.bpobgyn.2019.01.009, indexed in Pubmed: 30837118.
6. Li YX, Bai Z, Long DJ, et al. Predicting the success of vaginal birth after caesarean delivery: a retrospective cohort study in China. BMJ Open. 2019; 9(5): e027807, doi: 10.1136/bmjopen-2018-027807, indexed in Pubmed: 31129593.
7. Dy J, DeMeester S, Lipworth H, et al. No. 382-Trial of Labour After Caesarean. J Obstet Gynaecol Can. 2019; 41(7): 992–1011, doi: 10.1016/j.jogc.2018.11.008, indexed in Pubmed: 31227063.
8. Sentilhes L, Vayssière C, Beucher G, et al. Delivery for women with a previous cesarean: guidelines for clinical practice from the French College of Gynecologists and Obstetricians (CNGOF). Eur J Obstet Gynecol Reprod Biol. 2013; 170(1): 25–32, doi: 10.1016/j.ejogrb.2013.05.015, indexed in Pubmed: 23810846.
9. Reif P, Brezinka C, Fischer T, et al. Labour and Childbirth After Previous Caesarean Section: Recommendations of the Austrian Society of Obstetrics and Gynaecology (OEGGG). Geburtshilfe Frauenheilkd. 2016; 76(12): 1279–1286, doi: 10.1055/s-0042-118335, indexed in Pubmed: 28017971.
10. American College of Obstetricians and Gynecologists. Practice bulletin no. 205: vaginal birth after cesarean delivery. Obstet Gynecol. 2019; 133(2): e110–27.
11. Gupta JK, Smith GCS, Chodankar RR. RCOG Green-top guideline no. 45: Birth after previous caesarean birth. Royal College of Obstetricians and Gynaecologists 2015.

12. Guise JM, Denman MA, Emeis C, et al. Vaginal birth after cesarean: new insights on maternal and neonatal outcomes. Obstet Gynecol. 2010; 115(6): 1267–1278, doi: 10.1097/AOG.0b013e3181df925f, indexed in Pubmed: 20502300.
13. Gibbins KJ, Weber T, Holmgren CM, et al. Maternal and fetal morbidity associated with uterine rupture of the unscarred uterus. Am J Obstet Gynecol. 2015; 213(3): 382.e1–382.e6, doi: 10.1016/j.ajog.2015.05.048, indexed in Pubmed: 26026917.
14. Bujold E, Mehta SH, Bujold C, et al. Interdelivery interval and uterine rupture. Am J Obstet Gynecol. 2002; 187(5): 1199–1202, doi: 10.1067/mob.2002.127138, indexed in Pubmed: 12439503.
15. Grobman WA, Lai Y, Landon MB, et al. National Institute of Child Health and Human Development (NICHD) Maternal-Fetal Medicine Units Network (MFMU). Development of a nomogram for prediction of vaginal birth after cesarean delivery. Obstet Gynecol. 2007; 109(4): 806–812, doi: 10.1097/01.AOG.0000259312.36053.02, indexed in Pubmed: 17400840.
16. Metz TD, Stoddard GJ, Henry E, et al. Simple, validated vaginal birth after cesarean delivery prediction model for use at the time of admission. Obstet Gynecol. 2013; 122(3): 571–578, doi: 10.1097/AOG.0b013e31829f8ced, indexed in Pubmed: 23921867.
17. Lydon-Rochelle M, Holt VL, Easterling TR, et al. Risk of uterine rupture during labor among women with a prior cesarean delivery. N Engl J Med. 2001; 345(1): 3–8, doi: 10.1056/NEJM200107053450101, indexed in Pubmed: 11439945.
18. Elkousy MA, Sammel M, Stevens E, et al. The effect of birth weight on vaginal birth after cesarean delivery success rates. Am J Obstet Gynecol. 2003; 188(3): 824–830, doi: 10.1067/mob.2003.186, indexed in Pubmed: 12634665.
19. Kok N, Wiersma IC, Opmeer BC, et al. Sonographic measurement of lower uterine segment thickness to predict uterine rupture during a trial of labor in women with previous Cesarean section: a meta-analysis. Ultrasound Obstet Gynecol. 2013; 42(2): 132–139, doi: 10.1002/uog.12479, indexed in Pubmed: 23576473.
20. The Ministry of Health of Turkey. Turkey Demographic and Health Survey p. 109, 2018.
21. Akçay T, Göl K, Şahin İ, et al. The safety of vaginal birth after cesarean. Turkiye Klinikleri J Gynecol Obst. 2001; 11(4): 224–227.
22. Senturk MB, Cakmak Y, Atac H, et al. Factors associated with successful vaginal birth after cesarean section and outcomes in rural area of Anatolia. Int J Womens Health. 2015; 7: 693–697, doi: 10.2147/IJWH.S83800, indexed in Pubmed: 26203286.
23. Takmaz T, Dural HR, Gorchıyeva I, et al. The Obstetrics Outcomes of Vaginal Birth After Cesarean Section in a Cohort with High Induction of Labor Rate. J Clin Obstet Gynecol. 2020; 30(4): 146–152.
24. Sahin S, Ozkaya E, Eroglu M, et al. Predictors of successful vaginal birth after a caesarean in women with a previous single caesarean delivery. Eur Rev Med Pharmacol Sci. 2022; 26(5): 1594–1600.
25. Brick A, Layte R, Farren M, et al. Recent Trends in Vaginal Birth After Caesarean Section. Ir Med J. 2016; 109(10): 482, indexed in Pubmed: 28644587.
26. Kwee A, Cohlen BJ, Kanhai HHH, et al. Caesarean section on request: a survey in The Netherlands. Eur J Obstet Gynecol Reprod Biol. 2004; 113(2): 186–190, doi: 10.1016/j.ejogrb.2003.09.017, indexed in Pubmed: 15063958.
27. Appleton B, Targett C, Rasmussen M, et al. Knowledge and attitudes about vaginal birth after Caesarean section in Australian hospitals. VBAC Study Group. Vaginal Birth After Caesarean. Aust N Z J Obstet Gynaecol. 2000; 40(2): 195–199, doi: 10.1111/j.1479-828x.2000.tb01146.x, indexed in Pubmed: 10925909.
28. Lazarou A, Oestergaard M, Netzl J, et al. Vaginal birth after cesarean (VBAC): fear it or dare it? An evaluation of potential risk factors. J Perinat Med. 2021; 49(7): 773–782, doi: 10.1515/jpm-2020-0222, indexed in Pubmed: 34432969.
29. Macones GA, Peipert J, Nelson DB, et al. Maternal complications with vaginal birth after cesarean delivery: a multicenter study. Am J Obstet Gynecol. 2005; 193(5): 1656–1662, doi: 10.1016/j.ajog.2005.04.002, indexed in Pubmed: 16260206.
30. Cahill AG, Tuuli M, Odibo AO, et al. Is vaginal birth after cesarean (VBAC) or elective repeat cesarean safer in women with a prior vaginal delivery? Am J Obstet Gynecol. 2006; 195(4): 1143–1147, doi: 10.1016/j.ajog.2006.06.045, indexed in Pubmed: 16846571.
31. Practice Bulletin No. 184: Vaginal Birth After Cesarean Delivery. Obstet Gynecol. 2017; 130(5): e217–e233, doi: 10.1097/AOG.0000000000002398, indexed in Pubmed: 29064970.
32. Martel MJ, MacKinnon CJ. No. 155-Guidelines for Vaginal Birth After Previous Caesarean Birth. J Obstet Gynaecol Can. 2018; 40(3): e195–e207, doi: 10.1016/j.jogc.2018.01.014, indexed in Pubmed: 29525045.
33. Haas J, Barzilay E, Chayen B, et al. Safety of low-dose prostaglandin E2 induction in grandmultiparous women with previous cesarean delivery. J Matern Fetal Neonatal Med. 2014; 27(5): 445–448, doi: 10.3109/14767058.2013.818651, indexed in Pubmed: 23841832.
34. López-Jiménez N, García-Sánchez F, Pailos RH, et al. Induction of Labor with Vaginal Dinoprostone (PGE) in Patients with a Previous Cesarean Section: Obstetric and Neonatal Outcomes. J Clin Med. 2021; 10(22), doi: 10.3390/jcm10225221, indexed in Pubmed: 34830502.
35. Cieminski A. Induction and augmentation of labor after prior cesarean delivery. Ginekologia i Poloznictwo. 2012; 23(1): 18–24.
36. Sakala EP, Kaye S, Murray RD, et al. Epidural analgesia. Effect on the likelihood of a successful trial of labor after cesarean section. J Reprod Med. 1990; 35(9): 886–890, indexed in Pubmed: 2231564.
37. Mizrachi Y, Barber E, Kovo M, et al. Prediction of vaginal birth after one ceasarean delivery for non-progressive labor. Arch Gynecol Obstet. 2018; 297(1): 85–91, doi: 10.1007/s00404-017-4569-4, indexed in Pubmed: 29052016.
38. Kyvernitakis I, Reichelt J, Kyvernitakis A, et al. Trends of vaginal birth after cesarean delivery in Germany from 1990 to 2012: a population-based study. Z Geburtshilfe Neonatol. 2014; 218(5): 203–209, doi: 10.1055/s-0034-1385920, indexed in Pubmed: 25353214.
39. Tahseen S, Griffiths M. Vaginal birth after two caesarean sections (VBAC-2)-a systematic review with meta-analysis of success rate and adverse outcomes of VBAC-2 versus VBAC-1 and repeat (third) caesarean sections. BJOG. 2010; 117(1): 5–19, doi: 10.1111/j.1471-0528.2009.02351.x, indexed in Pubmed: 19781046.
40. Guise JM, Eden K, Emeis C, et al. Vaginal birth after cesarean: new insights on maternal and neonatal outcomes. Obstet Gynecol. 2010; 115(6): 1267–1278, doi: 10.1097/AOG.0b013e3181df925f, indexed in Pubmed: 20502300.
41. Takeya A, Adachi E, Takahashi Y, et al. Trial of labor after cesarean delivery (TOLAC) in Japan: rates and complications. Arch Gynecol Obstet. 2020; 301(4): 995–1001, doi: 10.1007/s00404-020-05492-8, indexed in Pubmed: 32185554.

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A novel prenatal index predicting the probability of neonatal intensive care in pregnants: amnion progesterone receptor to alfa fetoprotein rate

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ABSTRACT

Introduction: Amniocentesis (AC) is the most used interventional procedure for prenatal diagnosis. The study aims to evaluate the pregnancy outcomes undergoing AC and the potential of amnion progesterone receptor (aPR) to alfa fetoprotein (AFP) rate for predicting the probability of neonatal intensive care unit (NICU).

Material and methods: This prospective cross-sectional study population consisted of 85 pregnant women who underwent mid-trimester AC. All cases were screened by ultrasound before AC. Maternal venous and amniotic samples were obtained simultaneously to evaluate the serum progesterone (sPRG), aPR, and aAFP and analyzed with patient results.

Results: Unlike sPRG and aAFP, aPR showed a positive correlation with NICU and a negative correlation with parity. In linear regression, the aPR-AFP rate showed strong linearity with NICU and parity. In an aPR-AFP rate analysis, we saw a strong predictivity for NICU compared to the other three parameters. It presented 73.4% specificity and 79% sensitivity at 0.0075 cut-off (AUC: 0.78; p = 0.003; 95% CI: 0.608–0.914).

Conclusions: Evaluating the PR either alone or in a rational combination with AFP will provide physicians with valuable information about the advanced process of pregnancy and postpartum complications. The physicians might use the aPR-AFP rate to predict NICU potential for pregnancy and need further studies to make more vital predictions on postpartum complications.

Keywords: amnion progesterone receptor; alfa fetoprotein; neonatal; intensive care

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INTRODUCTION

Amniocentesis (AC) is the oldest known and most commonly used interventional procedure for prenatal diagnosis [1]. The primary purpose of prenatal diagnosis is to have information about the fetus's health at the earliest time. Since the fetus plays a crucial role in forming amniotic fluid (AF), AC is proper for evaluating fetal health and the prenatal diagnosis of hereditary diseases [2]. The most common indications for AC are advanced maternal age, high risk in maternal serum screening test, family history of neural tube defect, stillbirth, two or more spontaneous abortions, a family history of metabolic or molecular genetic disease, and fetal birth defect [3]. To date, AF was the first method for biochemical analysis. Studies are used for prenatal diagnosis of congenital disorders to determine fetal well-being and predict fetal maturity.

Progesterone (PRG) is an essential steroid sex hormone for required to maintain a healthy pregnancy. It helps physicians on detecting and understanding abnormalities of pregnancy period [4, 5]. The corpus luteum

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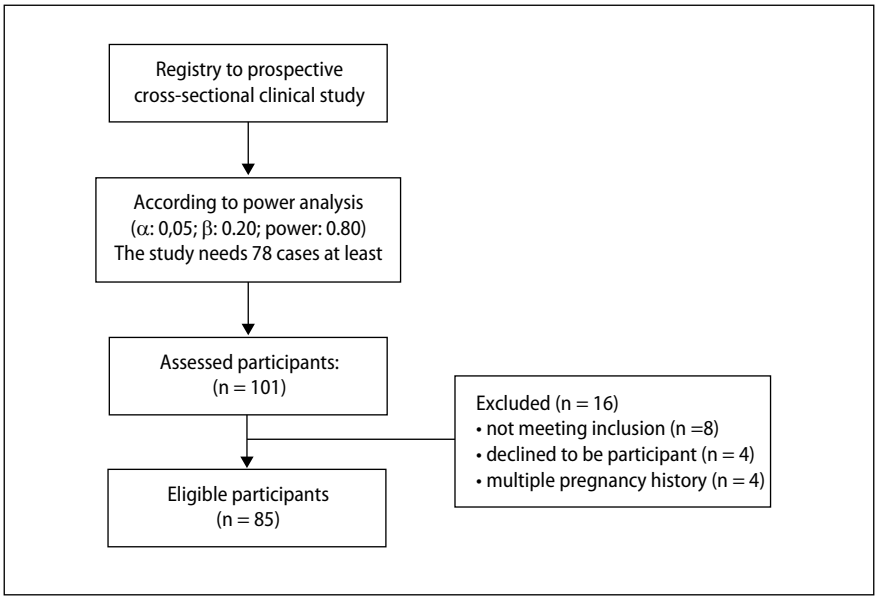

Figure 1. Flow chart for the selection and enrollment of the participants

produces it in the first eight weeks of pregnancy, but the placenta plays this role from 8 to 12 weeks [6–8]. Progesterone prepares the tissue lining of the endometrium for stimulating glands in the early endometrium. It suppresses uterine contractions and protects pregnancy as well. It regulates the mother's immune response to prevent embryo rejection and improves uteroplacental circulation and luteal phase support. Fetal membranes and decidua are potential target tissues for PRG [6, 7, 9, 10]. Eventually, for delivery, PRG effectiveness on the myometrium must change for the myometrium to switch from silent to active. The tissue achieves this change with neither peripheral maternal blood nor myometrial PRG but with the shift in myometrial progesterone receptor (PR). The interaction with PR primarily mediates the physiological effects of PRG [7, 9–12]. Progesterone receptors are in at least three functional isoforms in the tissues of the human reproductive system: PR-A, PR-B, and PR-C [9, 10, 12, 13]. These hormones pass through plasma membranes by simple diffusion in target cells, and the specific receptor in the nucleus binds [10]. There may be efficacy differences in PR isoforms. For example, PR-B was the dominant PR type in the decidua, while PR-C was efficient in the amnion [12].

Amniocentesis is the most used interventional procedure for prenatal diagnosis. The study aims to evaluate the pregnancy outcomes undergoing AC and the potential of amnion progesterone receptor (aPR) to alfa fetoprotein (AFP) rate for predicting the probability of neonatal intensive care unit (NICU).

MATERIAL AND METHODS

Study design

This research is a prospective cross-sectional clinical study performed in the University Hospital setting between August 2020 and February 2021. A total of 85 pregnant women with a singleton pregnancy who are willing to join the present research with their demographic/outpatient data joined the study. The Ethical Committee approved the current study (Date: 10.07.2020 — ID: E-20/311). All the participants gave written consent before contributing to the study.

Patient selection

The study population consisted of pregnant women who underwent mid-trimester AC between 16–20 gestations for different indications. All cases were screened by ultrasound for fetal anomalies before AC. As given in the flowchart (Fig. 1), we performed a power analysis for the participants. We recorded gestational age by the concordant menstrual period or via the earliest ultrasound if the last menstrual period was discordant or unsure. The indications for AC were; major fetal anomalies (Ventriculomegaly, Cleft lip/palate, Cardiac defects, Omphalocele, Cystic hygroma) (n = 10; 11.7%), high risk in non-invasive prenatal testing (NIPT) (n=4; 5%), ultrasound-determined soft signs (Second-Trimester Sonographic Markers Associated with Fetal Trisomy 21: Nuchal fold thickening, Single umbilical artery, Echogenic intracardiac focus, Renal pelvis dilation, Aberrant right subclavian artery, Echogenic bowel, Nasal bone absence or hypoplasia) (n = 30; 35.2%), maternal factors (maternal request, anxiety and advanced maternal age

(if the mother > 35 years)(n = 9; 10.5%), abnormal biochemical marker results in the first or second-trimester aneuploidy screening test results, a family background of chromosomal abnormalities such as; structural rearrangements in one of the parents or previous fetus or child with a de novo chromosomal anomalies (n = 30; 35.2%), abnormal ultrasound scan in the first or second trimester of the pregnancy (n = 3; 3.5%). We followed the patients and prospectively collected their data regarding pregnancy complications. Preexisting medical problems and demographics were collected elaborately for each patient. None of the patients were in the labor stage. The study excluded the followings: pregnancies who received hormonal medications, twin pregnancies, determined fetal aneuploidies incompatible with life, or fetal death following AC procedure.

Amniocentesis procedure

Each participant gave informed consent to the AC procedure, an approach under ultrasound guidance between 15 and 20 weeks. We performed a fetus scan before the amniocentesis to assess fetal condition. The puncture was done with a 22-gauge (9 cm) spinal-needle, apart from the fetus's body and free from the fetal cord. The first 1 mL of amniotic fluid was discarded, and another 25 mL of amniotic fluid was withdrawn for chromosome and PR assessment. Following the procedure, the color and clarity of the fluid are documented. The patients were discharged 20 minutes after the process was complete unless they encountered complications. All the women were informed to directly attend our gynecology and obstetrics ward if any complications occurred following the discharge. The same maternal and fetal unit specialist in our clinic performed all procedures in the study.

Blood collection and laboratory tests

Maternal venous blood specimens were obtained simultaneously as the AF to evaluate the serum progesterone (sPRG) levels. The collected samples were immediately processed and stored at –80ºC until thawed for assessment. Both serum and AF samples were not subjected to freeze-thaw cycles before evaluation. sPRG, amniotic AFP (aAFP) was measured using the competitive immunoassay method (Roche Diagnostics, Indianapolis, IN 46250). Amniotic fluids were collected via the AC procedure from each patient. The samples were centrifuged at 2000 rpm for 12 min, and the supernatant was kept in -80C conditions until the analysis time. AF supernatant was evaluated for PR levels using ELISA kits (Bioassay Technology Human Progesterone Receptor ELISA Kit, Shangai, China). The amniotic PR (aPR) was assessed using the ELISA according to the manufacturer's instructions. Inter & intra-assay variability were < 8% and 14%, respectively.

Statistical analysis

The significance level of statistical hypothesis tests was < 0.05 for the current research. The SPSS version 22.0 (IBM Soft. Comp.,USA) statistical software conducted the statistical analysis. For normally distributed variables, results were expressed as mean and standard deviation. Categorical data were compared using chi-square analysis or Fisher's exact test. Two groups with continuous variables were compared with an unpaired t-test, and three groups were compared using a one-way analysis of variance followed by Tukey's multiple comparison test. Non-normally distributed data are presented as the median. Using Dunn's multiple comparison test, groups were compared using the Kruskal–Wallis with post-hoc analysis. Additionally, stepwise linear regression was performed to identify potential clinical preoperative confounders for the comparisons. A receiver operating characteristic (ROC) curve assessed the potential of amnion progesterone receptor to alfa fetoprotein rate (aPR-AFP) for predicting the probability of neonatal intensive care.

RESULTS

Demographics

As given in Table 1 with details, the participant's mean age was 32.6 ± 5 years (n = 85, range: 19–44). Thirty-nine of the deliveries were by cesarean section, 46 were delivered by standard delivery, and 45 of the babies were boys, while 40 were girls. Seven babies required neonatal intensive care.

Regression analysis

In the analysis of sPRG and aAFP, there was no correlation on factors such as post-pregnancy NICU, gravida, birth week, smoking, a/s indication, gender, mode of delivery, third-trimester complication, chromosomal anomaly, abortion, weight, parity (p > 0.05). Unlike sPRG and aAFP, aPR showed a positive correlation with NICU and a negative correlation with parity. This correlation was not strong. We observed linear regression analysis that the aPR-AFP rate showed strong linearity with NICU and pregnancy parity, as in Table 2.

ROC analysis

The receiver operating characteristic (ROC) analysis we did for the predictability of NICU, given in Table 3 with details and Figure 2 with graphic, showed that sPRG (AUC: 0.42; p = 0.341) and aAFP (AUC: 0.41; p = 0.283) have no diagnostic efficiency in terms of predicting NICU. Unlike, aPR showed a predictive potential for NICU with 74,1% specificity and 67,2% sensitivity at 59,7 cut-off values [AUC: 0.69; p = 0.044; 95% confidence interval (CI) 0.472–0.881]. In the aPR-AFP rate analysis, we saw a strong predictivity for NICU compared to the other three unique parameters. It presented 73,4% specificity and 79% sensitivity at 0,0075 cut-off value (AUC: 0.78; p = 0.003; 95% CI 0.608–0.914).

Table 1. Demographic and clinical features of the participants

Variables	Mean/frequency	Range/percent
Age [years]	32.6 ± 5.9	19–44
Maternal weigh [kg]	67.4 ± 13	41–103
Height [m]	159.9 ± 6.4	140–180
aPR [ng/mL]	69.8 ± 101	13–746
aAFP [ng/mL]	9470 ± 7402	474–43150
aPR-AFP rate	0.011 ± 0.0001	0.001–0.087
Birth weigh [g]	2770 ± 1110	125–4180
NICU period [days]	1.6 ± 7.7	0–64
Gender		
Male	45	52.9%
Female	40	47.1%
Delivery		
Normal	46	54.1%
Caesarean	39	45.9%
Cigarette		
No	73	85.9%
Yes	12	14.1%
Gravida		
1	18	21.2%
2	27	31.8%
3	12	14.1%
4	17	20.0%
5	9	10.6%
6	2	2.4%
Parity		
0	24	28.2%
1	28	32.9%
2	21	24.7%
3	10	11.8%
4	2	2.4%
AC indication		
MFA	10	11.8%
NIPT	4	4.7%
Soft Signs	29	34.1%
Test Risk	36	42.4%
Maternal	6	7.1%
Abortus		
0	58	68.2%
1	14	16.5%
2	10	11.8%
3	1	1.2%
4	2	2.4%

aPR — amnion progesterone; aAFP — amnion alfa fetoprotein; aPR-AFP — amnion progesterone to alfa fetoprotein rate; NICU — neonatal intensive care unit; AC — amniocentesis; MFA — major fetal anomaies; NIPT — non-invasive phetal test

DISCUSSION

In the present analysis, we predicted that the study of the amniotic hormones in the early pregnancy period might be informative for the pregnancy and postpartum processes. Evaluating the PR in the AF alone or in rational combination with AFP will provide physicians with useful information about the advanced pregnancy and postpartum complications process.

Before the onset of labor, there is a substantial decrease in maternal PR, which is essential in decreasing the effects of PRG in the initiation of delivery in animals [14]. Unlike animals, this is different in the human fetus. According to the analysis of PRG values, maternal and AF concentrations do not show any change before the labor [15]. According to recent studies, if PRG support is given as an external supplement, it causes a decrease in the frequency of uterine contractions [16, 17]. For these reasons, new research has focused on mechanisms that may explain the effect of PRG more strongly, especially at the myometrium or decidua level. In this sense, the relationship between AF and PRG has become a focal point for us physicians to analyze the course of pregnancy and the possibility of complications after it.

Amniotic fluid, which is the habitat of the fetus, is a liquid substance of diagnostic importance not only in the nutrition of the fetal membranes but also in the homeostasis of pregnancy. During pregnancy, there are changes in electrolyte values in the AF of the pregnant, and hormones are produced by fetal trophoblastic cells and secreted into the maternal circulation [18]. In a study by Mazor et al. [19], maternal and serum PRG was correlated, though the study of Nagamani et al. [20] found that they did not find any correlation. Norwitz et al. [21] showed the in-vitro homeostasis role of PR in the fetalmembrane. So-Youhun et al. [22] reported uterine PR and its relationship to labour, and PR-A and B types were described by them. According to Leonhardt et al. [23], changes in PR can have a role in labor at term delivery. A shift in PR expression may mediate PRG withdrawal. In the present study, we would be able to obtain information about both the pregnant and the baby in the later stages of pregnancy by measuring aPR and aAFP, unlike serum measurements. We analyzed total PR instead of sub-receptor analysis.

In our analysis, sPRG and aAFP showed no significant correlation with post-pregnancy NICU, gravida, birth week, smoking, gender, mode of delivery, third-trimester complication, chromosomal anomaly, abortion, weight, or parity. Unlike sPRG and aAFP, aPR showed a positive correlation with NICU and a negative correlation with pregnancy parity. In linear regression analysis, the aPR-AFP rate showed strong linearity with NICU and pregnancy parity. In the aPR-AFP rate analysis, we saw a strong predictivity for NICU compared to other parameters. It presented 73.4% specificity and 79%

Table 2. Linear regression analysis of amnion progesterone receptor to alfa fetoprotein rate

Variables	Beta	T	p value	95% confidence interval	
				Lower	Upper
Constant	–	6.179	0.0001	0.008	0.017
NICU	0.445	4.592	0.0001	0.01	0.024
Pregnancy parity	–0.271	–2.798	0.006	–0.006	–0.001

Dependent variable: amnion progesterone receptor to alfa fetoprotein rate (aPR-AFP); Predictors: NICU, gravida, smoking, chromosomal anomaly, delivery (Caesarean or normal), gender, third-trimester complication, abortion, parity; NICU — eonatal intensive care unit

Table 3. The receiver operating characteristic (ROC) curve analysis for neonatal intensive care unit (NICU) possibility

Variables	Area	SE	p value	95% confidence interval	
				Lower	Upper
sPRG [µg/L]	0.42	0.09	0.341	0.219	0.608
aAFP [ng/mL]	0.41	0.08	0.283	0.243	0.562
aPR [ng/mL]	0.69	0.11	0.044	0.472	0.881
aPR-AFP	0.78	0.07	0.004	0.608	0.914

Variables: sPRG, aAFP, aPR, aPR-AFP; sPRG — serum progesterone; aAFP — amnion alfa fetoprotein; aPR — amnion progesterone; aPR-AFP — amnion progesterone to alfa fetoprotein rate

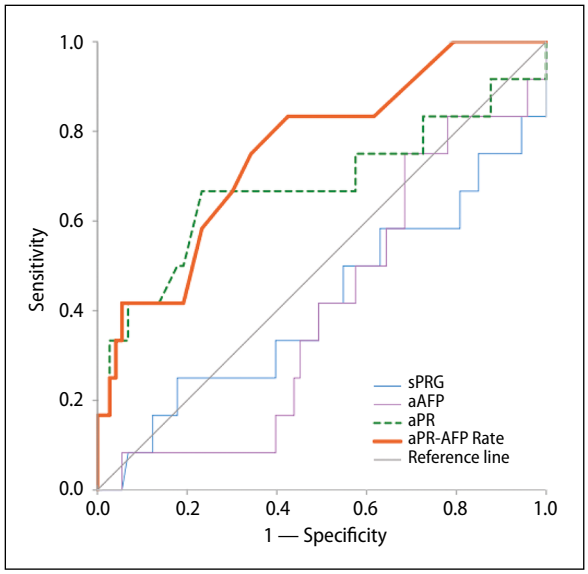

Figure 2. The receiver operating characteristic (ROC) curve of amniotic hormones for predicting neonatal intensive care unit (NICU); sPRG — serum progesterone; aAFP — amniotic alfa fetoprotein; aPR — amnion progesterone receptor; aPR-AFP — amnion progesterone to alfa fetoprotein

sensitivity; hence, physicians might use this novel index to predict NICU potential for pregnant women.

This prospective clinical research had some limitations. The major limitation is the inability to correlate amniotic hormone levels with maternal levels in these samples. Changing PR levels influences gestational length in humans, which is particularly important to research on regulating PR isoform expression. We measured total PR instead of all lower Progesterone receptors (PR-A, PR-B, and PR-C), which allowed us to reach a generalizable result over total PR rather than a specific PR effect. The efficacy and NICU specificity of the results may be increased in a study with all specific receptors. As a minor limitation, we analyzed samples of hormones at different times.

CONCLUSIONS

Amniotic hormones are essential to obtain information about both the pregnant and the baby in the later stages of pregnancy by measuring PR and AFP, unlike serum measurements. Evaluating the PR alone or in rational combination with AFP will provide physicians with useful information about the advanced pregnancy and postpartum complications process. The physicians might use the aPR-AFP rate to predict NICU potential for pregnancy and need further studies to make more vital predictions on postpartum complications. The data are preliminary and require further analysis.

Article information and declarations

Acknowledgments

None.

Ethics statement

The Ethical Committee's approval of the study was obtained (Date: 10.07.2020 — ID: E-20/311). All procedures performed in those studies involving human participants were following the ethical standards of the institutional and national

research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. For studies using human participants, state whether written informed consent was obtained from participants to participate.

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Author's contributions

S.B.A.: study concept and design; S.A., T.A., and G.S.Y.: data acquisition, data analysis, and interpretation; S.B.A, T.E., and O.S.: manuscript preparation; T.A.: correspondence.

Data availability statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

Conflict of interest

The authors declare no conflicts of interest.

REFERENCES

1. American College of Obstetricians and Gynecologists. ACOG Practice Bulletin No. 88, December 2007. Invasive prenatal testing for aneuploidy. Obstet Gynecol. 2007; 110(6): 1459–1467, doi: 10.1097/01.AOG.0000291570.63450.44, indexed in Pubmed: 18055749.
2. Alfirevic Z, Navaratnam K, Mujezinovic F. Amniocentesis and chorionic villus sampling for prenatal diagnosis. Cochrane Database Syst Rev. 2017; 9(9): CD003252, doi: 10.1002/14651858.CD003252.pub2, indexed in Pubmed: 28869276.
3. Jummaat F, Ahmad S, Mohamed Ismail NA. 5-Year review on amniocentesis and its maternal fetal complications. Horm Mol Biol Clin Investig. 2019; 40(2), doi: 10.1515/hmbci-2019-0006, indexed in Pubmed: 31539354.
4. Nizard J. Amniocentesis: technique and education. Curr Opin Obstet Gynecol. 2010; 22(2): 152–154, doi: 10.1097/GCO.0b013e32833723a0, indexed in Pubmed: 20098324.
5. Simpson JL, Rechitsky S. Preimplantation diagnosis and other modern methods for prenatal diagnosis. J Steroid Biochem Mol Biol. 2017; 165(Pt A): 124–130, doi: 10.1016/j.jsbmb.2016.03.022, indexed in Pubmed: 27108943.
6. Czyzyk A, Podfigurna A, Genazzani AR, et al. The role of progesterone therapy in early pregnancy: from physiological role to therapeutic utility. Gynecol Endocrinol. 2017; 33(6): 421–424, doi: 10.1080/09513590.2017.1291615, indexed in Pubmed: 28277122.
7. Di Renzo GC, Giardina I, Clerici G, et al. Progesterone in normal and pathological pregnancy. Horm Mol Biol Clin Investig. 2016; 27(1): 35–48, doi: 10.1515/hmbci-2016-0038, indexed in Pubmed: 27662646.
8. Weiss G. Endocrinology of parturition. J Clin Endocrinol Metab. 2000; 85(12): 4421–4425, doi: 10.1210/jcem.85.12.7074, indexed in Pubmed: 11134087.
9. Garg D, Ng SS, Baig KM, et al. Progesterone-Mediated Non-Classical Signaling. Trends Endocrinol Metab. 2017; 28(9): 656–668, doi: 10.1016/j.tem.2017.05.006, indexed in Pubmed: 28651856.
10. Zakar T, Hertelendy F. Progesterone withdrawal: key to parturition. Am J Obstet Gynecol. 2007; 196(4): 289–296, doi: 10.1016/j.ajog.2006.09.005, indexed in Pubmed: 17403397.
11. Nadeem L, Shynlova O, Matysiak-Zablocki E, et al. Molecular evidence of functional progesterone withdrawal in human myometrium. Nat Commun. 2016; 7: 11565, doi: 10.1038/ncomms11565, indexed in Pubmed: 27220952.
12. Wu SP, DeMayo FJ. Progesterone Receptor Signaling in Uterine Myometrial Physiology and Preterm Birth. Curr Top Dev Biol. 2017; 125: 171–190, doi: 10.1016/bs.ctdb.2017.03.001, indexed in Pubmed: 28527571.
13. Merlino A, Welsh T, Erdonmez T, et al. Nuclear progesterone receptor expression in the human fetal membranes and decidua at term before and after labor. Reprod Sci. 2009; 16(4): 357–363, doi: 10.1177/1933719108328616, indexed in Pubmed: 19196877.
14. Smith R, Mesiano S, McGrath S. Hormone trajectories leading to human birth. Regul Pept. 2002; 108(2-3): 159–164, doi: 10.1016/s0167-0115(02)00105-2, indexed in Pubmed: 12220740.
15. Tenore JL. Methods for cervical ripening and induction of labor. Am Fam Physician. 2003; 67(10): 2123–2128, indexed in Pubmed: 12776961.
16. Astle S, Slater DM, Thornton S. The involvement of progesterone in the onset of human labour. Eur J Obstet Gynecol Reprod Biol. 2003; 108(2): 177–181, doi: 10.1016/s0301-2115(02)00422-0, indexed in Pubmed: 12781407.
17. Klebanoff MA, Meis PJ, Dombrowski MP, et al. National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network, National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network. Prevention of recurrent preterm delivery by 17 alpha-hydroxyprogesterone caproate. N Engl J Med. 2003; 348(24): 2379–2385, doi: 10.1056/NEJMoa035140, indexed in Pubmed: 12802023.
18. Fahlbusch FB, Heussner K, Schmid M, et al. Measurement of amniotic fluid steroids of midgestation via LC-MS/MS. J Steroid Biochem Mol Biol. 2015; 152: 155–160, doi: 10.1016/j.jsbmb.2015.05.014, indexed in Pubmed: 26047555.
19. Mazor M, Hershkowitz R, Ghezzi F, et al. Maternal plasma and amniotic fluid 17 beta-estradiol, progesterone and cortisol concentrations in women with successfully and unsuccessfully treated preterm labor. Arch Gynecol Obstet. 1996; 258(2): 89–96, doi: 10.1007/BF00626029, indexed in Pubmed: 8779616.
20. Nagamani M, McDonough PG, Ellegood JO, et al. Maternal and amniotic fluid steroids throughout human pregnancy. Am J Obstet Gynecol. 1979; 134(6): 674–680, doi: 10.1016/0002-9378(79)90649-5, indexed in Pubmed: 463959.
21. Norwitz ER, Caughey AB. Progesterone supplementation and the prevention of preterm birth. Rev Obstet Gynecol. 2011; 4(2): 60–72, indexed in Pubmed: 22102929.
22. Oh SY, Kim CJ, Park I, et al. Progesterone receptor isoform (A/B) ratio of human fetal membranes increases during term parturition. Am J Obstet Gynecol. 2005; 193(3 Pt 2): 1156–1160, doi: 10.1016/j.ajog.2005.05.071, indexed in Pubmed: 16157129.
23. Leonhardt SA, Boonyaratanakornkit V, Edwards DP. Progesterone receptor transcription and non-transcription signaling mechanisms. Steroids. 2003; 68(10-13): 761–770, doi: 10.1016/s0039-128x(03)00129-6, indexed in Pubmed: 14667966.

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Epidural analgesia: effect on labor duration and delivery mode — a single-center cohort study

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ABSTRACT

Objectives: Parturients in labor experiencing severe pain may develop several complications, which could be avoided using various forms of labor analgesia. Researchers hold divergent opinions about the effect of epidural analgesia (EA) on labor duration and delivery mode. This paper aims to establish if EA affects the duration of the 1st and the 2nd phase of labor and the percentage of emergency Cesarean sections (CS) and instrumental delivery.

Material and methods: The patients in this cohort study were recruited at St. Sophia's Specialist Hospital in Warsaw, between January 1st, 2020, and June 1st, 2020 . We used following inclusion criteria: patients aged 18–40 with singleton pregnancies and cephalic presentation of the fetus who gave live birth at a gestational age of 37–42 weeks to neonates with birthweight 2500–4250 g and received EA at the cervical dilation between three and six centimeters. The control group didn't receive anesthesia. We excluded planned CS and vaginal births after CS. Data analysis was performed for all parturients and separately for multiparas and nulliparas.

Results: Out of 2550 deliveries, we included 1052 patients — 443 participants with EA and 609 in the control group. Patients with epidural analgesia experienced longer labor 415 vs 255 min ($p < 0.01$), longer 1st and 2nd stage ($p < 0.01$). They had a lower risk of emergency CS (OR = 0.56) ($p < 0.01$) but were more likely to have instrumental delivery.

Conclusions: Epidural analgesia prolongs the first and the second stage of labor yet doesn't affect neonatal outcomes. Moreover, the risk of emergency CS in nulliparas with EA is three times lower.

Keywords: cesarean section; parturition; epidural anesthesia; parity

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INTRODUCTION

Parturients describe labor pain as the worst pain they have ever endured [1]. This is because during childbirth, their body, due to pain, is exposed to hyperventilation, the release of catecholamines, and cortisol. This may cause respiratory alkalosis and uterine vasoconstriction [2], reducing oxygen transfer to the fetus and metabolic acidosis [3]. In addition, exposure to severe pain may cause mental health problems of the mother that affect relationship with the child or even with a partner [4].

To provide a comfortable birthing experience and prevent those adverse effects, healthcare professionals offer patients various forms of labor analgesia. The ideal anesthesia for childbirth should have minimal impact on the progress or outcome of labor, the fetus or newborn, and minimal maternal side effects [5]. Neuraxial analgesia meets many of these criteria [3–5] and is regarded as the gold standard [6]. However, the commonly used epidural anesthesia (EA) carries the risk of complications related to the procedure or side effects of the administered drugs [3].

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Some reports suggest that EA is associated with prolonged labor, increasing the risk of instrumental delivery and caesarean section (CS) [7–13]. However, as there is no clear standpoint on this topic, more research is needed to provide detailed and established information for the laboring parturients to facilitate their decision on labor analgesia.

Objectives

This paper aims to determine whether EA prolongs the 1st and the 2nd phase of labour and if it affects the ratio of vaginal and instrumental delivery and C-section both in nulliparas and multiparas. We hypothesize that anaesthesia prolongs the duration of labour, particularly the second phase, and increases the rate of caesarean sections and instrumental deliveries.

MATERIAL AND METHODS

Between January 1st, 2020, and June 1st, 2020, we conducted a single-center cohort study at St. Sophia's Specialists Hospital in Warsaw, obstetrics, and gynecology tertiary referral healthcare facility, to investigate the correlation between epidural analgesia and duration and mode of delivery. We followed parturients in labor and their neonates from the beginning of the 1st phase up to hospital discharge. The study has received approval from the Centre of Postgraduate Medical Education Bioethics Committee (No. 101/PB/2019). Because of retrospective analysis of anonymized data, individual patient consent was not needed. STROBE guideline for cohort studies was used to ensure proper reporting of data and outcomes [14].

Labor anesthesia and obstetric care

Our center uses EA for labor analgesia. The patients were given pain relief on demand regardless of cervical dilation. The type, volume, and concentration of administered drugs were chosen individually for each parturient by an experienced anesthesiologist. The anesthetics administered included: fentanyl (10%, 0.5%, 0.2%), lidocaine (1%), bupivacaine (0.5%, 0.1%, 1%), bupivacaine with adrenaline (0.1%, 0.5%, 0.125%, 0.625%), ropivacaine (0.2%). Detailed description of anesthetic use was presented in Supplementary Table 1. Obstetric care was similar in both groups, and a vaginal examination was performed every two hours. A specialist obstetrician made decisions concerning assisted vaginal delivery and CS according to maternal or fetal indications.

Study population

Patients were retrospectively evaluated by dividing them into groups with anesthesia (EA) and without anesthesia (no EA). Into the EA group we included only those patients, who received EA at the cervical dilatation between three to six cm. Finally, we performed an additional analysis where we stratified participants by parity (nulliparas and multiparas) within EA and no EA groups.

Data collection

Our primary outcome was the duration of labor defined as the sum of the 1st and 2nd phases and the mode of delivery (vaginal or operative childbirth). We defined the beginning of the 1st stage of labor as the mother's impression that the contractions are regular and the end as a complete cervical dilation (10 cm). The 2nd stage of labor is the time between full dilatation of the cervix and the birth of the neonate[15]. Our secondary outcomes were maternal (perineal rupture, duration of hospitalization, postpartum hemorrhage) and neonatal outcomes (Apgar score ≤ 7 points in 1st and 5th min. admission to the ICU). According to the World Health Organization (WHO) definition, postpartum hemorrhage was diagnosed as blood loss of ≥ 500 mL after vaginal delivery and ≥ 1000 mL after cesarean section [16]. We obtained individual patient data from the electronic health records and anesthesia documentation.

Study size

The number of labors in our center determined the sample size. We included all single live births at term (37––42 weeks), women aged 18–40, with the fetus in the cephalic presentation and birth weight between 2500 g and 4250 g. We excluded patients with scheduled caesarean sections and vaginal deliveries after caesarean section.

Data analysis

All statistical analyses were performed using STATISTICA 13.3 version (StatSoft Inc.). Data were demonstrated as average ± standard deviation (SD). The relationship of quantitative variables across the groups was calculated using the t-student or U Mann-Whitney test. The significance of qualitative variables was calculated using the chi-square test. Logistic regression was performed to calculate the correlation between the individual factors, and the OR (odds ratio) was calculated. For adjusted OR (aOR) calculation was performed. In all calculations, significant values were assessed for $p < 0.05$ and when 95% confidence interval (CI) did not include 1. Missing data were omitted from calculations.

RESULTS

A total of 2550 births were conducted in our centre between January 1st and June 1st. 2020. We excluded 1498 records. Out of 1052 patients included in the analysis, 443 (42.1%) participants received EA (nulliparous — 67.5%, multiparous — 32.5%) and 609 (57.9%) delivered without EA (nulliparous — 35.5%, multiparous — 64.5%). These results are shown in Figure 1. Patients in both groups had

Table 1. Demographic and clinical characteristics of parturients and their infants included in the study[a]

Characteristics	No epidural anaesthesia n = 609 [%] A ± SD	Epidural anaesthesia n = 443 [%] A ± SD	p value
Maternal age [years]	31.8 ± 4.1	30.8 ± 4.0	< 0.01
BMI before pregnancy	22.3 ± 3.9	22.8 ± 4.2	0.08
Neonatal birth weight [g]	3440.2 ± 374.2	3461.1 ± 358.2	0.36
Head circumference [cm]	34.5 ± 2.4	34.5 ± 1.5	0.82
Gestational age at delivery [weeks]	39.3 ± 1.1	39.4 ± 1.1	0.04
Parity			
Nulliparous	216 (35.5)	299 (67.5)	< 0.01
Multiparous	393 (64.5)	144 (32.5)	
Number of pregnancies			
1	184 (30.2)	258 (58.2)	
2	248 (40.7)	126 (28.5)	< 0.01
3	106 (17.4)	43 (9.7)	
> 4	71 (11.7)	16 (3.6)	
Labour induction	286 (47.0)	310 (70.0)	< 0.01
Oxytocin administration	137 (22.5)	209 (47.2)	< 0.01
Education			
Higher	338 (55.5)	224 (50.6)	
Secondary	38 (6.3)	31 (7.0)	0.55
Primary	5 (0.8)	2 (0.4)	
Missing data	228 (37.4)	186 (42.0)	
Marital Status			
Married	464 (76.2)	288 (65.0)	
Single	76 (12.5)	109 (24.6)	
Divorced	10 (1.6)	5 (1.2)	< 0.01
Widowed	0 (0.0)	1 (0.2)	
Other	3 (0.5)	1 (0.2)	
Missing data	56 (9.2)	39 (8.8)	

[a]missing data, n (%): BMI before pregnancy, 89 (9.2); head circumference, 39 (3.8); BMI — body mass index

a comparable body mass index (BMI) before pregnancy and education level. We also did not observe any significant differences in neonatal characteristics (birth weight and head circumference). In our study, more nulliparas than multiparas received EA 67.5% vs 32.5% among the EA group. Also, patients in the EA group more often had induction of labour (70% vs 47%) and administration of oxytocin (47.2% vs 22.5%) (Tab. 1). Drugs administered for EA along with doses are shown in Table S1 in the Supplementary Table.

Several factors were found to be statistically significant in the population characteristics. The induction of labour and oxytocin administration may have influenced the results, as discussed below. There were slight variations in maternal age and gestational age, but they were not clinically significant. Differences between the groups regarding marital status appear to be insignificant. From a clinical point of view, it is more important whether a patient is nulliparous or not.

Table 2 shows the comparison between EA and non-EA groups. One of the primary outcomes was the mean duration of labour which was longer in patients who received EA than those without analgesia (415 min vs 255 min). In addition, the 1st and the 2nd stages of labour were also prolonged in the EA group. In the EA group, parturients were twice more likely to give birth naturally than by caesarean section. However, they were more likely to have instrumental delivery with vacuum extraction, and their hospital stay was longer. The number of clinically significant 3rd-degree perineal lacerations did not differ between the groups. There was no association between EA and blood loss, postpartum haemorrhage, and admission to the Neonatal Intensive Care Unit. There were also no differences in Apgar scores ≤ 7 between the two groups.

The analysis shows statistically significant differences between nulliparas and multiparas with and without EA (Tab. 3). The duration of the first and second stages of labour was longer in the group with EA in nulliparas and multiparas (Fig. 2). Nulliparas who received EA were almost three times less likely to deliver by caesarean section than those without EA ($p < 0.01$). In the group of multiparas, there were no significant differences in the rate of emergency caesarean sections, but the patients with EA were more likely to give birth naturally ($p = 0.22$). In the group of nulliparas, EA did not increase the risk of longer hospitalization. However,

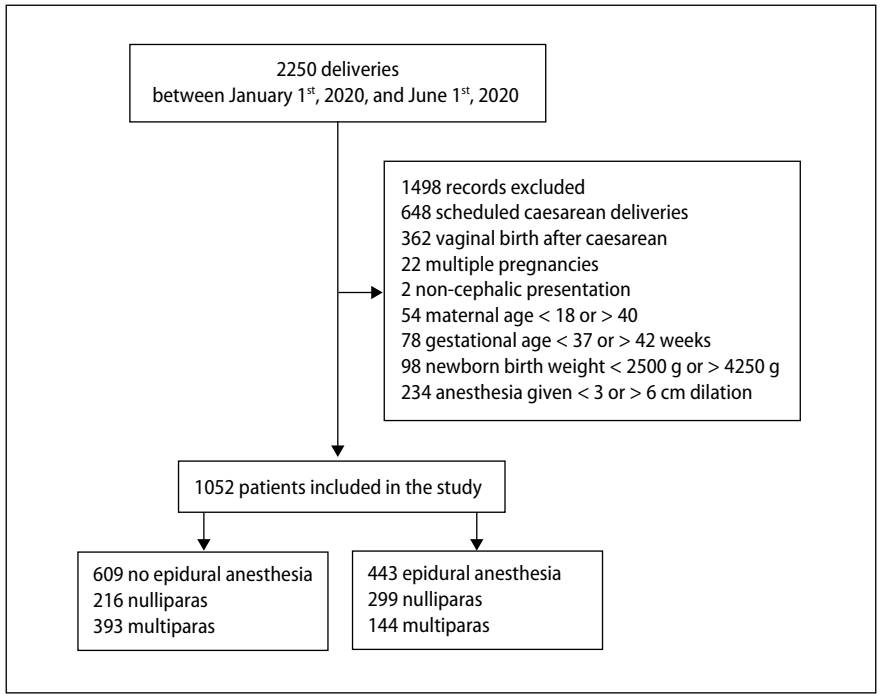

Figure 1. Study flow chart

Table 2. Outcomes correlated with epidural anaesthesia (all patients)[a]

Outcomes	No epidural anaesthesia n = 609 [%] A ± SD	Epidural anaesthesia n = 443 [%] A ± SD	p value	OR (95% CI)
Duration of labour [min]	255 ± 129	415 ± 170	< 0.01	1.006 (1.005–1.006)
Duration of 1st stage [min]	235 ± 121	379 ± 152	< 0.01	1.008 (1.007–1.010)
Duration of 2nd stage [min]	21 ± 19	35 ± 31	< 0.01	1.032 (1.024 to 1.039)
Caesarean section	107 (17.6)	47 (11)	< 0.01	0.56 (0.39–0.80)
Instrumental delivery Vacuum Forceps	15 (2.5) 15 (2.5) 0 (0.0)	24 (5.4) 22 (5.0) 2 (0.5)	0.02 0.02 1.00	2.27 (1.18–4.38) 2.07 (1.0–4.04) –
Postpartum haemorrhage	137 (22.5)	102 (23.02)	0.84	1.03 (0.77–1.38)
Blood loss [mL]	410 ± 188	417 ± 126	0.54	1.000 (0.999 to 1.001)
3rd degree perineal laceration	1 (0.2)	1 (0.2)	0.82	1.38 (0.09–22.05)
Apgar score < 7 at 1st min at 5th min	 5 (0.8) 1 (0.2)	 4 (0.9) 0 (0.0)	 0.88 1.00	 1.10 (0.29–4.12) –
Admission to neonatal intensive care unit	39 (6.4)	25 (5.6)	0.61	0.87 (0.52–1.47)
Mother's postnatal hospital stay [days]	3.76 ± 2.11	4.33 ± 2.09	< 0.01	1.14 (1.07–1.21)

[a]missing data, n (%): duration of labour, 1 (0.2); duration of 1st stage, 156 (14.8); duration of 2nd stage, 161 (15.3); blood loss, 13 (1.2); Apgar score at 1st min, 1 (0.2); Apgar score at 5th min, 2 (0.4)

in the group of multiparas, those who received EA were at a higher risk of longer hospitalization than parturients without EA. The groups did not differ significantly in the rate of instrumental deliveries, blood loss and perineal injury, Apgar score < 7, and admission to the neonatal intensive care unit. Nulliparas in the EA group were at a lower risk of postpartum haemorrhage.

DISCUSSION

This cohort study involving 1052 patients aimed to determine the effect of epidural analgesia on labor duration and delivery mode. The study showed that EA independently of the group prolongs the 1st and 2nd phase of labor. Furthermore, in the group with anesthesia, we observed a lower number of caesarean sections, higher incidence of

Table 3. Outcomes correlated with epidural anaesthesia after stratification according to parity

Outcomes	Nulliparas[a]			Multiparas[b]		
	No epidural anaesthesia N = 216 [%] A ± SD	Epidural anaesthesia N = 299 [%] A ± SD	p value	No epidural anaesthesia n = 393 [%] A ± SD	Epidural anaesthesia n = 144 [%] A ± SD	p value
Duration of labour [min]	346 ± 153	471 ± 175	< 0.01	219 ± 102	323 ± 146	< 0.01
Duration of 1st stage [min]	310 ± 145	429 ± 169	< 0.01	206 ± 100	294 ± 101	< 0.01
Duration of 2nd stage [min]	36 ± 22	43 ± 34	< 0.01	14.8 ± 12	19.6 ± 12	< 0.01
Caesarean section	66 (30.6)	39 (13.0)	< 0.01	41 (10.4)	8 (5.6)	0.22
Instrumental delivery Vacuum Forceps	 11 (5.1) 0 (0.0)	 20 (6.7) 2 (0.7)	 0.55 1.00	 4 (1.0) 0	 2 (1.4) 0	 0.77 1.00
Postpartum haemorrhage	81 (37.5)	86 (28.8)	0.04	56 (14.2)	16 (11.1)	0.43
Blood loss [mL]	451 ± 278	430 ± 131	0.60	389 ± 103	390 ± 108	0.86
3rd degree perineal laceration	0 (0.0)	0 (0.0)	1.0	1 (0.3)	1 (0.7)	0.49
Apgar score < 7 at 1st min at 5th min	 1 (0.5) 0 (0.0)	 2 (0.7) 0 (0.0)	 0.76 1.00	 4 (1.0) 1 (0.3)	 2 (1.4) 0 (0.0)	 0.73 0.54
Admission to neonatal intensive care unit	19 (8.8)	15 (5.0)	0.09	16 (5.1)	10 (6.9)	0.43
Mother's postnatal hospital stay [days]	4.25 ± 2.2	4.53 ± 2.1	0.16	3.49 ± 2.0	3.9 ± 2.0	0.02

[a]missing data, n (%): duration of labour, 1 (0.2); duration of 1st stage, 104 (20.2); duration of 2nd stage, 104 (20.2); blood loss, 7 (1.4); Apgar score at 5th min, 1 (0.2); [b]missing data, n (%): duration of 1st stage, 52 (9.7); duration of 2nd stage, 57 (10.6); blood loss, 6 (1.1); Apgar score at 1st min, 1 (0.2); Apgar score at 5th min, 1 (0.2)

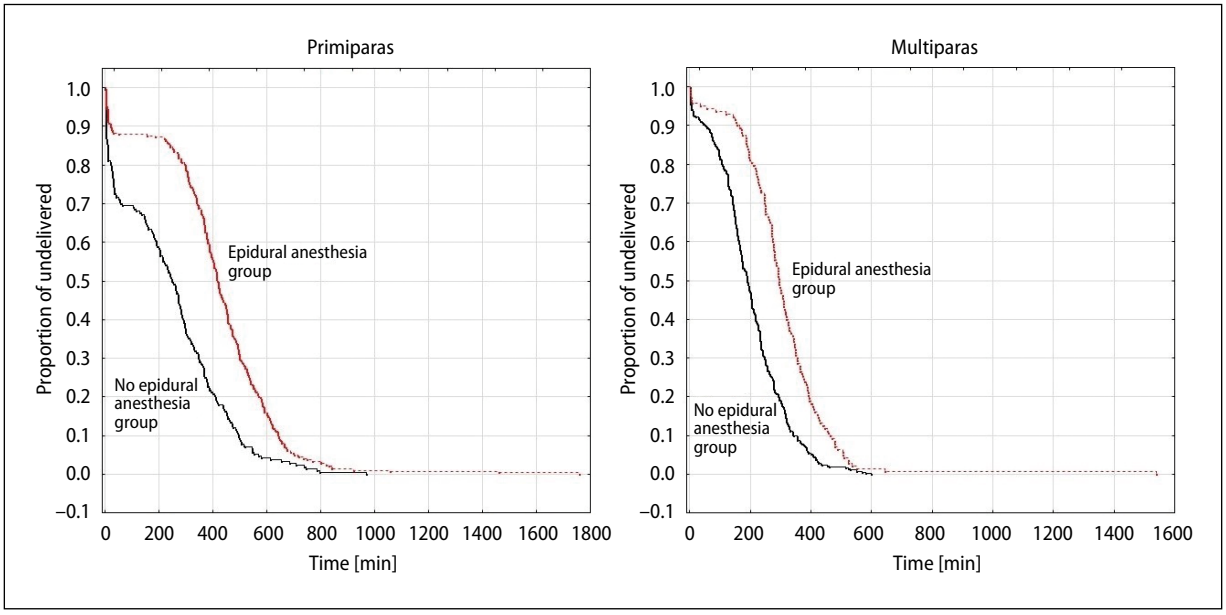

Figure 2. Kaplan–Meier survival analysis of labor duration

instrumental deliveries (vacuum), prolonged labor duration, and maternal hospitalization. In nullipara, EA remarkably lowered the number of emergency caesarean sections and was associated with a lower risk of postpartum hemorrhage. Thus, our hypothesis was confirmed in the aspect of labor duration, but the hypothesis that EA increases the rate of caesarean sections was proven false.

To date, many papers have reviewed the association between EA and the mode of delivery. In our study, EA resulted in a two-fold reduction in risk of CS in the general population and a threefold reduction/decrease in the nulliparous group. The effect of EA on the risk of CS has been reported in the literature. A study of 1733 low-risk nulliparas showed up to four times higher rates of

caesarean sections in the group of parturients who received anaesthesia [7]. In another study, the caesarean section rate was 9.2% vs 4% in the group with and without EA, respectively, but the p value was 0.06 [9]. Another randomized cohort study showed that the effect of anesthesia depends on the concentration of analgesic drugs used [17]. In our study, the analgesics and their concentrations were, heterogeneous and differed from those used in the study quoted above, they were selected by specialized anesthetists to allow patients to walk around the delivery room. This could potentially be one explanation for the differences in the results obtained.

On the other hand, no association between anaesthesia and caesarean section was demonstrated in a 2018 systematic review based on 33 randomized cohort studies (moderate-quality evidence) [8]. In the 2018 study of 207,525 births, a significantly lower rate of caesarean sections was observed in seven groups. These included multiparas labor induction, while the rate of caesarean sections was slightly higher in those with spontaneous onset of labor. So, induction of labor seems to be associated with a higher rate of caesarean section. In our study, more patients in the EA group had labor induction (70% vs 47%). Another study on the effect of EA on labor induction showed more caesarean sections among participants with anesthesia (26% vs 10.1%) [18]. However, there were more frequent post-term pregnancies in this population and significantly higher birth weight in the group with EA compared to the group without EA, which may have influenced the results. Nevertheless, other factors besides EA may likely influence the rate of emergency caesarean sections, and further research on this topic is needed.

For instrumental deliveries, we observed a twofold increase in the rate of vacuum deliveries in the group that received anesthesia. However, a separate analysis of a group of nulliparas and multiparas did not confirm this. The literature concerning the effect of EA on the rate of instrumental deliveries is more consistent. There is an abundance of papers reporting increased rates of instrumental deliveries in the group with EA [8, 10]. On the other hand, a systematic review and meta-analysis of randomized controlled trials found no association between EA (with low analgesic concentrations) and instrumental delivery. However, this meta-analysis was based on small studies of low quality [19].

In our study, the longer duration of the first and second phases of labor shown in the nulliparous and multiparas in the EA group is statistically significant. These differences showed no correlation with any serious maternal or neonatal adverse effects and can therefore be considered clinically irrelevant. The literature on the impact of EA on length of labor is inconsistent. A correlation between EA and longer duration of the 1st and the 2nd phase of labor was observed in a study involving 645 parturients in labor [9]. Other studies have also shown longer duration of labor in the group with EA [11–13]. However, the meta-analysis provides evidence that EA may even shorten the second phase of labor, depending on the combination of drugs used [20]. According to recent studies, the use of oxytocin may be associated with longer labor, which might have influenced the results of the study [21].

In our study, patients who received EA had a longer hospital stay. However, this effect was statistically significant only for multiparas, and the difference was less than half a day. In the study of Liu et. al. [22] any adverse outcomes of child and mother were found significant. The longer hospital stay was also observed in a study of Yin and Hu [23], and was probably related to increased rate of maternal intrapartum fever.

The study showed that the incidence of hemorrhage was lower in nulliparas with EA. At the same time, there was no difference in the amount of blood loss among nulliparas in the group with and without EA. We did not find similar results in the available literature. After correction, this result was not found to be statistically significant. Some studies indicate that the duration of labor affects the incidence of maternal hemorrhage [24]. However, others do not confirm an increased incidence of hemorrhage with anesthesia. Due to the discrepancy in results, further studies on this topic are needed.

In the present study, EA did not affect neonatal outcomes — neither Apgar scores at 1st and 5th minute nor the rate of ICU admissions, which is consistent with the available literature [2, 8, 24].

A key strength of this study is its applicability which is determined by a few factors. The setting of this study included a tertiary care hospital, a broad choice of analgesics dependent on anesthesiologist's discretion as in many other facilities worldwide. A large group of patients was included in the study and their range is wide — both nulliparas and multiparas. We included young adolescents as well as more mature patients.

This study has several limitations. These are primarily related to the observational retrospective character of the study as there may be other factors affecting the outcome which are not included, such as maternal position during the first [25] or second stage of labor [26]. We did not rule out any BMI category nor participants with labor induction as this is a procedure often performed in parturients. Finally, patients were given different combinations of drugs and at different concentrations, which represents the situation daily at different hospitals in Poland and worldwide.

Moreover, we could not obtain data on the participants' reasons for their decision on labor anesthesia. For example, parturients with initially longer deliveries could request for administration of anesthesia more often because of longer-lasting pain. Moreover, assessment of the onset of the 1st phase of labor is potentially subject to recall bias among the patients who initiated labor out of the hospital. In these

cases, the onset of regular contractions was subjectively estimated. Also, missing data could have affected the results.

CONCLUSIONS

Even though EA prolongs the delivery time, it is clinically irrelevant as it does not affect maternal or neonatal outcomes, whereas it provides comfort. Our study shows that EA may play a protective role and reduce the number of Cesarean sections in a particular group of patients. Statistical analysis suggests that confounders can affect the mode of delivery. Further research is therefore needed to evaluate these factors and provide parturients pain-free labor that is safe for them and their infants.

Article information and declarations

Ethics statement

The study has received approval from the Centre of Postgraduate Medical Education Bioethics Committee (No. 101/PB/2019).

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Conflict of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Supplementary material

Supplementary Table S1. Combination of drugs used to EA with doses.

REFERENCES

1. Beigi NM, Broumandfar K, Bahadoran P, et al. Women's experience of pain during childbirth. Iran J Nurs Midwifery Res. 2010; 15(2): 77–82, indexed in Pubmed: 21589784.
2. Reynolds F. Labour analgesia and the baby: good news is no news. Int J Obstet Anesth. 2011; 20(1): 38–50, doi: 10.1016/j.ijoa.2010.08.004, indexed in Pubmed: 21146977.
3. Labor S, Maguire S. The Pain of Labour. Rev Pain. 2008; 2(2): 15–19, doi: 10.1177/204946370800200205, indexed in Pubmed: 26526404.
4. Wong CA. Advances in labor analgesia. Int J Womens Health. 2010; 1: 139–154, doi: 10.2147/ijwh.s4553, indexed in Pubmed: 21072284.
5. Silva M, Halpern SH. Epidural analgesia for labor: Current techniques. Local Reg Anesth. 2010; 3: 143–153, doi: 10.2147/LRA.S10237, indexed in Pubmed: 23144567.
6. Sng BL, Sia AT. Maintenance of epidural labour analgesia: The old, the new and the future. Best Pract Res Clin Anaesthesiol. 2017; 31(1): 15–22, doi: 10.1016/j.bpa.2017.01.002, indexed in Pubmed: 28625301.
7. Lieberman E, Lang JM, Cohen A, et al. Association of epidural analgesia with cesarean delivery in nulliparas. Obstet Gynecol. 1996; 88(6): 993–1000, doi: 10.1016/s0029-7844(96)00359-6, indexed in Pubmed: 8942841.
8. Anim-Somuah M, Smyth RMd, Cyna AM, et al. Epidural versus non-epidural or no analgesia for pain management in labour. Cochrane Database Syst Rev. 2018; 5(5): CD000331, doi: 10.1002/14651858.CD000331.pub4, indexed in Pubmed: 29781504.
9. Mock PM, Santos-Eggimann B, Clerc Bérod A, et al. Are women requiring unplanned intrapartum epidural analgesia different in a low-risk population? Int J Obstet Anesth. 1999; 8(2): 94–100, doi: 10.1016/s0959-289x(99)80005-3, indexed in Pubmed: 15321152.
10. Lucovnik M, Blajic I, Verdenik I, et al. Impact of epidural analgesia on cesarean and operative vaginal delivery rates classified by the Ten Groups Classification System. Int J Obstet Anesth. 2018; 34: 37–41, doi: 10.1016/j.ijoa.2018.01.003, indexed in Pubmed: 29501538.
11. Naito Y, Ida M, Yamamoto R, et al. The effect of labor epidural analgesia on labor, delivery, and neonatal outcomes: a propensity score-matched analysis in a single Japanese institute. JA Clin Rep. 2019; 5(1): 40, doi: 10.1186/s40981-019-0260-z, indexed in Pubmed: 32026970.
12. Heesen M, Böhmer J, Klöhr S, et al. The effect of adding a background infusion to patient-controlled epidural labor analgesia on labor, maternal, and neonatal outcomes: a systematic review and meta-analysis. Anesth Analg. 2015; 121(1): 149–158, doi: 10.1213/ANE.0000000000000743, indexed in Pubmed: 25902319.
13. Shmueli A, Salman L, Orbach-Zinger S, et al. The impact of epidural analgesia on the duration of the second stage of labor. Birth. 2018; 45(4): 377–384, doi: 10.1111/birt.12355, indexed in Pubmed: 29790194.
14. von Elm E, Altman DG, Egger M, et al. STROBE Initiative. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. Ann Intern Med. 2007; 147(8): 573–577, doi: 10.7326/0003-4819-147-8-200710160-00010, indexed in Pubmed: 17938396.
15. ACOG. Safe Prevention of the Primary Cesarean Delivery. https://www.acog.org/clinical/clinical-guidance/obstetric-care-consensus/articles/2014/03/safe-prevention-of-the-primary-cesarean-delivery (6.05.2021).
16. WHO recommendations for the prevention and treatment of postpartum haemorrhage. https://apps.who.int/iris/bitstream/handle/10665/75411/9789241548502_eng.pdf;jsessionid=F0830D159686A8906BBDDCCCD7D26822?sequence=1 (6.05.2021).
17. Baliuliene V, Macas A, Rimaitis K. The optimal concentration of bupivacaine and levobupivacaine for labor pain management using patient-controlled epidural analgesia: a double-blind, randomized controlled trial. Int J Obstet Anesth. 2018; 35: 17–25, doi: 10.1016/j.ijoa.2018.05.002, indexed in Pubmed: 29914785.
18. Antonakou A, Papoutsis D. The effect of epidural analgesia on the delivery outcome of induced labour: a retrospective case series. Obstet Gynecol Int. 2016; 2016: 5740534, doi: 10.1155/2016/5740534, indexed in Pubmed: 27990163.
19. Wang TT, Sun S, Huang SQ. Effects of epidural labor analgesia with low concentrations of local anesthetics on obstetric outcomes: a systematic review and meta-analysis of randomized controlled trials. Anesth Analg. 2017; 124(5): 1571–1580, doi: 10.1213/ANE.0000000000001709, indexed in Pubmed: 27828798.
20. Li Y, Hu C, Fan Y, et al. Epidural analgesia with amide local anesthetics, bupivacaine, and ropivacaine in combination with fentanyl for labor pain relief: a meta-analysis. Med Sci Monit. 2015; 21: 921–928, doi: 10.12659/MSM.892276, indexed in Pubmed: 25816849.
21. Espada-Trespalacios X, Ojeda F, Perez-Botella M, et al. Oxytocin administration in low-risk women, a retrospective analysis of birth and neonatal outcomes. Int J Environ Res Public Health. 2021; 18(8), doi: 10.3390/ijerph18084375, indexed in Pubmed: 33924137.
22. Liu X, Zeng R, Chen Q, et al. The effect of epidural analgesia on maternal-neonatal outcomes: a retrospective study. Ginekol Pol. 2021 [Epub ahead of print], doi: 10.5603/GP.a2021.0007, indexed in Pubmed: 33914328.
23. Yin H, Hu R. A cohort study of the impact of epidural analgesia on maternal and neonatal outcomes. J Obstet Gynaecol Res. 2019; 45(8): 1435–1441, doi: 10.1111/jog.13988, indexed in Pubmed: 31131486.
24. Li CJ, Xia F, Xu SQ, et al. Concerned topics of epidural labor analgesia: labor elongation and maternal pyrexia: a systematic review. Chin Med J (Engl). 2020; 133(5): 597–605, doi: 10.1097/CM9.0000000000000646, indexed in Pubmed: 32032081.
25. Lawrence A, Lewis L, Hofmeyr GJ, et al. Maternal positions and mobility during first stage labour. Cochrane Database Syst Rev. 2009(2): CD003934, doi: 10.1002/14651858.CD003934.pub2, indexed in Pubmed: 19370591.
26. Gupta JK, Sood A, Hofmeyr GJ, et al. Position in the second stage of labour for women without epidural anaesthesia. Cochrane Database Syst Rev. 2017; 5(5): CD002006, doi: 10.1002/14651858.CD002006.pub4, indexed in Pubmed: 28539008.

SUPPLEMENTARY MATERIAL

Supplementary Table S1. Combination of drugs used to EA with doses

Drugs combination	Patients n = 443 [%]	Fentanyl (F) A ± SD [mcg]	Lidocaine (L) A ± SD [mg]	Bupivacaine (B) A ± SD [mg]	Bupivacaine with adrenaline (BA) A ± SD [mg]	Ropivacaine (R) A ± SD [mg]
F + BA	107 (24.2)	142.1 ± 88.0	–	–	9.3 ± 4.2	–
F + L + BA	94 (21.1)	113.6 ± 95.8	32.5 ± 14.7	–	10.6 ± 4.03	–
F + R	81 (18.3)	145.1 ± 86.4	–	–	–	21.9 ± 7.0
F + L + R	58 (13.1)	131.6 ± 96.8	45.0 ± 30.8	–	–	21.5 ± 7.3
F + L + B	48 (10.8)	184.0 ± 63.3	31.7 ± 12.8	15.5 ± 12.6	–	–
F + B	45 (10.2)	52.4 ± 86.9	–	16.7 ± 7.2	–	–
Other combination	6 (1.4)	152.5 ± 82.3	35.0 ± 11.2	37.5 ± 27.5	12.0 ± 0.0	24.8 ± 7.8

*missing data, n (%): drugs combination, 4 (0.9); F 16 (3.6); L, 7 (1.6); B, 4 (0.9); BA, 16 (3.6); R, 7 (1.6)

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The efficacy of three regimes of uterotonic agents for prevention of postpartum blood loss at undergoing cesarean section: a prospective randomized clinical trial

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ABSTRACT

Objectives: To compare the efficacy of three regimes of uterotonic agents on PPH in women undergoing cesarean section in our RCT.

Material and methods: This study was a randomized controlled study (NCT05083910) performed at the Bezmialem Vakif University between July 2021 and January 2022. All women were randomly allocated into three groups: Group I (n = 52) — oxytocin only; Group II (n = 52) — the combination of oxytocin plus intrauterine misoprostol; Group III (n = 52) — carbetocin only. The primary outcome measures were: PPH to evaluate with the change between the concentrations of preoperative and postoperative hemoglobin, hematocrit and intraoperative blood loss.

Results: The blood loss characteristics, including the change in hemoglobin and the change in hematocrit concentration, intraoperative blood loss, intraoperative additional hemostatic uterine sutures and the need for additional uterotonics, were lowest in group III, although all groups were comparable in terms of blood loss parameters. Group III had the highest blood loss ratio, exceeding 1000 mL. For the combination of oxytocin and intrauterine misoprostol, the ARR was 3.8% (95% CI 20.02–12.33), with a RR of 1.18 (95% CI 0.58–2.39) and a NNT of 26 (95% CI 8.1–4.9); for carbetocin, the ARR was 5.8% (95% CI 22.15–10.61), with a RR of 1.27 (95% CI 0.63–2.53) and a NNT of 17 (95% CI 9.41–4.51).

Conclusions: Our results demonstrate that carbetocin shows no superiority in the prevention of PPH in women undergoing cesarean section. Oxytocin still seems to be a highly effective alternative to prevent PPH.

Keywords: postpartum hemorrhage; oxytocin; uterotonic agents

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INTRODUCTION

Postpartum hemorrhage (PPH) is a serious but rare condition when a woman has heavy bleeding after giving birth. This is a prominent factor contributing to maternal morbidity and mortality on a global scale [1] .

Various modern technological (*e.g.*, intrauterine balloon tamponade, interventional radiological procedures) and pharmacological (*e.g.*, anti-fibrinolytic agents, recombinant factor VIIa) advancements have been made in the management of postpartum hemorrhage (PPH). Nevertheless, the primary focus remains on preventing PPH through active management of the third stage of labor. This involves routinely administering uterotonic agents to enhance uterine contractions, reducing maternal morbidity and mortality [2–4] .

Indeed, recent guidelines suggested the routine preventive administration of uterotonic agents during the third stage of labour for all births, regardless of the route of delivery, to reduce the incidence of PPH: the Royal College of Obstetricians and Gynaecologists guidelines recommend

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5 IU of slow intravenous oxytocin injection; the World Health Organization recommend 10 IU of oxytocin injection (IU, IV/ /IM); French guidelines recommend 5 or 10 IU of oxytocin (IV or IM) [5–7] .

In the past few decades, many studies have focused on improving the preventive regimes of uterotonic agents for PPH. Oxytocin (produced in the hypothalamus), misoprostol (a prostaglandin E1 analogue) and carbetocin (a synthetic long-acting oxytocin analogue) are the most popular uterotonic agents to have been evaluated in studies, in terms of their effectiveness in preventing PPH.

As the first-line prophylactic drug, oxytocin is still recommended to prevent PPH; however, there is currently no consensus in the literature for the optimal dose and infusion rate of oxytocin. A single 100 μg dose of intravenous carbetocin can provide a prolonged uterine contraction of up to an hour, while carbetocin has a longer half-life than oxytocin (41 min), which gives it an advantage [8, 9].

The efficacy of vaginal or rectal misoprostol has also been demonstrated in the prevention of PPH [10] .

Moreover, it can be administrated by the sublingual route after rectal or vaginal administration. Some studies have assessed the effectiveness of intrauterine misoprostol in preventing postpartum hemorrhage (PPH) in women undergoing cesarean section (CS) [11, 12].

Our randomized controlled trial aimed to assess whether there were any distinctions among the three regimens of uterotonic agents concerning the primary outcome of postpartum hemorrhage occurring in women who have undergone a cesarean section.

MATERIAL AND METHODS

Participants

This study was a randomized controlled study (NCT05083910) performed at the Department of Obstetrics and Gynaecology of Medical Faculty of Bezmialem Vakif University between July 2021 and January 2022. The study received approval from the Ethical Committee of the Medical Faculty at Bezmialem Vakif University. (Ethic No: 20.05.2021-E.16677). All patients provided written informed consent for participation in the study. The inclusion criteria consisted of (1) women between 18–40 years old, (2) a caesarean section under spinal anaesthesia, (3) term single pregnancy, and (4) an American Society of Anesthesiology physical status of I or II. A total of 156 women were included in our study. The study was designed and reported in accordance with the Consolidated Standards of Reporting Trials (CONSORT) guidelines (Fig. 1).

The exclusion criteria consisted of emergency surgeries due to placental pathologies, including previa or abruptia, multiple pregnancies, women with a previous history of several medical problems, such as moderate to severe hypertension, preeclampsia diabetes mellitus, and any blood or thrombophilia disorders, a history of previous major abdominal surgeries and anticoagulation therapy. Data were collected relating to age, body mass index (BMI), gravida, parity, indication of CS, gestational age at birth, Apgar scores at 1 and 5 min, birth weight, neonatal intensive care unit (NICU) admission, blood loss parameters, including intraoperative blood loss as described in our previous study [13]. Intraoperative measurement of blood loss during cesarean section was done by combining the volume of the suction bottle containing blood-soaked sponges. During the procedure, two suctions were employed. The second suction was explicitly employed to collect the amniotic fluid at the incision of the amniotic sac. To calculate the blood loss accurately, the amniotic fluid volume in the second suction bottle was excluded from each case.

The same surgeons evaluated uterine tone in all cases, by palpating the uterine fundus (Pınar Özcan and Çağlar Çetin). Postpartum hemorrhage was diagnosed when the total blood loss reached 1000 mL or more or when there was evidence of blood loss accompanied by signs or symptoms of hypovolemia within 24 hours after delivery, including any intrapartum loss. The primary outcome measures were: PPH to evaluate with the change between the concentrations of preoperative and postoperative hemoglobin and hematocrit and intraoperative blood loss. The secondary outcomes were additional number of intraoperative hemostatic uterine sutures, operating time, the requirement for extra uterotonics, and the necessity for blood transfusion.

Interventions in groups

All participants were randomly assigned to one of three groups using a computer-based randomization number program (Fig. 1). Group I (n = 52) — oxytocin only (Synpitan forte®; Deva Pharma, Istanbul, Türkiye) (following the clamping of the umbilical cord, oxytocin was infused at a rate of 125 mL/h as 20 IU dissolved in 500 mL of normal 0.9% NaCl); Group II (n = 52) — the combination of oxytocin plus intrauterine misoprostol (Cytotec®; ARIS , Istanbul, Türkiye) (the oxytocin infusion was infused as previously described, and a 400 mg misoprostol tablet was inserted into the uterine cavity, at the fundal surface, after delivery of the placenta); Group III (n = 52) — carbetocin only (Pabal; Ferring Pharma, Istanbul, Türkiye) (immediately after delivery of the baby, 100 mg carbetocin was intravenously administered). Two surgeons (Pınar Özcan and Çağlar Çetin) performed all the surgeries.

Statistical analysis

When we take the difference in the variable "Reduction in hemoglobin" between the two groups as 0.74 (with a standard deviation of 1.39) with a 95% confidence level

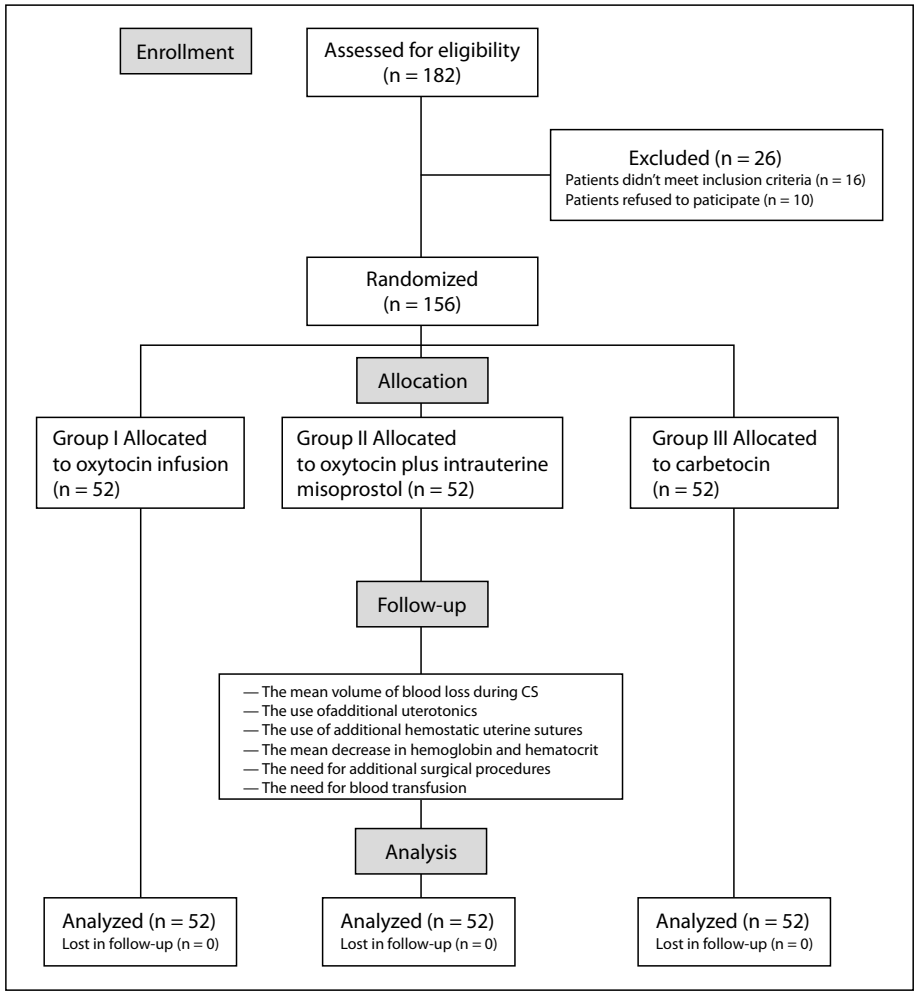

Figure 1. Study flowchart; CS — cesarean section

and 80% test power, we should include a minimum of 52 people in each group [12]. Variables were presented as mean ± standard deviation, number or percentage. The Pearson chi-square test and Fisher's exact test were used to compare categorical variables. Distribution of variables were tested by the Shapiro–Wilk test and histogram. For normally distributed variables, the Student t test was used to compare two independent groups in terms of the means. For non-normally distributed variables, the Mann-Whitney U test was used to compare two independent groups in terms of the means. The relative risk (RR), the relative risk reduction (RRR), the absolute risk reduction (ARR) and the number needed to treat (NNT) were calculated. In all cases, $p < 0.05$ was considered significant. All data were analysed using SPSS version 26 (IBM Corp., Armonk, NY, USA).

RESULTS

A total of 182 patients were initially enrolled in the study. However, 26 women were excluded from the study before randomization for various reasons: 16 did not meet the inclusion criteria, and 10 declined to participate. As a result, the analysis was performed on data from 156 women divided equally into three groups: 52 patients in Group I, 52 in Group II, and 52 in Group III. No patients were excluded after randomization. The flowchart of our study and the patient requirements are presented in Figure 1. The baseline demographic and obstetric characteristics of the patients in all groups are presented in Table 1. No statistically significant differences were observed among the groups concerning BMI, age, gestational age at birth, gravida, parity, and the indication for cesarean section.

The comparison of primary outcomes; intra-operative, post-operative and hemorrhage characteristics between groups are presented in Table 2. The blood loss characteristics, including the change in hemoglobin and the change in hematocrit concentration, intraoperative blood loss, intraoperative additional hemostatic uterine sutures and the requirement for additional uterotonics, were lowest in

Table 1. Baseline obstetric and demographic characteristics of groups

Characteristics	Group I (n = 52)	Group II (n = 52)	Group III (n = 52)	p value
Age [years]	30.37 ± 4.87	31.94 ± 5.01	32.29 ± 5.78	0.15
Body mass index [kg/m^2]	29.28 ± 4.24	31.24 ± 6.29	29.59 ± 4.56	0.24
Gravida	2.17 ± 1.26	2.04 ± 1.02	2.12 ± 1.33	0.9
Parity	0.75 ± 0.9	0.6 ± 0.77	0.79 ± 1.14	0.65
Gestational age at birth [day]	268.67 ± 7.83	269.13 ± 6.8	269.56 ± 7.65	0.83
Indication of CS				
Previous CS	50% (26)	42.3% (22)	40.4% (21)	0.33
Fetal Distress	19.2% (10)	11.5% (6)	7.7% (4)	
Malpresentation	9.6% (5)	9.6% (5)	19.2% (10)	
Macrosomia	3.8% (2)	5.8% (3)	5.8% (3)	
Failure to progress	0% (0)	9.6% (5)	5.8% (3)	
Others	17.3% (9)	21.2% (11)	21.2% (11)	

Values are reported as mean ± standard deviation; p < 0.05, statistically significant difference; CS — cesarean section

Table 2. Comparison of operative characteristics, hemorrhage and post-operative characteristics between groups

Characteristics	Group I (n = 52)	Group II (n = 52)	Group III (n = 52)	p value
The pre-operative hemoglobin concentration [g/dL]	11.81 ± 1.24	12.05 ± 1.29	11.9 ± 1.21	0.600
The pre-operative hematocrit concentration [%]	35.60 ± 3.63	36.25 ± 3.4	35.94 ± 3.3	0.630
The changing of the hemoglobin concentration [g/dL]	1.05 ± 0.93	1.08 ± 0.89	0.97 ± 0.88	0.640
The changing of the hematocrit concentration [%]	3.33 ± 3.41	3.13 ± 2.78	2.9 ± 2.89	0.590
Operating time [min]	49.65 ± 17.05	46.00 ± 12.14	44.13 ± 12.71	0.120
Intraoperative blood loss [mL]	721.96 ± 370.06	810.60 ± 556.18	755.52 ± 533.3	0.840
Intraoperative additional hemostatic uterine sutures	9.6% (5)	15.4% (8)	19.2% (10)	0.379
Need for additional uterotonics	21.2% (11)	28.8% (15)	11.5% (6)	0.090
Need for blood transfusion	0% (0)	1.9% (1)	0% (0)	1

Values are reported as mean ± standard deviation; p < 0.05, statistically significant difference

group III, although all groups were comparable in terms of blood loss parameters. According to these parameters, a trend towards decreased intraoperative hemorrhage was observed in group III. However, 21.1% (11) of Group I, 25% (13) of Group II and 26.9% (14) of Group III had blood loss > 1000 mL, while all groups were similar in terms of blood loss (p = 0.78). Group III exhibited the highest proportion of blood loss exceeding 1000 mL. In Group III, only one case necessitated additional surgical intervention, specifically uterine artery ligation, due to intraoperative bleeding. In contrast, only one case in Group II required a blood transfusion. 13 (25%) in Group II and 14 (26,9%) in Group III have PPH while 11 (21.2%) in the control group have PPH (p = 0.6 and p = 0.4, respectively). For the combination of Oxytocin and intrauterine misoprostol, The ARR was 3.8% (95% CI: 20.02–12.33) with RR of 1.18 (95% CI: 0.58–2.39) and NNT 26 (95% CI: 8.1–4.9) and for carbetocin, The ARR was 5.8% (95% CI: 22.15–10.61) with RR of 1.27 (95% CI: 0.63–2.53) and NNT 17 (95% CI: 9.41–4.51) (Tab. 4).

No drug adverse effects were observed in any of the groups, and there were no major postoperative complications in any of the groups. The neonatal outcomes of the groups are shown in Table 3. All three groups showed comparable Apgar scores at 1 and 5 minutes after birth, and there were no significant differences in neonatal intensive care unit (NICU) admissions among the groups.

DISCUSSION

Researchers have generally focused on determining the best choice of either pharmacological or non-pharmacological interventions by achieving favourable uterine contractions during CS, because of the significance of PPH in terms of its mortality and morbidity. Every evaluation of the choices, in terms of efficacy, potential adverse events

Table 3. The neonatal outcomes of the study

Characteristics	Group I (n = 52)	Group II (n = 52)	Group III (n = 52)	p value
Birth weight [g]	3203.37 ± 606.56	3308.65 ± 405.44	3235.87 ± 522.45	0.341
Apgar score at 1 minute	7.9 ± 0.95	7.85 ± 1.22	8.06 ± 1.14	0.390
Apgar score at 5 minute	9.33 ± 0.61	9.35 ± 0.81	9.48 ± 0.72	0.290
NICU admission	11.5% (6)	71.9% (1)	3.8% (2)	0.084

Values are reported as mean ± standard deviation; $p < 0.05$, statistically significant difference; NICU — neonatal intensive care unit

Table 4. Incidence of postpartum hemorrhage

Variables	Group II (n = 52)	Group III (n = 52)
Postpartum hemorrhage	13	14
Relative risk (RR)	1.18 (0.58–2.39)	1.27 (0.63–2.53)
Relative risk reduction (RRR)	18.2% (139.2–41.6%)	27.3% (153.7–36.19%)
Absolute risk reduction (ARR)	3.8% (20.02–12.33%)	5.8% (22.15–10.61%)
Number needed to treat (NNT)	26 (8.1–4.9)	17 (9.41–4.51)
p value	0.642	0.491

and cost-effectiveness, should be beneficial for the management and prevention of PPH. Possible agents used for the prophylaxis of PPH include tranexamic acid, oxytocin, methyloergometrine, misoprostol and carbetocin. Oxytocin is the primary choice of uterotonic medication for preventing and treating uterine atony. Methylergonovine remains the secondary option for uterotonic treatment in preventing and managing PPH [14]. Methylergonovine is a synthetic alkaloid that induces powerful contractions of the myometrium. However, when administered parenterally, especially intravenously, it may lead to transient but significant elevation in blood pressure [15]. In our randomized controlled trial, we focused on the efficacy and potential adverse events of the three most used pharmacological uterotonics (oxytocin, misoprostol, which is highly cost-effective, and carbetocin, which is long acting and single dose) in women who underwent caesarean section, although oxytocin has routinely been suggested as the primary treatment option for the prevention of PPH, because of its efficacy and safety profile.

Oxytocin and the combination of oxytocin plus misoprostol are generally the two most used uterotonic agents in Türkiye. In the daily routine practice of our department, oxytocin is prophylactically used during CS to prevent PPH, as recommended. When an additional uterotonic is needed, we generally use misoprostol as the second agent. Carbetocin seems to be more expensive in Türkiye, compared to oxytocin and misoprostol. Thus, we would like to especially focus on the efficacy of carbetocin, to establish whether it has any superiority over the other drugs for the prevention of PPH. Our results demonstrated that carbetocin has no overall advantage on other alternatives regarding prevention of PPH. Contrary to the literature, we did not report any severe adverse effects related to misoprostol, because we used intrauterine misoprostol, whereas other studies generally used sublingual misoprostol tablets. According to our results, the combination of misoprostol and oxytocin is no more effective than oxytocin alone.

A double-blind randomized controlled study including 263 women evaluated the efficacy and safety of oxytocin, misoprostol and carbetocin for the prevention of PPH. Their results demonstrated that carbetocin was similar to oxytocin (RR 0.41, 95% CI: 0.14–1.25) and superior to misoprostol (RR 0.21, 95% CI: 0.07–0.58) in terms of the prevention of uterine atony during elective CS. Moreover, the requirement for extra uterotonics was found to be less in the carbetocin group when compared to the other groups. They also showed that the ratio of adverse effects, such as abdominal pain resulting from uterine contractions, were lower with carbetocin. In this study, the misoprostol was used as a sublingual 400 µg misoprostol tablet following the caesarean delivery [16] .

The results from misoprostol may be due to the use of sublingual tablets, as well as the use of misoprostol alone, as another trial including 380 women concluded that the combination of misoprostol with oxytocin was as effective as IV carbetocin [17].

The latter trial evaluated the prevention of PPH using a combination of oxytocin infusion and sublingual misoprostol versus IV carbetocin in high-risk women undergoing caesarean delivery. Another randomized controlled trial

including 300 women compared the use of the combination of oxytocin and intrauterine misoprostol versus oxytocin alone in terms of the incidence of PPH in women undergoing elective CS. Their results indicated that the combination of 400 µg intrauterine misoprostol tablets with oxytocin is safe and effective for the prevention of PPH in elective CS delivery (ARR 5.3%, 95% CI: 0.8–10.6, with RR 0.20, 95% CI: 0.05–0.90; 95% CI: 125–9, NNT 19) [12] .

There was a trend towards the use of intrauterine misoprostol to prevent PPH after the publication by Quiroga Díaz et al. [11]. They reported good efficacy of intrauterine misoprostol (800 µg), with few adverse events in the prevention of PPH. A systematic review and meta-analysis including 17 studies (3174 women) assessed the efficacy and safety of use of prophylactic misoprostol to reduce blood loss during either intraoperative or postoperative haemorrhage in women undergoing CS, concluding that the combination of misoprostol with oxytocin appears to be more effective than oxytocin alone, based on a few trials with methodological limitations. It also reported a higher risk of pyrexia and shivering in women who receive misoprostol alone or the combination of misoprostol and oxytocin [18].

A double-blind, randomised, single-centre study including 114 women who underwent non-elective CS under general anaesthetic compared the efficacy of carbetocin versus oxytocin [19].

Their results showed no significant differences regarding the change of haemoglobin concentration, estimated blood loss, the rates of PPH and blood transfusions. Based on this, they concluded that the efficacy of oxytocin and carbetocin is similar for haemoglobin drop, estimated blood loss, additional uterotonics and blood transfusions. They also showed that there was a trend towards the need for additional uterotonics in the carbetocin group, although this was not statistically significant. Finally, they concluded that carbetocin showed no superiority to oxytocin. Furthermore, a double-blinded RCT, which included 180 obese nulliparous women undergoing emergency CS, evaluated the efficacy and safety of carbetocin versus oxytocin to prevent PPH. They showed that carbetocin is more effective than oxytocin, with a similar safety profile, in the prevention of PPH while maintaining adequate uterine contractility in obese nulliparous women undergoing emergency CS [20]. A meta-analysis including seven studies involving 2012 women compared the efficacy of oxytocin and carbetocin to prevent PPH in CS [21]. According to the results of this meta-analysis, the use of carbetocin results in a significant reduction in PPH ($p < 0.009$, RR 0.79, 95% CI: 0.66–0.94), in the need for additional uterotonics ($p < 0.001$, RR 0.57, 95% CI: 0.49–0.65) and in the need for transfusion ($p < 0.002$, RR 0.31, 95% CI: 0.15–0.64) when compared to oxytocin. They concluded that carbetocin is effective in reducing PPH, the need for transfusion and the need for additional uterotonics during CS. Meanwhile, they suggested a locoregional cost-effectiveness analysis before adopting carbetocin in routine prophylaxis, because of the disparity between the cost of oxytocin and the cost of carbetocin. A multicentre, double-blind, RCT from Canada including 694 patients undergoing elective CS assessed the efficacy of carbetocin with oxytocin to prevent uterine atony [22].

They demonstrated that carbetocin appears to be more effective when compared to continuous IV oxytocin infusion and has a similar safety profile.

One limitation of the present study is that there is no group involving misoprostol alone. This is because we would not prophylactically use misoprostol alone to prevent PPH in our department. If we had used misoprostol alone, carbetocin may have been superior, whereas the combination of both drugs (oxytocin and misoprostol) may have produced a comparable effect to the carbetocin. The strength of our study is that it is a RCT with power calculations. Additionally, there are no other current studies comparing carbetocin and intrauterine misoprostol.

CONCLUSIONS

In conclusion, our findings indicate that carbetocin does not exhibit superiority in preventing postpartum hemorrhage in women undergoing cesarean section. Furthermore, a notable difference exists in the cost between oxytocin and carbetocin. Considering its efficacy, affordability, and favorable safety profile, oxytocin remains a highly effective option for preventing postpartum hemorrhage. We recommend maintaining the routine use of oxytocin in cesarean section procedures until substantial evidence of carbetocin's superiority over oxytocin is established. Oxytocin should remain the preferred option until such proof is demonstrated conclusively.

Article information and declarations

Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Ethics

This study was a prospective, randomized, controlled study (NCT05083910) conducted at the Department of Obstetrics and Gynaecology of Medical Faculty of Bezmialem Vakif University between July 2021 and January 2022.

Conflict of interest

The authors declare that they have no conflict of interest.

REFERENCES

1. Say L, Chou D, Gemmill A, et al. Global causes of maternal death: a WHO systematic analysis. Lancet Glob Health. 2014; 2(6): e323–e333, doi: 10.1016/S2214-109X(14)70227-X, indexed in Pubmed: 25103301.
2. Wang CY, Chen YC, Lin CH, et al. Successful treatment with recombinant blood factor VIIa in severe postpartum hemorrhage-induced disseminated intravascular coagulation. Taiwan J Obstet Gynecol. 2016; 55(2): 301–302, doi: 10.1016/j.tjog.2014.11.027, indexed in Pubmed: 27125421.
3. Alkış İ, Karaman E, Han A, et al. The fertility sparing management of postpartum hemorrhage: A series of 47 cases of Bakri balloon tamponade. Taiwan J Obstet Gynecol. 2015; 54(3): 232–235, doi: 10.1016/j.tjog.2014.03.009, indexed in Pubmed: 26166332.
4. Purwosunu Y, Sarkoen W, Arulkumaran S, et al. Control of Postpartum Hemorrhage Using Vacuum-Induced Uterine Tamponade. Obstet Gynecol. 2016; 128(1): 33–36, doi: 10.1097/AOG.0000000000001473, indexed in Pubmed: 27275795.
5. World Health Organization WHO recommendations for the prevention and treatment of postpartum haemorrhage. Geneva (Switzerland), 2012.
6. Mavrides E, Allard S, Chandraharan E, et al. Prevention and management of postpartum haemorrhage: Green-top Guideline No 52. BJOG. 2016; 358: 106–149.
7. Sentilhes L, Vayssière C, Deneux-Tharaux C, et al. Postpartum hemorrhage: guidelines for clinical practice from the French College of Gynaecologists and Obstetricians (CNGOF): in collaboration with the French Society of Anesthesiology and Intensive Care (SFAR). Eur J Obstet Gynecol Reprod Biol. 2016; 198: 12–21, doi: 10.1016/j.ejogrb.2015.12.012, indexed in Pubmed: 26773243.
8. Rath W. Prevention of postpartum haemorrhage with the oxytocin analogue carbetocin. Eur J Obstet Gynecol Reprod Biol. 2009; 147(1): 15–20, doi: 10.1016/j.ejogrb.2009.06.018, indexed in Pubmed: 19616358.
9. Leduc D, Senikas V, Lalonde AB, et al. CLINICAL PRACTICE OBSTETRICS COMMITTEE. Active management of the third stage of labour: prevention and treatment of postpartum hemorrhage. J Obstet Gynaecol Can. 2009; 31(10): 980–993, doi: 10.1016/S1701-2163(16)34329-8, indexed in Pubmed: 19941729.
10. Hofmeyr GJ, Gülmezoglu AM. Misoprostol for the prevention and treatment of postpartum haemorrhage. Best Pract Res Clin Obstet Gynaecol. 2008; 22(6): 1025–1041, doi: 10.1016/j.bpobgyn.2008.08.005, indexed in Pubmed: 18786863.
11. Quiroga DR, Cantú MR, Tello GHE, et al. Misoprostol intrauterino para la prevención de la hemorragia postcesárea [Intrauterine misoprostol for the prevention of bleeding cesarean]. Ginecol Obstet Mex. 2009; 77(10): 469–474.
12. Alalfy M, Lasheen Y, Elshenoufy H, et al. The efficacy of intrauterine misoprostol during cesarean section in prevention of primary PPH, a randomized controlled trial. J Matern Fetal Neonatal Med. 2020; 33(9): 1459–1465, doi: 10.1080/14767058.2018.1519796, indexed in Pubmed: 30176758.
13. Takmaz T, Ozcan P, Sevket O, et al. Less Blood Loss by Earlier Oxytocin Infusion in Cesarean Sections? A Randomized Controlled Trial. Z Geburtshilfe Neonatol. 2020; 224(5): 275–280, doi: 10.1055/a-1108-2017, indexed in Pubmed: 32120445.
14. Manrique Muñoz S, Munar Bauzà F, Francés González S, et al. [Update on the use of uterotonic agents]. Rev Esp Anestesiol Reanim. 2012; 59(2): 91–97, doi: 10.1016/j.redar.2012.02.019, indexed in Pubmed: 22480555.
15. Moertl MG, Friedrich S, Kraschl J, et al. Haemodynamic effects of carbetocin and oxytocin given as intravenous bolus on women undergoing caesarean delivery: a randomised trial. BJOG. 2011; 118(11): 1349–1356, doi: 10.1111/j.1471-0528.2011.03022.x, indexed in Pubmed: 21668768.
16. Elbohoty AEH, Mohammed WE, Sweed M, et al. Randomized controlled trial comparing carbetocin, misoprostol, and oxytocin for the prevention of postpartum hemorrhage following an elective cesarean delivery. Int J Gynaecol Obstet. 2016; 134(3): 324–328, doi: 10.1016/j.ijgo.2016.01.025, indexed in Pubmed: 27350226.
17. Elgafor el Sharkwy IA. Carbetocin versus sublingual misoprostol plus oxytocin infusion for prevention of postpartum hemorrhage at cesarean section in patients with risk factors: a randomized, open trail study. Arch Gynecol Obstet. 2013; 288(6): 1231–1236, doi: 10.1007/s00404-013-2896-7, indexed in Pubmed: 23689739.
18. Conde-Agudelo A, Nieto A, Rosas-Bermudez A, et al. Misoprostol to reduce intraoperative and postoperative hemorrhage during cesarean delivery: a systematic review and metaanalysis. Am J Obstet Gynecol. 2013; 209(1): 40.e1–40.e17, doi: 10.1016/j.ajog.2013.03.015, indexed in Pubmed: 23507545.
19. Whigham CA, Gorelik A, Loughnan TE, et al. Carbetocin versus oxytocin to reduce additional uterotonic use at non-elective caesarean section: a double-blind, randomised trial (.). J Matern Fetal Neonatal Med. 2016; 29(23): 3866–3869, doi: 10.3109/14767058.2016.1149564, indexed in Pubmed: 26940081.
20. El Behery MM, El Sayed GA, El Hameed AA, et al. Carbetocin versus oxytocin for prevention of postpartum hemorrhage in obese nulliparous women undergoing emergency cesarean delivery. J Matern Fetal Neonatal Med. 2016; 29(8): 1257–1260, doi: 10.3109/14767058.2015.1043882, indexed in Pubmed: 25946576.
21. Voon HY, Suharjono HN, Shafie AA, et al. Carbetocin versus oxytocin for the prevention of postpartum hemorrhage: A meta-analysis of randomized controlled trials in cesarean deliveries. Taiwan J Obstet Gynecol. 2018; 57(3): 332–339, doi: 10.1016/j.tjog.2018.04.002, indexed in Pubmed: 29880160.
22. Dansereau J, Joshi AK, Helewa ME, et al. Double-blind comparison of carbetocin versus oxytocin in prevention of uterine atony after cesarean section. Am J Obstet Gynecol. 1999; 180(3 Pt 1): 670–676, doi: 10.1016/s0002-9378(99)70271-1, indexed in Pubmed: 10076146.

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Depression and anxiety in patients with pelvic floor disorders

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ABSTRACT

Pelvic floor disorders are very common health problems in adult women affecting their quality of life in many aspects. One of them, still poorly recognised, is depression as well as anxiety. As the main goal of treatment is achievement of improvement of life quality we have to be aware of the incidence and severity of mood disorders in urogynecological patients. It is very important to be sure whether treatment of main disease is enough to solve depression and anxiety or we have to cope with them separately. The review sums up current knowledge on that very important topic.

Keywords: depression; anxiety; stress urinary incontinence; overactive bladder syndrome; pelvic organ prolapse

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INTRODUCTION

Depression and anxiety stand for the biggest percentage of mental illness in the world, and is recognized as the rising problem in global health [1]. Very often it is connected with disturbances in social functioning, poor self-esteem and generates costs as far as micro and macroeconomics expenditure are concerned. The frequency of depressive symptoms in older population (over 65 years old) is estimated as to be over 40% [2]. There are known risk factors for developing depression, among others cardiometabolic disorders, obesity, metabolic syndrome, type 2 diabetes, and CVD (cardiovascular disease) [3–5].

Pelvic floor disorders are known as serious risk factor for lowering quality of life in many aspects, and it is postulated that they may be a cause of depression, anxiety as well as sleep disorders. The incidence of pelvic floor disorders in women population is very wide and vary from 30–50% as far as stress urinary incontinence is concerend, 30% with overactive bladder syndrome (OAB) and up to 25% with pelvic organ prolaps in women over their 50s. Therefore, the problem of mental health similarly to other aspects of lowering of quality of life, should be taken into concideration during discussion on the importance of urogynecological treatment, education and the social awarenes in this field.

THE CURRENT KNOWLEDGE ON THE CONNECTION BETWEEN PELVIC FLOOR DISORDERS, ANXIETY AND DEPRESSION

The aim of the review is to summerize the current knowledge on the influence of pelvic floor disorders on mental health problems as well as to recognize whether there are evidences of influence of the uroginecological treatment on above problems.

The most commonly occurring pelvic floor disorders are: overactive bladder, stress urinary incontinence, pelvic organ prolapse and combinations of the above.

Overactive bladder syndrome (OAB) is syndrome characterized three symptoms: urgency, frequent micturition during active hours and nocturia, with or without urge incontinence. OAB symptoms increase with advancing age. The incidence of this condition is estimated In the United States at over 35% of women aged 75 or older [6]. Overactive bladder symptom influence quality of life, professional performance, family and sexual lives [7].

In systematic meta-analysis of Melotti et al. [8] the authors showed an existance of correlation between OAB symptoms psychiatric disorders such as depression and anxiety. Both sexes suffered from simillar severity of depression while men were more frequently diagnosed with

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OAB related anxiety. The results of above paper should get attention of medical professionalist to coexistance of those problems and be aware of potential need for psychiatric intervention.

In cross-sectional population study conducted by Coyne in UK, Sweden and USA similar results were shown. The prevalence of bothering OAB was 22.5% and 33.7% for women in the UK and Sweden, and in the same time patients with OAB were significantly more likely to seek treatment, undergo psychiatric therapy for anxiety and depression compared healthy subjects [9].

In another Melotti's et al. study [10] 274 women with confirmed diagnose of OAB underwent questionnaire survey [International Consultation on Incontinence Questionnaire-Overactive Bladder (ICIQ-OAB), the Beck Depression Inventory (BDI), and the Beck Anxiety Inventory (BAI)]. The authors showed that severe or moderate depressive symptoms were appeared in 59.8% of patients and severe or moderate anxiety was cinfirmed in 62.4%. High scores of depression and anxiety were correlated with OAB severity. Very important finding was that the patients with severe depression had higher nocturia score than those with mild depressive symptoms. Authors also showed that patients with urge incontinence had higher depression score as compared to those with milder leakages ($p = 0.0261$). Similar findings were described as far as anxiety was concerned. Patients diagnosed with severe anxiety had more frequent night micturitions than those without anxiety and women with moderate anxiety had higher urgency incontinence score than with minimal anxiety [10]. Above study indicated that there are two major factors that matter in depression and anxiety development in case of OAB syndrome, that is nocturia and severe and frequent leakage of urine.

In Jacomo et al. [11] study 260 women with a clinical diagnosis of OAB were examined. It was observed that 50% had mild depression. The authors divided the study group to the cases with and without history of previous gynaecological surgeries. They confirmed that women with OAB and with a history of gynaecological surgery were 1.08 times more likely to demonstrate depression symptoms as compared to women who had ever been operated for gynaecological diseases, adding therefore previous medical intervention as an additional risk factor for depression in OAB patients.

Once the connection between OAB and depression and anxiety has been confirmed the influence of the comorbidity of them on medical cost was analyzed in Shiozawa study [12]. In case-control cohort study authors compared costs, professional performance among women with depression and OAB (case) and patients with depression without OAB (control). Emergency room (ER) visits, and percentage of using antidepressive medications were statistically higher (all $p < 0.05$) among OAB patients. Patients with co-existance of OAB and depression also generated 13% higher total costs ($p < 0.0001$) and a higher seak leave days compared to controls (21.3% vs 16.9%; $p < 0.0001$) confirming that psychiatric disorders stand for a growing costs for the system in patients with incontinence [12].

Current studies additionally focus on the influence of treatment of OAB on the improvement of *lower urinary tract symptoms* (LUTS) and depression in the same time. Kim et al. [13] performed a prospective study of patients with overactive bladder. The examined patients were divided into two groups (with and without depressive symptoms) based on the Beck Depression Inventory (BDI) questionnaire. Then, 5 mg of solifenacin was prescribed for three months. In the group with depression statistically significant decreases in the BDI score were observed in 12-week period. The authors concluded that successful treatment of OAB symptoms with anti-muscarinic drugs may improve depression and quality of life.

The study conducted by Ahn et al. [14] focused on rarely examined aspect of OAB patient's mental health. Authors showed that patients with OAB were more likely to present obsessive symptoms than controls on the Korean version of the Maudsley Obsessional-Compulsive Inventory Questionnaire total score ($p = 0.006$). They postulated therefore that obsessive-compulsive symptoms may be an co-existing clinical problem OABs patients. Moreover, the authors shoved the correlation between the severity of obsessive-compulsive symptoms and the severity of overactive bladder syndrome we should to pay more attention to psychiatric status of overactive bladder syndrome patients.

As shown above the overactive bladder syndrom the association with depression and anxiety is well documented.

Nevertheless, we cannot forget that also other pelvic floor disorders may have an influence on anxiety and depressive disorders. There are quite a few reports concerining the topic as far as stress urinary inconinence and pelvic organ prolapse are concerned.

Most authors focus on the stress urinary incontinence as a risk factor for depression in postpartum period as it is frequently recognized condition in young mothers. Jurascova et al. [15] tried to find risk factors in the Czech population for incidence of stress urinary incontinence (SUI) and postnatal depression (PD). Patients completed questionnaires six weeks and six months after birth. During the first six months after birth, 17.6% developed SUI and 17.3% displayed signs of PD. Severity of stress urinary incontinence at six weeks was not very intense but correlated with onset of postnatal depression after six months. On the other hand, PD at six weeks was not correlated to the appearance of SUI at six months. The study suggests that both directions of stress

urinary incontinence and postpartum depression correlations exists but there is a need for further studies.

There are even fewer reports on above problem in elderly or middle-aged women who suffer from SUI and the strength of the associations varies widely. Norwegian authors conducted a cross-sectional population-based survey study, and analyzed questionnaire data on UI, depression and anxiety from 5,321 women between 40 and 44 years. Among women with UI, the adjusted OR for depression was 1.64 (95% CI, 1.32–2.04) and for anxiety 1.59 (95% CI, 1.36–1.86) compared with women without UI. The authors noticed that UI was associated with both anxiety and depression it was stronger associated for mixed and urgency UI than for SUI [16]. Similar results were obtained by the same research group on the basis of over 16000 patients inquire [17]. In the study collecting data from patients who turned to eHealth with incontinence problems the prevalence of anxiety and depression in women with SUI was 12.4% and 3.2% respectively as in women with MUI/UUI, 13.8% had anxiety and 10.6% had depression. In multivariate analyses, the odds ratio of having depression was 4.2 (95% CI = 1.4–12.3) for women with MUI/UUI compared with SUI when controlling for other risk factors [18]. On the contrary in the Siddiqui [19] study there were no correlation? between the existence of urinary leakage, depression and sleep disorders but in cases with incontinence the severity of depression was correlated with the severity of incontinence.

In the Polish study, the authors also showed the correlation between stress urinary incontinence, depression and anxiety. The observations revealed that 33.3% of patients showed significant levels of depression before SUI surgery. After 12 months the symptoms of depression were present in smaller number of subjects, i.e., 11.7% and anxiety was present in 13.3% of the entire group. The results may indicate that SUI itself may be a cause of mood disorders and its successful treatment may reduce the depressive symptoms [20].

Similar results were obtained by the Japanese authors [21]. They showed that at baseline, proportions of the patients with anxiety and depression and SUI were 21.6% (22/102) and 24.5% (25/102), respectively. The median ICIQ-SF (International Consultation on Incontinence Questionnaire--Urinary Incontinence Short Form) score, HADS (Hospital Anxiety Depression Scale) — Anxiety score, and HADS--Depression score were significantly higher after 12 months after surgery as compared to pre-operative period. Improvement od ICIQ-SF and depressive symptoms score in HADS were significantly correlated after one-year observation.

Another group of researchers showed that surgery in SUI gives better results also as far as depression and anxiety is concerned than the pelvic floor training. In a prospective longitudinal study, patients with confirmed/diagnosed SUI (no 32) were examined with standardized questionnaires (sociodemographic data sheet, FACT-G [sociodemographic data sheet, Functional Assessment of Cancer Therapy — General (FACT-G), Incontinence Quality of Life Questionnaire (I-QOL), HADS] before and two months after surgery. Women in the conservative group [21] underwent eight, once-weekly supervised pelvic floor training exercises. The authors showed that SUI surgery was more efficient as physiotherapy as far as anxiety and quality of life was concerned [22].

Another very interesting problem that has still been poorly recognized is the correlation or co-existence between pelvic organ prolapse (POP), depression and anxiety. Still there is no consensus on the relationship between those problems.

There are few studies examining co-existence depression and/or anxiety with pelvic organ prolapse evaluating impact of this comorbidity on quality of life and the outcomes in postoperative period. In one of them authors compared patients with bothering POP and healthy controls. Patients were examined with the Pelvic Floor Impact Questionnaire (PFIQ), Pelvic Floor Distress Inventory, and the Patient Health Questionnaire-9 (PHQ-9) at before and six months post-operatively. The authors showed that POP patients had depression five times more frequent than women without pelvic organ symptoms. In addition, patients with depression had higher PFIQ scores showing their worse quality of life. Surgery also improved PHQ-9 scores. The authors therefore concluded that depressive symptoms are common in women with prolapse with tendency to regression following surgical treatment. The important remark is that the patients with depression seems to assess their symptoms as more bothering than subjects without POP [23].

Pizzarro-Berdichevsky et al. [24] in order to find possible correlation divided POP patients into two groups: with and without depression. All patients underwent physical examination: POP quantification (POP-Q), pelvic ultrasound (US), voiding diaries, stress test, pad test as well as inventory questionnaires (Pelvic Floor Distress Inventory [PFDI-20], Prolapse QoL [P-QoL] and the Goldberg Health Questionnaire [GHQ-12]). GHQ-12 was positive in 47 (51.6%) patients. The authors showed that patients with POPQ have similar GHQ-12 scores as compared to healthy subjects. However, GHQ-12 was positively correlated with PFDI-20 GHQ-12 was shown as an strong risk factor for lower quality of life. Similarly, to previously cited authors they concluded that patients with depression or anxiety interpret their symptoms differently, usually as more bothering [24].

Larouche et al. in prospect cohort study, investigated the role of succesful POP surgery as a factor influencing depresion and axiety in operated subjects. Patients underwent questionnaire survey before and six weeks after surgery (Beck Depression and Beck Anxiety Inventories, Pain Catastrophizing Scale, Pelvic Floor Distress Inventory, Pelvic Floor Impact Questionnaire). The first observations

showed that depression and anxiety symptoms were not severe in examined group but the final analysis confirmed that surgery caused improvement in preoperative scores for Beck Anxiety Inventory, Pelvic Floor Distress Inventory, and Pelvic Floor Impact Questionnaire [25].

In Collin's study evaluating the influence of anxiety trait on the subjective result of the POP reconstruction, patients underwent examination using the Spielberger State-Trait Anxiety Inventory and the Pelvic Floor Distress Inventory 20 before and over three months after the surgrey. Authors showed that the anxiety trait was not an independent risk factor for wors subjective results of POP surgery. Unfortunately, the authors did not analyse the influence of surgery success rate with the anxiety improvement, nevertheless the result show above patients are not at risk of worsening the anxiety symptoms [26].

CONCLUSIONS

The analysis of current literature indicates the connection between pelvic floor disorder, depression and anxiety. It shows the interpenetration of symptoms, suggests the positive influence of proper treatment of urogynegological disorders on mental health, nevertheless does not show the whole picture of the problem. Therefore, there is a need for further studies and analysis as the improvement of quality of live is the major goal in pelvic floor disorders treatment.

Article information and declarations

Conflict of interest

All authors declare no conflict of interest.

REFERENCES

1. GBD 2019 Diseases and Injuries Collaborators. Global burden of 369 diseases and injuries in 204 countries and territories, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019. Lancet. 2020; 396(10258): 1204–1222, doi: 10.1016/S0140-6736(20)30925-9, indexed in Pubmed: 33069326.
2. Zhao Y, Hu Y, Smith JP, et al. Cohort profile: the China Health and Retirement Longitudinal Study (CHARLS). Int J Epidemiol. 2014; 43(1): 61–68, doi: 10.1093/ije/dys203, indexed in Pubmed: 23243115.
3. Pan A, Keum N, Okereke OI, et al. Bidirectional association between depression and metabolic syndrome: a systematic review and meta-analysis of epidemiological studies. Diabetes Care. 2012; 35(5): 1171–1180, doi: 10.2337/dc11-2055, indexed in Pubmed: 22517938.
4. Mezuk B, Eaton WW, Albrecht S, et al. Depression and type 2 diabetes over the lifespan: a meta-analysis. Diabetes Care. 2008; 31(12): 2383–2390, doi: 10.2337/dc08-0985, indexed in Pubmed: 19033418.
5. Lippi G, Montagnana M, Favaloro EJ, et al. Mental depression and cardiovascular disease: a multifaceted, bidirectional association. Semin Thromb Hemost. 2009; 35(3): 325–336, doi: 10.1055/s-0029-1222611, indexed in Pubmed: 19452408.
6. Stewart WF, Van Rooyen JB, Cundiff GW, et al. Prevalence and burden of overactive bladder in the United States. World J Urol. 2003; 20(6): 327–336, doi: 10.1007/s00345-002-0301-4, indexed in Pubmed: 12811491.
7. Raquel H, Alves AT, Garcia PA, et al. Risk factors for mild depression in older women with overactive bladder syndrome — A cross sectional study. PLoS One. 2020; 15(1): e0227415, doi: 10.1371/journal.pone.0227415.
8. Melotti IG, Juliato CR, Coelho SC, et al. Is there any difference between depression and anxiety in overactive bladder according to sex? A systematic review and meta-analysis. Int Neurourol J. 2017; 21(3): 204–211, doi: 10.5213/inj.1734890.445, indexed in Pubmed: 28954462.
9. Coyne KS, Sexton CC, Kopp ZS, et al. The impact of overactive bladder on mental health, work productivity and health-related quality of life in the UK and Sweden: results from EpiLUTS. BJU Int. 2011; 108(9): 1459–1471, doi: 10.1111/j.1464-410X.2010.10013.x, indexed in Pubmed: 21371240.
10. Melotti IG, Juliato CR, Tanaka M, et al. Severe depression and anxiety in women with overactive bladder. Neurourol Urodyn. 2018; 37(1): 223–228, doi: 10.1002/nau.23277, indexed in Pubmed: 28407347.
11. Jacomo RH, Alves AT, Garcia PA, et al. Risk factors for mild depression in older women with overactive bladder syndrome — A cross sectional study. PLoS One. 2020; 15(1): e0227415, doi: 10.1371/journal.pone.0227415, indexed in Pubmed: 31999718.
12. Shiozawa A, Hopson S, Fuldeore R, et al. Increased healthcare resource utilization and direct and indirect costs in patients with depression and comorbid overactive bladder: evidence from a retrospective, matched case-control cohort analysis. Adv Ther. 2020; 37(11): 4599–4613, doi: 10.1007/s12325-020-01485-w, indexed in Pubmed: 32910419.
13. Kim KS, Moon HS. Antimuscarinic agent treatment affecting patient-reported outcomes in overactive bladder syndrome with depressive symptoms. Int Neurourol J. 2016; 20(4): 349–355, doi: 10.5213/inj.1624678.339, indexed in Pubmed: 28043114.
14. Ahn KS, Hong HP, Kweon HJ, et al. Correlation between overactive bladder syndrome and obsessive compulsive disorder in women. Korean J Fam Med. 2016; 37(1): 25–30, doi: 10.4082/kjfm.2016.37.1.25, indexed in Pubmed: 26885319.
15. Jurášková M, Piler P, Kukla L, et al. Association between stress urinary incontinence and depressive symptoms after birth: the czech ELSPAC study. Sci Rep. 2020; 10(1): 6233, doi: 10.1038/s41598-020-62589-5, indexed in Pubmed: 32277088.
16. Felde G, Bjelland I, Hunskaar S. Anxiety and depression associated with incontinence in middle-aged women: a large Norwegian cross-sectional study. Int Urogynecol J. 2012; 23(3): 299–306, doi: 10.1007/s00192-011-1564-3, indexed in Pubmed: 22068320.
17. Felde G, Ebbesen MH, Hunskaar S. Anxiety and depression associated with urinary incontinence. A 10-year follow-up study from the Norwegian HUNT study (EPINCONT). Neurourol Urodyn. 2017; 36(2): 322–328, doi: 10.1002/nau.22921, indexed in Pubmed: 26584597.
18. Hansson Vikström N, Wasteson E, Lindam A, et al. Anxiety and depression in women with urinary incontinence using E-health. Int Urogynecol J. 2021; 32(1): 103–109, doi: 10.1007/s00192-020-04227-2, indexed in Pubmed: 32095954.
19. Zalewski M, Kołodyńska G, Fink-Lwow F, et al. The relationship between anxiety and depression levels and general health status before and 12 months after SUI treatment in postmenopausal women from the lower silesian population. Int J Environ Res Public Health. 2022; 19(9), doi: 10.3390/ijerph19095156, indexed in Pubmed: 35564551.
20. Siddiqui NY, Wiseman JB, Cella D, et al. LURN. Mental health, sleep and physical function in treatment seeking women with urinary incontinence. J Urol. 2018; 200(4): 848–855, doi: 10.1016/j.juro.2018.04.076, indexed in Pubmed: 29730202.
21. Kinjo M, Masuda K, Nakamura Yu, et al. Effects on depression and anxiety after mid-urethral sling surgery for female stress urinary incontinence. Res Rep Urol. 2020; 12: 495–501, doi: 10.2147/RRU.S270915, indexed in Pubmed: 33117749.
22. Innerkofler PC, Guenther V, Rehder P, et al. Improvement of quality of life, anxiety and depression after surgery in patients with stress urinary incontinence: results of a longitudinal short-term follow-up. Health Qual Life Outcomes. 2008; 6: 72, doi: 10.1186/1477-7525-6-72, indexed in Pubmed: 18823552.
23. Ghetti C, Lowder JL, Ellison R, et al. Depressive symptoms in women seeking surgery for pelvic organ prolapse. Int Urogynecol J. 2010; 21(7): 855–860, doi: 10.1007/s00192-010-1106-4, indexed in Pubmed: 20333505.
24. Pizarro-Berdichevsky J, Hitschfeld MJ, Pattillo A, et al. Association between pelvic floor disorder symptoms and QoL scores with depressive symptoms among pelvic organ prolapse patients. Aust N Z J Obstet Gynaecol. 2016; 56(4): 391–397, doi: 10.1111/ajo.12467, indexed in Pubmed: 27135639.
25. Larouche M, Brotto LA, Koenig NA, et al. Depression, anxiety, and pelvic floor symptoms before and after surgery for pelvic floor dysfunction. Female Pelvic Med Reconstr Surg. 2020; 26(1): 67–72, doi: 10.1097/SPV.0000000000000582, indexed in Pubmed: 29688899.
26. Collins AF, Doyle PJ, Duecy EE, et al. Do anxiety traits predict subjective short-term outcomes following prolapse repair surgery? Int Urogynecol J. 2019; 30(3): 417–421, doi: 10.1007/s00192-018-3734-z, indexed in Pubmed: 30116845.

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A rare case of uniparental isodisomy of chromosome 7 without phenotypic anomalies

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ABSTRACT

Uniparental disomy (UPD) is a well-known epigenomic anomaly with both copies of a homologous pair of chromosomes (or part thereof) inherited from the same parent. Unlike numerical or structural chromosomal aberrations, UPD has no effects on chromosome number or structure, thereby escaping cytogenetic detection. However, UPD detection could be performed by the microsatellite analysis or SNP-based chromosomal microarray analysis (CMA) method. UPD may cause diseases in humans by disrupting normal allelic expression of genes undergoing genomic imprinting, homozygosity in case of autosomal recessive traits, or mosaic aneuploidy. Here we present the first case of parental UPD for chromosome 7 with a normal phenotype.

Keywords: uniparental disomy; chromosomal microarray analysis; prenatal diagnosis

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A 38-year-old gravida 2 para 0 female had amniocentesis at pregnancy week 19 due to advanced maternal age. Cytogenetic assessment of amniocyte culture showed a normal karyotype, 46, XY. Chromosomal microarray analysis (CMA) assessing uncultured amniocytes was carried out with the Affymetrix CytoScan 750 K chip that comprises 200k SNP markers and 550k non-polymorphic. CMA revealed a 7.1-Mb uniparental isodisomy of chromosome 7, arr 7p22.3p22.1(44,166–7,152,131) × 2 hmz [GRCh37(hg19)] (Fig. 1) [1, 2]. Both parents had normal karyotypes and CMA findings. Microsatellite analysis indicated uniparental disomy (UPD) of chromosome 7 from the father. Laboratory findings of both parents were unremarkable. Ultrasound revealed the absence of facial dysmorphism or intrauterine growth restriction (fetal weight approximating 650 g and 1600 g at pregnancy weeks 24 and 30, respectively, with abdominal circumferences of 19.4 and 25.7 cm, head circumferences of 21.8 and 27.8 cm, femur lengths of 4.2 and 5.6 cm, and fetal heart rates of 150 and 145 bpm, respectively) [3]. Following genetic counseling, whole-exome sequencing (WES) was carried out to examine uncultured amniocytes. A Novaseq6000 platform (Illumina, USA), in the 150 bp pair-end sequencing mode, was utilized to sequence genomic DNA samples from the family members. The human reference genome (hg38/GRCh38) was utilized for aligning reads, with the Burrows-Wheeler Aligner tool. WES showed no homozygous mutations of reported recessive pathogenic genes for inherited diseases on chromosome 7p22. The parents opted for pregnancy continuation. At pregnancy week 39, a 3450 g boy was born *via* natural delivery, with Apgar scores of 9/9/10. He underwent full physical examination with no remarkable findings. At 36 months, he showed normal development (Intelligence Quotient, 112; weight, 14.8 kg; height, 98 cm; head circumference, 50.1 cm).

Maternal UPD of chromosome 7 is associated with Russell-Silver syndrome, which features pre- and post-natal growth retardation, macrocephaly and limb, body, and/or facial asymmetries [4]. Paternal UPD of chromosome 7 is extremely rare, with only seven cases reported so far [5]. Four of the latter cases were associated with autosomal-recessive diseases likely associated with growth retardation, two with an overgrowth phenotype, and one with cystic fibrosis and

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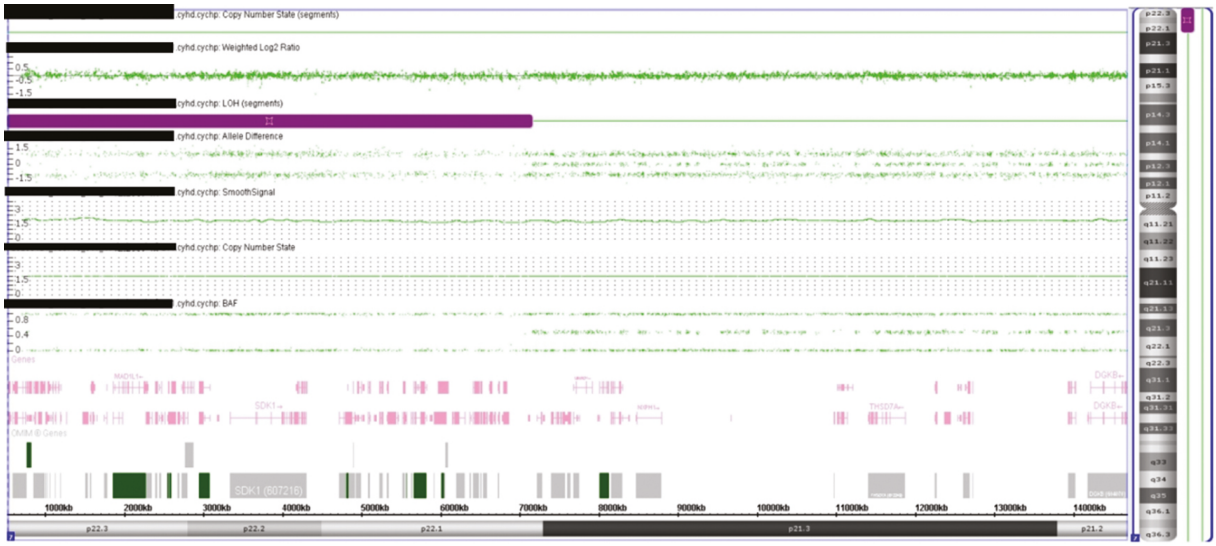

Figure 1. Uniparental isodisomy of chromosome 7, arr 7p22.3p22.1 (44,166–7,152,131) × 2 hmz [GRCh37(hg19)]

normal growth [5]. The present patient represents the first case of UPD of chromosome 7 with a normal phenotype.

UPD may cause several clinical phenotypes because of the homozygosity of recessive mutations or abnormal imprinting patterns [1]. Imprinting-related diseases affect epigenetic regulation and DNA methylation as well as histone modifications [5]. The broad utilization of the microsatellite analysis and SNP-based CMA assay has promoted UPD detection [2]. For most chromosomes, UPD causes no symptoms. However, for chromosomes 6, 7, 11, 14, 15 and 20, parent-of-origin or imprinting changes in gene expression exist in case of UPD, likely causing phenotypic anomalies [6]. Multiple suspected recessive pathogenic genes involved in inherited diseases are found on chromosome 7p22, including FAM20C, LFNG, and BRAT1. In the current boy, CMA and WES revealed no pathogenic mutations or homozygous recessive pathogenic genes.

Overall, we describe the first case of paternal UPD of chromosome 7 with no phenotypic anomaly.

Article information and declarations

Ethics statement

This research had approval from the Ethics Committee of Shiyan Renmin Hospital. The patient's guardians provided informed consent to the study.

Conflicts of interest

There are no conflicts of interest relevant of this article.

REFERENCES

1. Robinson WP. Mechanisms leading to uniparental disomy and their clinical consequences. Bioessays. 2000; 22(5): 452–459, doi: 10.1002/(SICI)1521-1878(200005)22:5<452::AID-BIES7>3.0.CO;2-K, indexed in Pubmed: 10797485.
2. Eggermann T. Prenatal detection of uniparental disomies (UPD): intended and incidental finding in the era of next generation genomics. Genes (Basel). 2020; 11(12), doi: 10.3390/genes11121454, indexed in Pubmed: 33287348.
3. Oğlak SC, Bademkıran MH, Obut M. Predictor variables in the success of slow-release dinoprostone used for cervical ripening in intrauterine growth restriction pregnancies. J Gynecol Obstet Hum Reprod. 2020; 49(6): 101739, doi: 10.1016/j.jogoh.2020.101739, indexed in Pubmed: 32251738.
4. Zhang C, Hao S, Zhang Q, et al. Maternal UPD of chromosome 7 in a patient with Silver-Russell syndrome and Pendred syndrome. J Clin Lab Anal. 2020; 34(9): e23407, doi: 10.1002/jcla.23407, indexed in Pubmed: 32666542.
5. Nakamura A, Muroya K, Ogata-Kawata H, et al. A case of paternal unipaternal isodisomy for chromosome 7 associated with overgrowth. J Med Genet. 2018; 55(8): 567–570, doi: 10.1136/jmedgenet-2017-104986, indexed in Pubmed: 29455159.
6. Del Gaudio D, Shinawi M, Astbury C, et al. ACMG Laboratory Quality Assurance Committee. Diagnostic testing for uniparental disomy: a points to consider statement from the American College of Medical Genetics and Genomics (ACMG). Genet Med. 2020; 22(7): 1133–1141, doi: 10.1038/s41436-020-0782-9, indexed in Pubmed: 32296163.

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Optimization of the cosmetic appearance of skin scar after caesarean section — part I: obstetric practice

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ABSTRACT

Caesarean section (CS) is a surgical way of child delivery by cutting the abdomen and uterus. Although compared to natural childbirth, it carries a greater risk of complications, the percentage of performed cuts is still increasing. The consequence of this procedure is the surgical skin scar. The appearance of this scar depends on many factors, including appropriate pre- and intraoperative procedure, operator skills and experience. The aim of the work is to present actions aimed at increasing the aesthetics of the skin scar after CS including pre-, intra- and postoperative procedures.

Keywords: skin scar; caesarean section; wound healing

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INTRODUCTION

The surgical wound after a caesarean section is a cut wound, leaving a linear scar. Initially, a sterile wound is surgically sutured with edges of the wound placed close together, healing by primary intention. Wounds with infection or significant tissue loss heal by secondary intention, resulting in larger scars. Scars differ in appearance and structure from skin, and changes in their appearance reflect remodeling and maturation processes. Immature scars are characterized by a disorganized collagen fiber system and the presence of blood vessels (up to 6 months after injury). They are red, slightly raised scars. Mature scars are characterized by a pale color (usually lighter than the surrounding tissue), lack of pigmentation, lack of hair, and less elasticity (replacement of type III collagen with type I collagen — thicker fibers arranged in an orientation corresponding to the lines of skin tension). The maturation process of scars leads to a significant increase in mechanical strength. It can last up to 12 months after injury or even up to 2 years. Despite these intense remodeling processes, scars never reach the strength of unharmed skin [1, 2]. Maturation disorders can lead to uncontrolled scar growth, which becomes hard, thickened, less elastic and strongly reddened (keloid, hypertrophic scar) or lack of filling the entire tissue defect (the bottom of the scar lies below the skin surface — atrophic scar). Such forms of scars not only disfigure, but can also provoke pain, burning and can lead to body deformities. Women with hypertrophic skin scares and depressed hypopigmented scars are more likely to have adhesions in the abdominal region [3, 4]. The process of proper wound healing depends on many factors: the patient's age, nutritional status, the presence of diabetes (weakened expression of cytokines, delayed epithelialization), the presence of obesity [healing disorders with a body mass index (BMI) > 30–35 kg/m^2 or subcutaneous tissue thickness > 3 cm], smoking, individual tendencies to keloid scars. Factors that are independent of the patient include the technique used for the procedure, the duration of the procedure, and postoperative care that includes wound care [5, 6].

Disturbed wound healing after CS can be result of partial or total wound dehiscence, hematoma within the wound, tissue necrosis due to ischemia, increased abdominal pressure or wound infection. A common complication that significantly affects cosmetic appearance of the scar is surgical site infection (SSI). This results in abnormal wound healing, often accompanied by separation of wound edges. It prolongs hospitalization and can be the cause of re-suturing the wound. There are significant differences in the frequency of

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SSI after CS (1.8–11.3% even up to 15%), as well as wound dehiscence (0.4–1.2%) [2]. Based on 3-year observations conducted in five Polish hospitals, the frequency of SSI was determined to be 0.5% (differences between facilities ranging from 0.1% to 1.8%), with a predominance of deep infections (61.5%) [7]. Delayed wound healing is observed more frequently in case of emergency CS [8]. Preventing SSI requires implementing appropriate perioperative procedures. Postoperative factors have been considered to play a relatively minor role in causing SSI. The aims of this review were to appraise actions aimed at increasing the cosmetic appearance of the skin scar after CS with regard to pre-, intra- and postoperative procedures. To identify the risk factors and preventive strategies, a literature search with no date restrictions was conducted using the terms: scar, wound care, wound management, surgical site infections, C-section.

PREOPERATIVE CARE

Preoperative care aims to minimize risk of wound infection by implementing procedures to protect the continuity of skin, and the and reduce the bacterial flora present on the patient's skin. It is not recommended to shave or remove pubic hair at least one week before the surgery, as it may cause skin microdamage (Tab. 1). If hair removal is required, it is recommended to use an electric clipper with a single-use head, and shaving should be done as close to the procedure as possible, but outside the operating room [5, 9]. Using a razor increases the risk of SSI [10]. At the latest, the day before the surgery and on the day of the surgery, it is recommended to wash the entire body, including head, with special attention to areas characterized by significant bacterial colonization (skin folds, armpits, navel, groin, and perineum). Using mild, regular soap, wiping patient's body with a fresh towel, and avoiding moisturizers or oily cosmetics is a common practice. There are no recommendations for shower or bath optimal time, and the amount or type of cleaning agents used [8]. It is acceptable to use soap and antiseptic solution, usually chlorhexidine. However, there is no evidence of their greater effectiveness in reducing SSI [5, 11, 12]. Heavy smokers are also advised to quit or reduce smoking at least 30 days before the procedure [10]. Smoking increases the risk of complications after surgical procedures. Nicotine impairs blood flow through tissues, which disrupts the wound healing process.

An important element of preoperative prevention is antibiotic therapy. According to the guidelines in every case of CS (elective, emergency), a single dose of cefazolin in a dose adjusted to the patient's body weight (80 kg — 1 g, above 80 kg — 2 g) should be administered within 30 minutes before skin incision. Prolonging perioperative prophylaxis beyond 24 hours does not reduce the risk of infectious complications but may increase the risk of antibiotic resistance and side effects. Prophylactic antibiotic therapy in women undergoing CS reduces the frequency of wound and endometrium infections and serious infectious complications by 60–70% [13, 14]. However, this method of drug administration raises concerns due to their potential impact on the newborn (disruption of intestinal microflora formation, disruption of immune system development, development of antibiotic resistance, masking of infections). In both methods of administration Jyothirmay et al. [15] found no differences in the condition of newborns. The long-term impact of antibiotics administered before CS on the child's body has not yet been analyzed.

INTRAOPERATIVE CARE

Intraoperative care aimed at minimizing the risk of SSI includes skin disinfection, ensuring hemostasis, avoiding prolonging anesthesia, avoiding hypothermia (maintaining body temperature above 36°C), controlling blood glucose levels in patients with diabetes (< 11 mmol/L) [5, 6, 9, 16]. Operator- related factors: experience and technical ability are essential for wound healing process. The skin scar aesthetics also depend on the choice of incision localization, tools and suture materials selection and appropriate suturing technique. World Health Organization recommends using alcohol solutions of antiseptic preparations based on chlorhexidine for skin preparation [17]. Their effectiveness is compared to preparations with povidone-iodine. In the case of CS, the most effective method of skin preparation has not yet been determined, and the results of studies are varied. There are also no guidelines regarding the methods and time of antiseptic agents application. Skin should be prepared at the surgical site immediately before the incision. The antiseptic solutions should dry in the air [9, 17, 18]. Caissutti et al. [19] recommend vaginal cleansing before CS (sponge stick preparation of povidone-iodine 10% for at least 30 seconds). This procedure has not been shown to decrease the frequency of postoperative wound infections in elective cases [20]. It mainly counteracts postpartum endometrial infection, especially in patients who had a rupture of the fetal membranes. Due to short time of the procedure and low cost, it can be considered for routine practice [20, 21].

Different types of skin incisions of the abdominal wall can be used for CS. For better cosmetic appearance transverse abdominal incision in accordance with the course of Langer's lines is recommended. Incision made transversely to Langer's lines (vertical incision), is associated with postoperative wound dehiscence, postoperative hernia development, and formation of scar contractures. The Pfannenstiel incision ("bikini incision", "smiley incision") is an 8–12 cm curved incision made at a distance of the thickness of two fingers above the pubic symphysis, ending 2–3 cm medially

Table 1. Procedures aimed at optimizing wound healing process and postoperative skin scar cosmetic appearance (compiled by this review authors)

Preoperative care	Intraoperative care	Postoperative care
• Proper hygiene (shower, bath) • Prohibition of shaving pubic hair 7 days before surgery • Shaving pubic hair with clippers as close to the surgery as possible • Giving up or limiting smoking (at least 30 days before surgery) • Providing single-use hospital underwear during surgery • Antibiotic prophylaxis	• Skin preparation (chlorhexidine) • Preoperative vaginal irrigation (optional) • Maintaining appropriate body temperature and saturation • Glucose control • Localization and length of the incision • Subcutaneous tissue suturing in case of thickness above 2 cm • Skin closure (non-absorbable sutures), avoiding excessive tension on the wound edges • Dressing application	• Dressing removal after 24–48 hours following the procedure • Proper hygiene and wound care • Appropriate ways of changing body position (without tensing the abdominal muscles) • Stabilizing the wound during activities that cause abdominal pressure (coughing, sneezing, laughing, pushing) • Wound healing process evaluation

from the anterior superior iliac spine. It provides good surgical access and satisfactory cosmetic results. The Joel-Cohen incision is a 15–17 cm straight incision, about 3 cm below the line connecting the anterior superior iliac spines, made more cranially compared to the Pfannenstiel incision. The Pfannenstiel incision is used in Pfannenstiel-Kerr method and the modified Misgav-Ladach method. The Joel-Cohen incision is used in the Joel-Cohen and Misgav-Ladach method [4, 22–24]. When comparing CS techniques with regard to skin scar appearance, it is assumed that better cosmetic effects are obtained with the Pfannenstiel incision [22]. In the case scar is located lower, often hidden in a natural skin depression, may partly be covered by pubic hair, and its length is shorter. On the other hand, the Joel-Cohen technique brings other benefits such as shorter operation time, fewer occurrences of fever and pain, and reduced blood loss. Preparation of tissues with blunt technique reduces the risk of nerve and blood vessel damage, which affects the healing rate of the wound [25, 26]. Therefore, chronic pain in skin scar area is more commonly reported in patients after the Pfannenstiel incision [27]. Less invasive CS performed using the Joel-Cohen technique and its modifications are associated with shorter procedure time, and better postoperative patient's condition, but or worse cosmetic appearance. The results of research comparing the type of abdominal incision technique with the healing of the postoperative wound are inconsistent [23–28].

The length of incision is important for scar aesthetics, but it must be sufficient for the quick and safe delivery of the baby. The minimum length of the incision with the Pfannenstiel method is 150 mm, and the Allis forceps of the same length can be used to determine it (the "Allis test") [29]. Ulubay et al. [29] among the important factors affecting length of the incision, mention operator's experience (residents: 159.5 ± 13.1 mm; min–max, 132–195 mm, specialists 154.5 ± 14.8 mm; min–max, 127–195 mm) and the patient's BMI. Sutton [30] analyzed the relationship between length of the incision and postoperative wound complications. The average and median lengths of incision were similar (15.3 cm and 15 cm). Longer incisions were not associated with an increased risk of postoperative complications. They were more frequent in overweight patients.

Excessing tension on the wound increases the risk for dehiscence, and decreasing perfusion to the healing wound. Mechanical forces (stretching, compression, hydrostatic pressure and osmotic pressure) acting on a healing wound can also disrupt the scar formation process and lead to the formation of keloids or hypertrophic scars. The risk of pathological scarring is reduced by the use of fascia sutures (deep and superficial fascia). Natural, and tension-free wound adhesion is achieved by bringing the edges of deeper structures together [31].

Absorbable and non-absorbable sutures, staples, surgical tapes, and tissue adhesives are used for skin closure after CS. An optimal method is still being sought (fast, technically easy, without any complications, and with good cosmetic results). The choice of type for skin closure potentially influences the risk of wound infection and complications. No guidelines have been developed in this area yet. The selection of skin closure method depends on the operator's preferences. It is recommended to suture the subcutaneous tissue if its thickness is greater than 2 centimeters. This is associated with a lower rate of wound complications, specifically infection and wound separation. Routine subcutaneous tissue drainage and re-disinfection of the skin before suturing is not recommended [32–35]. Studies evaluating different methods of skin closure analyze the frequency and type of complications (SIS, wound separation), pain and cosmetic effect. Metal staples and absorbable sutures are the two methods most commonly used and compared. Routine staple skin closure is not recommended, although staples significantly reduce time of skin closure [6, 33]. In Aabake et al. [35] research half of the skin incision was closed with subcuticular sutures and the other half was closed with staples. Significantly more women preferred the stapled side in terms of cosmetic effect and reported staples

as their preferred technique. Tissue adhesive is a more expensive and less commonly used method. The efficacy of tissue adhesive is comparable to conventional suture. No differences were noted in blood loss, surgical site infection, length of postpartum hospitalization, or wound disruption. Tissue adhesive can be used safely and effectively for skin closure after CS [36, 37]. Although absorbable sutures are recommended in areas that require a good aesthetic effect (plastic surgery, gynecology), from personal observations, a better result is achieved using non-absorbable sutures.

The surgical incision should be covered with an appropriate interactive dressing at the end of the operation [9]. In case of patients with a risk of abnormal wound healing (*e.g.* obese — BMI > 45 kg/m^2), prophylactic postoperative use of vacuum dressings might be considered [38].

POSTOPERATIVE CARE

In this stage, standard aseptic and antiseptic principles should be followed to prevent SIS. Because wound infections typically appear after leaving the hospital (postoperative days 4–7), patient education about wound healing, recognizing signs of infection, hygiene as well as care at home are very important [39, 40]. Additional measures to prevent wound separation and the formation of postoperative hernias include proper ways of changing positions and stabilizing the operated area with hands during activities that involve the abdominal muscles (coughing, sneezing, pushing, changing positions). The dressing is usually removed after 24–48 hours after the procedure. The results of studies evaluating the effects of earlier dressing removal are inconsistent. Kilic et al. [41] compared dressing removal 24 hours versus 48 hours after surgery. At the six-week follow-up, the wound score (the ASEPSIS score system) was significantly less in the 48-hour group, indicating better wound healing in this group. On the other hand, Peleg et al. [42] did not observe any differences in the wound healing process in the group with dressing removal 6 hours after CS versus 24 hours. The wound should be kept clean and dry, without any dressing. Frequent hand washing is recommended, particularly before and after using the toilet and before touching the wound. Soaking the wound is not recommended. Showers with pouring water over the wound area are advised. Soap, including chlorhexidine soap, is allowed, but skin should not be scrubbed. Wearing cotton, breathable underwear and loose clothing, is also recommended. Depilation or pubic area shaving is not recommended within 3–4 weeks after CS [6, 9, 38].

CONCLUSIONS

Caesarean section is one of the most commonly performed major abdominal operations. With the increasing percentage of CS being performed women's awareness of the adverse health consequences of this procedure is growing. Proper pre- , intra-, and post-operative management combined with patient education are important for wound healing and cosmetic appearance of skin scar.

Article information and declarations

Conflict of interest

All authors declare no conflict of interest.

REFERENCES

1. Bagłaj M, Bagłaj M. Blizny jako problem kliniczny w praktyce dermatologa estetycznego. Dermatol Estet. 2014; 16(2): 80–85.
2. Stanirowski P, Sawicki W. Nowoczesne metody terapii trudno gojących się położniczo-ginekologicznych ran pooperacyjnych – analiza przydatności i skuteczności stosowania. Post Nauk Med. 2013; 26(7): 475–487.
3. Kokanalı D, Kokanalı MK, Topcu HO, et al. Are the cesarean section skin scar characteristics associated with intraabdominal adhesions located at surgical and non-surgical sites. J Gynecol Obstet Hum Reprod. 2019; 48(10): 839–843, doi: 10.1016/j.jogoh.2019.03.026, indexed in Pubmed: 30928543.
4. Elprince M, Taha OT, Ibrahim ZM, et al. Prediction of intraperitoneal adhesions using striae gravidarum and scar characteristics in women undergoing repeated cesarean sections. BMC Pregnancy Childbirth. 2021; 21(1): 286, doi: 10.1186/s12884-021-03763-z, indexed in Pubmed: 33836692.
5. Knight J, Escobar PF. Strategie zmierzające do zminimalizowania powikłań w trakcie gojenia się rany pooperacyjnej. Ginekol Dypl. 2012; 6: 33–38.
6. Kawakita T, Landy HJ. Surgical site infections after cesarean delivery: epidemiology, prevention and treatment. Matern Health Neonatol Perinatol. 2017; 3: 12, doi: 10.1186/s40748-017-0051-3, indexed in Pubmed: 28690864.
7. Różańska A, Jarynowski A, Kopeć-Godlewska K, et al. Polish Society of Hospital Infections Team. Does surgical site infection after caesarean section in Polish hospitals reflect high-quality patient care or poor postdischarge surveillance? Results from a 3-year multicenter study. Am J Infect Control. 2018; 46(1): 20–25, doi: 10.1016/j.ajic.2017.07.025, indexed in Pubmed: 28967511.
8. Pomorski M, Woytoń R, Woytoń P, et al. Cięcia cesarskie a porody siłami natury – aktualne spojrzenie. Ginekol Pol. 2010; 81: 347–351.
9. Welsh Healthcare Associated Infection Programme (WHAIP). Caesarean Section Surgical Site Wound Care and Management Public Health Wales 2015.
10. Tanner J, Norrie P, Melen K. Preoperative hair removal to reduce surgical site infection. Cochrane Database Syst Rev. 2011(11): CD004122, doi: 10.1002/14651858.CD004122.pub4, indexed in Pubmed: 22071812.
11. Webster J, Osborne S. Preoperative bathing or showering with skin antiseptics to prevent surgical site infection. Cochrane Database Syst Rev. 2015, doi: 10.1002/14651858.cd004985.pub5.
12. Chlebicki MP, Safdar N, O'Horo JC, et al. Preoperative chlorhexidine shower or bath for prevention of surgical site infection: a meta-analysis. Am J Infect Control. 2013; 41(2): 167–173, doi: 10.1016/j.ajic.2012.02.014, indexed in Pubmed: 22722008.
13. Smaill FM, Gyte GMI. Antibiotic prophylaxis versus no prophylaxis for preventing infection after cesarean section. Cochrane Database Syst Rev. 2010(1): CD007482, doi: 10.1002/14651858.CD007482.pub2, indexed in Pubmed: 20091635.
14. Mackeen AD, Packard RE, Ota E, et al. Timing of intravenous prophylactic antibiotics for preventing postpartum infectious morbidity in women undergoing cesarean delivery. Cochrane Database Syst Rev. 2014(12): CD009516, doi: 10.1002/14651858.CD009516.pub2, indexed in Pubmed: 25479008.
15. Jyothirmayi CA, Halder A, Yadav B, et al. A randomized controlled double blind trial comparing the effects of the prophylactic antibiotic, Cefazolin,

administered at caesarean delivery at two different timings (before skin incision and after cord clamping) on both the mother and newborn. BMC Pregnancy Childbirth. 2017; 17(1): 340, doi: 10.1186/s12884-017-1526-y, indexed in Pubmed: 28974203.
16. WHO Guidelines Development Group. Global Guidelines for the Prevention of Surgical Site Infection. WHO, Geneva 2016: 15–21.
17. Hadiati DR, Hakimi M, Nurdiati DS, et al. Skin preparation for preventing infection following caesarean section. Cochrane Database Syst Rev. 2012; 10(9): CD007462, doi: 10.1002/14651858.CD007462.pub2, indexed in Pubmed: 22972109.
18. Huang H, Li G, Wang H, et al. Optimal skin antiseptic agents for prevention of surgical site infection in cesarean section: a meta-analysis with trial sequential analysis. J Matern Fetal Neonatal Med. 2018; 31(24): 3267–3274, doi: 10.1080/14767058.2017.1368481, indexed in Pubmed: 28817989.
19. Caissutti C, Saccone G, Zullo F, et al. Vaginal cleansing before cesarean delivery: a systematic review and meta-analysis. Obstet Gynecol. 2017; 130(3): 527–538, doi: 10.1097/AOG.0000000000002167, indexed in Pubmed: 28796683.
20. Aref NK. Vaginal cleansing prior to caesarian section: To do or not to do?: A randomized trial. J Gynecol Obstet Hum Reprod. 2019; 48(1): 65–68, doi: 10.1016/j.jogoh.2018.11.002, indexed in Pubmed: 30447348.
21. Haas DM, Morgan S, Contreras K, et al. Vaginal preparation with antiseptic solution before cesarean section for preventing postoperative infections. Cochrane Database Syst Rev. 2013; 7(1): CD007892, doi: 10.1002/14651858.CD007892.pub3, indexed in Pubmed: 23440819.
22. Bolla D, Schöning A, Drack G, et al. Technical aspects of the cesarean section. Gynecol Surg. 2010; 7(2): 127–132, doi: 10.1007/s10397-010-0560-9.
23. Vitale SG, Marilli I, Cignini P, et al. Comparison between modified Misgav-Ladach and Pfannenstiel-Kerr techniques for cesarean section: review of literature. J Prenat Med. 2014; 8(3-4): 36–41, indexed in Pubmed: 26265999.
24. Gizzo S, Andrisani A, Noventa M, et al. Caesarean section: could different transverse abdominal incision techniques influence postpartum pain and subsequent quality of life? A systematic review. PLoS One. 2015; 10(2): e0114190, doi: 10.1371/journal.pone.0114190, indexed in Pubmed: 25646621.
25. Hofmeyr GJ, Mathai M. Techniques for caesarean section. Cochrane Database of Syst Rev. 2004, doi: 10.1002/14651858.cd004662.
26. Karanth KL, Sathish N. Review of advantages of Joel-Cohen surgical abdominal incision in caesarean section: a basic science perspective. Med J Malaysia. 2010; 65(3): 204–208, indexed in Pubmed: 21939169.
27. Loos MJ, Scheltinga MR, Mulders LG, et al. The Pfannenstiel incision as a source of chronic pain. Obstet Gynecol. 2008; 111(4): 839–846, doi: 10.1097/AOG.0b013e31816a4efa, indexed in Pubmed: 18378742.
28. Şahin N, Genc M, Turan GA, et al. A comparison of 2 cesarean section methods, modified Misgav-Ladach and Pfannenstiel-Kerr: a randomized controlled study. Adv Clin Exp Med. 2018; 27(3): 357–361, doi: 10.17219/acem/66215, indexed in Pubmed: 29533540.
29. Ulubay M, Öztürk M, Fidan U, et al. Skin incision lengths in caesarean section. Cukurova Medical Journal. 2016; 41(1): 82, doi: 10.17826/cutf.147190.
30. Sutton A. 548: Impact of cesarean skin incision length on post-operative wound complications. Am J Obstet Gynecol. 2018; 218(1): S327–S328, doi: 10.1016/j.ajog.2017.11.075.
31. Ogawa R, Akaishi S, Huang C, et al. Clinical applications of basic research that shows reducing skin tension could prevent and treat abnormal scarring: the importance of fascial/subcutaneous tensile reduction sutures and flap surgery for keloid and hypertrophic scar reconstruction. J Nippon Med Sch. 2011; 78(2): 68–76, doi: 10.1272/jnms.78.68, indexed in Pubmed: 21551963.
32. Poprzeczny AJ, Grivell RM, Louise J, et al. Skin and subcutaneous fascia closure at caesarean section to reduce wound complications: the closure randomised trial. BMC Pregnancy Childbirth. 2020; 20(1): 606, doi: 10.1186/s12884-020-03305-z, indexed in Pubmed: 33032560.
33. Dahlke JD, Mendez-Figueroa H, Rouse DJ, et al. Evidence-based surgery for cesarean delivery: an updated systematic review. Am J Obstet Gynecol. 2013; 209(4): 294–306, doi: 10.1016/j.ajog.2013.02.043, indexed in Pubmed: 23467047.
34. Dhama V, Chaudhary R, Singh S, et al. Three techniques for skin closure in caesarean section (stapler, absorbable subcuticular, non-absorbable subcuticular suture). Indian J Obstet Gynecol Res. 2016; 3(1): 68–72, doi: 10.5958/2394-2754.2016.00014.x.
35. Aabakke AJM, Krebs L, Pipper CB, et al. Subcuticular suture compared with staples for skin closure after cesarean delivery: a randomized controlled trial. Obstet Gynecol. 2013; 122(4): 878–884, doi: 10.1097/AOG.0b013e3182a5f0c3, indexed in Pubmed: 24084548.
36. Kwon JiY, Yun HG, Park InY. n-Butyl-2-cyanoacrylate tissue adhesive (Histoacryl) vs. subcuticular sutures for skin closure of Pfannenstiel incisions following cesarean delivery. PLoS One. 2018; 13(9): e0202074, doi: 10.1371/journal.pone.0202074, indexed in Pubmed: 30216337.
37. Daykan Y, Sharon-Weiner M, Pasternak Y, et al. Skin closure at cesarean delivery, glue vs subcuticular sutures: a randomized controlled trial. Am J Obstet Gynecol. 2017; 216(4): 406.e1–406.e5, doi: 10.1016/j.ajog.2017.01.009, indexed in Pubmed: 28153666.
38. Mosoń K. Rana po cięciu cesarskim – jak zmniejszyć ryzyko nieprawidłowego gojenia? Post N Med. 2016; 29(7): 448–451, doi: 10.5604/08606196.1210324.
39. Zuarez-Easton S, Zafran N, Garmi G, et al. Postcesarean wound infection: prevalence, impact, prevention, and management challenges. Int J Womens Health. 2017; 9: 81–88, doi: 10.2147/IJWH.S98876, indexed in Pubmed: 28255256.
40. Zarei M, Rostami F, Bozorghnejad M, et al. Effect of self-care training program on surgical incision wound healing in women undergoing cesarean section: a quasi-experimental study. Med Surg Nurs J. 2021; 9(4): e108800, doi: 10.5812/msnj.108800.
41. Kilic GS, Demirdag E, Findik MF, et al. Impact of timing on wound dressing removal after caesarean delivery: a multicentre, randomised controlled trial. J Obstet Gynaecol. 2021; 41(3): 348–352, doi: 10.1080/01443615.2020.1736015, indexed in Pubmed: 32312139.
42. Peleg D, Eberstark E, Warsof SL, et al. Early wound dressing removal after scheduled cesarean delivery: a randomized controlled trial. Am J Obstet Gynecol. 2016; 215(3): 388.e1–388.e5, doi: 10.1016/j.ajog.2016.03.035, indexed in Pubmed: 27018465.

VIA MEDICA

RECCOMENDATIONS

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Recommendations of the Polish Society of Gynaecologists and Obstetricians, Polish Paediatric Society, Polish Society of Family Medicine, Polish Society of Vaccinology, Polish Society of Oncological Gynaecology and Polish Society of Colposcopy and Pathophysiology of the Uterine Cervix on prophylactic vaccinations against infections with human papillomaviruses in Poland

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ABSTRACT

Several hundred million people are infected with genital genotypes of the human papillomavirus (HPV) annually in the world. The infections transmitted mainly through sexual routes are usually asymptomatic, but can lead to the development of cervical, vulvar, vaginal, anal, penile cancers, some head and neck cancers and genital warts (condylomas). The fraction HPV-related cancers range from nearly 100% in the case of cervical cancer to several/over a dozen percent in the case of other cancers and diseases. There are no effective drugs against HPV, but prophylactic HPV vaccines are available free of charge in immunization programmes in many countries around the world. In Poland, HPV vaccinations have so far been executed out on the pocket or in free-of-charge, local-governmental prevention programs, but the vaccination coverage of the target population does not exceed 10%. From November 2021, one of the vaccines is available with a 50% reimbursement, work is underway to reimburse the next ones, and the National Oncology Strategy assumes the implementation of the HPV immunization programmes and vaccination of 60% of the teen population by 2028. Three prophylactic HPV vaccines are registered. All of them are safe and their effectiveness in the prevention of diseases caused by vaccine genotypes reaches almost 100%, provided that full post-vaccination immunity is obtained before the contact with the virus. Girls aged 11–13 are the priority target cohort for HPV vaccination in Poland. The implementation of routine, free-of-charge HPV immunization in the Preventive Immunization Program (PIP) for all adolescents should be pursued. Persons over the age of 13 may also benefit from HPV vaccination and should be vaccinated according to product specifications. In addition to free access under the PIP, the key element for the success of the implementation of HPV vaccinations in Poland will be the education of medical personnel and parents of adolescents to be vaccinated.

Keywords: human papillomavirus; prophylactic vaccination; cervical cancer

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HUMAN PAPILLOMAVIRUSES AS AN ETIOLOGICAL FACTOR OF DISEASES

Human papillomavirus (HPV) infections are one of the most common genital organ infections in humans, mostly asymptomatic and spontaneously regressing. However, in a few to a dozen or so percent of those infected, lesions develop in various anatomical locations. It is estimated that HPV is responsible for the development of nearly 100% of precancerous lesions and cervical cancers, approximately 64–100% of precancerous conditions and vaginal cancers, 90% of anal cancers, 30% of penile cancers, 15–30% of vulvar cancers [1–4]. Human papillomavirus also causes some cases of head and neck cancers (oral cavity — approx. 3.7%; nasopharynx - approx. 11%; base of tongue, tonsil — approx. 19.9%; unspecified part of the throat — approx. 25%) [2, 3]. Human papillomavirus is the etiological factor of genital warts and recurrent laryngeal papillomatosis. So far, around 200 HPV genotypes have been classified, of which currently 14 (designated as: 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68) are considered high risk genotypes of neoplastic lesions. The so-called low-risk genotypes 6 and 11 are responsible for the development of most genital warts and recurrent laryngeal papillomatosis. The infection frequency, carrier status, and distribution of HPV genotypes varies depending on the anatomical location of the infection, sex, age, and geographic region and population. About 70% of cervical cancers in the world are caused by HPV 16 and 18 [5] and genotype 16 dominates in all HPV-dependent neoplasms [1]. In Polish material, it was estimated that genotypes 16 and 18 are responsible for the development of approx. 83% of HPV-DNA positive cervical cancers, and approx. Eighty-five percent of high-grade intraepithelial lesions (direct precancers) are etiologically associated with HPV 16, 33, 31, 52, 45 and 58 [6]. It is estimated that 690 thousand cases of cancer globally in 2020 [7] and about three thousand in Poland in 2015 [2] were associated with HPV infections. Cervical cancer is by far the biggest problem for public health in Poland among the diseases etiologically related to HPV due to the highest incidence, and the threat to health and life of young women. There are no official registers in Poland, but by extrapolating world data [8], the incidence of genital warts and recurrent laryngeal papillomatosis can be estimated at several dozen thousand and several hundred cases per year, respectively.

PROPHYLACTIC HPV VACCINES

Currently, three vaccines are registered in most countries of the world and in Poland. All of them contain virus-like particles (VLPs) made of purified protein of the main viral capsid L1, produced by recombinant DNA technology, and adjuvants. Vaccines do not contain live viruses or their DNA material. Vaccines cannot cause infection, and the non-infectious VLPs included in vaccines are not replicative. The mechanism of action of HPV vaccines is based on induction a humoral immune response and the presence of neutralizing antibodies and their activity at the site of infection. Antibody concentrations obtained after vaccination decrease with the time interval after vaccination and then remain at a stable level, many times higher than those recorded after natural infection, for many years [9]. Prophylactic HPV vaccines do not have therapeutic properties, do not change the course of the ongoing infection or the

clinical course of lesions caused by the virus. Therefore, to obtain the immunity of individual people and the maximum population effect, they should be given to individuals before contact with the virus, *i.e.*, before sexual debut. From a meta-analysis of data covering 60 million vaccinated people over a period of eight years of follow-up, the highest effectiveness in the prevention of high-grade precancerous conditions of the cervix and genital warts was demonstrated in the group of girls vaccinated up to 19 years of age (lower, but also significant in women up to 29 years of age) [10]. A brief summary of the approved vaccines is presented in Table 1.

Table 1. Characteristics of registered prophylactic human papillomavirus (HPV) vaccines (in order of registration in Europe)

Brand name	Gardasil (formerly Silgard)	Cervarix	Gardasil 9
Year of registration in Europe	2006	2007	2015
Composition of one dose (0.5 mL)	20 µg of L1 HPV 6 protein, 40 µg of L1 HPV 11 protein, 40 µg of L1 HPV 16 protein, 20 µg of L1 HPV 18 protein, adsorbed on amorphous aluminium hydroxyphosphate sulphate adjuvant (0.225 mg Al)	20 µg of L1 HPV 16 protein, 20 µg of L1 HPV 18 protein with AS04 adjuvant system	30 µg of L1 HPV 6 protein, 40 µg of L1 HPV 11 protein, 60 µg of L1 HPV 16 protein, 40 µg of L1 HPV 18 protein, 20 µg of L1 HPV 31 protein, 20 µg of L1 HPV 33 protein, 20 µg of L1 HPV 45 protein, 20 µg of L1 HPV 52 protein, 20 µg of L1 HPV 58 protein, adsorbed on amorphous aluminium hydroxyphosphate sulphate adjuvant (0.5 mg Al)
Indications for use	Prevention of precancerous lesions of the genital organs (cervix, vulva and vagina), precancerous lesions of the anus, cervical cancer and cancer of the anus, genital warts (genital warts)	Prophylaxis of precancerous lesions of the genital organs and anus (cervix, vulva, vagina and anus) as well as cervical and anal cancer	Active immunization against precancerous lesions and cancer of the cervix, vulva, vagina and anus, genital warts (condylomas)
Dosage	Persons 9 through 13 years of age inclusive: Gardasil can be given according to a 2-dose schedule (0.5 mL at 0.6 months). If the second dose is given earlier than 6 months after the first dose, a third dose should always be given. Gardasil can also be given in another schedule — 3 doses (0.5 mL at 0, 2, 6 months). The second dose should be administered at least one month after the first dose and the third dose should be administered at least 3 months after the second dose. All three doses should be administered within 1 year. Individuals 14 years of age and older: Gardasil should be administered according to a 3-dose schedule (0.5 mL at 0, 2, 6 months). The second dose should be administered at least one month after the first dose and the third dose should be administered at least 3 months after the second dose. All three doses should be administered within 1 year	Adults and adolescents from 15 years of age: 3 doses (0.5 mL each) in months 0, 1 and 6; if flexibility in the vaccination schedule is required, the second dose may be administered between 1 and 2.5 months after the first dose and the third dose between 5 and 12 months after the first dose. Children and adolescents 9 to 14 years of age: 2 doses (0.5 mL each) — the second dose administered between 5 and 13 months after the first dose. If the second dose of vaccine is given less than 5 months after the first dose, a third dose of vaccine will be required. The need for a booster dose has not been established	Patients 9 to 14 years of age inclusive at the time of first dose: 2-dose schedule (0, 6–12 months). The second dose should be given between 5 and 13 months after the first dose. If the second dose of vaccine is administered more than 5 months after the first dose, a third dose should always be given. 3-dose regimen (0, 2, 6 months). The second dose should be given at least one month after the first dose and the third dose should be given at least 3 months after the second dose. All 3 doses should be given within 1 year. Patients 15 years of age and over at the time of first dose: 3-dose schedule (0, 2, 6 months). The second dose should be given at least one month after the first dose and the third dose should be given at least 3 months after the second dose. All 3 doses should be given within 1 year. The vaccine should be used according to official recommendations. It is recommended that patients who receive a first dose of Gardasil 9 complete the vaccination course with Gardasil 9. It has not been established whether a booster dose is needed
The route of administration	Intramuscular	Intramuscular	Intramuscular
Contraindications	Hypersensitivity to the active substance or to any of the excipients. Individuals who develop symptoms indicative of hypersensitivity after receiving a dose of Gardasil should not receive further doses of Gardasil	Hypersensitivity to the active substance or to any of the excipients	Hypersensitivity to the active substances or to any of the excipients. Individuals who have developed hypersensitivity after previous administration of Gardasil 9 or Gardasil/Silgard should not receive Gardasil 9

SAFETY

Vaccination safety is a key aspect of ensuring an appropriate balance of benefits against the potential risks of this form of prophylaxis in populations of young, healthy people. All three HPV vaccines have undergone appropriate pre-approval studies, have passed regulatory agencies' positive assessment of their safety, and are subject to ongoing post-approval surveillance (bivalent — HPV2 and quadrivalent — HPV4 vaccines for over 15 years, and nine-valent — HPV9 for 9 years). Post-Vaccine Adverse Reactions (VARs) observed in clinical trials with all three vaccines were similar in profile and incidence. For HPV4, the most common local post-vaccination symptoms were pain (84%), erythema (< 25%), and swelling (25%) at the injection site, with pain more frequent than with placebo (saline — 49%; placebo containing aluminium — 75%). These symptoms occurred more frequently after the use of HPV2 and HPV9 [8]. Transient low-grade fever/fever is the only systemic adverse reaction that occurs more frequently (> 10%) in individuals vaccinated with HPV vaccines than in vaccinated with placebo [8]. Common but rapidly reversing VARs after HPV vaccinations include headache and dizziness (> 10%), muscle and joint pain, abdominal pain, nausea and vomiting (frequency 1–10%). The HPV vaccines, as with other vaccines administered to adolescents, have also been associated with syncope, which is classified as a psychogenic needle-stick reaction. Anaphylaxis after HPV vaccinations occurs with a similar frequency as after administration of other vaccines. Data on the safety of HPV vaccination have been collected in people from nine years of age and are still collected and analysed, as in case of other preventive vaccines [11].

In post-registration reports, a cause-and-effect relationship was suggested between HPV vaccinations and the occurrence of Guillain-Barre syndrome, complex regional pain syndrome (CRPS), postural orthostatic tachycardia syndrome (POTS), premature ovarian insufficiency (POI) or autoimmune diseases and others. Due to these reports and the related media controversy, HPV vaccines are among the most thoroughly examined and constantly monitored in terms of safety. So far, none of the suspicions has been confirmed in analyses carried out on large, vaccinated populations [12–14]. However, they remain the subject of further observations and debates [15–17]. In the HPV4 safety analysis including data from clinical trials and databases, in the 9-year post-marketing period, only syncope and local skin reactions were associated with vaccinations [18]. Compared to HPV4, local VARs were more frequent after HPV9, but the incidence of serious VARs was the same [20]. Vaccination against HPV is not recommended in pregnant women, however, no differences in the incidence of complications during pregnancy were found in vaccinated and unvaccinated women during pregnancy [19–21].

IMMUNOGENICITY

The immunogenicity of HPV vaccines has been assessed in many clinical trials. Bridging studies of antibody levels formed the basis of vaccination registration in adolescents (in whom efficacy studies could not be conducted) and a 2-dose vaccination schedule (antibody titres not lower than after the 3-dose schedule) in young people [9]. The percentage of people with seroconversion after receiving the full vaccination course significantly exceeds 90%, and the achieved titres of neutralizing antibodies are many times higher than those observed after natural infection [9]. The highest titres are recorded four weeks after the last dose, then antibody concentrations reach a plateau significantly exceeding those after natural infection [22]. The duration of post-vaccination protection is predicted for several dozen years [22]. The minimum protective level of antibodies against infection and the need and timing of a booster dose have not yet been established.

EFFECTIVENESS

The effectiveness of vaccines assessed in clinical trials depended on many factors, such as: current or past HPV infection, age and sex of the vaccinated person, end point (type, severity, anatomical location of the lesion caused by HPV infection), and the follow-up period after vaccination [23–26]. The highest, up to 100%, efficacy, was observed in the prevention of advanced precancerous lesions caused by vaccine HPV genotypes in people without indicators of current and previous infection [23, 27, 28]. For HPV4, the efficacy against high-grade intraepithelial lesions of the cervix (CIN2+), vagina/vulva (VaIN2+/VIN2+) caused by vaccine types 6, 11, 16, 18 was assessed in a combined analysis of three phase II/III clinical trials at 98.2% (95% CI: 93.3–99.8) and 100% (95% CI: 82.6–100), respectively, in HPV-DNA and seronegative women for vaccine types [23]. In the cohort of women with no previous/current infection markers, the effectiveness of HPV2 in preventing HPV-16/18-dependent lesions of CIN3 + and CIN2 + was 100% (95% CI: 85.5–100) [24] and 89.8% (95 % CI: 39.5–99.5) [25]. The efficacy of HPV2 in preventing CIN3 + caused by all HPV genotypes (also not included in the vaccine) was 93.2% (95% CI: 78.9–98.7) [24] in previously uninfected women. High effectiveness of HPV9 in the prevention of diseases caused by HPV 31, 33, 45, 52, 58 was demonstrated in comparative studies with HPV4 [19]. The effectiveness of HPV4 in the prevention of HPV-6/11/16/18-dependent lesions of the external genitalia in young men with no previous indicators of infection was estimated at 90.4% (95% CI: 69.2–98.1) [26] and the effectiveness in the prevention of advanced precancerous anal lesions reached 74.9% (95% CI: 8.8–95.4). The effectiveness of HPV2 in the prevention of HPV 16/18, HPV 31/45, HPV 31/33/45 infections in the oropharyngeal cavity reached

82.4% (95% CI: 47.3–94.1), 75.3 % (95% CI: 12.7–93.0) and 69.9% (95% CI: 29.6–87.1) [29].

POPULATION EFFECTS

High effectiveness of HPV vaccines in clinical trials in reducing the incidence of HPV infections and their clinical manifestations has an impact on the reduction of the incidence of HPV-related infections and diseases, which has been demonstrated not only in models [30] but proven also in meta-analyses of population studies [10]. Recently published English data showed a reduction in the risk of invasive cervical cancer and CIN3 by 87% (95% CI: 72–94) and 97% (95% CI: 96–98) respectively in vaccinated girls aged 12–13 years [31]. Nearly 90% reduction in the incidence of cervical cancer has recently also been reported among Swedish girls vaccinated before the age of 17 [32]. In Denmark, after the implementation of the population-based, free-of-charge HPV vaccination programme, a significant decrease in the incidence of cervical cancer was noted, especially in the populations that received vaccines before the age of 16 [33]. The effectiveness of HPV4 in the prevention of genital warts at the population level was estimated at 74% (95% CI: 68–79) in the Valencia region [34]. Eight years after the introduction of population-based HPV vaccination in Australia, a reduction in the incidence of preterm labour (3.2% 95% CI: 1.1–5.3%) and low birth weight new-borns (9.8% 95% CI 8.2–11.4) was noticed, which may be associated with a reduction in the frequency of cervical excisional procedures in young women [35]. After the implementation of the population-based, free-of-charge HPV vaccination before the age of 16, the risk of developing high-grade intraepithelial neoplasia of the vagina and vulva, respectively, was reduced by 85% and 78%, in an analysis of over 500,000 patients [36]. Demonstration of the effectiveness of HPV vaccines in reducing the incidence of less common HPV-dependent cancers such as head and neck, vulva and vagina, and other pathological lesions such as recurrent laryngeal papillomatosis will require longer observations and large cohorts of subjects. So far, an almost 90% reduction in HPV 16/18/6/11 infections in the oral cavity has been demonstrated in vaccinated versus unvaccinated young Americans [37].

VACCINATION AGAINST HPV IN SPECIAL COHORTS AND CLINICAL SITUATIONS

Immunodeficiency *e.g.*, during HIV infections and the use of immunosuppressants, is the strongest known risk factor for the acquisition, maintenance and progression of HPV infections to lesions (precancerous conditions, neoplasms, papillary lesions) [38–40]. It therefore seems that immunocompetent individuals may benefit from HPV vaccination, although there are no results of large, prospective studies in this area. Although prophylactic vaccines have no therapeutic effect, there is a body of evidence showing a lower rate of recurrence of precancerous cervical lesions after treatment in HPV vaccinated than in unvaccinated women [41–43]. The observations of some of the authors of this position show that Polish women diagnosed and treated due to cervical precancerous conditions are a group willing to undergo HPV vaccinations. These women very often ask their gynaecologists about the possibility of vaccinating their children. Partial reimbursement gives additional opportunities to make use of the vaccination potential in this group of patients.

RECOMMENDATIONS OF OTHER ORGANIZATIONS AND SOCIETIES

Due to very favourable data from clinical trials regarding the immunogenicity, effectiveness and safety of HPV vaccinations and the registration of the first vaccine in 2006, starting from 2007, HPV vaccinations were recommended by influential societies and organizations, and they began to be implemented in immunization programs in a number of countries in world. So far, Poland has not joined the group of nearly 90% of high-income countries according to the World Bank classification, which have implemented HPV vaccination in PIPs [44]. The Global Strategy to Accelerate the Elimination of Cervical Cancer as a Public Health Problem announced by WHO in 2020, among the three key goals included the one to fully vaccinate 90% of the population of girls up to 15 years of age by year 2030 [44]. The key points of the previous WHO position from 2017 are as follows: 1) HPV vaccinations should be implemented in national immunization programmes, 2) the prevention of cervical cancer is a priority, 3) HPV vaccinations should be carried out in girls prior to sexual initiation, 4) vaccination should be implemented as part of a coordinated strategy including, inter alia, education on the risk of HPV infections, training of medical personnel and information for women on screening tests, 5) the priority cohort for vaccination is girls between 9–14 years of age, 6) vaccination of secondary target groups (girls > 15 years of age and boys) it is only recommended if it is feasible, cost effective and does not limit the funding of priority cohort vaccinations and cervical cancer screening programs [8]. The position of the European Centre for Disease Prevention and Control from 2020 is mainly devoted to the vaccination of people with HIV, boys and the introduction of HPV9 [45]. Among the key conclusions, it points to: 1) the effectiveness of HPV9 in the prevention of infections and lesions related to HPV 31, 33, 45, 52 and 58 (high quality data) and HPV 6, 11, 16, 18 (indirect data, moderate quality) 2) no direct data in effectiveness of HPV2 in men (evidence of its high immunogenicity), 3) high dependence of cost-effectiveness on priorities and local

situation in a given country (if the priority is cervical cancer prevention, the most cost-effective strategy is to maximize vaccination of girls; vaccination of boys may improve effectiveness cost-effective with a low coverage of the cohorts of girls; universal vaccination of girls and boys is recommended if the goal is to prevent various consequences of HPV infections). The United States Advisory Committee on Immunization Practices: 1) recommends routine immunization of 11–12-year-olds and catch-up vaccinations for unvaccinated people up to 26 years of age, 2) points to minimal public health benefits of vaccinating people between 26 and 45 years of age and recommends taking combined (doctor-patient) decisions in this regard, as these individuals may benefit from vaccination in individual situations [46]. The National Oncological Strategy for 2020–2030 in Poland assumes the commencement of the vaccination process for girls and boys in 2021 and 2026, respectively, and vaccinating at least 60% of adolescents by 2028, and points to the need to conduct an information campaign on the benefits of HPV vaccination [47]. Human papillomavirus vaccines have the recommendation of the President of the Agency for Health Technology Assessment and Tariff System [48, 49] and, according to the opinion of experts from 2020, they should constitute an integral part of the comprehensive prevention of cervical cancer in Poland [50].

POLISH RECOMMENDATIONS FOR VACCINATION AGAINST HPV

Previous positions of Polish scientific societies on HPV vaccination are over 10 years old. They emphasized that prophylactic vaccinations should be a practice complementary to regular cytological screening [51]. The important role of paediatricians and family doctors in education and primary prevention of cervical cancer in Poland was also indicated [52].

LOCAL GOVERNMENT HPV VACCINATION PROGRAMS IN POLAND AND THEIR EXPERIENCES

Vaccinations against HPV in the years 2010-1017 were the most frequently implemented local government prevention programmes with a positive opinion from the Agency for Health Technology Assessment (currently the Agency for Health Technology Assessment and Tariff System). However, the overall vaccination coverage of the target female population was very low, ranging from just 1% to 1.5% between 2015 and 2017. The highest number of vaccinations in this period was carried out in the Dolnośląskie, Pomorskie, Śląskie, Wielkopolskie and Mazowieckie voivodships (63% of all vaccinations in Poland). In 2017, HPV vaccines were reimbursed by 223 local governments, including nine also for boys. During the 10 years of operation of local government programmes, approximately 180,000 girls were vaccinated. Immunization coverage depended on the region of Poland — higher in the west than in the east of the country — on average about 55% of the eligible individuals [53]. In 12 editions of the Wrocław HPV vaccination programme, in 2010–2021, on average 75.2% of 13-year-old female students (n = 16.301) were vaccinated. The schoolgirls were vaccinated in district clinics. Every year, the implementation of the programme was accompanied by comprehensive educational activities aimed at parents, students of both sexes, teachers, doctors and nurses from vaccination centres. 28,632 parents (60% on average) and 33,949 students (70% on average) participated in educational meetings. In the first five years, the average vaccination coverage was 83% [54]. During the peak period of media anti-vaccination propaganda and the broadcast of the film "Vaxxed" in the 2016/17 and 2017/18 editions of the program, the percentage of vaccinated people fell to the critical level of 62%. Studies among parents, students and vaccinating nurses were executed. It has been shown that nurses participating in the program were not sufficiently aware of their role in building acceptance of immunization. Among the determinants of doubts regarding vaccination against HPV among the inhabitants of Wrocław the fear of side effects of vaccinations and a lack of trust in the effectiveness of vaccination were identified. Contrary to the results of studies on doubts regarding HPV vaccination from other countries, the respondents from Wrocław did not report any concerns related to the alleged promotion of promiscuity as a result of vaccination [55]. Changes in educational programs were introduced, which were extended with elements of training in the field of communication skills with the patient, and the monitoring of doubts concerning HPV vaccination was intensified. These changes resulted in a renewed increase in vaccination coverage to a satisfactory level of 70% [56]. Similar conclusions can be drawn from vaccination programs in Europe and the USA. The highest vaccination rates in the target population were achieved through organized school vaccinations [57], combined with consistent medical recommendations and public education [58, 59].

RECOMMENDATIONS FOR POLAND

1. Prophylactic HPV vaccinations should be an integral part of the comprehensive cervical cancer prevention in Poland. Human papillomavirus vaccines enable the reduction of the incidence of other diseases etiologically related to HPV infections.
2. The priority target group for HPV vaccination are girls aged 11–13 years.
3. As the next step, girls over 13 years of age and boys 11–13 years of age should be vaccinated.

4. We should strive for the fastest possible implementation of free-of-charge HPV vaccinations of adolescents aged 11–13 years Preventive Immunization Programme.
5. Population-based vaccinations against HPV should be ultimately implemented within the framework of the existing, proven, organizational solutions in Preventive Immunization Programme in order to cover the target cohorts as widely as possible.
6. The qualification for HPV vaccination does not differ from other vaccinations. According to the general recommendations, the only permanent, absolute contraindication to further vaccination, including HPV, is an anaphylactic reaction that occurred after the previous dose of the vaccine or administration of any of its components. Mild or moderate reactions following the administration of the previous dose of the vaccine, such as pain, redness and swelling at the injection site, slight or moderate fever after the previous dose of the vaccine, are not a contraindication for vaccination. There is no need to do a pregnancy test before administration. The use of hormonal contraceptives has no effect on the immune response. Temporary/relative contraindications include moderate or severe acute illness, whether with or without fever, *e.g.*, streptococcal angina, influenza, acute bronchitis or acute diarrhoea. Moreover, the exacerbation of the chronic disease process is a relative temporary contraindication. In these cases, vaccination is postponed until the acute symptoms subside, and in chronic diseases until remission is achieved and the patient's condition is stabilized.
7. Human papillomavirus vaccines can be administered concurrently or at any intervals with other vaccines, but in a different site — *e.g.*, the opposite arm, or with a minimum distance of 2.5 cm from the site of the first vaccine injection. The safety of concurrent administration of HPV vaccines with pertussis, diphtheria, tetanus, inactivated polio vaccines, hepatitis A and B vaccines, Meningococcal, Covid 19 has been tested and demonstrated. As part of the vaccination campaign of whole groups of adolescents, VARs may develop in the form of fainting, which in this case is triggered by pain or anxiety. People who pass out can fall and injure themselves if they don't sit or lie down. Giving patients a drink, a snack, ensuring the safety of the procedure and vaccinating while lying or sitting has been shown to prevent syncope associated with the vaccination procedure. In addition, patients should be observed for 30 minutes after vaccination. If a patient faints after vaccination, he or she should be monitored by a healthcare professional until he regains consciousness (usually within a few minutes) so that the need for any further medical treatment can be determined.
8. In order to achieve optimal population effects, if it is necessary to select one product for vaccination under the Preventive Immunisation Programme, the selection of the vaccine should be made based on an independent pharmaco-economic analysis taking into account, inter alia, data from clinical trials in terms of efficacy against key endpoints, vaccine price achieved in a tender/auction and distribution of HPV genotypes in lesions in Poland.
9. People older than planned for the free-of-charge immunization in the Preventive Immunisation Programme may also benefit from HPV immunization and should be vaccinated in line with the prescribing information for all three approved vaccines.
10. Human papillomavirus vaccination should be recommended to women diagnosed and treated for precancerous conditions of the cervix, as they may benefit from a lower risk of recurrence of lesions.
11. An extremely important element of the implementation of HPV vaccines are educational activities in target populations for vaccinations and their guardians, for medical personnel and the entire society, which should be conducted both centrally (media campaigns, etc.), regionally/locally (scientific and educational conferences, educational and information activities of producers, etc.) and individually (in clinics and offices) in order to provide maximum information about the benefits of HPV vaccination.

Frequently asked questions and answers on vaccination against HPV will be published on the website of the Polish Society of Family Medicine.

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Conflict of interests

AN — advisory board, lectures (GSK); MS — lectures (MSD); AN-O — advisory board, lectures (GSK, MSD).

REFERENCES

1. https://hpvcentre.net/ (20.10.2021).
2. https://www.mp.pl/szczepienia/artykuly/przegladowe/186457,co-wiadomo-o-populacyjnych-efektach-szczepien-przeciwko-hpv (20.10.2021).

3. de Martel C, Plummer M, Vignat J, et al. Worldwide burden of cancer attributable to HPV by site, country and HPV type. Int J Cancer. 2017; 141(4): 664–670, doi: 10.1002/ijc.30716, indexed in Pubmed: 28369882.
4. Robenek M, Olejek A, Witek L, et al. Presence of human papilloma virus in Caucasian women living in the central Europe diagnosed with vulvar intraepithelial neoplasia. Ginekol Pol. 2020; 91(4): 181–184, doi: 10.5603/GP.a2020.0035, indexed in Pubmed: 32236934.
5. de Sanjose S, Quint WGv, Alemany L, et al. Retrospective International Survey and HPV Time Trends Study Group. Human papillomavirus genotype attribution in invasive cervical cancer: a retrospective cross-sectional worldwide study. Lancet Oncol. 2010; 11(11): 1048–1056, doi: 10.1016/S1470-2045(10)70230-8, indexed in Pubmed: 20952254.
6. Nowakowski A, de Souza SC, Jach R, et al. HPV-type distribution and reproducibility of histological diagnosis in cervical neoplasia in Poland. Pathol Oncol Res. 2015; 21(3): 703–711, doi: 10.1007/s12253-014-9877-4, indexed in Pubmed: 25547828.
7. https://gco.iarc.fr/causes/infections/tools-pie?mode=2&sex=0&population=who&continent=0&country=0&population_group=0&cancer=0&key=attr_cases&lock_scale=0&pie_mode=1&nb_results=5, accessed on 20th October 2021.
8. World Health Organization. Weekly Epidemiological Record. 2017; 92(19): 241–268.
9. Stanley M. HPV vaccines: alternative dosage schedules. Expert Rev Vaccines. 2019; 18(12): 1309–1316, doi: 10.1080/14760584.2019.1704261, indexed in Pubmed: 31847625.
10. Drolet M, Bénard É, Pérez N, et al. HPV Vaccination Impact Study Group. Population-level impact and herd effects following the introduction of human papillomavirus vaccination programmes: updated systematic review and meta-analysis. Lancet. 2019; 394(10197): 497–509, doi: 10.1016/S0140-6736(19)30298-3, indexed in Pubmed: 31255301.
11. Gidengil C, Goetz MB, Newberry S, et al. Safety of vaccines used for routine immunization in the United States: An updated systematic review and meta-analysis. Vaccine. 2021; 39(28): 3696–3716, doi: 10.1016/j.vaccine.2021.03.079, indexed in Pubmed: 34049735.
12. Andrews N, Stowe J, Miller E. No increased risk of Guillain-Barré syndrome after human papilloma virus vaccine: A self-controlled case-series study in England. Vaccine. 2017; 35(13): 1729–1732, doi: 10.1016/j.vaccine.2017.01.076, indexed in Pubmed: 28245941.
13. Hviid A, Thorsen NM, Valentiner-Branth P, et al. Association between quadrivalent human papillomavirus vaccination and selected syndromes with autonomic dysfunction in Danish females: population based, self-controlled, case series analysis. BMJ. 2020; 370: m2930, doi: 10.1136/bmj.m2930, indexed in Pubmed: 32878745.
14. Barboi A, Gibbons CH, Axelrod F, et al. American Autonomic Society, American Autonomic Society. Human papillomavirus (HPV) vaccine and autonomic disorders: a position statement from the American Autonomic Society. Clin Auton Res. 2020; 30(1): 13–18, doi: 10.1007/s10286-019-00608-w, indexed in Pubmed: 31475305.
15. Gøtzsche PC, Jørgensen KJ. EMA's mishandling of an investigation into suspected serious neurological harms of HPV vaccines. BMJ Evid Based Med. 2022; 27(1): 7–10, doi: 10.1136/bmjebm-2020-111470, indexed in Pubmed: 33514652.
16. Tatang C, Arredondo Bisonó T, Bergamasco A, et al. Human Papillomavirus Vaccination and Premature Ovarian Failure: A Disproportionality Analysis Using the Vaccine Adverse Event Reporting System. Drugs Real World Outcomes. 2022; 9(1): 79–90, doi: 10.1007/s40801-021-00271-6, indexed in Pubmed: 34510402.
17. Bonaldo G, Vaccheri A, D'Annibali O, et al. Safety profile of human papilloma virus vaccines: an analysis of the US Vaccine Adverse Event Reporting System from 2007 to 2017. Br J Clin Pharmacol. 2019; 85(3): 634–643, doi: 10.1111/bcp.13841, indexed in Pubmed: 30569481.
18. Vichnin M, Bonanni P, Klein NP, et al. An Overview of Quadrivalent Human Papillomavirus Vaccine Safety: 2006 to 2015. Pediatr Infect Dis J. 2015; 34(9): 983–991, doi: 10.1097/INF.0000000000000793, indexed in Pubmed: 26107345.
19. Joura EA, Giuliano AR, Iversen OE, et al. Broad Spectrum HPV Vaccine Study. A 9-valent HPV vaccine against infection and intraepithelial neoplasia in women. N Engl J Med. 2015; 372(8): 711–723, doi: 10.1056/NEJMoa1405044, indexed in Pubmed: 25693011.
20. Goss MA, Lievano F, Buchanan KM, et al. Final report on exposure during pregnancy from a pregnancy registry for quadrivalent human papillomavirus vaccine. Vaccine. 2015; 33(29): 3422–3428, doi: 10.1016/j.vaccine.2015.04.014, indexed in Pubmed: 25869893.
21. Scheller NM, Pasternak B, Mølgaard-Nielsen D, et al. Quadrivalent HPV Vaccination and the Risk of Adverse Pregnancy Outcomes. N Engl J Med. 2017; 376(13): 1223–1233, doi: 10.1056/NEJMoa1612296, indexed in Pubmed: 28355499.
22. Schwarz TF, Huang LM, Lin TY, et al. Long-term immunogenicity and safety of the HPV-16/18 AS04-adjuvanted vaccine in 10- to 14-year-old girls: open 6-year follow-up of an initial observer-blinded, randomized trial. Pediatr Infect Dis J. 2014; 33(12): 1255–1261, doi: 10.1097/INF.0000000000000460, indexed in Pubmed: 24978856.
23. Kjaer SK, Sigurdsson K, Iversen OE, et al. A pooled analysis of continued prophylactic efficacy of quadrivalent human papillomavirus (Types 6/11/16/18) vaccine against high-grade cervical and external genital lesions. Cancer Prev Res (Phila). 2009; 2(10): 868–878, doi: 10.1158/1940-6207.CAPR-09-0031, indexed in Pubmed: 19789295.
24. Lehtinen M, Paavonen J, Wheeler C, et al. Overall efficacy of HPV-16/18 AS04-adjuvanted vaccine against grade 3 or greater cervical intraepithelial neoplasia: 4-year end-of-study analysis of the randomised, double-blind PATRICIA trial. Lancet Oncol. 2012; 13(1): 89–99, doi: 10.1016/s1470-2045(11)70286-8.
25. Hildesheim A, Wacholder S, Catteau G, et al. CVT Group. Efficacy of the HPV-16/18 vaccine: final according to protocol results from the blinded phase of the randomized Costa Rica HPV-16/18 vaccine trial. Vaccine. 2014; 32(39): 5087–5097, doi: 10.1016/j.vaccine.2014.06.038, indexed in Pubmed: 25018097.
26. Giuliano AR, Palefsky JM, Goldstone S, et al. Efficacy of quadrivalent HPV vaccine against HPV Infection and disease in males. N Engl J Med. 2011; 364(5): 401–411, doi: 10.1056/NEJMoa0909537, indexed in Pubmed: 21288094.
27. Olsson SE, Restrepo JA, Reina JC, et al. Long-term immunogenicity, effectiveness, and safety of nine-valent human papillomavirus vaccine in girls and boys 9 to 15 years of age: Interim analysis after 8 years of follow-up. Papillomavirus Res. 2020; 10: 100203, doi: 10.1016/j.pvr.2020.100203, indexed in Pubmed: 32659510.
28. Kjaer SK, Nygård M, Sundström K, et al. Final analysis of a 14-year long-term follow-up study of the effectiveness and immunogenicity of the quadrivalent human papillomavirus vaccine in women from four nordic countries. EClinicalMedicine. 2020; 23: 100401, doi: 10.1016/j.eclinm.2020.100401, indexed in Pubmed: 32637895.
29. Lehtinen M, Apter D, Eriksson T, et al. Effectiveness of the AS04-adjuvanted HPV-16/18 vaccine in reducing oropharyngeal HPV infections in young females-Results from a community-randomized trial. Int J Cancer. 2020; 147(1): 170–174, doi: 10.1002/ijc.32791, indexed in Pubmed: 31736068.
30. Brisson M, Bénard É, Drolet M, et al. Population-level impact, herd immunity, and elimination after human papillomavirus vaccination: a systematic review and meta-analysis of predictions from transmission-dynamic models. Lancet Public Health. 2016; 1(1): e8–ee17, doi: 10.1016/S2468-2667(16)30001-9, indexed in Pubmed: 29253379.
31. Falcaro M, Castañon A, Ndlela B, et al. The effects of the national HPV vaccination programme in England, UK, on cervical cancer and grade 3 cervical intraepithelial neoplasia incidence: a register-based observational study. Lancet. 2021; 398(10316): 2084–2092, doi: 10.1016/S0140-6736(21)02178-4, indexed in Pubmed: 34741816.
32. Lei J, Ploner A, Elfström K, et al. HPV Vaccination and the Risk of Invasive Cervical Cancer. N Engl J Med. 2020; 383(14): 1340–1348, doi: 10.1056/nejmoa1917338.
33. Kjaer SK, Dehlendorff C, Belmonte F, et al. Real-World Effectiveness of Human Papillomavirus Vaccination Against Cervical Cancer. J Natl Cancer Inst. 2021; 113(10): 1329–1335, doi: 10.1093/jnci/djab080, indexed in Pubmed: 33876216.
34. Muñoz-Quiles C, López-Lacort M, Díez-Domingo J, et al. Human papillomavirus vaccines effectiveness to prevent genital warts: A population-based study using health system integrated databases, 2009-2017. Vaccine. 2022; 40(2): 316–324, doi: 10.1016/j.vaccine.2021.11.062, indexed in Pubmed: 34865874.
35. Yuill S, Egger S, Smith M, et al. Has Human Papillomavirus (HPV) Vaccination Prevented Adverse Pregnancy Outcomes? Population-Level Analysis After 8 Years of a National HPV Vaccination Program in Australia. J Infect Dis. 2020; 222(3): 499–508, doi: 10.1093/infdis/jiaa106, indexed in Pubmed: 32386228.
36. Dehlendorff C, Baandrup L, Kjaer SK. Real-World Effectiveness of Human Papillomavirus Vaccination Against Vulvovaginal High-Grade Precancerous Lesions and Cancers. J Natl Cancer Inst. 2021; 113(7): 869–874, doi: 10.1093/jnci/djaa209, indexed in Pubmed: 33377930.

37. Chaturvedi AK, Graubard BI, Broutian T, et al. Effect of Prophylactic Human Papillomavirus (HPV) Vaccination on Oral HPV Infections Among Young Adults in the United States. J Clin Oncol. 2018; 36(3): 262–267, doi: 10.1200/JCO.2017.75.0141, indexed in Pubmed: 29182497.
38. Denny LA, Franceschi S, de Sanjosé S, et al. Human papillomavirus, human immunodeficiency virus and immunosuppression. Vaccine. 2012; 30 Suppl 5: F168–F174, doi: 10.1016/j.vaccine.2012.06.045, indexed in Pubmed: 23199960.
39. Tanweer MS, Aljurf M, Savani BN, et al. Lower Genital Tract Precancer and Cancer in Hematopoietic Cell Transplant Survivors and the Role of HPV: A Systematic Review and Future Perspectives. Clin Hematol Int. 2019; 1(3): 142–153, doi: 10.2991/chi.d.190519.001, indexed in Pubmed: 34595424.
40. Wielgos AA, Pietrzak B. Human papilloma virus-related premalignant and malignant lesions of the cervix and anogenital tract in immunocompromised women. Ginekol Pol. 2020; 91(1): 32–37, doi: 10.5603/GP.2020.0008, indexed in Pubmed: 32039466.
41. Gómez de la Rosa AG, Quesada López-Fe A, Vilar Chesa M, et al. Efficacy of Human Papillomavirus Vaccination 4 Years After Conization for High-Grade Cervical Neoplasia. J Low Genit Tract Dis. 2021; 25(4): 287–290, doi: 10.1097/LGT.0000000000000625, indexed in Pubmed: 34456270.
42. Di Donato V, Caruso G, Petrillo M, et al. Adjuvant HPV Vaccination to Prevent Recurrent Cervical Dysplasia after Surgical Treatment: A Meta-Analysis. Vaccines (Basel). 2021; 9(5), doi: 10.3390/vaccines9050410, indexed in Pubmed: 33919003.
43. Sand FL, Frederiksen K, Kjaer SK, et al. Risk of cervical intraepithelial neoplasia grade 2 or worse after conization in relation to HPV vaccination status. Int J Cancer. 2020; 147(3): 641–647, doi: 10.1002/ijc.32752, indexed in Pubmed: 31648368.
44. World Health Organization. Global strategy to accelerate the elimination of cervical cancer as a public health problem. WHO, Geneva 2020.
45. European Centre for Disease Prevention and Control. Prevention and Control. Guidance on HPV vaccination in EU countries: focus on boys, people living with HIV and 9-valent HPV vaccine introduction. European Centre for Disease Prevention and Control, Stockholm 2020.
46. Meites E, Szilagyi PG, Chesson HW, et al. Human Papillomavirus Vaccination for Adults: Updated Recommendations of the Advisory Committee on Immunization Practices. MMWR Morb Mortal Wkly Rep. 2019; 68(32): 698–702, doi: 10.15585/mmwr.mm6832a3, indexed in Pubmed: 31415491.
47. Uchwała nr 10 Rady Ministrów z dnia 4 lutego 2020 r. w sprawie przyjęcia programu wieloletniego pn. Narodowa Strategia Onkologiczna na lata 2020-2030, Dz.U. 2019 poz. 969.
48. Rekomendacja nr 128/2021 z dnia 25 listopada 2021 r. Prezesa Agencji Oceny Technologii Medycznych i Taryfikacji w sprawie oceny leku Gardasil, szczepionka przeciw wirusowi brodawczaka ludzkiego [typy 6, 11, 16, 18] we wskazaniu: zapobieganie wystąpienia u osób w wieku od 9 lat: zmian przednowotworowych narządów płciowych (szyjki macicy, sromu i pochwy), zmian przednowotworowych odbytu, raka szyjki macicy oraz raka odbytu, związanych przyczynowo z zakażeniem pewnymi onkogennymi typami wirusa brodawczaka ludzkiego (HPV); brodawek narządów płciowych (kłykcin kończystych) związanych przyczynowo z zakażeniem określonymi typami wirusa brodawczaka ludzkiego.
49. Rekomendacja nr 54/2021 z dnia 18 maja 2021 r. Prezesa Agencji Oceny Technologii Medycznych i Taryfikacji w sprawie objęcia refundacją leku Cervarix, szczepionka przeciw wirusowi brodawczaka ludzkiego [typy 16 i 18] we wskazaniu: profilaktyka zmian przednowotworowych narządów płciowych i odbytu (szyjki macicy, sromu, pochwy i odbytu) oraz raka szyjki macicy i raka odbytu związanych przyczynowo z określonymi onkogennymi typami wirusa brodawczaka ludzkiego (HPV) u osób od ukończenia 9. roku życia.
50. Nowakowski A, Arbyn M, Turkot MH, et al. A roadmap for a comprehensive control of cervical cancer in Poland: integration of available solutions into current practice in primary and secondary prevention. Eur J Cancer Prev. 2020; 29(2): 157–164, doi: 10.1097/CEJ.0000000000000528, indexed in Pubmed: 31517672.
51. Bidziński M, Debski R, Kedzia W, et al. Stanowisko zespołu ekspertów Polskiego Towarzystwa Ginekologicznego na temat profilaktyki raka gruczołowego szyjki macicy. Ginekol Pol. 2008; 79(10): 710–714.
52. Pediatria Polska. 85; 4(Lipiec-Sierpień 2010).
53. Agencja Oceny Technologii Medycznych i Taryfikacji, Wydział Oceny Technologii Medycznych. Profilaktyka zakażeń wirusem brodawczaka ludzkiego (HPV) w ramach programów polityki zdrowotnej Warszawa. Raport w sprawie zalecanych technologii medycznych, działań przeprowadzanych w ramach programów polityki zdrowotnej oraz warunków realizacji tych programów polityki zdrowotnej – materiały dla Rady Przejrzystości AOTMiT. Warszawa, 2019. https://bipold.aotm.gov.pl/assets/files/ppz/2019/RPT/19.10.29_raport_zalec_techn_art_48aa_profilaktyka_hpv.pdf (20.10.2021).
54. Wydział Zdrowia i Spraw Społecznych Urzędu Miejskiego Wrocławia. Wrocławski program profilaktyki zakażeń wirusem brodawczaka ludzkiego. https://hpv.um.wroc.pl/?p=561 (20.10.2021).
55. Ludwikowska KM, Szenborn L, Krzyżanowska I, et al. Potrzeba, bezpieczeństwo oraz realizacja szczepień przeciwko HPV - perspektywa wrocławska. Klin Pediatr . 2018; 26(1): 26–30.
56. Ludwikowska KM, Biela M, Szenborn L. HPV vaccine acceptance and hesitancy - lessons learned during 8 years of regional HPV prophylaxis program in Wroclaw, Poland. Eur J Cancer Prev. 2020; 29(4): 346–349, doi: 10.1097/CEJ.0000000000000556, indexed in Pubmed: 31770346.
57. Nguyen-Huu NH, Thilly N, Derrough T, et al. HPV Policy working group. Human papillomavirus vaccination coverage, policies, and practical implementation across Europe. Vaccine. 2020; 38(6): 1315–1331, doi: 10.1016/j.vaccine.2019.11.081, indexed in Pubmed: 31836255.
58. Brown B, Gabra MI, Pellman H. Reasons for acceptance or refusal of Human Papillomavirus Vaccine in a California pediatric practice. Papillomavirus Res. 2017; 3: 42–45, doi: 10.1016/j.pvr.2017.01.002, indexed in Pubmed: 28720455.
59. Facciolà A, Visalli G, Orlando A, et al. Vaccine hesitancy: An overview on parents' opinions about vaccination and possible reasons of vaccine refusal. J Public Health Res. 2019; 8(1): 1436, doi: 10.4081/jphr.2019.1436, indexed in Pubmed: 30997357.

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A case report of laparoscopic pectopexy in a patient with an ectopic kidney and POP-Q III grade apical prolapse

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A 70-year-old woman [gravida 2, para 2, body mass index (BMI) 27 kg/m^2] was referred to the hospital due to clinically symptomatic POP-Q III grade apical prolapse (Aa –1, Ba +2, C +5, Ap –2, Bp –2; TVL 9 cm). The patient presented with a congenital renal anomaly: asymptomatic, left pelvic kidney located below the iliac fossa, with the left ureter located approximately 4 mm from the uterus (confirmed by a preoperative CT scan — Figure 1). The patient completed the PFDI-20, PFIQ-SF, and ISI questionnaires at baseline and one month postoperatively, and reported no symptoms of urinary or fecal incontinence.

Medical history revealed the following comorbidities: hypertension, paroxysmal atrial fibrillation, ulcerative colitis, and colonic diverticulosis. The patient underwent uterine curettage before pectopexy, which is a standard procedure at our center if the uterine corpus is to be removed. Preoperatively, a vaginal cube pessary was attempted but this conservative management was ineffective due to intolerance of the pessary and pain, which significantly affected the quality of the patient life.

Laparoscopic pectopexy was performed, as described in the literature [1]. Total operative time was 155 min., and included adhesion dissection, removal of the uterine corpus with the right adnexa, and suturing of a synthetic mesh (polypropylene, 20/35 × 159 mm) to the cervical stump (4 nonabsorbable, braided, polyester sutures) and iliopectineal ligaments (1 braided, polyester suture). At the final stage of the surgery, total mesh peritonization was performed using absorbable, continuous intracorporeal suturing (Fig. 2). The postoperative course was uneventful. The patient was discharged on postoperative day 2. At one-month follow-up, urogynecologic examination revealed no evidence of apical prolapse recurrence (Aa –3, Ba –3, C –8, Ap –2, Bp –2; TVL 9 cm) and the patient had no complaints.

To the best of our knowledge, this has been the first report about a laparoscopic pectopexy in a patient with congenital renal anomaly. Considerable interest in the topic of apical defect and a growing number of reports about complications following sacrocolpo(cervico)pexy prompted the researchers to search for new and effective methods of apical defect treatment [2–4]. Sacrocolpo(cervico)pexy is not recommended in patients with obesity and limited access to the promontory, *e.g.*, in case of colonic diverticulosis [5]. The worldwide incidence of ectopic kidney has been estimated at approximately 1 in 1000 live births [6]. The choice of surgery in such patients should take into consideration possible complications associated with the presence of an ectopic kidney [7]. In our case, we believe that laparoscopic pectopexy will not affect any future surgical treatment due to renal causes. Additional, safety-related procedures like peritonization of the synthetic mesh may reduce the risk of complications such as mesh exposure, organ perforation, or future urinary or bowel issues.

In summary, laparoscopic pectopexy seems to be a promising surgical treatment for apical defect in patients with congenital kidney defects.

Article information and declarations

Conflict of interest

The authors declare no conflict of interest.

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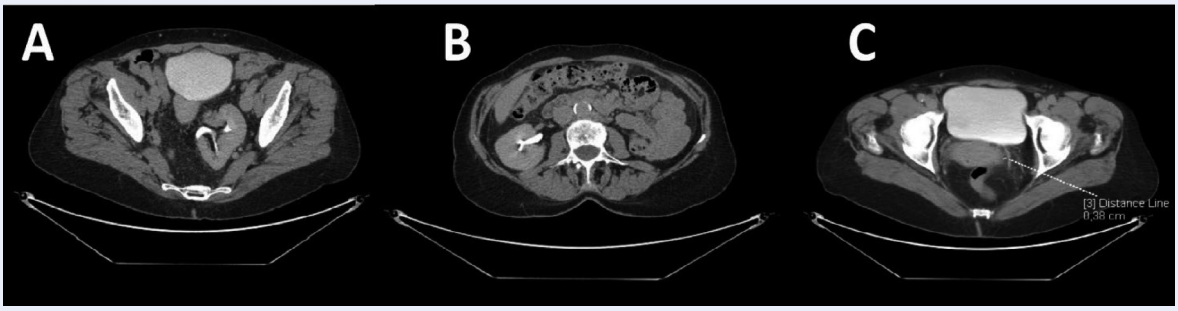

Figure 1. Preoperative CT scan – the location of left kidney (**A**) and right kidney (**B**). The renal pelvis is white because iodinated contrast has filled the collecting system. Noteworthy is the position of the left kidney - the pelvic kidney (**B**). The last scan showed the location of the left ureter in relation to the uterus (**C**)

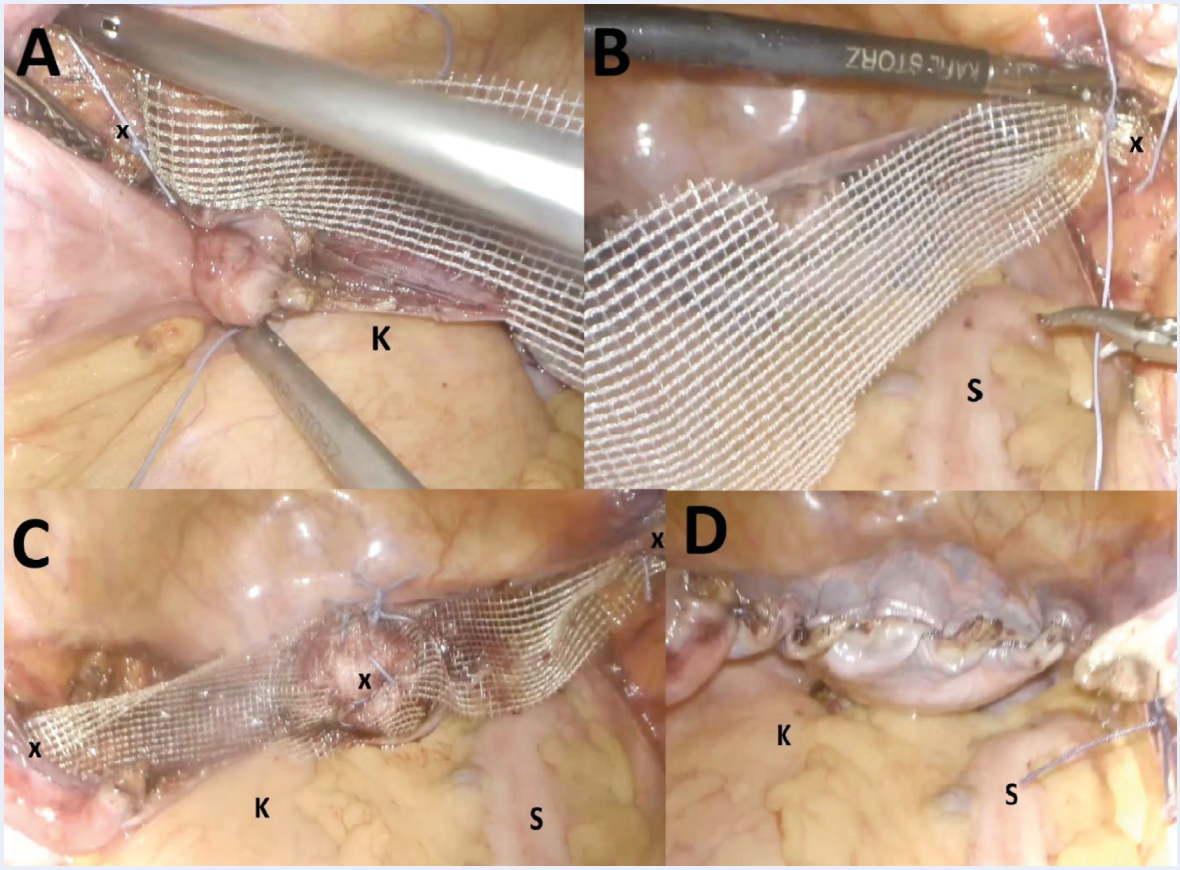

Figure 2. Laparoscopic pectopexy: mesh fixation to the left (**A**) and right (**B**) iliopectineal ligaments (x), to the cervical stump (**C**) and the final view (**D**) of the operation; K — ectopic kidney; S — sigmoid colon

REFERENCES

1. Szymczak P, Grzybowska ME, Sawicki S, et al. Laparoscopic Pectopexy-CUSUM Learning Curve and Perioperative Complications Analysis. J Clin Med. 2021; 10(5), doi: 10.3390/jcm10051052, indexed in Pubmed: 33806294.
2. Noé KG, Schiermeier S, Alkatout I, et al. Laparoscopic pectopexy: a prospective, randomized, comparative clinical trial of standard laparoscopic sacral colpocervicopexy with the new laparoscopic pectopexy-postoperative results and intermediate-term follow-up in a pilot study. J Endourol. 2015; 29(2): 210–215, doi: 10.1089/end.2014.0413, indexed in Pubmed: 25350228.
3. Galczyński K, Nowakowski L, Romanek-Piva K, et al. Laparoscopic mesh procedures for the treatment of pelvic lorgan prolapse--review of the literature. Ginekol Pol. 2014; 85(12): 950–954, doi: 10.17772/gp/1888, indexed in Pubmed: 25669066.
4. Baranowski W, Stangel-Wojcikiewicz K, Grzybowska ME, et al. Urogynecology Section of the Polish Society of Gynecologists and Obstetricians Guidelines on the management of recurrent pelvic organ prolapse. Ginekol Pol. 2022 [Epub ahead of print], doi: 10.5603/GP.a2021.0218, indexed in Pubmed: 35072263.
5. Banerjee C, Noé KG. Laparoscopic pectopexy: a new technique of prolapse surgery for obese patients. Arch Gynecol Obstet. 2011; 284(3): 631–635, doi: 10.1007/s00404-010-1687-7, indexed in Pubmed: 20941503.
6. Bingham G, Leslie SW. Pelvic Kidney [Updated 2022 Sep 26]. In: StatPearls [Internet]. StatPearls Publishing, Treasure Island 2022.
7. Eid S, Iwanaga J, Loukas M, et al. Pelvic Kidney: A Review of the Literature. Cureus. 2018; 10(6): e2775, doi: 10.7759/cureus.2775, indexed in Pubmed: 30109168.