Edited since 1922

POLISH GYNECOLOGY

GINEKOLOGIA POLSKA

no 3/vol 92/2021

ORGAN POLSKIEGO TOWARZYSTWA GINEKOLOGÓW I POŁOŻNIKÓW
THE OFFICIAL JOURNAL OF THE POLISH SOCIETY OF GYNECOLOGISTS AND OBSTETRICIANS

IF: **0.941,** MNiSW: **40**

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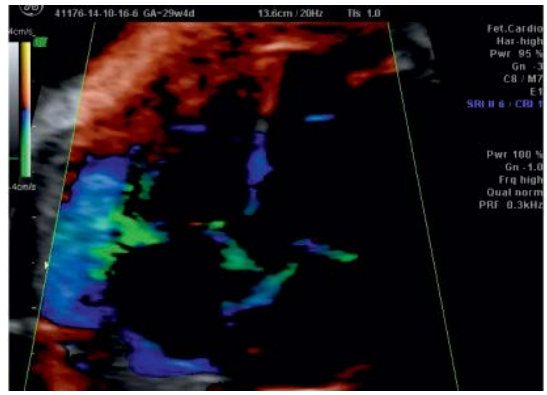

GINEKOLOGIA POLSKA 2021, VOL 92, NO 3, PAGES 175–256

ISSN 0017–0011
e-ISSN 2543–6767

VIA MEDICA

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Ginekologia Polska is published monthly, twelve volumes a year, by VM Media sp. z o.o. VM Group sp.k.,
73 Świętokrzyska St, 80–180 Gdańsk, Poland, phone: (+48 58) 320 94 94, fax: (+48 58) 320 94 60,
e-mail: redakcja@viamedica.pl, marketing@viamedica.pl, http://www.viamedica.pl

Editorial office address: Woman's Health Institute, School of Health Sciences, Medical University of Silesia in Katowice, 12 Medyków St, 40–752 Katowice, e-mail: ginpol@viamedica.pl

Indexed in: CrossRef, DOAJ, Index Copernicus, Ministry of Science and Higher Education (40), POL-Index, Polish Medical Bibliography, PubMed, Science Citation Index Expanded (0.941), Scimago Journal Rank, Scopus, Ulrich's Periodicals Directory

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POLISH GYNECOLOGY
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Ginekologia Polska
2021, vol. 92, no. 3, 175–182

ISSN 0017–0011, e-ISSN 2543–6767

DOI 10.5603/GP.a2021.0022

The impact of multimodal therapies on the comfort and safety of patients in the immediate post-anaesthetic period following gynaecological procedures — part II

Agnieszka Biskup[1], Katarzyna Plagens-Rotman[2], Maria Polocka-Molinska[2], Piotr Merks[3, 4]

[1]*Independent Public Clinical Hospital No. 1, Szczecin, Poland*
[2]*Hipolit Cegielski State University of Applied Sciences, Gniezno, Poland*
[3]*Faculty of Medicine, Collegium Medicum, Cardinal Stefan Wyszyński University, Warsaw, Poland*
[4]*Department of Pharmaceutical Technology, Faculty of Pharmacy, Collegium Medicum in Bydgoszcz, Poland*

ABSTRACT

Objectives: The second part of the study was to assess the effects of the types of anaesthesia along with multimodal analgesia on the stability of vital functions at the critical moment of awakening from anaesthesia.

Materials and methods: The material comprised the medical records at the Department of Anaesthesiology and Intensive Care in Szczecin. The anaesthesia record forms and recovery room observation charts of 150 patients from the Gynaecology Clinic who had undergone category III and IV surgical procedures between October 2018 and January 2019 were selected for analysis. The patients were divided into three groups:

1. Patients given multimodal analgesia with non-opioid and opioid analgesics.
2. Patients given multimodal analgesia with non-opioid analgesics and adjuvants.
3. Patients given multimodal analgesia with non-opioid and opioid analgesics, as well as neuraxial anaesthesia.

Results: The average minimum heart rate in the operating room was 63.92 in group I, 61.48 in group II, and 62.34 in group III. The most common cause of bradycardia during surgery was insufflation. The average SBP prior to surgery was similar in groups I and II — 128.74 and 128.66, respectively. The average maximum values during surgery were 135.24 in group I, 139.34 in group II, and 142.32 in group III.

At the time of discharge from the post-anaesthetic care unit, all the patients from the study group had achieved an Aldrete score of 10. Following the anaesthesia, 24% of the patients in group I, 22% in group II, and 28% in group III required oxygen therapy.

Conclusions: When using multimodal analgesia, the time required to fully awaken even after extensive surgical procedures was no longer than two hours.

Key words: multimodal therapies; tachycardia; bradycrdia

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INTRODUCTION

The ERAS protocol, first outlined by Danish surgeon Henrik Kehlet in the 1990s, assumes that the development of post-operative complications is influenced not only by the surgical procedure and anaesthesia, but also by the perioperative management. Older age increases the likelihood of diseases requiring surgical treatment, thus the number of older patients undergoing surgeries is increasing. Old age is an additional independent risk factor for increased perioperative mortality.

Therefore, the implementation of comprehensive post-operative care increases the chance of an uncomplicated postoperative course. The elements of such care include analgesic treatment, prevention of nausea and vomiting, as well as maintenance of normothermia.

Corresponding author:
Katarzyna Plagens-Rotman
Hipolit Cegielski State University of Applied Sciences, 38 Stefana Wyszynskiego St, 62–200 Gniezno, Poland
e-mail: plagens.rotman@gmail.com

The aim of the second part of the study was to assess the effects of the types of anaesthesia along with multimodal analgesia on the stability of vital functions at the critical moment of awakening from anaesthesia.

MATERIAL AND METHODS

The material comprised the medical records at the Department of Anaesthesiology and Intensive Care at one of the clinical hospitals in Szczecin. The anaesthesia record forms and recovery room observation charts of 150 patients from the Gynaecology Clinic who had undergone category III and IV surgical procedures between October 2018 and January 2019 were selected for analysis. The patients were divided into three groups:

1. Patients given multimodal analgesia with non-opioid and opioid analgesics.
2. Patients given multimodal analgesia with non-opioid analgesics and adjuvants.
3. Patients given multimodal analgesia with non-opioid and opioid analgesics, as well as neuraxial anaesthesia.

RESULTS

During the surgical procedures and in the post-anaesthetic care unit, all the patients were monitored for heart rate, blood pressure and oxygen saturation. These values were compared with those prior to the anaesthesia, the average values during surgery and in the post-anaesthetic care unit, and the minimum and maximum values during surgery and in the recovery room (Fig. 1–3).

The average minimum heart rate in the operating room was 63.92 in group I, 61.48 in group II, and 62.34 in group III. The most common cause of bradycardia during surgery

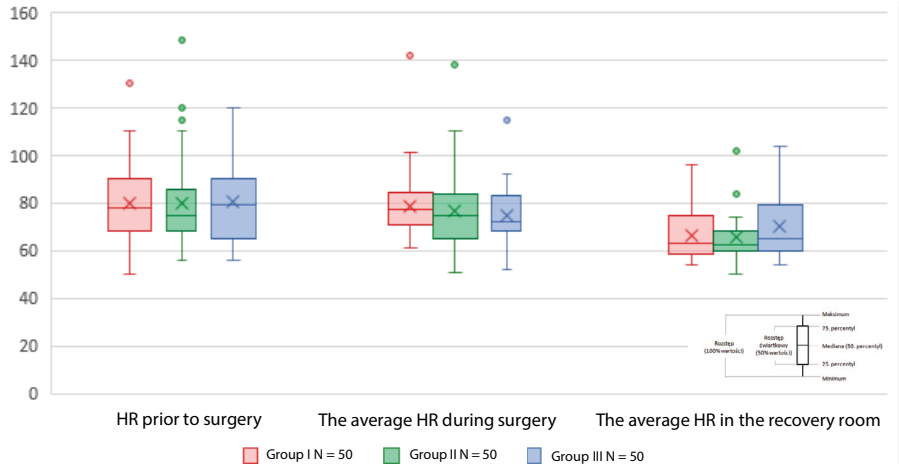

Figure 1. HR (pulse) in the perioperative period

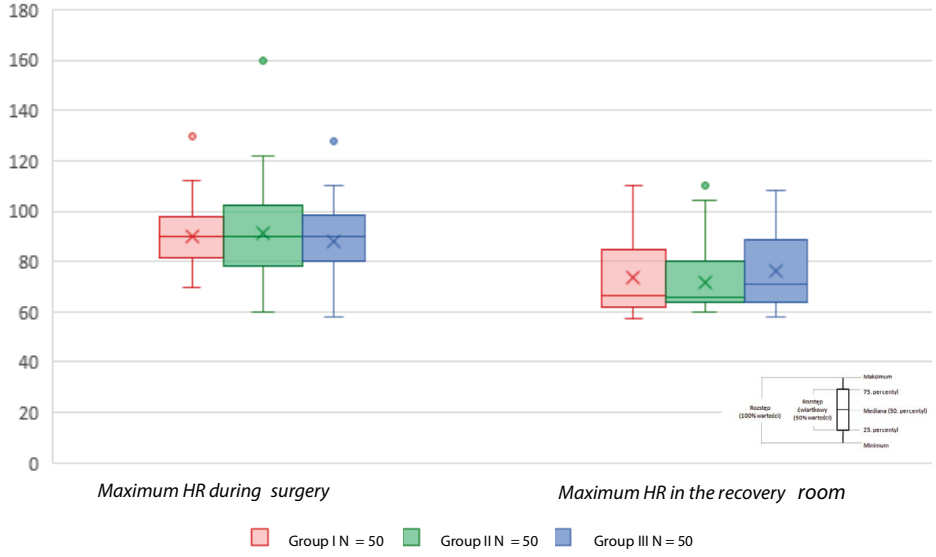

Figure 2. Maximum HR (pulse) in the perioperative period

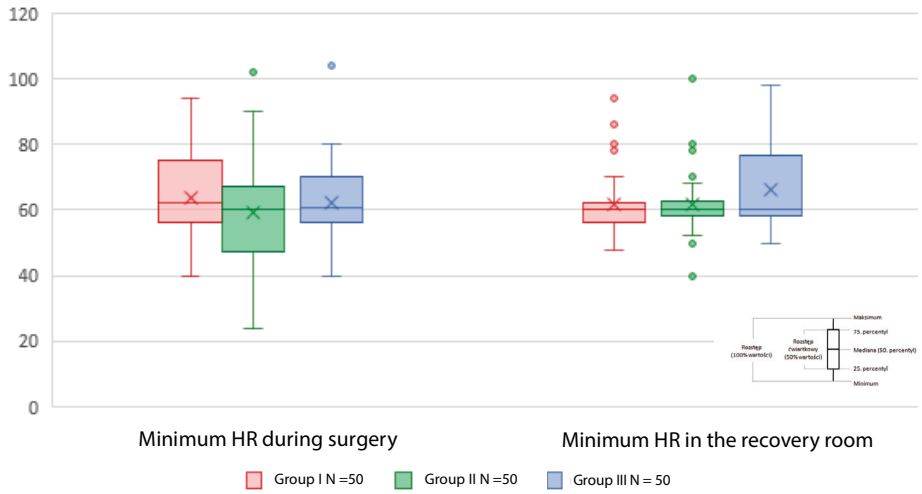

Figure 3. HR (pulse) in the perioperative period

Table 1. Causes of tachycardia in the operating room

Cause of tachycardia in the operating room	Group I N = 50	Group II N = 50	Group III N = 50
Medical History	1	1	0
Stress	10	12	15
Intubation	1	0	0
Pain	7	7	6
Haemorrhage	1	2	1
Insufflation	2	2	1
Medications (atropine)	1	1	1
Anaemia	0	0	1
Awakening	3	0	0
Total	26	25	25

Source: own study

Table 2. Causes of bradycrdia in the operating room

Cause of bradycardia in the operating room	Group I N = 50	Group II N = 50	Group III N = 50
Medical History	3	2	3
Intubation/Induction of anaesthesia	1	3	5
Insufflation	2	7	0
Opioids	0	1	0
Sympathetic blockade	–	–	2
Unknown	0	0	1
Total	6	13	11

Source: own study

was insufflation. The detailed causes of tachycardia and bradycardia are presented in Tables 1–3.

Systolic blood pressure (SBP) values prior to anaesthesia, average values during surgery and in post-anaesthetic

Table 3. Causes of tachycardia and bradycardia in the recovery room

Recovery room	Group I	Group II	Group III
Tachycardia	On entry — 2	On entry — 1	On entry — 1
			Pain — 1
			Hypovolemia – 1
			Anaemia — 1
Total	2	1	4
Bradycardia	On entry — 3	On entry — 3	0

Source: own study

care, as well as the minimum and maximum values during surgery and in the recovery room were compared (Fig. 4–6). The average SBP prior to surgery was similar in groups I and II — 128.74 and 128.66, respectively. The average maximum values during surgery were 135.24 in group I, 139.34 in group II, and 142.32 in group III.

In more than half of the patients from group III (64%), an SBP of 140 mmHg or higher was noted at least once during the intraoperative period.

Similarly, to tachycardia, the most common cause of a higher SBP was preoperative stress (30% of the patients in each group). The remaining causes of elevated or lowered SBP in the intraoperative period are presented in Tables 4 and 5.

In the post-anaesthetic care unit, an elevated SBP was recorded in 7 patients from groups I and II, and in 5 patients from group III immediately after awakening, at the first measurement taken after leaving the operating room. A pain-related elevated blood pressure was observed in 3 patients from group I and 2 patients from group III (Tab. 6).

In the operating room, oxygen saturation of 92–94% (Fig. 7) was noted prior to surgery in 1 patient from groups

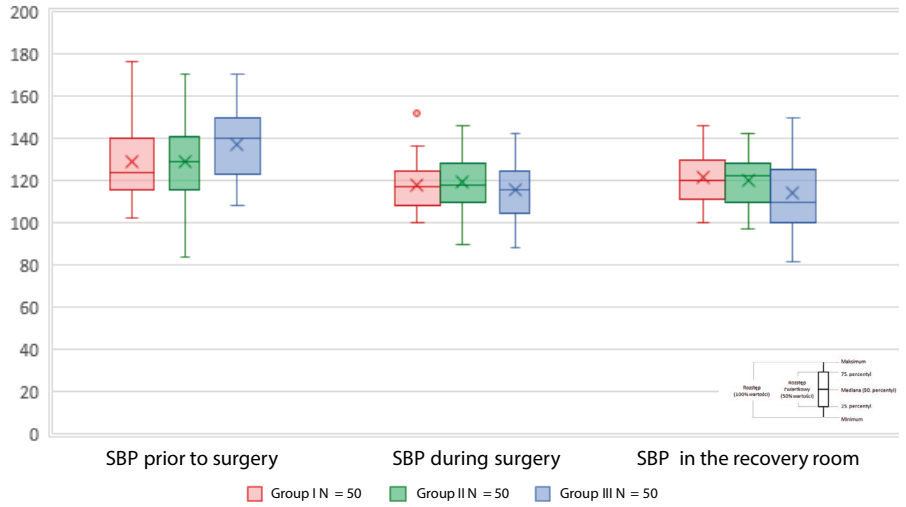

Figure 4. Systolic blood pressure in the perioperative period; SBP — systolic blood pressure

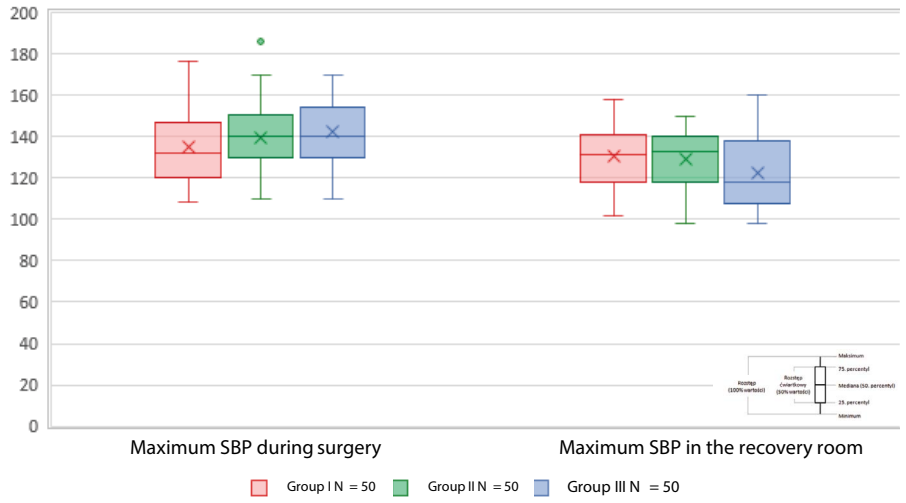

Figure 5. Maximum systolic blood pressure in the perioperative period; SBP — systolic blood pressure

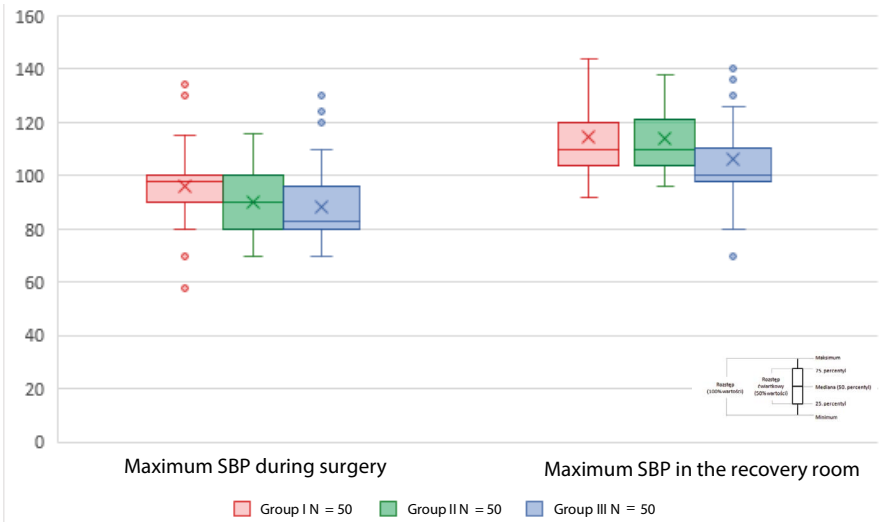

Figure 6. Minimum systolic blood pressure in the perioperative period; SBP — systolic blood pressure

Table 4. Causes of elevated SBP in the operating room

Cause of elevated SBP in the operating room	Group I N = 50	Group II N = 50	Group III N = 50
History of HA	2	2	1
Stress	17	19	19
Intubation/Induction of anaesthesia	3	2	0
Pain	9	11	7
Instability/Other causes	1	1 – before bradycardia	1
Awakening	0	1	2
Total	32	36	30

Source: own study; HA — Hypertonia arterialis

Table 5. Causes of hypotonia in the operating room

Cause of hypotonia in the operating room	Group I N = 50	Group II N = 50	Group III N = 50
Induction	3	9	2
Opioids	3	4	1
Hypovolemia	1	1	1
Insufflation	0	2	0
Awakening	1	1	0
Sympathetic blockade	–	–	25
Instability/other causes	1	2	2
Total	9	19	31

Source: own study

Table 6. Causes of elevated and lowered SBP in the recovery room

Recovery room	Group I	Group II	Group III
Elevated SBP	On entry — 7	On entry — 7	On entry — 5
	Pain — 3		Pain — 2
	Nausea — 1		Nausea — 1
	Total — 11		Total — 8
Lowered SBP	0	0	Hypovolemia — 1 Blockade — 1

Source: own study; SBP — systolic blood pressure

I and II, and in 2 patients from group III, and was caused by stress-induced vasoconstriction (Tab. 7).

In the recovery room, low oxygen saturation was recorded in all the patients immediately after leaving the operating room due to the residual effects of the anaesthetics.

Hypothermia prevention methods included: fluid warming, passive warming and a convective warm-air system. Passive warming is a standard method applied in every patient. Fluid warming with flow-through heaters was used for 60% of the patients in group I, 92% in group II, and 82%

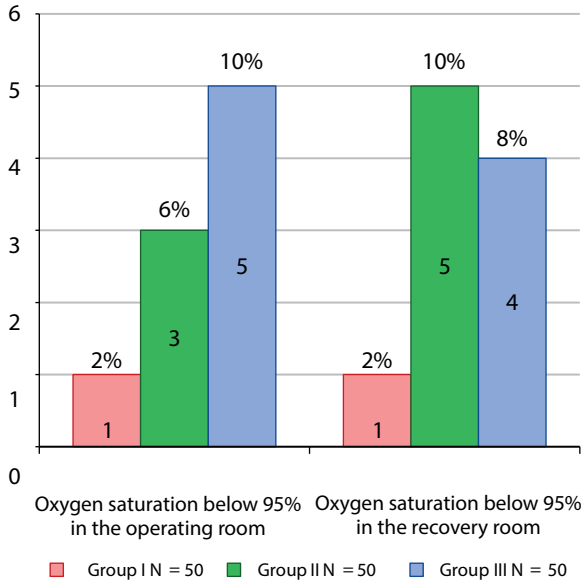

Figure 7. Oxygen saturation in the perioperative period

Table 7. Causes of low oxygen saturation in the perioperative period

	Grupa I N = 50	Grupa II N = 50	Grupa III N = 50
Causes of oxygen saturation below 95% in the operating room	Prior to surgery — cold hands — 1	Prior to surgery — cold hands — 1	Prior to surgery — cold hands — 2
		Haemorrhagic shock — 1	During intubation — 1
		Bronchospasm during desflurane anaesthesia — 1	Anaesthetics in spontaneously breathing patients — 2
Causes of oxygen saturation below 95% in the recovery room	After awakening	After awakening	After awakening

Source: own study

in group III. The convective warming system was used for 60% of the patients from group III, where the longest and extensive surgeries were recorded. Warm air was used for 12% of the patients from group I and 8% from group II. A detailed distribution of hypothermia prevention methods is presented in Figure 8.

The Aldrete scoring system is an important measurement of recovery after anaesthesia. In group II, 1 patient achieved a score of 7 points — she was drowsy, with poor activity, and required oxygen therapy. Eight patients (16%) from group III and 4 patients (8%) from groups I and II achieved a score of 8 points. 20% of the patients from group II and 18% (9) from group I achieved a maximum score of 10 (Fig. 9).

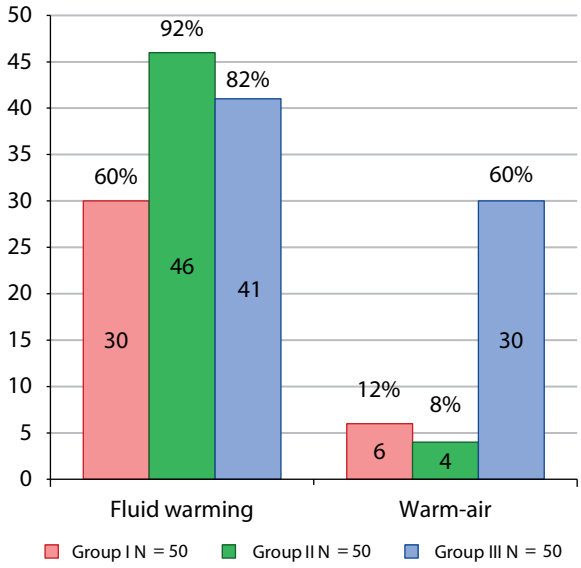

Figure 8. Warming during surgery

At the time of discharge from the post-anaesthetic care unit, all the patients from the study group had achieved an Aldrete score of 10. Following the anaesthesia, 24% of the patients in group I, 22% in group II, and 28% in group III required oxygen therapy.

DISCUSSION

Preventing hypothermia is one element in providing the best perioperative care possible, in compliance with the ERAS protocol. Analysis of the medical charts showed that fluid warming as a method to prevent unintended hypothermia was used in 60% of the patients from group I, 92% from group II, and 82% from group III. The temperature in the operating room was centrally controlled and oscillated around 23–25°C, which is within the limits recommended for the operating room. Bernthal showed that if the temperature in the operating room is less than 21°C, heat loss in the patient increases significantly in the first hour of the surgery, and up to 90% of patients will have hypothermia unless they are protected [1]. All the patients were warmed, either by passive methods or by means of a convective warming system. Warm air was used for 60% of the patients from group III (with the longest surgeries and the oldest patients with a higher surgical risk), 12% from group I, and 8% from group II. After surgery, warm air was used for all the patients. Unfortunately, the temperature was not monitored after surgery, so assessment of its effectiveness was not possible. Studies [2] show that active intraoperative warming methods are most effective at preventing intraoperative hypothermia. The effectiveness of the convective warming system at preventing unintended intraoperative hypothermia has been proven in numerous clinical studies among adults and children, and only when the warmed body surface area was not too limited.

Monitoring during anaesthesia aims at early detection of hazards, identification of the adverse effects of anaesthesia, early corrective actions, and provision of safe anaesthesia.

The most common cause of tachycardia and an elevated SBP noted in the anaesthesia record forms was emotional arousal prior to the induction of anaesthesia. Anxiety can have a negative impact on physiological parameters prior to and during anaesthesia, and patients with high levels of preoperative anxiety have problems with the induction of general anaesthesia and conduction anaesthesia [3]. Besides, patients with high stress levels are more difficult to undergo anaesthesia [4].

Emotional arousal, which is a derivative of the activity of the central nervous, endocrine and sympathetic system, increases the perception of pain [5]. Preoperative tachycardia was observed in 20% of the patients in group I, 24% in group II, and 38% in group III. An elevated SBP was noted in 34% of the women from group I, and 38% from groups II and III. We examined whether preoperative stress impacted

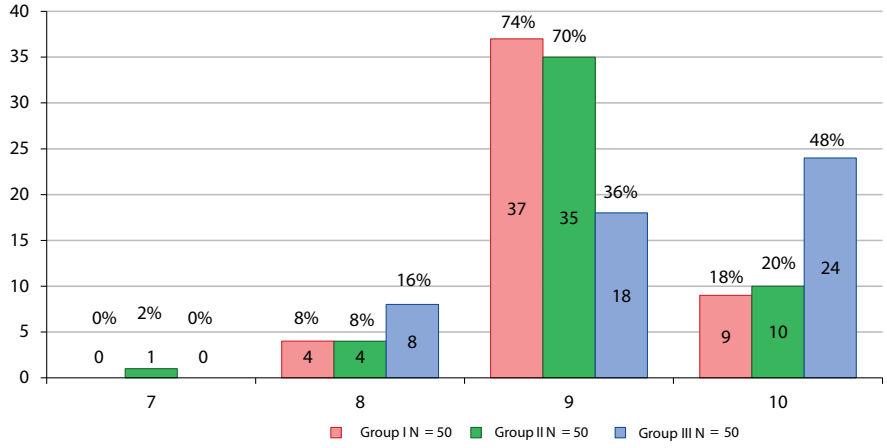

Figure 9. Evaluation of patients immediately after surgery, aldrete score

on the pain qualified as severe (above 5 points according to the NRS scale) in the recovery room, yet the analysis did not show any statistically significant differences between the groups. A similar study was carried out by Sioma-Markowska U et al. [6]. This prospective study included 184 women aged 18–80 years undergoing surgeries for gynaecological diseases. The average postoperative pain value assessed using the Visual Analog Scale (VAS) was significantly higher in the group of patients with general anaesthesia than in the group with epidural anaesthesia [6]. Studies [7–11] show that intense anxiety can have a negative influence on physiological parameters in the early postoperative period, which results in more complications, intensified postoperative pain and extended length of hospital stay. Due to the highly diversified groups and the short time spent in the post-anaesthetic care unit, it was difficult to form any conclusions as to whether multimodal analgesia had an impact on a lack of association between preoperative anxiety and postoperative pain intensity. This is certainly an issue worth further research in this area.

Other causes affecting the cardiovascular system in the study group included factors connected with anaesthesia and surgery.

The anaesthetic-related factors include the type of anaesthetic, its concentration and duration of action. Halogen-containing anaesthetics can cause cardiac depression and even cardiac arrest. At the time of maintenance of the anaesthesia and the lack of surgical stimulation, desflurane and sevoflurane lower the blood pressure [12]. Deep and long anaesthesia can cause tachycardia. Sympathetic blockades result in hypotonia. Surgical stimuli increase the blood pressure and heart rate in the case of all volatile halogen-containing anaesthetics [13]. Conscious responses to pain are not present under general anaesthesia, yet the activation of sympathetic neural and autonomic humoral pathways results in a range of physiological (*e.g.*, haemodynamic) changes that can indirectly indicate intensified surgical stress and inappropriate analgesia [14].

Intubation is also a very strong stimulus that can cause bradycardia, tachycardia, disturbed heart rate, and an elevated blood pressure [15].

Surgery-related factors affecting the cardiovascular system include haemorrhage, insufflation in the case of laparoscopic surgeries, and surgical stimulation of the cranial nerve [15].

In our own study, in the intraoperative period, patients had cardiovascular disorders due to both anaesthetic and surgical reasons, causing instability of vital parameters. In the recovery room, a much higher stability of the cardiovascular system was observed. The average maximum SBP values were significantly lower, particularly in group III — by 20 mmHg, by 10 mmHg in group II, and by 7 mmHg in group I. The average minimum SBP values also were more stable in the recovery room — the average minimum SBP increased by 18 mmHg in groups I and III, and by 23 mmHg in group II. The average maximum heart rate values in the recovery room decreased by 20 beats per minute in groups I and II, and by 12 in group III.

In the post-anaesthetic care unit, a lot of stimuli ceased upon completion of the surgery, yet the moment of awakening is still critical and requires a lot of attention and observation on the part of the nurse, as disorders of the cardiovascular and respiratory systems can appear.

Delayed awakening from anaesthesia is most often associated with the overall bad condition of the patient in the preoperative period, extensive and long surgery accompanied by a lot of anaesthetics, opioids and neuromuscular blockers, as well as the traumatic course of the surgery resulting in a haemorrhage or damage to important organs. In our own study, most patients were discharged from the post-anaesthetic care unit within two hours, *i.e.*, 92% in group I, 88% in group II, and 84% in group III. The causes of lengthened stay in the post-anaesthetic care unit, for more than two hours, were analysed and only in two cases were connected with the patient's condition. Based on the conducted analysis, it can be stated that anaesthesia adjusted to the patient as well as to the extent and technique of the surgery largely contributes to a safe perioperative period and patient comfort.

CONCLUSIONS

Preoperative stress causing an elevated blood pressure and accelerated heart rate did not result in a higher level of pain in the post-anaesthetic care unit.

When using multimodal analgesia, the time required to fully awaken even after extensive surgical procedures was no longer than two hours.

Haemodynamic disorders during surgery do not have to occur in the recovery room.

Temperature control in the perioperative period should be a standard.

Conflict of interest

None.

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VIA MEDICA

ORIGINAL PAPER / GYNECOLOGY

Ginekologia Polska
2021, vol. 92, no. 3, 183–187

ISSN 0017–0011, e-ISSN 2543–6767

DOI 10.5603/GP.a2021.0025

The assessment of selected parameters of bioelectric and mechanical activity of the uterus during pharmacologic treatment of threatening preterm delivery

Marek Tomialowicz[1], Mariusz Zimmer[1], Tomasz Fuchs[1], Adam Matonia[2]

[1]2nd Department of Gynecology and Obstetrics, Wroclaw Medical Univesity, Poland
[2]Lukasiewicz Research Network, Institute of Medical Technology and Equipment, Zabrze, Poland

ABSTRACT

Objectives: To analyze and compare the bioelectric and mechanical activity of the uterus in pregnant women with threatening preterm delivery treated with tocolysis. Additionally, auxiliary parameters of the bioelectric signal, as registered by electrohysterography and characteristic only for this method, were measured and analyzed.

Material and methods: Forty-five women with pregnancies from 24 to 36 weeks of gestation with typical clinical symptoms of threatening preterm delivery were given tocolytic therapy. Registration and analysis of bioelectric activity with electrohysterography was performed simultaneously with registration and analysis of mechanical activity with tocography.

Results: After administration of tocolytic treatment, the presence of bioelectric activity was accompanied by the lack of or minimal occurrence of mechanical activity. All parameters of contraction recorded by electrohysterography had significantly greater values than those recorded by tocography.

Conclusions: Measurement of bioelectric activity is more sensitive than measurement of mechanical activity of the uterus. Elevated bioelectric activity of the uterine muscle was observed despite the use of tocolysis, a lack of symptoms of threatening preterm delivery, as well as a lack of contraction in tocography. The presence of bioelectric activity may precede the occurrence of mechanical activity of the uterus, but further research is required on larger groups of patients.

Key words: electrohysterography; tocography; uterine constrictions; preterm delivery; tocolysis

Ginekologia Polska 2021; 92, 3: 183–187

INTRODUCTION

Despite huge advances in perinatal medicine, the frequency of premature deliveries is part of a continuously increasing trend. Preterm births account for 9.6% of all deliveries. Prematurity constitutes one of the most important causes of neonatal mortality and currently, it is among the most difficult health care problems worldwide [1].

The great number of factors that may cause uterine contraction activity makes prophylaxis or the creation of proper therapeutic management challenging despite the constant development of diagnostic methods. It must be noted that the physiology of contraction activity of the pregnant uterus is still poorly understood and is the subject of many scientific studies [2]. As a result, it is necessary to make a diagnosis of threatening preterm delivery before the onset of the mechanical activity of the uterus which would lead to cervical effacement and cervical dilation. Regardless of the etiologic factor leading to premature delivery, the basic mechanism responsible for the occurrence of contraction activity of the uterus tied to the 200 billion cells of smooth muscle tissue which undergo hypertrophy while adapting during pregnancy, remains unclear [3, 4]. In the process of generating a functional electrical current, each of the those 200 billion cells becomes an individual pacemaker and transmitter, and thus an action potential may be produced in any part of the uterine muscle cell in various locations. From the physiology, it appears that the uterine contraction wave originates in the uterine horns near the uterine ostium of the fallopian tubes. As the wave propagates from the ostium of the tube to the cervix, its

Corresponding author:
Marek Tomialowicz
2nd Department of Gynecology and Obstetrics, Wroclaw Medical Univesity, Poland
e-mail: marektomialowicz@wp.pl

intensity decreases. The magnitude of uterine muscle stimulation depends on the number of gap junction intercellular channels, which are responsible for the metabolic and functional contact between cells. The number of gap junctions increases as the pregnancy advances, with the greatest number being observed at term [5].

Classic and widely used external tocography allows obstetricians only to detect and monitor the final effect of very complicated biochemical and electrophysiological processes, such as the contractions of the uterus. It must be remembered that tocography as a diagnostic method is used in nearly all obstetric hospitals worldwide; however, it does not allow for measurement of the bioelectric signal (electrohysterogram), which is the primary source of contractile activity of the uterus. Because sensors can be placed all over the surface of the maternal abdominal wall in electrohysterography (EHG), it can determine the source and paths of propagation of separate contractions, which classic tocography (TOCO) cannot do.

EHG was introduced in two studies by Steer and Hertsch in 1950 as a method of measurement of bioelectric activity of the uterus [6]. It can be used not only to diagnose threatening preterm delivery but also as a method of monitoring uterine contraction activity during labor [7, 8]. In comparison to TOCO, EHG allows for faster and more precise registration of bioelectric activity as it covers almost the whole surface of the uterine muscle. Additionally, it can determine characteristics of the contractions such as dynamics, place of origin and propagation pattern [9]. Another important aspect in diagnosing threatening preterm delivery is that the bioelectric activity of the muscle of the uterine fundus occurs before an increase in the intrauterine pressure but at the same time as the electric activity of the cervix [10].

Threatening preterm delivery is characterized by diversified clinical symptoms. Pregnant women may experience pain of varying intensity, which often is difficult for patients to localize. Non-specific symptoms make the decision about tocolytic treatment difficult. It should be emphasized that in many cases the diagnosis of threatening preterm delivery is completely groundless and, as a result, tocolytic therapy is being used on healthy subjects, creating a complicated clinical problem. Measuring bioelectric activity of the uterine muscle with EHG in cases of where different types of tocolytic therapy are being used (among them: beta adrenergic receptor agonists, calcium channel blockers, oxytocin receptor antagonists) might be helpful in monitoring the results of the therapy as well as determining its duration and the proper drug dosage.

In our study, we performed an analysis of the bioelectric activity of the uterine muscle during tocolytic treatment, which allowed us to evaluate the impact of tocolysis on contractile activity of the uterus, as registered on EHG recordings. Tocolytic drugs reduce intracellular calcium concentration in the myometrial cells, which activates cyclic adenosine monophosphate (cAMP), which then blocks the production of prostaglandins or the oxytocin receptor directly. The final effect of above-mentioned processes is the hampering of the actin-myosin interaction, thus making cells of the uterine muscle unresponsive to stimulation [11].

Aim of the study

The aim of the study was to analyze and compare the bioelectric and mechanical activity of the uterus in pregnant women with threatening preterm delivery treated with tocolysis. Additionally, auxiliary parameters of the bioelectric signal, as registered by EHG and characteristic only for this method, were measured and analyzed.

MATERIAL AND METHODS

The study group consisted of 45 women whose pregnancies ranged from 24 to 36 weeks of gestation who were hospitalized in the II Department of Obstetrics and Gynecology of the Wrocław Medical University. All patients had singleton pregnancy with vertex presentation of the fetus. All patients also presented clinical symptoms of threatening preterm delivery, such as lower abdominal or lower back pain, vaginal bleeding or cervical effacement. Patients presenting symptoms of threatening preterm delivery were given the following medications: beta adrenergic receptor agonists, calcium channel blockers and progesterone.

Pregnant women were simultaneously subjected to diagnosis of mechanical (TOCO) and bioelectric (EHG) contractile activity of the uterine muscle. The fetal surveillance system MONAKO (ITAM, Zabrze, Poland) and system for registration and analysis of bioelectric activity KOMPOREL (ITAM, Zabrze, Poland) were used to simultaneously register and analyze the activity of the uterus.

All the pregnant women were informed about the study procedures and gave written informed consent to participate in the study. The study was approved by the Commission of Bioethics at Wroclaw Medical University.

KOMPOREL is a measurement system using an external bioelectric signal recorder and a computer. It allows for the simultaneous registration of four signals (electrohysterograms) of electric uterine activity with measuring sensors located on the surface of the maternal abdomen. Collected bioelectric signals were processed into a digital form, transmitted to the computer system, analyzed, presented graphically on a computer screen, and stored by the KOMPOREL software. The analysis was performed based on four EHG signals and used to determine the slow frequency component of the contraction that corresponds to the TOCO signal, which then served as the basis for detecting contractions and determining their basic descriptive parameters [12]. Mechanical

activity of the uterus (TOCO) was registered by the MONAKO system connected to the traditional fetal and maternal monitor Avalon FM20 (Philips, Eindhoven, Netherlands). The TOCO signal was obtained with a tensiometric sensor placed on the maternal abdomen and registered by a tocograph. Next, the signal was transmitted by a transmission system to the computer for quantitative analysis (detection of contractions and calculation of their descriptive parameters).

The analysis of registered mechanical and bioelectric activity examined the following parameters of contractile activity [12]: contraction rate (R), defined as the number of detected contractions per 10 minutes; duration of contractions (TD); duration of maximal contractile amplitude (TA); surface (S); and contraction amplitude (A). Additional analysis was performed on a contraction parameter characteristic only for bioelectric activity, contraction intensity (I), as well as on a set of parameters from the analysis of the frequency domain: power (P), median frequency (Fmed) and frequency of maximum contractile power (Fmax) [13, 14]. A model of contraction wave is presented on Figure 1.

First, the duration of mechanical and bioelectric activity of the uterine muscle was compared. Next, the mean, standard deviation, median, and maximum and minimum values were calculated for the analyzed variables. Comparative analysis of the mean values between the corresponding parameters was also performed. Normality of distribution of the contraction parameters was verified using the Shapiro-Wilk test. Before the statistical analysis, variance equality was confirmed with the F-test. For sets of data with a normal distribution, the significance of difference between mean values was analyzed with Student's t-test. In case of significant differences in variances, a modified Student's t-test called Welch's t-test was employed. For variables with a non-Gaussian distribution, the nonparametric Mann-Whitney U test was used. The criteria for statistical significance were set at $p < 0.05$ and $p < 0.001$. Statistical analysis was carried out with Statistica software v. 5.5 (StatSoft, Tulsa, OK, USA).

RESULTS

The mean duration of recordings was almost 32 minutes (1906 s) and the total duration of recordings was 24 hours and 21 minutes (87691 s). All parameters of contraction — such as the mean and maximal contractile amplitude, rate and duration of contractions, and mean surface of contractions — recorded by EHG had significantly greater values than those recorded by TOCO. Further analysis was performed for parameters such as contraction intensity, power, median frequency and frequency of maximum contractile power. The values of descriptive parameters of contractions calculated both for the bioelectric and mechanical signals, along with their comparative analysis as well as values of auxiliary parameters for contractions as assessed by measuring the bioelectric signal are presented in Table 1.

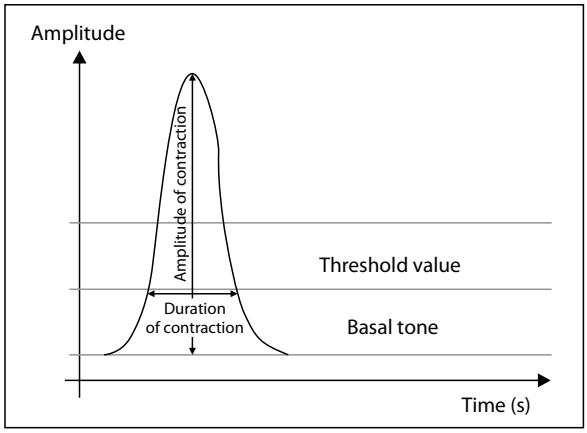

Figure 1. A model of contraction wave. The figure was adapted from Zietek J, Sikora J, Horoba K, et al. [Mechanical and electrical uterine activity. Part II. Contractions parameters. Ginekol Pol 2008; 79 (11): 798–804]

None of the pregnant women reported any side effects.

DISCUSSION

In perinatal medicine, new diagnostic tools which enable the identification of pregnancies with a high risk of preterm contractile activity of the uterus are constantly being sought. In our study, we compared two methods of detecting contractile activity of the uterus. We found that measurement of bioelectric activity is more sensitive than measurement of mechanical activity of the uterus. Additionally, the presence of bioelectric activity precedes the occurrence of mechanical activity of the uterus. We also observed the presence of bioelectric activity along with an absence of or minimal occurrence of mechanical activity in women undergoing tocolytic treatment.

As prematurity is the major cause of neonatal morbidity and mortality, tools for predicting premature labor are needed [15]. The basic diagnostic tool for the assessment of the contractile activity of the uterus is external tocography, which is a subjective examination tool. The very low sensitivity of tocography has encouraged researchers to search for more sensitive diagnostic methods. One of the alternatives is the assessment of bioelectric activity in the uterus, which can be detected starting at 19 weeks of gestation [10, 16]. Our study included only pregnant women at 24 weeks of gestation and above. In this group, a bioelectric signal was easy to detect in all patients. An additional advantage of EHG is its effective detection of contractions during labor [17, 18].

Contractions of the uterine muscle are induced by myogenic stimulation, which leads to a change in potential in muscle cell membranes. The rise in bioelectric voltage is the effect of the difference in the concentration of ions between the extracellular space and those inside myocytes. In the

Table 1. Comparison contraction parameters based on analysis of mechanical and bioelectric activity of the uterine muscle with characteristics of contractions based on analysis of bioelectric activity of the uterine muscle

Parameter	Mean	SD	Median	Min	Max	Significance
Xomparison of contraction parameters — mechanical and bioelectric activity						
R_{EHG} [l/10 min]	2.19	0.82	2.281	0.3920	4.9	$p < 0.001$
R_{TOCO} [l/10 min]	1.39	1.08	0.939	0.2560	3.9	
T_{D_EHG} [sek]	83.86	22.13	80.493	41.1000	130.3	$p < 0.05$
T_{D_TOCO} [sek]	66.38	26.14	59.632	32.5000	149.8	
T_{A_EHG} [sek]	43.99	12.11	45.247	24.3750	70.2	$p < 0.05$
T_{A_TOCO} [sek]	33.27	17.55	33.125	11.5000	107.8	
A_{EHG} [μV]	96.61	106.38	56.325	0.1590	453.1	$p < 0.001$
A_{TOCO} [–]	15.01	10.31	11.560	5.0300	50.9	
S_{EHG}	5301.38	6253.42	2603.055	11.9870	24226.4	$p < 0.001$
S_{TOCO}	656.63	549.79	458.925	134.5000	2522.5	
Descriptive statistics of auxiliary parameters — bioelectric activity						
I_{EHG} [l/1 min]	14.79	5.33	14.227	3.9290	30.5	
P_{EHG} [μV^2]	12412.06	23779.87	3240.189	0.0210	141666.6	
F_{MED_EHG} [Hz]	0.30	0.36	0.160	0.1140	1.7	
F_{MAX_EHG} [Hz]	0.22	0.29	0.118	0.0660	1.5	

A — contraction amplitude; EHG — electrohysterography; Fmax — frequency of maximum contractile power; Fmed — median frequency; I — contraction intensity; P — power; R — contraction rate; TA — duration of maximal contractile amplitude; TD — duration of contractions; TOCO — tocography; S — surface

resting state, the value of bioelectric voltage ranges from 65 to 80 mV [19]. Stimulation leads to an increase in the permeability of the cell membrane for sodium ions and thus to the flow of the sodium ion current, which results in an increase in the amount of positively charged sodium ions inside the cell and a decrease in membrane potential. When a threshold potential is reached (from –40 to –60 mV), stimulation of the cell and a further increase in the amount of intracellular positive ions occurs — this last for about 1 ms. Because potassium ions rush out of the cell, the cell membrane again becomes charged to about +20 mV, creating an action potential which stimulates contraction [16]. Action potentials initiate contractions that then propagate along the uterine muscle. The pattern, direction and speed of electrical activity change as the pregnancy advances [20].

Parameters of the bioelectric signal from the uterus itself or in comparison with other methods may help in predicting delivery but attempts to find associations among the bioelectric parameters of uterine contractions gave inconclusive results. Aviram et al. [21] found a significant difference between contraction rate and time to delivery. Kandil et al. observed significant differences in the duration of electrical bursts and the amplitude of action potentials between women in active labor and those not in labor, while other researchers found the amplitude of measurements not to be predictive for preterm labor [22–24].

We observed a different character of electric and mechanical activity of the uterine muscle in the studied women. The frequency of contractions noted using EHG was significantly greater than that resulting from mechanical activity of the uterine muscle registered in TOCO. This observation is in line with data from the literature [25]. The obtained results indicate that measurement of the bioelectric activity is more sensitive and precedes the occurrence of mechanical stimulation that results in contractile activity leading to threatening preterm delivery. In our study, in most cases, bioelectric activity of the uterine muscle persisted despite the application of a tocolytic treatment; bioelectric stimulation could be detected along with a complete lack of mechanical contraction. The tocolytic treatment had no effect on the inhibition of bioelectric activity although the studied women presented low contractile mechanical activity. In the literature, reports on the impact of tocolysis on bioelectric activity of the uterus are scarce. Aviram et al. [21] found similar electrical activity in women with imminent preterm labor who received a tocolytic treatment and those without tocolysis, while Kandil et al. [26] observed a different pattern of bioelectric activity in women who responded to tocolytic treatment than in non-responders. However, mechanical activity of the uterus was not assessed in either study.

In clinical practice, the assessment of contractile activity of the uterus is based on registration of mechanical activity in tocography and does not include an evaluation of bioelectric parameters. The presence of bioelectric activity may be evidence of contractile readiness and precedes the occurrence of uterine contractions [24]. Moreover, analysis

of parameters characteristic solely for bioelectric activity such as contraction intensity, power, median frequency and frequency of maximum contractile power indicated intensified bioelectric activity preceding mechanical contractile activity [25, 27]. Another diagnostic problem revealed by our study was the lack of clinical symptoms of threatening preterm delivery in pregnant women with elevated bioelectric activity.

Registration of bioelectric activity has some advantages, including its completely noninvasive character and low cost of examination. Additionally, the lack of side effects in any of the studied women demonstrates its high safety.

Parallel registration and analysis of mechanical and bioelectric activity allows for assessment and comparison of the same descriptive parameters of contractions using both diagnostic methods. Therefore, it seems to be reasonable to conduct studies on larger populations of pregnant women, which can enable the identification of groups of women at high risk for mechanical contractile activity and eventual cervical dilation, based on intensified bioelectric activity.

CONCLUSIONS

Elevated bioelectric activity of the uterine muscle was observed despite the use of tocolytic therapy, a lack of symptoms of threatening preterm delivery, as well as a lack of contraction in tocography. The use of tocolytic therapy for threatening preterm delivery does not cease bioelectric activity of the uterus. All parameters of bioelectric activity were significantly higher than those of mechanical activity.

Conflict of interest

None.

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VIA MEDICA

ORIGINAL PAPER / GYNECOLOGY

Ginekologia Polska
2021, vol. 92, no. 3, 188–194

ISSN 0017–0011, e-ISSN 2543–6767

DOI 10.5603/GP.a2020.0174

Amniotic fluid metabolic fingerprinting indicated metabolites which may play a role in the pathogenesis of foetal Down syndrome — a preliminary report

Ewa Parfieniuk[1], Karolina Pietrowska[1], Paulina Samczuk[1], Adam Kretowski[1, 2], Michal Ciborowski[1], Monika Zbucka-Kretowska[3]

[1]*Metabolomics Laboratory, Clinical Research Centre, Medical University of Bialystok, Bialystok, Poland*
[2]*Department of Endocrinology, Diabetology and Internal Medicine, Medical University of Bialystok, Poland*
[3]*Department of Gynecological Endocrinology and Adolescent Gynecology, Medical University of Bialystok, Poland*

ABSTRACT

Objectives: Down syndrome is the most common human chromosomal aberration. It is commonly known that it is a genetic-based disease, but still, pathomechanisms which lead to observed disorders have not been explained. The objective of this study was to determine the metabolic fingerprinting of the amniotic fluid women carrying foetuses with Down syndrome (DS).

Material and methods: The study and control groups consisted of women who underwent routine amniocentesis between the 15th and 18th week of gestation. After analysis of the karyotyping results, 13 women with foetal DS were chosen. For the control group, 13 healthy patients with uncomplicated pregnancies who delivered healthy newborns at term was selected. Amniotic fluid was analyzed using liquid chromatography combined with high resolution mass spectrometry.

Results: In the amniotic fluid of women with foetal DS compared to patients with healthy foetuses, we reported significant differences in the level of four metabolites: methylhistidine, hexanoylcarnitine, diacetylspermine and p-cresol sulfate which may be connected with improper development of nervous system and muscles. We detected bacterial metabolite, which support the latest thesis about non-sterile intrauterine environment.

Conclusions: Based on our findings, we hypothesise that differences in the level of four metabolites in the amniotic fluid may play role in the pathogenesis of DS. Defining their potential as biochemical pathogenic factors of DS requires further investigation of the biological pathways involving in the foetal development.

Key words: Down Syndrome; amniotic fluid; metabolomics

Ginekologia Polska 2021; 92, 3: 188–194

INTRODUCTION

Chromosomal aberrations are the main cause of many congenital malformations. The most common is trisomy 21, also known as Down Syndrome (DS). It is estimated that 1:700 live births in the United States were affected with this chromosomal abnormality between 2010 and 2014 [1]. This is the most recent report on the incidence of DS, but according to the World Health Organization data, incidence rates have not changed to date. Individuals with DS are affected by many disorders, which may occur in different combinations. According to the National Institute of Child Health and Human Development, the most common problems include mental retardation, heart defects, vision problems, hearing loss, infections, hypothyroidism, blood disorders, hypotonia (poor muscle tone), cervical spine abnormalities, disrupted sleep patterns and sleeping disorders, gum disease and dental problems, epilepsy, digestive problems, celiac disease and mental health and emotional problems [2]. Such a diversity of defects complicates the explanation of how an additional chromosome may affect the whole organism.

The newest "omics" technologies may serve as potentially useful tools in providing an explanation of molecular mechanisms leading from chromosomal aberration to observed malformations [3]. Metabolomics, in particular, which aims to measure all small molecules below 1000 Da, is a powerful tool, as it shows the current status of an organism. In the case of research on human beings, it is commonly used to compare individuals affected by a studied parameter (*e.g.*

Corresponding author:
Monika Zbucka-Kretowska
Department of Gynecological Endocrinology and Adolescent Gynecology, Medical University of Bialystok, Poland
e-mail: monikazbucka@wp.pl

disease or treatment) with an appropriate control group [3]. Observed changes provide a comprehensive view of alterations in the metabolome caused by the studied factor. Consequently, metabolomics can be applied to study different aspects of disease and/or treatment including a search for diagnostic markers, explanation of disease pathogenesis, treatment strategy (personalized medicine) or monitoring of treatment efficacy. Nuclear magnetic resonance (NMR) or mass spectrometry (MS) are analytical techniques which are most commonly used in metabolomics research. To improve its sensitivity, MS is often used in combination with one of the separation techniques: liquid chromatography (LC), gas chromatography (GC) or capillary electrophoresis (CE). The methods complement one another as each provides information about different compound classes [4]. However, as a single analytical platform, LC-MS provides the highest metabolome coverage [5] and therefore it was used in our study.

Metabolomics has previously been used to evaluate mechanisms which are the basis of impaired development of a foetus with DS or to find new indicators which may improve the prenatal diagnostic process [3, 6–10]. Maternal blood has been analysed using LC-MS [3] and NMR [6]. A panel of fatty amides (palmitic amide, linoleamide and oleamide), which can be connected with foetal brain and central nervous system development, discriminated DS-affected maternal plasma from the plasma of healthy pregnant women [3]. In a similar study performed with the use of NMR, Bahado-Singh et al. [6] found that 2-hydroxybutyrate, 3-hydroxybutyrate, 2-hydroxyisovalerate, acetamide, acetone, carnitine, lactate, pyruvate and L-methylhistidine were increased while dimethylamine and methionine were decreased in the plasma of women with a DS-affected pregnancy. These compounds can also be connected with brain development (brain myelination), hypotonia, learning disability, seizure disorders, brain atrophy or oxidative stress. Maternal urine, biological material which can be obtained in an entirely non-invasive way, was also analysed using metabolomics [9, 10]. Using LC-MS, Trivedi et al. [9] found that dihydrouracil was significantly elevated in the urine of women with a DS-affected pregnancy. A similar study, but focused on DS, other chromosomal disorders and poor pregnancy outcomes was conducted by Diaz et al. using the NMR technique. In the study, urine levels of 2-ketoglutarate, 1-methylhistidine, 3-hydroxybutyrate, 4-OH-hippurate and dimethylamine were found to discriminate pregnant women carrying a foetus affected with a chromosomal disorder from the control group, but none of the significant metabolites were found to be specific to DS [10]. These studies provide some information regarding the way in which metabolic pathways are affected by the presence of DS in a foetus. To complete the picture, we focused on amniotic fluid (AF) in our study. AF is routinely used for karyotyping and was a biofluid of choice for our research since it reflects the condition of both the mother and the foetus. AF composition changes dynamically during gestation. In early pregnancy, it contains a low amount of proteins and enzymes, which increases with foetal development (in mid- and late pregnancy) [7, 8]. AF was analysed using different "omics" platforms (metabolomics, proteomics and genomics) to investigate a variety of pregnancy-related abnormalities [8, 11–14]. Those in which a metabolomics approach was used have recently been reviewed by Bardanzellu et al. [15].

Objectives

The aim of the study was to explore metabolic pathways affected by the additional chromosome 21. A LC-MS-based metabolomic approach was utilised to study AF samples obtained from women with a DS-affected pregnancy and women carrying a foetus with normal karyotype.

MATERIAL AND METHODS

Study group

The study and control groups consisted of women who underwent routine amniocentesis between the 15th and 18th week of gestation at the Department of Reproduction and Gynecological Endocrinology of the Medical University of Bialystok, Poland. Exclusion criteria were as follows: chronic or acute diseases, hormonal treatment, anti-inflammatory treatment, high-risk pregnancy or preterm delivery in the patient's medical history. All participants were informed about potential risks prior to the procedure and received relevant information regarding the study. Moreover, study participants were matched according to the course of pregnancy and BMI values. Details of the study group are presented in Table 1. Following karyotype test results analysis, 13 women carrying foetuses affected with DS and 13 women with healthy foetuses were enrolled in the study. The study was approved by the Ethics Committee of the Medical University of Bialystok (No. R-I-002/134/2018). Prior to inclusion in the study, all participants signed informed consent forms.

Materials

Deionised water was obtained in-house using the Milli-Q Integral 3 system (Millipore SAS, Molsheim, France). LC-MS grade acetonitrile (ACN), methanol (MeOH) and formic acid (FA) were purchased from Sigma-Aldrich Chemie GmbH

Table 1. The characteristics of the study participants

	case (n = 13)	control (n = 13)
Maternal age (mean ± SD)	38 ± 4 years	36 ± 5 years
Maternal BMI (mean ± SD)	24 ± 3.8	24 ± 1.8
Gestation age (mean ± SD)	16 ± 1 weeks	16 ± 1 weeks

SD — standard deviation; BMI — body mass index

(Steinheim, Germany). LC grade ethanol was purchased from POCH (Gliwice, Poland). The API TOF reference mass solution kit (G1969-850001) and tuning solutions, ESI-L low concentration tuning mix (G1969-850000) and ESI-TOF Biopolymer Analysis reference masses (G1969-850003) were purchased from Agilent Technologies (Santa Clara, California, USA).

Sample preparation

The obtained 10 mL of AF was divided into smaller portions and stored at –80°C until the day of analysis. On the day of analysis, samples were thawed on ice and vortex-mixed. Then, to extract metabolites and remove proteins, 100 µL of methanol and ethanol mixture (1:1) was added to 100 µL of the sample. It was again vortex-mixed (1 min) and incubated on ice for 10 min. After that time, samples were centrifuged at 21000 × g for 20 min at 4°C. The obtained pellet was removed and the supernatant was filtered through a 0.22 µm nylon filter into glass vials. Quality control (QC) samples were prepared by mixing equal volumes of all analysed samples. The mixture was extracted following the same procedure as that used with other samples and analysed together in the intervals.

Metabolic fingerprinting

Samples were analysed using the 1290 Infinity UHPLC system combined with the 6550 QTOF mass spectrometer (both Agilent Technologies). Chromatographic separation was obtained with a Poroshell 120 EC-C18 column (3.0 × 100 mm, 2.7 µm particle size). Deionised water (phase A) and acetonitrile (phase B), both with 0.1 % formic acid, were used as mobile phases. Proportion of mobile phases was changing with the following gradient: analyses commenced with 1% of phase B and it was kept for 1 min, then the gradient started reaching 100% of B at 10 min. After that, the gradient moved back to the starting condition in 10.1 min and the system was re-equilibrated before the next injection for the next 5 min. Electrospray ionisation (ESI) was used and the samples were analysed separately in both positive and negative ion modes. The mass spectrometer was operated in full scan mode in the range 50––1000 *m/z* at a scan rate of 2 spectra per second. To ensure high accuracy of *m/z* measurements, reference mass solution was continuously delivered by an isocratic pump. The following compounds were observed: protonated purine (*m/z* 121.0509), protonated hexakis (1H,1H,3H-tetrafluoropropoxy) phosphazine (*m/z* 922.0098) in positive ion mode; proton abstracted purine (*m/z* 119.036) and formate adduct of HP-921 (*m/z* 966.0007) in negative ion mode.

Data processing and statistical analysis

Raw data collected by analytical instrumentation were cleaned of background noise and unrelated ions by the molecular feature extraction (MFE) tool in Mass Hunter Qualitative Analysis Software (B.07.00, Agilent, Santa Clara, CA, USA). The MFE creates a list of all possible components described by mass, retention time (RT) and abundance. To identify co-eluting adducts of the same feature, the following adduct settings were applied: +H, +Na, +K for positive ion mode, and –H, +HCOO, +Cl for negative ion mode. Dehydration neutral losses were also allowed in both ionisation modes. Obtained data were aligned allowing for 1% shift in RT and 15 ppm variation in mass measurement. To maintain proper data quality, a quality assurance (QA) protocol was applied. Only features detected in more than 50% of QC samples and with adequate repeatability (CV < 25%) were kept. Additionally, data were filtered based on their presence in studied groups, i.e. metabolites present in at least 80% of the samples from at least one of the groups were kept. Sample alignment, data filtering and QA protocol were performed using Mass Profiler Professional 12.6.1 (Agilent, Santa Clara, CA, USA). To check data quality based on the projection of QC samples, principal component analysis (PCA) was used. To visualize differences in AF metabolic profiles between the studied groups, partial least squares discriminant analysis (PLS-DA) was used. SIMCA P+ 13.0.3 (Umetrics) was used to create multivariate plots. To select metabolites discriminating studied groups, univariate statistical analysis was used. Depending on normality of data distribution (checked using the Shapiro-Wilk test), the Student t test (normally distributed data) or the Mann-Whitney U test (data without a normal distribution) were applied. Obtained *p*-values were corrected by the Benjamini-Hochberg false discovery rate (FDR). Values lower than 0.05 were considered significant.

Statistically significant compounds were putatively identified by searching for potential hits in online databases (METLIN, HMDB and LIPIDMAPS), accessed through CEU Mass Mediator (http://ceumass.eps.uspceu.es/) [16]. The identity of metabolites was confirmed by matching the experimental MS/MS spectra to MS/MS spectra from databases. Experiments were repeated with chromatographic conditions identical to those in the primary analysis. Ions were targeted for collision-induced dissociation (CID) fragmentation on the fly based on previously determined accurate mass and RT.

RESULTS

As a result of the QA procedure and data filtering, 1410 and 940 metabolic features remained in positive and negative ion modes, respectively. Based on these data, PCA models were created showing a close clustering of QC samples (Fig. 1), which indicates good data quality. The same data were used to build PLS-DA models. As shown in Figure 2, study groups can be discriminated on the basis of the metabolic profiles obtained in positive (panel A) and negative (panel B) ion modes. Statistical analysis and metabolite identification were performed as described in the

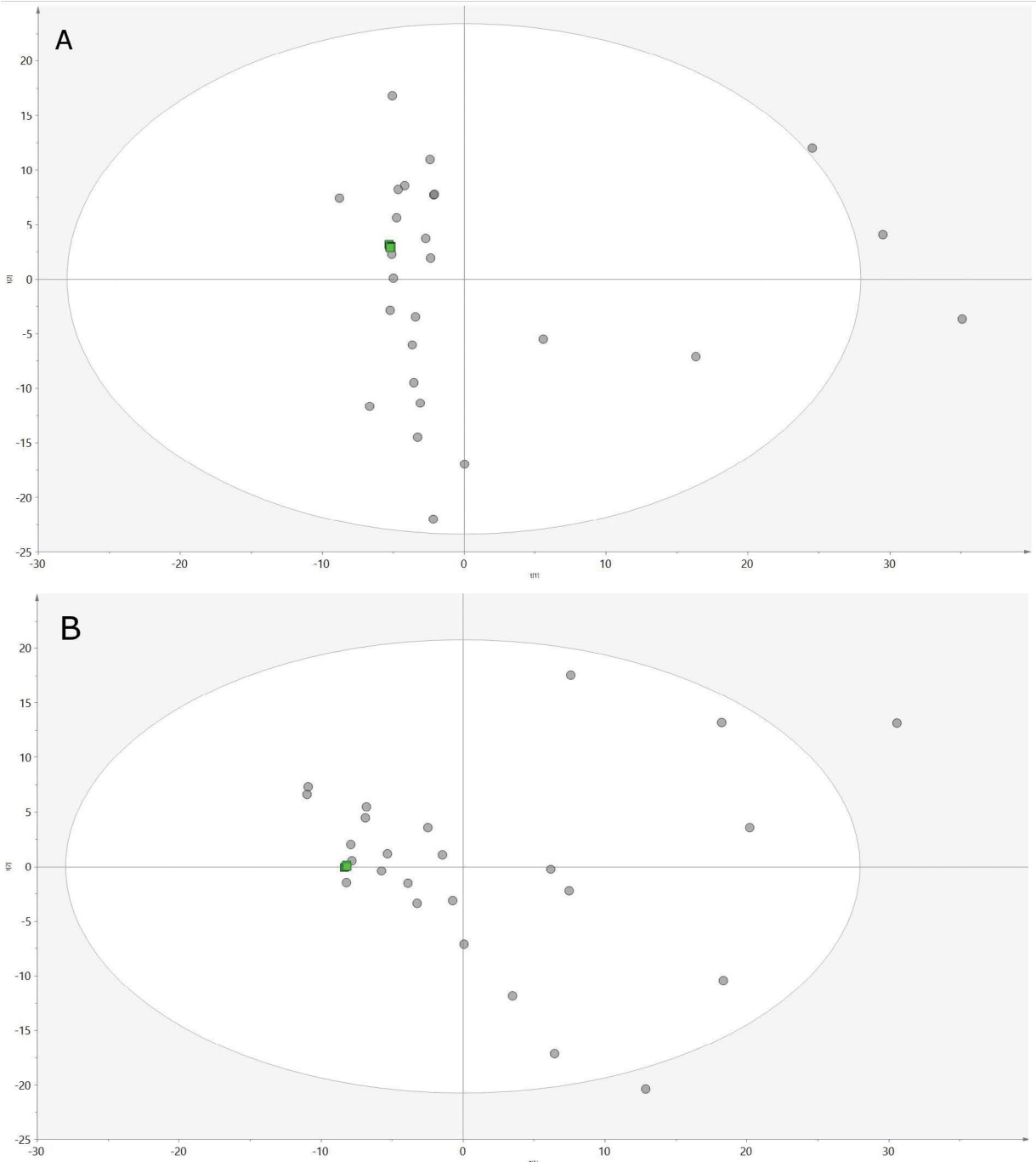

Figure 1. Classification of quality control samples (marked in green) on a principal component analysis (PCA) model. Panel A shows a PCA model based on data generated in positive while panel B in negative ion mode. Data was log transformed and Ctr scaled

Materials and Methods section. Identified metabolites are presented in Table 2.

DISCUSSION

To date, alterations in metabolic pathways evoked by foetal DS have been studied with the metabolomic approach using, primarily, maternal blood or urine samples [3, 6, 9, 10, 17]. Therefore, data obtained from our analysis of AF samples may complement previous reports on the subject. AF has been analysed by Liu et. al. [7] and Huang et. al. [8] who observed similar changes in the levels of cortisol, free amino acids (arginine, histidine and glutamate) and pregnenolone sulfate. Liu et al. [7] used different types of chromatographic separation, which resulted in a discovery of a larger number of differentiating compounds (151 metabolites). These metabolites were grouped into the following metabolic pathways: *gamma*-glu-

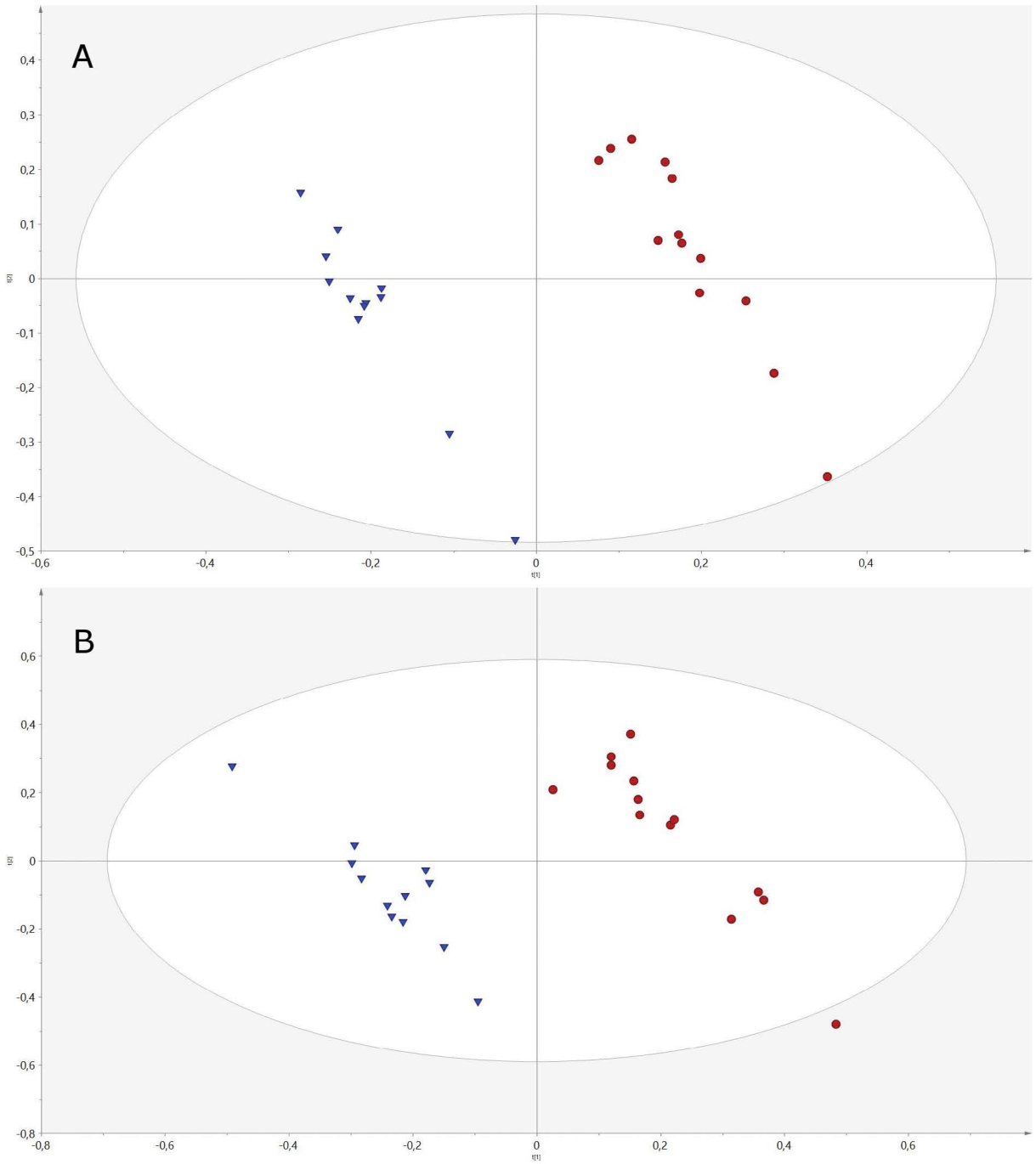

Figure 2. Partial least squares discriminant analysis (PLS-DA) score plots showing separation between patients with foetal Down syndrome and control group. PLS-DA models based on data generated in positive (Panel A, $R^2 = 0.991$, $Q^2 = 0.509$, Par scaling and log-transformed data) and in negative (Panel B, $R^2 = 0.972$, $Q^2 = 0.58$, Par scaling, log transformed) ion modes; ● DS pregnancy; ▼ healthy pregnancy

Table 2. Significant metabolites

Compound name	Monoisotopic mass	Ionisation mode	Retention time	*p* value	Change
Methylhistidine	169.0855	positive	0.97	0.0484	–27.09
Hexanoylcarnitine	259.1787	positive	4.65	0.0464	–38.66
Diacetylspermine	286.2369	positive	1.09	0.0464	+42.92
p-cresol sulfate	188.0146	negative	4.73	0.021	–40.94

tamyl amino acids metabolism, phospholipid metabolism, fatty acid and dicarboxylate, pentose metabolism, glycogen metabolism, disaccharides and olilgosaccharides, fructose, mannose and galactose metabolism, aminosugar metabolism and tricarboxylic acid cycle. In the study by Huang et al., a smaller number of metabolites differed significantly, but the obtained results were confirmed with a validation set. Moreover, some of the metabolites, *i.e.* coproporphyrin-III, taurochenodeoxycholate, taurocholate and glycocholic acid, were not reported by Liu et al. [7].

In our study, similarly to the study by Liu et. al. [7], an increase in diacetylspermine was observed. This metabolite has been indicated as a factor connected with maternal exposure to nicotine [18] and as a marker of breast and colorectal cancer [19], but its association with metabolic changes evoked by foetal DS has not been elucidated [7].

According to our knowledge, the present study is the first to demonstrate differences in AF composition between DS-affected pregnancies and pregnancies with foetuses with normal karyotype in the Caucasian race. Both studies mentioned above [7, 8] concern Asian people, but as shown by Taylor et. al. [20], race of the study group is an important factor affecting the results. Observed interracial differences may not only have a genetic background, but also could be the result of specific maternal and dietary habits as well as environmental factors. A Western-style diet, based on processed food, impacts both the foetus (amniotic fluid volume and composition [21]) and the mother (gut microbiota composition [22]). A high-fat diet promotes excessive weight gain or can even induce maternal obesity, which may result in hypertension or preterm delivery [21]. Neither Liu et. al. [7] nor Huang et. al. [8] included information on the BMI of study participants. The hypothesis that research results may be related to the ethnicity of the population studied can be supported by our observation of changes in p-cresol sulfate. While p-cresol is a product of bacterial fermentation of aromatic amino acids [23], p-cresol sulfate is produced in colonic mucosa and the liver as a result of detoxification of p-cresol. The dogma of sterile intrauterine environment has recently been challenged [24–28]. It has postulated that bacterial colonisation of the foetus, amniotic fluid and placenta in utero potentially comes from the maternal oral cavity via the bloodstream, from vagina via translocation across the choriodecidual plate or from the maternal intestine [25]. The last source is particularly interesting when we try to explain differences observed in p-cresol sulfate. As mentioned above, a high-fat diet (which is a typical Western-style diet) may affect maternal gut microbiota and may be associated with poor maternal health outcomes. Our observation of microbial metabolite presence in AF may provide additional confirmation that the intrauterine environment is not sterile. Moreover, the presence of bacteria in utero allows for the prenatal development of foetal gut microbiota [27–31]. Borre et. al. [26] highlighted parallels between microbiota and brain (or more generally, the nervous system) development. Their theory is related to the brain-gut axis which coordinates interactions between gut microbiota and the central nervous system in postnatal life (CNS).

Our study was the first to detect methylhistidine in AF. It is excreted with urine, which can explain its presence in AF. Methylhistidine was found to be decreased in the AF of DS-affected pregnancies. It is a product of methylation of histidine, which occurs mainly in skeletal muscle cells during methylation of actin and myosin. Therefore, the observed presence of methylhistidine can be connected with hypotonia, a neuromuscular disorder that affects almost all individuals with DS [32]. In the third trimester, the amount of methylhistidine in maternal urine increases, which is connected with the protein cost of pregnancy [33]. Moreover, it has been demonstrated that methyhistidine concentration is elevated in the urine of women carrying foetuses affected by a chromosomal disorder. The increase was observed in the second trimester before the expected rise in a methylhistidine level related to the natural course of pregnancy [10]. Interestingly, Bahado-Singh et al. also observed elevated methylhistidine levels in the serum of women with a DS-affected pregnancy in the first trimester (11^{th}–13^{th} week of gestation) [6]. Similar changes in methylhistidine concentration were observed in maternal blood when women with a pregnancy affected with trisomy 18 were studied [34].

Another metabolite whose concentration in AF was decreased in our study group in comparison to the control group was hexanoylcarnitine. Long-chain fatty acids in the form of acylcarnitines are transported to mitochondria for β-oxidation. However, apart from this function, this group of metabolites has a neuroprotective role and affects brain metabolism [35]. Therefore, the observed changes in hexanoylcarnitine concentration may reflect on foetal brain and CNS development. Parfieniuk et al. and Bahado-Singh et al. have also observed significant differences in the level of particular acylcarnitines when blood metabolic profiles of women carrying a foetus affected with DS were compared with those of women carrying a foetus with normal karyotype [3, 6]. Despite the fact that carnitines are excreted with urine, no statistically significant differences in their levels were found when similar studies on urine samples from DS-affected and healthy pregnancies were performed [9, 10].

CONCLUSIONS

The present study increases current knowledge regarding the impact of an extra copy of chromosome 21 on metabolic imbalance. The compounds detected in our study may be related to disturbed foetal brain and CNS development. During the second trimester, the composition of AF changes and the concentration of many molecules increases as the foetus

excretes them. A decrease in the majority of significant metabolites observed in our study may be the result of differences in the pathological pathways of disturbed foetal development.

Acknowledgments

This work was supported by the Medical University of Bialystok, Poland. The study was conducted with the use of equipment purchased by the Medical University of Bialystok as part of the RPOWP 2007–2013 Funding, Priority I, Axis 1.1, Contract no. UDA-RPPD.01.01.00-20-001/15-00 dated 26.06.2015.

Conflict of interest

None.

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VIA MEDICA

ORIGINAL PAPER / OBSTETRICS

Ginekologia Polska
2021, vol. 92, no. 3, 195–204

ISSN 0017–0011, e-ISSN 2543–6767

DOI 10.5603/GP.a2020.0175

Investigation of fetal cardiac function using tissue doppler imaging in fetuses compromised by growth restriction

Rabia Merve Palalioglu[1], Halil Ibrahim Erbiyik[2], Basak Kaya[3], Huseyin Kiyak[3], Ali Gedikbasi[3]

[1]Department of Obstetrics and Gynecology, University of Health Sciences, Umraniye Training and Research Hospital, Elmalıkent Mah. Adem Yavuz Cad. Trt Sok. Umraniye, Istanbul, Turkey

[2]Uskudar University, Istanbul, Turkey

[3]Department of Obstetrics and Gynecology, University of Health Sciences, Kanuni Sultan Suleyman Training and Research Hospital, Istanbul, Turkey

ABSTRACT

Objectives: The primary aim of this study was to evaluate fetal cardiac systolic and diastolic function using the tissue Doppler technique in pregnancies with complications of fetal growth restriction (FGR) and to examine the relationship between FGR with umbilical artery Doppler parameters and fetal cardiac function in complicated pregnancies.

Material and methods: This study included 30 pregnant women with FGR complications and 46 pregnant women without FGR complications. Both groups were at 24–34 gestational weeks. Fetal cardiac examination was performed using pulsed Doppler and tissue Doppler imaging (TDI) in all pregnancies. In the analysis of myocardial tissue by tissue Doppler, the tracing obtained from the junction of the tricuspid valve annulus with the right ventricle was recorded by measuring the duration of the isovolumetric contraction wave (IVC), ejection time (ET), and isovolumetric relaxation time (IVR). Furthermore, we calculated the myocardial performance index (MPI) and then measured and recorded the early diastolic annular rate.

Results: Based on the TDI studies, the mean IVC and IVR values were significantly longer and the ET values were significantly shorter in the study group than those in the control group. The study group also had significantly longer MPI measurements.

Conclusions: Because TDI is a considerably more sensitive method than cardiac sonographic evaluation using pulsed Doppler, tissue Doppler parameters facilitate the detection of cardiac dysfunction at a relatively early stage. In addition, TDI and myocardial evaluation in fetuses with FGR can be noninvasively performed in clinical practice.

Key words: fetal cardiac function; FGR; myocardial performance index; tissue Doppler imaging

Ginekologia Polska 2021; 92, 3: 195–204

INTRODUCTION

Fetal growth restriction (FGR) is usually expressed as the statistical deviation of fetal size based on a population-based reference, with a typical threshold at the 10th, 5th, or 3rd centile; such a threshold is designed better to demonstrate a "small-for-gestational-age" (SGA) fetus [1, 2]. In a significant proportion of cases, low birth weight was found to be a cardiovascular risk factor, and the onset of cardiovascular diseases coincided with the prenatal period [3, 4].

Placental insufficiency with increased vascular resistance is a significant cause of FGR-related to hypoxia, premature birth, fetal acidemia, and even fetal death [5, 6]. Hypoxic environment frequently affects cardiac diastolic function, occurring earlier in the spectrum of FGR-related cardiac disorders [7]. Fetal cardiac involvement has been found in the late stages with developmental retardation, as supported by various studies; accordingly, the fetal heart is the main organ involved in adaptation mechanisms to placental insufficiency, and fetal development retardation plays a central role in physiopathology [8–13]. Moreover, echocardiographic and biochemical findings of subclinical cardiac dysfunction are mainly associated with diastolic dysfunction [8, 9, 14]. Tissue Doppler imaging (TDI) allows direct measurement of regional myocardial velocities [15]. Various studies using angiography

Corresponding author:
Rabia Merve Palalioglu
Department of Obstetrics and Gynecology, University of Health Sciences, Umraniye Training and Research Hospital, Elmalıkent Mah. Adem Yavuz Cad. Trt Sok. Umraniye, 34764 Istanbul, Turkey
e-mail: drmerbiyik@gmail.com

in adults have shown that the systolic myocardial velocity of the mitral valve annulus along the left axis of the LV is closely related to the changes in the LV pressure and the EF [10].

In fetuses with FGR, pulmonary and systemic vasoconstriction causes an increase in right ventricular (RV) afterload, thereby displacing the cardiac output to the left ventricle (LV); these outcomes indicate diastolic dysfunction [7]. The etiology of neonatal mortality and morbidity caused by pathological conditions such as FGR and fetal anemia is fetal cardiac failure. Parameters such as ejection fraction (EF), ventricular ejection force, ratio of early diastole rate (E) to atrial systole rate (A) (E/A), cardiac output, and myocardial performance index (MPI) are generally employed for examining fetal cardiac function [5, 6, 11, 12]. Thus, the ratio of flow rate (E) to annular rate (E') **(**E/E'**)** in early diastole is also closely related to filling pressures. Therefore, regional myocardial rates reflect global cardiac function and can be used to predict systolic and diastolic functions in both ventricles [10].

Considering the importance of detecting fetal cardiac function related to FGR, TDI can be used as an additional method for evaluating ventricular diastolic function because it improves the decision-making process and helps determine neonatal prognosis [13]. This study aimed to investigate fetal cardiac functions by TDI in pregnancies complicated with FGR to compare these with the control group.

MATERIAL AND METHODS

Study design, setting and participants

In this prospective study, we included 30 pregnant women complicated with FGR without known fetal anomaly and additional maternal disease as the study group and 46 pregnant women without FGR complication as the control group. All were at 24–34 gestational weeks and applied to the Perinatology Clinic of Kanuni Sultan Suleyman Training and Research Hospital between May 2016 and May 2017. The exclusion criteria were as follows: multiple pregnancies, diabetes, cholestasis, preeclampsia, chromosomal or structural fetal anomaly, FGR diagnosis below the viability limit, early membrane rupture, oligohydramnios, fetal heart complication, or any maternal medical illness. Before starting the study, all volunteers received an informed consent form. The study was approved by the local ethics committee (date: December 1, 2016; approval number: 2016/2/10).

The small fetus is explained as an estimated fetal weight (EFW) below the 10th percentile. Small fetuses were defined as fetal growth restriction or SGA according to estimated fetal weight (EFW), umbilical artery pulsatility index (PI), cerebroplacental ratio (CPR) and uterine artery PI.

FGR was described as an EFW < 3rd percentile, or EFW < 10th percentile with umbilical artery (UA) PI > 95th percentile and/or cerebroplacental ratio (CPR) < 5th percentile and/or mean UtA-PI > 95th percentile.

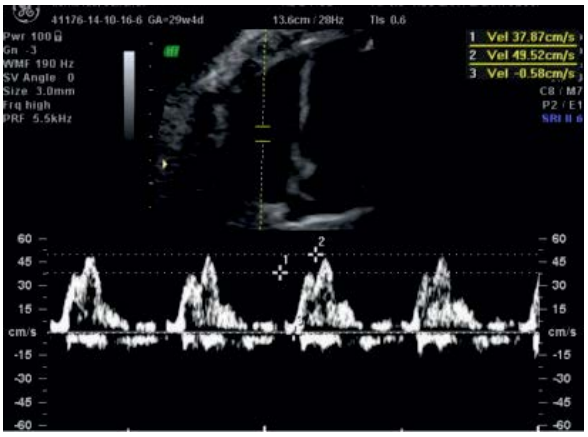


Figure 1. Measurement of E- and A-wave velocity; 1 — E-wave velocity; 2 — A-wave velocity

SGA was characterized as an EFW between 3rd and 9th percentile with normal Doppler indicators.

The obstetric and gynecological anamnesis, maternal age, body mass indexes (BMIs), smoking history, and gestational ages according to CRL of all participating pregnant women were recorded. Umbilical artery Doppler was measured when the fetus was immobile, from the free angle of the umbilical artery to the angle of sound waves less than 20°. PIs were grouped into above and below the 90th percentile according to gestational week. All of them underwent fetal cardiac examination using pulse Doppler and TDI. The fetal heart was evaluated in four apical or basal chamber views. Using pulse Doppler, we measured the early (E) and late (A) transvalvular filling rates (Fig. 1). Atrioventricular flow velocity waveforms were obtained from four apical or basal chamber views. The sample volume was acquired from the tip of the tricuspid valve leaves and measured thrice. In fetal echocardiographic examination, arterial and venous Doppler parameters (umbilical artery, middle cerebral artery, and ductus venous) and RV MPIs were studied in both groups without major anomaly. Measurements were calculated by examining the tricuspid valve annulus for the RV in four apical or basal quadrant images and measuring the peak flow rates. The PVE', PVA', and E'/A' ratio reflected the diastolic function of RV, whereas the PVS' value reflected the systolic function; then, the MPIs were documented. In the analysis of myocardial tissue with tissue Doppler, the tricuspid valve annulus was measured by identifying the duration of the isovolumetric contraction wave (IVC), ejection time (ET), and isovolumetric relaxation time (IVR). The MPI was also calculated. Moreover, the early diastolic annular velocity (E') was measured and recorded. Meanwhile, eight patients with increased umbilical artery PI from fetuses with FGR were compared with 22 patients with normal umbilical artery PI. A further comparison was made with and without a history of FGR.

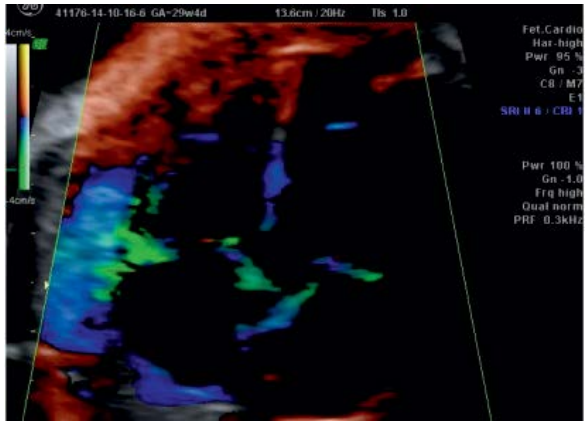


Figure 2. Doppler imaging view

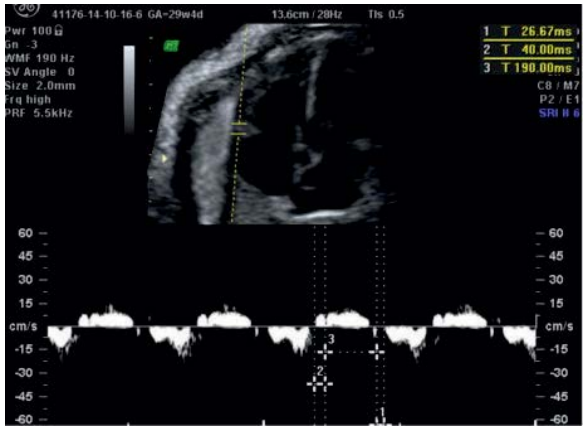


Figure 3. Isovolumetric contraction wave (IVR), isovolumetric relaxation time (IVC) and ET′ measurements; 1 — IVR; 2 — IVC; 3 — ET′ MPI′ is the ratio of the sum of IVR and IVC to ET

TDI was performed in real time using probes with a 2 to 10 MHz frequency. The device settings for pulsed tissue Doppler were as follows: flow rate (sweep speed), 5 cm/s; gain, 10 dB; wall motion filter (WMF), 210 Hz (Fig. 2). At the plane where the tricuspid valve annulus joins the right ventricle in the four apical or basal chamber sections, a sampling interval was maintained between 2 and 4 mm, and myocardial tissue was analyzed using pulse tissue Doppler. The angle between the RV free wall and probe was maintained at < 20°, with no angle correction.

In the trace obtained using pulsed tissue Doppler, the duration of the first positive wave; the IVC, beginning after the late diastolic annular velocity wave (A'); the ET', which is the second positive wave; and the IVR, which is the click between the end of systole and the tricuspid valve, were measured. Each measurement was obtained thrice and then averaged. MPI' was calculated, which indicates the ratio of the sum of the IVC and IVR values to the ET' value (Fig. 3). E' velocity was measured. The ratio of the E value to E' value (E/E') measured using pulse Doppler was calculated (Fig. 4).

Statistical analysis

The statistical analyses were performed using the Statistical Package for the Social Sciences, version 20 (SPSS Inc.). The chi- square and Student's t tests were used for statistical comparisons. $p < 0.05$ was considered statistically significant.

RESULTS

The mean abdominal circumference (AC) percentile measurements of the patients in the study group were significantly lower than those of patients in the control group: 2.47 ± 0.75 and 50.71 ± 22.05, respectively ($p = 0.0001$). Moreover, the EFW percentile measurements were 3.37 ± 0.77 in the study group and 45.82 ± 21.55 in the control group, and the difference was significant ($p = 0.0001$). Furthermore,

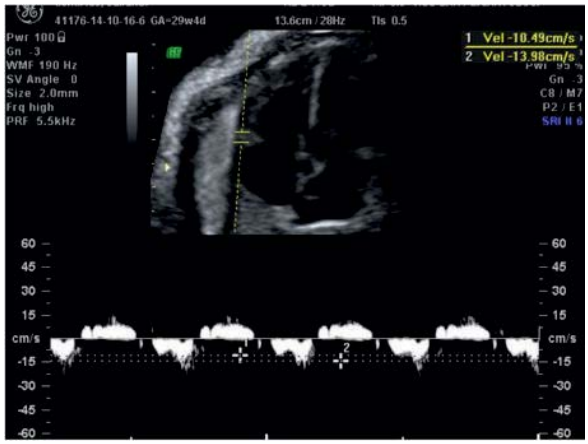


Figure 4. E′ (**1**) and A′ (**2**) wave velocity measurements

E, A, IVC, IVR, ET′, MPI′, E′ and umbilical artery values were statistically significant in the study group (Tab. 1).

The mean gestational period, as determined by the birth week measurement, was significantly lower in patients in the study group (35.8 ± 3.02 weeks) than in the control group (38.61 ± 2.27 weeks; $p = 0.0001$). In addition, the mean birth weight was significantly lower in the study group (2011 ± 701.21 g) than in the control group (3319.07 ± 517.21 g; $p = 0.0001$). The study group showed a higher incidence of NICU hospitalization than the control group [16 (53.33%) vs 3% (6.52%); $p = 0.0001$] (Tab. 2).

The mean gestational period, mean birth weight, mean 1-min Apgar score, and mean 5-min Apgar score of the PI Low group were significantly higher than the PI High group. The duration of NICU stay and the incidence of NICU hospitalization of the PI Low group were significantly lower than the PI High group (Tab. 3).

There was no statistically significant difference between the gestational weeks of the groups ($p > 0.05$). MCA PI and

Table 1. Evaluation of ultrasound variables by group

		Control (n = 46)	Case (n = 30)	p
AC percentiles	Mean ± SD	50.71 ± 22.05	2.47 ± 0.75	[b]0.0001***
	Min–Max (Median)	48.2 (32. 65–69.2)	2 (2–2.925)	
EFW percentiles	Mean ± SD	45.82 ± 21.55	3.37 ± 0.77	[b]0.0001***
	Min–Max (Median)	41 (27.65–58.88)	3 (3–3.35)	
E	Mean ± SD	38.37 ± 6.2	34.08 ± 9.36	[a]0.019
	Min–Max (Median)	38.45 (35. 1–42.9)	36.53 (28.15–40.32)	
A	Mean ± SD	52.51 ± 7.96	45.4 ± 10.94	[a]0.002
	Min–Max (Median)	51.99 (45. 4–57.73)	45.63 (40.14–52.86)	
E/A	Mean ± SD	0.73 ± 0.08	0.74 ± 0.1	[a]0.557
	Min–Max (Median)	0.72 (0. 68–077)	0.73 (0.68–0.83)	
IVC	Mean ± SD	0.037 ± 0.007	0.047 ± 0.012	[b]0.0001***
	Min–Max (Median)	0.037 (0.03–0.04)	0.047 (0.04–0.05)	
IVR	Mean ± SD	0.030 ± 0.007	0.052 ± 0.011	[b]0.0001***
	Min–Max (Median)	0.03 (0.03–0.03)	0.05 (0.04–0.06)	
ET'	Mean ± SD	0.19 ± 0.01	0.16 ± 0.01	[a]0.0001***
	Min–Max (Median)	0.19 (0.18–0.2075)	0.17 (0.16–0.18)	
MPI'	Mean ± SD	0.34 ± 0.07	0.61 ± 0.16	[a]0.0001***
	Min–Max (Median)	0.35 (0.31–0.38)	0.6 (0.5–0.7)	
E'	Mean ± SD	9.52 ± 1.4	8.25 ± 1.19	[a]0.0001**
	Min–Max (Median)	9.44 (8.39–10.49)	8.24 (7.4–9.08)	
E/E'	Mean ± SD	4.12 ± 0.91	4.18 ± 1.18	[a]0.800
	Min–Max (Median)	4.11 (3.38–4.88)	4.24 (3.64–5.14)	
UA PI	Mean ± SD	0.93 ± 0.13	1.3 ± 0.55	[a]0.0001***
	Min–Max (Median)	0.9 (0.84–1.025)	1.07 (0.99–1.475)	
UA PI Percentile	Mean ± SD	35.37 ± 15.13	62.37 ± 25.26	[a]0.0001***
	Min–Max (Median)	32 (24.5–45.75)	57 (45.5–92.25)	

[a]Independent t Test; [b]Mann–Whitney U Test; [c]Fisher's Exact Test; *p < 0.05; **p < 0.01; ***p < 0.0001; SD — standard deviation; AC — abdominal circumference; EFW — estimated fetal weight; E — early diastole rate; A — atrial systole rate; E/A — ratio of early diastole rate (E) to atrial systole rate (A); IVC — isovolumetric contraction wave; IVR — isovolumetric relaxation time; ET' — ejection time; MPI' — myocardial performance index; E' — early diastolic annular velocity; E/E' — the ratio of flow rate (E) to annular rate (E'); PI — pulsatility index; UA — umbilical artery

Table 2. Evaluation of infant variables by group

		Control (n = 46)	Case (n = 30)	p
Sex	Male	25 (54.35)	16 (43.33)	**[c]0.931**
	Female	21 (45.65)	14 (46.67)	
Birth week	Mean ± SD	38.61 ± 2.27	35.8 ± 3.02	**[a]0.0001*** **
	Median (IQR)	39 (38–40)	37 (34–38)	
Birth weight	Mean ± SD	3319.07 ± 517.21	2011 ± 701.21	**[a]0.0001*** **
	Median (IQR)	3400 (2992.5–3585)	2140 (1517.5–2632.5)	
Birth weight percentile	Mean ± SD	54.22 ± 28.49	7.1 ± 7.6	**[b]0.0001*** **
	Median (IQR)	50 (25–75)	3 (3–10)	
Apgar 1st minute	Mean ± SD	8.46 ± 1.03	7.7 ± 1.99	**[a]0.032***
	Median (IQR)	9 (8–9)	8.5 (7.75–9)	
Apgar 5th minute	Mean ± SD	9.76 ± 0.6	9.37 ± 1.07	**[a]0.043***
	Median (IQR)	10 (10–10)	10 (9–10)	

[a]Independent t Test; [b]Mann–Whitney U Test; *p < 0.05; **p < 0.01; ***p < 0.0001; SD — standard deviation; IQR — interquartile range

Table 3. Evaluation of variables according to umbilical artery pulsatility index percentile groups

UA PI > 90th percentile (n = 8)		UA PI percentile		p
		UA PI < 90th percentile (n = 22)		
Birth week	Mean ± SD	32.38 ± 3.07	37.05 ± 1.84	[a]**0.0001**
	Median (IQR)	33 (29.75–34.75)	37 (36–38)	
Birth weight	Mean ± SD	1218.13 ± 415.13	2299.32 ± 543.12	[a]**0.0001**
	Median (IQR)	1227.5 (785–1597.5)	2350 (2027.5–2727.5)	
Apgar 1st minute	Mean ± SD	6.25 ± 2.76	8.23 ± 1.34	[a]**0.013**
	Median (IQR)	8 (3.25–8)	9 (8–9)	
Apgar 5th minute	Mean ± SD	8.5 ± 1.51	9.68 ± 0.65	[a]**0.005**
	Median (IQR)	9 (8.25–9)	10 (9.75–10)	
Duration of NICU Hospitalization	Mean ± SD	52.57 ± 36.51	15.22 ± 11.55	[a]**0.011**
	Median (IQR)	47 (14–72)	13 (7.5–22)	
		n (%)	**n (%)**	
Delivery Method	SVD	7 (87.5)	14 (63.6)	[c]**0.1207**
	C-Section	1 (12.5)	8 (36.4)	
Sex	Male	5 (62.5)	11 (50)	[c]**0.544**
	Female	3 (37.5)	11 (50)	
NICU need	No	1 (12.5)	13 (59.1)	[c]**0.024**
	Yes	7 (87.5)	9 (40.9)	

[a]Independent t Test; [b]Mann–Whitney U Test; [c]Fisher's Exact Test; SD — standard deviation; PI — pulsatility index; UA — umbilical artery; SVD — spontaneous vaginal delivery; C-Section — cesarean section

MCA PI percentile measurements were found to be significantly lower in the study group ($p < 0.01$). CPR and CPR percentile measurements were also found to be statistically significantly lower in the study group ($p < 0.01$). DV PI and DV PI percentile measurements do not show statistically significant difference according to the groups ($p > 0.05$). UT mean PI and UT PI percentile measurements were found to be statistically significantly higher in the study group ($p < 0.01$). UA PI and UA PI percentile measurements were found to be statistically significantly higher in the study group ($p < 0.01$) (Tab. 4).

No statistically significant difference was found between the patients in the study group, Apgar 1 min, Apgar 5 min, Umbilical artery PH and NICU hospitalization periods compared to the CPR percentile groups ($p > 0.05$) (Tab. 5).

No statistically significant difference was found in the study group patients in terms of Apgar 1.min, Apgar 5 min, Umbilical artery PH and NICU hospitalization periods compared to Ut A PI percentile groups ($p > 0.05$) (Tab. 6).

MPI values have been shown to vary slightly during pregnancy and have an average of 0.36 MPI (between 0.28–0.44).

According to this study, the cut off value was calculated as 0.47 and below in the ROC curve. Fetuses whose cut off value was calculated as 0.47 and below were found to be compatible with gestational age at birth. In fetuses with cut off value above 0.47, FGR development sensitivity was 97.83% and specificity was 86.67% (Fig. 5).

DISCUSSION

Fetal cardiac involvement has been found in the late stages with developmental retardation, as supported by various studies; accordingly, the fetal heart is the main organ involved in adaptation mechanisms to placental insufficiency, and fetal development retardation plays a central role in physiopathology [8, 14–21]. The most accepted theory is "fetal metabolic programming," which causes diseases such as obesity, diabetes mellitus, and hypertension associated with cardiovascular diseases and secondarily increases cardiovascular risk [16, 17].

Ductus venosus is the most important indicator of perinatal death, implying the need for birth in preterm FGR [13, 22, 23]. However, MPI, which is a combined indicator of systolic and diastolic function, starts to rise in the early stages of FGR and increases proportionally with weight [14, 24]. Importantly, these parameters are affected by preload and afterload. Tissue Doppler imaging (TDI) reflects myocardial movement better than the conventional echocardiography, because it evaluates cardiac function directly on the myocardium and is also less affected by preload and afterload [25, 26]. Diastolic dysfunction is an earlier sign of cardiac failure. In the evaluation of fetal cardiac function, TDI practices are associated with increased gestational age and myocardial rate changes [27]. In addition, the E/E′ ratio is significantly higher in fetuses with RV heart failure. The TDI technique can measure the relaxation rate of myocardium directly

Table 4. Doppler indices of the groups				
		Control (n = 46)	**Case (n = 30)**	**p**
Gestational Age	Mean ± SD	30.34 ± 1.85	30.8 ± 2.08	[a]0.316
	Min–Max (median)	27–34 (30.4)	26.1–33.9 (31.2)	
MCA PI	Mean ± SD	1.98 ± 0.4	1.39 ± 0.24	[b]**0.001****
	Min–Max (median)	1.3–2.6 (2)	0.9–2 (1.4)	
MCA PI percentile	Mean ± SD	53.7 ± 37.21	7.27 ± 9.46	[b]**0.001****
	Min–Max (median)	1–99 (59)	1–44 (3)	
CPR	Mean ± SD	2.16 ± 0.57	1.16 ± 0.28	[b]**0.001****
	Min–Max (median)	0.9–3.9 (2.1)	0.4–1.5 (1.3)	
CPR percentile	Mean ± SD	63.85 ± 29.48	3.13 ± 2.27	[b]**0.001****
	Min–Max (median)	6–99 (71.5)	1–7 (2)	
	> 5; n (%)	46 (100)	6 (20.0)	[c]**0.001****
	< 5	0	24 (80.0)	
DV PI	Mean ± SD	0.56 ± 0.2	0.57 ± 0.22	[a]0.842
	Min–Max (median)	0.3–1.3 (0.5)	0.3–1.3 (0.5)	
DV PI percentile	Mean ± SD	49.74 ± 33.95	49.77 ± 34.17	[b]0.924
	Min–Max (median)	3–99 (42)	3–99 (41.5)	
Ut A PI	Mean ± SD	0.84 ± 0.11	1.46 ± 0.35	[b]**0.001****
	Min–Max (median)	0.6–1 (0.8)	1–2.4 (1.4)	
Ut A PI percentile	Mean ± SD	62.04 ± 18.57	97.5 ± 2.3	[b]**0.001****
	Min–Max (median)	14–88 (61.5)	91–99 (99)	
	< 95; n (%)	46 (100)	6 (20.0)	[c]**0.001****
	> 95	0	24 (80.0)	
UA PI	Mean ± SD	0.92 ± 0.12	1.3 ± 0.55	[b]**0.001****
	Min–Max (median)	0.7–1.2 (0.9)	0.7–2.9 (1.1)	
UA PI percentile	Mean ± SD	31.43 ± 23.92	62.37 ± 25.26	[b]**0.001****
	Min–Max (median)	1–88 (23)	11–99 (57)	
	< 90; n (%)	46 (100)	22 (73.3)	[c]**0.001****
	> 90	0	8 (26.7)	

[a]Independent t Test; [b]Mann–Whitney U Test; [c]Ki kare test; **p < 0.01; SD — standard deviation; MCA — middle cerebral artery; CPR — cerebroplacental ratio; DV — ductus venosus; Ut A — uterine artery; UA — umbilical artery; PI — pulsatility index

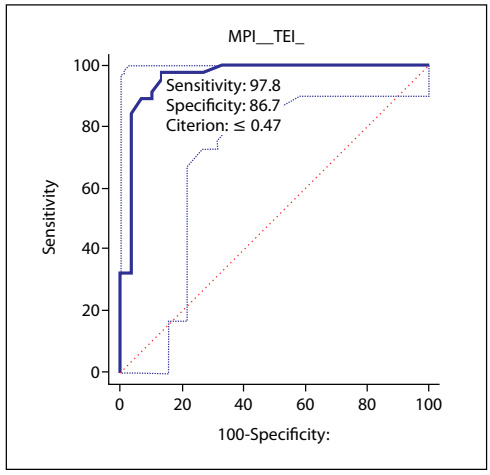
Table 5. Evaluation of neonatal outcomes according to cerebroplacental ratio percentile groups				
		CPR percentile		**p**
		> 5 (n = 6)	**< 5 (n = 24)**	
Apgar 1st minute	Mean ± SD	8.33 ± 1.21	7.54 ± 2.13	**0.432**
	Min–Max (median)	6–9 (9)	2–9 (8)	
Apgar 5th minute	Mean ± SD	9.67 ± 0.82	9.29 ± 1.12	**0.374**
	Min–Max (median)	8–10 (10)	5–10 (10)	
Umbilical Artery pH	Mean ± SD	7.37 ± 0.05	7.37 ± 0.05	**1.000**
	Min–Max (median)	7.3–7.4 (7.4)	7.2–7.5 (7.4)	
Duration of NICU Hospitalization	Mean ± SD	4 ± 9.32	20.04 ± 29.73	**0.230**
	Min–Max (median)	0–23 (0)	0–120 (9.5)	

Mann Whitney U test; SD — standard deviation; CPR — cerebroplacental ratio; NICU — neonatal intensive care unit

Table 6. Evaluation of neonatal outcomes according to uterine artery pulsatility index percentile groups

		Ut A PI percentile		p
		< 95	> 95	
Apgar 1st minute	Mean ± SD	6.5 ± 1.91	7.88 ± 1.97	**0.071**
	Min–Max (median)	4–8 (7)	2–9 (9)	
Apgar 5th minute	Mean ± SD	9 ± 0.82	9.42 ± 1.1	**0.200**
	Min–Max (median)	8–10 (9)	5–10 (10)	
Umbilical Artery pH	Mean ± SD	7.38 ± 0.05	7.37 ± 0.05	**0.791**
	Min–Max (median)	7.3–7.4 (7.4)	7.2–7.5 (7.4)	
Duration of NICU Hospitalization	Mean ± SD	18.75 ± 16.64	16.54 ± 29.09	**0.391**
	Min–Max (median)	0–40 (17.5)	0–120 (0.5)	

Mann Whitney U test; PI — pulsatility index; SD — standard deviation; NICU — neonatal intensive care unit



Area under the ROC curve (AUC)	0.964
Standard error[a]	0.0239
95% confidence interval[b]	0.894 to 0.993
z statistic	19.367
Significance level, p (area = 0.5)	< 0.0001

[a]DeLong et al., 1988
[b]Binomial exact

Youden index	
Youden index J	0.8449
Associated criterion	≤ 0.47
Sensitivity	97.83
Specificity	86.67

Figure 5. Area under the ROC curve (AUC)

and unlike conventional pulse Doppler studies, the diastolic function evaluated by TDI is considerably less affected by the loading state. TDI can also measure the myocardial systole and diastole rates without the limitations of transvalvular flow analysis performed with pulse Doppler, which is affected by high heart rate and preload and afterload conditions. Chan et al. [27] claimed that myocardial velocity determined by tissue Doppler varies with gestational age and constituted reference tables for the myocardial tissue Doppler with the result that diastolic function was evaluated more accurately with TDI in intrauterine fetal evaluation than transvalvular flow rates and concluded diastolic dysfunction may be an early marker of fetal hypoxia in FGR.

FGR progressing with fetal hypoxia and acidemia has been associated with long-term cardiovascular outcomes, leading to perinatal morbidity and even mortality. Conventional Doppler and mitral and tricuspid valve flow analyses are affected by heart rate, preload, and afterload. Considering the increased pulmonary and systemic vascular resistance in FGR, the RV afterload increases, and the cardiac flow shifts from the RV to the LV. These changes in cardiac output and afterload reduce the reliability of conventional Doppler analysis in fetuses with FGR. Despite that, myocardial velocities can be measured by the tissue Doppler technique without being affected by these parameters. Tissue Doppler technique allows for a quantitative evaluation of the myocardial activity. Changes in myocardial rates are a marker for mildly affected systolic and diastolic dysfunctions; thus, cardiac dysfunction can be detected early with tissue Doppler.

In our study, the IVC, IVR, and MPI increased in fetuses with FGR whose umbilical artery Doppler findings were either normal or affected, compared with the control group. In cases wherein the umbilical artery Doppler findings are not disrupted, an increase in MPI supports the view that diastolic dysfunction may be an early marker of hypoxia in fetuses with FGR. The prolongation of the isovolumetric contraction period in the fetal heart was associated with systolic dysfunction, whereas IVR prolongation was associated with diastolic dysfunction [14].

Similarly, decreased myocardial rates are early markers of systolic and diastolic dysfunctions. In our study, we detected a decrease in myocardial rates in fetuses with FGR. Ventricular filling rates determined by tissue Doppler technique were significantly lower in the study group than in the control group, supporting the presence of diastolic dysfunction in fetuses with FGR. However, in using the conventional Doppler, the E/A ratio used in detecting diastolic dysfunction was similar in both groups. In some studies, the E/A ratio determined by conventional Doppler can only be detected in severely affected fetuses with FGR having a reverse flow in the umbilical artery [7]. However, in our study, we found diastolic dysfunction in fetuses with FGR having normal umbilical artery Doppler findings by detecting an increase in IVR and a decrease in ventricular filling rates using the tissue Doppler technique.

Considering that TDI is considerably more sensitive than cardiac sonographic evaluation using pulse Doppler, tissue Doppler parameters allow to determine cardiac dysfunctions at a relatively earlier stage. Myocardial evaluation with TDI in fetuses with FGR can be used in clinical practice noninvasively. When we compared the cases with normal and abnormal umbilical artery Doppler findings, we could not find a difference between the groups in terms of parameters predicting cardiac systolic and diastolic functions. This situation can be explained by the view wherein in the early stages of hypoxia, the cardiac function was affected extending throughout various periods of fetal exposure. It can also be explained by the limited number of cases with impaired umbilical artery Doppler parameters. Our current study clearly shows that in fetuses with FGR, systolic and diastolic function changes were detected more sensitively by TDI than by pulse Doppler. Tissue Doppler parameters are important because they allow early monitoring by determining the cardiac dysfunction at an early stage. Another advantage is that through TDI, the findings of systolic and diastolic cardiac dysfunction in fetuses can be determined; such findings cannot be detected by pulse Doppler. Generally, the LV in the fetus is responsible for coronary circulation and cranium, whereas the RV is the main distributor of the lower trunk, lungs, and placenta. Considering this distribution, the afterload is different in both ventricles [10]. In this study, we used tricuspid annulus and tricuspid flow measurements to evaluate the RV, which is dominant in fetal circulation.

In addition, RV function evaluation is more accurate because myocardial velocity is evaluated only on the long axis in which the movement of the longitudinal myocardial fibers can be measured; meanwhile, the LV function depends on the lengthening and shortening of circumferential and longitudinal fibers at the appropriate degree and timing. However, the orientation of myocardial fibers of the RV is different and tends to contract along its long axis compared to the short axis. Therefore, the evaluation of systolic function on the long axis allows the LV function to appear less than expected and the RV function to be better evaluated. The anatomical alignment of myocardial fibers highly influences the systolic myocardial velocities of the RV and LV walls [10]. The most important limitation of the transvalvular flow rate is the indirect evaluation of diastolic function by measuring the flow of blood passing through the AV valves, which are also affected by fetal blood volume and vascular resistance, namely, preload and afterload. Direct measurement of myocardial relaxation rate in TDI is a more sensitive indicator of diastolic function. More importantly, TDI is less dependent on preload and afterload.

The MPI value measured from the tricuspid annulus in the study group was significantly higher than that in the control group. The MPI in FGR was previously evaluated in several studies [10, 28–30], and parallel to our study, it was found to be high in fetuses with FGR. In addition, increased right MPI values were detected in a study evaluating fetuses with heart failure. The E/E' ratio in early diastole is also closely related to filling pressures [10], and it is significantly higher in fetuses with RV heart failure. In our study, when comparing the E/E' ratio, no significant difference was found between the case and the control group, further supporting the view that other TDI parameters are impaired before heart failure develops and that TDI is a sensitive tool in evaluating cardiac function. When TDI measurements (IVC, IVR, ET', MPI, and E') were examined in pregnant women in different gestational weeks, no significant relationship was found between the gestational week and TDI values.

When the umbilical artery Doppler pulsatility index is> 95th percentile, CPR is very valuable in predicting adverse neonatal outcome.

However, in our study there are only 8 patients have seen UA PI > 90^{th} percentile. Hence, FGR was defined as an EFW < 10^{th} percentile, CPR < 5^{th} percentile and mean UtA-PI > 95^{th} percentile.

Abnormal CPR increases the level of abnormal fetal growth rate, significantly increased fetal distress rates at birth, relatively lower umbilical cord pH, and the need for neonatal intensive care unit support for fetuses with FGR [31]. An additional finding of abnormal CPR in such cases adds to adverse neonatal outcomes, umbilical artery end-diastolic flow deficiency, and signs of reversal.

If the end-diastolic flow does not increase during pregnancy and a small uterine artery notch is observed at the end of systole, the development of FGR for the fetus will have high risks. [32]. There may be no diastolic blood flow and reversal with excessive placental dysfunction. In our study, absent end-diastolic flow (AEDF) was observed in only 4 patients in the study group. No reversed end-diastolic flow (REDF) was observed.

With this study, we concluded that it is possible to achieve good perinatal outcomes without REDF.

The study group also had significantly higher umbilical artery PI and umbilical artery PI percentiles than the control group. Furthermore, birth weight percentiles and Apgar 1st- and 5th-minute measurements were statistically significantly lower in the study group. When NICU was compared in terms of duration of stay, no significant difference was found between the two groups, but the need for NICU hospitalization was significantly higher in the study group. Considering the limited access to the fetus, physicians find the evaluation of fetal well-being difficult.

Fetal diastolic dysfunction is an early marker of fetal hypoxia. Therefore, evaluation of diastolic function using TDI in any abnormal pregnancy should be the modality in determining fetal well-being. TDI is useful in early fetal delivery, determining the time of intrauterine interventions and/or close follow-up for such cases [27–30].

CONCLUSIONS

The fetal heart is the main organ involved in placental hypoperfusion, and hypoxia adaptation mechanisms, which play an important role in FGR pathogenesis, and early placental changes are not likely to affect the fetus. In our study, we detected the presence of cardiac systolic and diastolic dysfunctions in all fetuses who suffered from FGR with and without umbilical artery Doppler findings by using the tissue Doppler technique. Assessment of cardiac function using the tissue Doppler is applicable during the intrauterine period, repeatable, and useful in various fetal conditions. This technique is an indicator of early fetal adaptation to the fetal pathophysiological process and is more sensitive in predicting pregnancy outcomes and long-term cardiovascular outcomes in fetuses with FGR than the conventional Doppler. The ability to detect preclinical cardiac dysfunction is the superior aspect of the technique. However, in terms of its limitations, only clinicians experienced in fetal echocardiography can perform it, and its application can be challenging. TDI is a more sensitive tool than pulse Doppler in cardiac evaluation; thus, tissue Doppler parameters can determine cardiac dysfunction at an early stage, allowing for early monitoring. Myocardial evaluation using TDI should be used as a noninvasive method in fetuses with FGR.

Ethical approval

The study was approved by the local ethics committee (date: December 1, 2016; approval number: 2016/2/10).

Research involving human participants and/or animal

This article does not contain any studies with animals performed by any of the authors.

Sources of funding

None.

Conflict of interest

The authors report no conflict of interest.

Informed Consent

Informed consent was obtained from all individual participants included in the study.

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VIA MEDICA

ORIGINAL PAPER / OBSTETRICS

Ginekologia Polska
2021, vol. 92, no. 3, 205–209

ISSN 0017–0011, e-ISSN 2543–6767

DOI 10.5603/GP.a2020.0179

Collection of umbilical cord blood and the risk of complications in postpartum women after natural labour in the context of the possibility of umbilical cord stem cells usage in clinical practice

Jakub Mlodawski[1, 3], Marta Mlodawska[1], Natalia Przybysz[2], Aleksandra Bielak[2], Karolina Detka[3], Marcin Pasiarski[1], Wojciech Rokita[1, 3]

[1]Collegium Medicum, Jan Kochanowski Univeristy, Kielce, Poland
[2]Eskulap Student's Scientific Society, Collegium Medicum Jan Kochanowski University in Kielce, Poland
[3]Clinic of Obstetrics and Gynaecology, Provincial Combined Hospital in Kielce, Poland

ABSTRACT

Objectives: Comparison of changes in peripheral blood venous morphology and the frequency of select complications in patients who underwent umbilical cord blood collection during the third stage of labour by in the utero method compared to patients who did not undergo this procedure. Presentation of current therapeutic possibilities of cord blood stem cells.

Material and methods: The study involved 248 patients who had a vaginal delivery and had umbilical cord blood taken by in utero method during the third stage of labour. The control group consisted of the first 400 patients who gave vaginal delivery starting in 2019. Each patient had a venous peripheral blood count taken before delivery and 18 hours after delivery. Changes in the results of laboratory tests and the occurrence of adverse outcomes, such as postpartum curettage, postpartum haemorrhage and manual removal of placenta, in the 3rd and 4th stage delivery periods, were analysed.

Results: In the blood donor group there were significantly lower haemoglobin (11.32 g/L vs 11.61 g/L, p = 0.004) and haematocrit (32.83% vs 33.82% p = 0.001) concentrations after delivery. Umbilical cord donors had a greater difference in haemoglobin (postpartum minus prepartum) (–1.4 g/L vs –0.9 g/L, p = 000), and haematocrit (–4.05% vs –2.5% , p = 0.000). The study group had a higher percentage of patients with postpartum anaemia (haemoglobin concentration < 10 g/L) (15.9% vs 10.64%, p = 0.05), but the result were borderline significant. The groups did not differ in terms of the percentage of postpartum curettage, PPH, manual removal of placenta, percentage of severe anaemia (Hb < 7 g/L) or transfusion requirement.

Conclusion: Collection of umbilical cord blood during the 3rd stage of labour using the in utero method is associated with a statistically significant increase of blood loss and a higher probability of postpartum anaemia. The observed changes are minor and may have little clinical significance in otherwise healthy patients.

Key words: cord blood; private banking; public banking; delayed cord clamping; stem cells; perinatal care

Ginekologia Polska 2021; 92, 3: 205–209

INTRODUCTION

Umbilical cord blood banking became popular 30 years ago after the first allogeneic transplant of cord blood stem cells for the treatment of Fanconi anaemia [1]. The umbilical cord blood is an important source of allogeneic hematopoetic cells which can be used in the treatment of both cancer and non-cancerous diseases. Research is also being conducted concerning the use of allo- and autogenous stem cells derived from umbilical cord blood in regenerative medicine. Umbilical cord blood is collected during the third stage of vaginal delivery, or immediately after the cord clamping, in the case of a caesarean section. Most often, the procedure is performed "*in utero*," before the separation of the placenta. *In utero* collection increases the chance of collecting an appropriate volume of umbilical cord blood. This procedure is widely recognized as safe for the mother. However, there are few studies in literature assessing the impact of this procedure on maternal blood loss and the risk of adverse outcomes such as retained placenta, postpartum curettage and postpartum haemorrhage (PPH).

Corresponding author:
Jakub Mlodawski
Collegium Medicum, Jan Kochanowski Univeristy, Kielce, Poland
e-mail: jakub.mlodawski@ujk.edu.pl

Study Aims

This study aimed to compare changes in peripheral blood venous morphology and the frequency of select complications of third and fourth stage labour in patients whose umbilical cord blood was drawn *in utero* during the third stage of delivery with patients who did not undergo this procedure. The secondary aim was to present the current rationale for using stem cells from umbilical cord blood in the treatment of various diseases.

MATERIAL AND METHODS

This was a retrospective study of the medical records of all women who gave birth by vaginal delivery at the Department of Obstetrics and Gynaecology of the Provincial Combined Hospital in Kielce between November 1, 2016 and July 1, 2019 and had umbilical cord blood collected *in utero* for private or public banking (n = 248). The control group consisted of the first 400 patients who gave birth by vaginal delivery starting from January 1, 2019 and did not undergo cord blood sampling. All patients had the morphology of peripheral blood collected on one hour prior to delivery and 18 hours after delivery. The mean concentration of blood morphotic elements post-delivery and individual concentration differences for each patient were analysed. Adverse outcomes were the necessity of manual removal of placenta, postpartum curettage performed due to bleeding or incomplete placenta, or administration of tocomimetic drugs (carbetocin, methylergometin and misoprostol) due to postpartum bleeding. The incidence of postpartum anaemia, defined as haemoglobin (Hb) < 10 g/dL and severe postpartum anaemia defined as Hb < 7 g/dL was compared. Continuous variables were compared, the arithmetic mean as a measure of central tendency when the distribution is near normal, and the median, in the case of skewed distribution. The standard deviation and interquartile range were used as measures of spread. If assumptions of normal distribution and equal variance were met, then groups were compared using the Student's t-test. When there was a failure to meet the above-mentioned criteria, groups were compared using the Mann-Whitney U test. For qualitative variables, data were presented as a percentage of events in a given group. The groups were compared using the Pearson $\chi 2$ test, Yates correction was applied when low numbers were expected. Calculations were made using the Statistica 13.1 program (Stat Soft Poland). The number of patients in the control group was selected so that a 0.5 g/dL difference in the haemoglobin concentration between the groups could be detected at a test power of 90%. Current literature on the practical use of stem cells from umbilical cord blood in the treatment of various diseases is presented.

RESULTS

The study included 284 patients in the study group and 400 patients in the control group. The characteristics of the study and control groups are presented in Table 1. The groups did not differ in terms of parity, age, weight, length of the newborn, or haemoglobin concentration, haematocrit and platelet count before delivery. Patients from the study group had significantly lower haemoglobin concentration after delivery [mean difference (MD) = 0.28 g/dL] and lower haematocrit (MD = 0.99%), while platelet count did not differ significantly (Tab. 2). The difference between haemoglobin concentrations, hematocrits and platelet counts (postpartum value - prepartum value) was calculated for each patient individually. The value was then averaged and presented in the form of median and interquartile range due to a lack of normal distribution. The groups differed in terms of haemoglobin decrease (MD = 0.5 g/dL) (study group median –1.4 g/dL and control group median –0.9 g/dL, p = 0.000) and haematocrit (median = –4% vs –2.5%, respectively, p = 0.000). There were no observed differences in the platelet count reduction between the two cohorts of women. The occurrence of adverse effects during the third and fourth stage of labour was also analysed. The groups did not differ statistically in terms of post-partum curettage incidence (8.8% vs 10.5%, p = 0.74) or manual placenta removal (1.41%

Table 1. Demographic parameters of both groups

Parameters	Control group	Donor's group	p
Number of patients	400 (58.47%)	284 (41.52%)	total — 684
First delivery (percentage in group)	43.66% (n = 195)	56.34%(n=160)	p = 0.06
Age [years] (mean ± SD)	30.178 ± 4.83	30.79 ± 4.6	p = 0.29
Newborn weight [g] (mean ± SD)	3400.26 ± 410.9	3391.6 ± 368.5	p = 0.056
Newborn length [cm] (median, IQR)	54; 3	54; 3	p = 0.21
Hb before delivery [g/L] (mean ± SD)	12.52 ± 1.06	12.67 ± 0.95	p = 0.07
Hct before delivery [%] (mean ± SD)	36.5 ± 2.7	36.88 ± 2.50	p = 0.31
Plt before delivery [1000/mm^3] (median, IQR)	202 (68)	201 (68)	p = 0.79

Hb — haemoglobin concentration; Hct — haematocrit; PLT — platelets concentration; SD — standard deviation

Table 2. Outcome comparison

Parameters	Control group	Donor's group	p
Hb after delivery [g/dl] (mean+-SD)	11.61 ± 1.29	11.32 ± 1.32	p = 0.004
Hct after delivery [%] (mean ± SD)	33.82 ± 3.66	32.83 ± 3.97	p = 0.001
Plt after delivery [1000/mm^3] (median, IQR)	198 (67)	199 (62)	p = 0.90
diff Hb [g/dL] (median; IQR)	–0.90; 1.3	–1.40; 1.5	p < 0.001
diff Hct [%] (median; IQR)	–2.50; 4.1	–4.05; 4.6	p < 0.001
diff PLT (median; IQR)	–7; 31	–6.0; 27	p = 0.48
postapartum need for carbetocin administration	4%	3.52%	p = 0.74
postpartum need for methylergometrine administration	1.25%	0.35%	p = 0.21
postpartum need for misoprostol administration	5%	4.23%	p = 0.63
post-partum curettage	10.50%	8.80%	p = 0.46
manual removal of placenta	0.50%	1.41%	p = 0.20
Hb < 7 g/dL postpartum	0%	0%	not applicable
Hb < 10 g/dL postpartum	10.64%	15.90%	p = 0.05

Hb — haemoglobin concentration; Hct — haematocrit; PLT — platelets concentration; SD — standard deviation, IRQ – interquartile range; diff —difference

vs 0.5%, p = 0.2). The percentage of patients with postpartum anaemia (Hb < 10 g/dL) was compared, revealing that the percentage of patients with this diagnosis was over 5% higher in group with cord blood collection but difference had borderline statistical significance [15.9% vs 10.64%, p = 0.05, odds ratio (OR) = 1.63] (Tab. 2). In both groups, there were no patients with a post-delivery haemoglobin concentration below 7 g/dL and no patients who required a blood transfusion. The groups did not differ in terms of the percentage of patients receiving postpartum carbetocin, misoprostol and methylergomethin treatment (Tab. 2).

DISCUSSION

Cord blood unit (CBU) collection can potentially affect the third stage of delivery by prolonging duration and increasing the risk of blood loss in women. There are few reports in the literature discussing the occurrence of maternal risk associated with this procedure following vaginal delivery. One report showed an increase in the volume of blood lost among donors compared to the control group (321 ± 273 vs 255 ± 237 mL; p = 0.02), however, there was no increased risk of severe anaemia or need for blood transfusions in this group [2]. Our study did not assess the volume of blood lost by women giving birth but did assess the difference in haemoglobin concentration in peripheral venous blood before and after delivery. This comparison appears to be a more objective method than the inaccurate visual assessment of perinatal blood loss. The data we collected showed a greater loss in the study group as expressed by the difference in haemoglobin concentration before and after vaginal delivery (median difference in concentration in the two groups was 0.5 g/dL), and the percentage of postpartum anaemia not requiring blood transfusion was 5% larger in the donor group. Despite statistical significance or borderline statistical significance, the difference does not appear to be clinically significant in the otherwise healthy patient population. The results of our research may be the basis for designing a prospective randomized trial assessing the relative risk for cord blood donors. In our study, there were no differences in the percentage of retained placenta, however it is worth noting that this is a rare complication, therefore our statistical analysis has little power in detecting a difference (power = 25%). Therefore, the probability of not detecting a statistically significant difference, in the case of its actual existence, is as much as 75%. It is estimated that both groups would need to assess over 4.500 patients to detect a statistically significant difference between the groups, for this complication, with 90% power.

The idea of umbilical cord blood collection should be carefully considered. In addition to the potential impact on the course of the third and fourth stage of delivery and process of cord clamping, we should also consider relation between time of collection and quality of the collected material, as well as the long-term benefits of blood banking for the newborn, both in case of collection to private and public blood banks.

Blood sampling should take place after delayed cord clamping (DCC), which is recommended by WHO [3]. DCC (> 60 s) increases postnatal cord blood transfer to the baby. Studies have shown the benefits of this approach for full-term children, which include higher haemoglobin concentration (MD 1.49 g/dL, 95% CI –1.78 to –1.21) and lower risk of iron deficiency at 3–6 months [RR (relative risk) = 0.37, 95% CI 0.96–0.14] [4]. Some studies also indi-

cate a better psychomotor development of children aged four years old who had DCC after birth [5]. The benefits of this approach are especially apparent among premature babies, as delayed umbilical cord closure reduces hospital mortality by more than 30% (RR 0.68; 95% CI 0.52–0.90) [6]. Data in the literature regarding the risk of intraventricular haemorrhage, necrotizing enterocolitis and bronchopulmonary dysplasia, which remain contradictory [7, 8]. In the protocol, manufacturers of CBU collection sets suggest that it is not necessary to perform an early cord clamping during the CBU procedure. However, recent literature suggests that DCC may affect the quality and volume of CBU uptake. CBU quality is commonly assessed as the amount of total nuclear cells (TNCs) in the collected sample. A study by Ciubotariu et al. [9] showed that DCC > 60 s is associated with a small chance of obtaining a clinically useful CBU (TNC ≥ 1600×10^6). Of all CBUs collected 60–120 s after birth, only 2.6% met the criteria of clinical utility, and out of CBUs collected ≥ 120 s after birth, only 2.4%. DCC also affects the volume of CBUs collected — in the group of patients whose collection took place 60–120 seconds after childbirth, 38% of CBUs had a volume of less than 40 mL, and after 120 seconds, 46% of CBUs had a volume of less than 40 mL [8]. The volume of collected umbilical cord blood has a strong positive correlation with the CD34 + stem cell count in the sample ($r = 0.7618$, $p = 0.00$) [10]. Delayed collection reduces both the volume and the quality of the measured TNC of CBUs [11]. Given the above information, a potential conflict arises concerning DCC, the child's best interest and the medical staff's aspirations to collect as much CBU as possible. In the case of private collection, pressure to perform early cord clamping may be increased from parents who expect high quality material from the medical staff. In this research, we have not focused on the impact of DCC on the quality of CBUs, however there is an ongoing effort to focus on this subject.

Currently, around 800,000 CBUs are stored in public banks worldwide and around 4 million units in private banks [12]. Annually, the therapeutic use of cord blood is estimated at 3,300 units per year from public banks and 130 units from private banks. The chances of using each CBU for medical purposes are about 160 times greater for each unit donated to a public bank than for those donated to private banks [13]. In Poland, in 2018, 1188 hematopoietic cell transplants were performed and only in one case it was from CBU [14]. At the end of 2018, 3883 CBUs were deposited in public cord blood banks in Poland. At the same time, the Polish Organization and Coordination Centre for Transplantation "Poltransplant" has stated that public funds for banking CBU in the Central Register will not be increased due to increase transplants from haploidentical individuals [14]. It is difficult to estimate the number of units banked in private banks in Poland, but this number is certainly several times greater than CBUs stored in public banks. Worldwide, over 60% of CBU units issued from public banks are used to treat leukaemia [13], while most units issued from private banks (about 60%) are used in regenerative medicine [13]. Specifically, majority of the private bank CBUs (82%) are used to recover damage to the nervous system including hypoxemic ischemic encephalopathy, periventricular leukomalacia, cerebral palsy, apraxia, and traumatic brain injury [15]. Most units issued for regenerative purposes are used in clinical and experimental studies. Autogenous stem cell transplant is not the gold standard in any of the above-mentioned indications. A systematic review from 2019 [16], which collected controlled clinical studies from June 1, 2016 to April 1, 2018, investigated the use of stem cells in regenerative medicine. These authors identified four controlled studies treating cerebral palsy (CP), of which autogenic transplants were used in only one [17]. The study reported an improvement in motor function (GMFM-66) in children with CP one year after the use of allogeneic stem cell transplantation at a dose of ≥ 2×10^7/kg [17]. The authors of the review [16] found three additional studies assessing the usefulness of stem cell transplantation for children with type 1 diabetes, two of which included autogenous transplants. In the study, the authors did not report statistically significant differences in the main outcomes. A single study assessed the usefulness of using autologous CBU in the treatment of burns [18]. The authors of this study concluded that bone marrow and umbilical cord blood stem cells improve healing of burn injuries [18]. In total, out of 14 studies published in accordance with PRISMA standards over a two-year period, autogenic transplants were used in four studies and a moderate positive health effect was achieved in two of them. Limited scientific evidence indicating usefulness of CBU storage in private banks has been revealed in the guidelines and recommendations of major scientific societies. The American College of Obstetricians and Gynaecologists (ACOG), in 2019 indicated that routine cord blood donation to private banks is currently not supported by available scientific evidence [19]. The ACOG also strongly emphasizes the inability to use autologous CBU transplantation in the treatment of cancer due to the presence of genetic variants in transplanted cells. ACOG further points out that those who are most likely to achieve potential benefits from private banking of CBU are family members with a known disease where treatment with a hematopoietic cell transplant from a related donor is advised [19]. At the same time, ACOG accepts the societal benefit of public umbilical cord blood donation, while maintaining standards of perinatal care and DCC of neonate. The ACOG also recommends that healthcare professionals interested in private banking for financial reasons to disclose their conflict of interest to patients. The opinion of The Polish Society of Gynaecologists and Obstetricians was issued in

2010, positively reviewing umbilical cord blood collection, although not clearly indicating the type of donation (public or private) [20]. The current standards of perinatal care in Poland include an obligation to inform the patient about the possibility of depositing cord blood without distinguishing between types of banking (public or private) [21]. In the light of current medical knowledge, the position of The Polish Society of Gynaecologists and Obstetricians experts should be updated, and a patient who bears the costs associated with collecting and banking cord blood should be aware of the purposes for which cells can be used based on the method of banking (private vs public). Additionally, patients should be aware that most autologous CBUs are used in experimental therapy. In the public awareness, there is no differentiation between auto- and allogeneic stem cell transplants, and, in our opinion, private banking is misinterpreted not only by patients but also by doctors who with transplantation profesionally and consider it as remedy for childhood cancers. In the context of the scientifically proven benefits of DCC, the lack of strong research showing the benefits of private banking and the potential interference of collection with reducing the time to clamp the umbilical cord, the position of The Polish Society of Gynaecologists and Obstetricians should emphasize the priority of DCC in the third period of delivery.

CONCLUSIONS

Collection of umbilical cord blood using the "*in utero*" method after vaginal delivery is associated with a slight increased risk of blood loss in the third stage of delivery and a greater risk of postpartum anaemia. The observed changes are minor and likely have minimal clinical significance in otherwise healthy patients.

Currently, the possibilities of using umbilical cord blood stem cells in therapy are limited, resulting in a need to constantly update the recommendations regarding cord blood collection.

Funding

Project financed under the program of the Minister of Science and Higher Education called "Regional Initiative of Excellence" in the years 2019-2022, project no. 024/RID/2018/19, amount of financing 11 999 000,00 PLN.

Conflict of interest

None.

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VIA MEDICA

ORIGINAL PAPER / OBSTETRICS

Ginekologia Polska
2021, vol. 92, no. 3, 210–215

ISSN 0017–0011, e-ISSN 2543–6767

DOI 10.5603/GP.a2020.0180

The clinical evaluation of internal iliac arteries balloon occlusion for placenta accreta spectrum

Anna Rosner-Tenerowicz, Tomasz Fuchs, Michal Pomorski, Jakub Sliwa, Aleksandra Zimmer-Stelmach, Mariusz Zimmer

2nd Department of Gynecology and Obstetrics, Wroclaw Medical University, Wroclaw, Poland

ABSTRACT

Objectives: To evaluate the balloon occlusion of the internal iliac arteries during a caesarean section in the group of patients with placenta accreta spectrum.

Material and methods: We analysed 29 pregnant women with placenta accreta spectrum. The study group consisted of 15 patients, who underwent a caesarean delivery with temporary bilateral internal iliac artery occlusion. In the control group, we examined 14 women who had a standard caesarean delivery without any radiologic procedure. We compared pre- and post-operative haemoglobin level, necessity of blood transfusion, intraoperative blood loss, intensive care requirement, complications, duration of surgery, anaesthesia and hospital stay.

Results: The history and obstetric outcomes were similar in both groups. The study group required fewer blood transfusions than the control group (p = 0.0176). We administered less packed red blood cells and fresh frozen plasma. Complications were more frequent in the control group (p = 0.0014). Complications related to occlusion of the internal iliac arteries did not occur. The intensive care unit transfer was more frequent in the control group (p = 0.0329). The duration of surgery and hospital stay did not differ between groups. The anaesthesia time was longer in a study group, which related to the radiologic procedure.

Conclusions: Caesarean delivery for placenta accreta spectrum with bilateral balloon occlusion of the internal iliac arteries requires fewer transfusions. It contributes to a decrease in the complication rate and maternal morbidity.

Key words: internal iliac artery occlusion; placenta accreta spectrum

Ginekologia Polska 2021; 92, 3: 210–215

INTRODUCTION

The pathological implantation of the gestational ovum is responsible for placenta accreta spectrum. The improper placentation is associated with abnormal penetration of the villi into the uterine muscle. In placenta accreta chorionic villi are attached to the myometrium. Placenta increta invades into the myometrium. Placenta percreta penetrates the parametria and other adjacent tissues such as the bladder or rectum [1].

The main risk factors for placenta accreta spectrum are placenta previa and a history of surgery of the uterine muscle. The rate of this pathology has been increasing which is strictly associated with the rising level of caesarean section and the consequences of caesarean scar pregnancies. In the 1960s, it was diagnosed with an incidence of 1 per 4027 pregnancies. In the 1980s, it rose to 1 per 2510 pregnancies and again increased, to 1 per 500 pregnancies, in 2002 [1–3]. For this reason, there is a need for the assessment of the implantation site of pregnancy in the first trimester. Low implantation of the gestational sac at the uterine scar defect should be considered and treated as ectopic pregnancy. In case of low implantation outside of the scar defect, the pregnancy should be carefully monitored as this location of the placenta may be associated with placenta accreta spectrum [4].

According to the literature, invasive placentation may be detected by ultrasound with a sensitivity of 41% and a specificity of 88% in the first trimester of pregnancy [5, 6]. The accuracy of ultrasonography for the diagnosis of this pathology increases over time and reaches a sensitivity of 77–97% and specificity of 96–98% in the second and third trimesters of pregnancy [7–10]. There are also reports on the use of contrast-enhanced ultrasonography, which is permitted for use in pregnant women to improve blood flow through maternal-fetal interface visualisation and, at the same time, to determine the depth of penetration

Corresponding author:
Anna Rosner-Tenerowicz
2nd Department of Gynecology and Obstetrics, Wroclaw Medical University, Wroclaw, Poland
e-mail: annarosnertenerowicz@gmail.com

of the placental vascularity into the uterine muscle [11]. In more difficult cases, especially with a posterior location of the placenta, MRI can be useful [12, 13].

Invasive placentation is associated with severe complications in pregnancy and the peripartum period, including haemorrhage to various degrees, the necessity of hysterectomy, numerous blood transfusions, what can endanger the health and life of the patients. This condition qualifies as the most severe obstetric pathology [1]. In cases of placenta accreta spectrum the amount of blood loss during caesarean delivery is very often massive, reaching from 3000 to 5000 mL [14]. Ninety percent of these patients need transfusions, in whom 40% need more than 10 units packed red blood cells (PRBCs). The pathology of placentation is also one of the most common causes of peripartum hysterectomy.

In view of these facts, the early detection of placentation disorders is crucial for safety management. Determining the implantation site and degree of this abnormality enables proper prenatal surveillance and can help in avoiding emergency interventions which may lead to life-threatening situations with high maternal mortality, even of 7% [15, 16].

Early diagnosis allows for the best timing of pregnancy and planned delivery; concerning the preparation for operation and surgical technique to avoid severe consequences in the peripartum period. This paper presents the clinical evaluation of temporary bilateral balloon occlusion of internal iliac arteries in caesarean delivery with placenta accreta spectrum.

Objectives

The aim of this study is the clinical evaluation of the balloon occlusion of the internal iliac arteries in caesarean delivery in patients with diagnosis of placenta accreta spectrum.

MATERIAL AND METHODS

This work included clinical data of 29 patients with prenatal diagnosis of placenta accreta spectrum who underwent caesarean section in the 2nd Department of Gynaecology and Obstetrics of Medical University in Wroclaw. The study was approved by the review board of the Department and was conducted in accordance with the Declaration of Helsinki. The requirement to obtain informed consent was waived because of the retrospective nature of this clinically acquired data. Of the 29 analysed cases, 15 patients were referred for caesarean section with temporary balloon occlusion of the internal iliac arteries (study group). The remaining 14 women had caesarean section without balloon occlusion (control group). They were operated on without the possibility of using temporary occlusion of the internal iliac arteries because of the absence of interventional radiology unit. The control group included two patients without a prior diagnosis of placenta accreta spectrum.

In all cases, except two patients from the control group who were diagnosed intraoperatively, the diagnosis of placenta accreta spectrum was based on ultrasonography and, if needed, verified by magnetic resonance imaging (MRI). Currently, in our institution, all patients suspected of placenta percreta are scheduled to undergo elective caesarean section before term followed by hysterectomy.

Catheterisation and placement of the internal iliac balloons at the level of the uterine arteries were performed before the caesarean section in the interventional radiology unit in the University Hospital.

The perioperative plan included the following:

1. Ultrasound diagnosis — assessment of the placenta location, especially for determining the placental borders to establish the site of the uterus incision;
2. Caesarean delivery after 34 weeks of gestation or earlier in case of maternal or foetal complications
3. Elective caesarean section planned for the morning hours dictated by the presence of the entire experienced staff:
   a) 7:00 am: cardiotocography in the obstetric ward and the referral of the patient to the radiology unit;
   b) 7:00-8:00 am: catheterisation of the internal iliac arteries with balloon placement at the level of the opening of the uterine arteries; conducting a test inflation of the catheter balloons to check proper occlusion and to determine the volume of the required contrast material; transfer of the patient to the operating theatre;
   c) 8:00 am: beginning of the caesarean section:
      — The abdomen was entered through a midline vertical incision despite previous transverse scar.
      — After entering the abdomen, the following activities were performed: identification of the presence of any visible blood vessels leading to parametrium; identification of abnormal placentation; identification of the upper border of the placenta via palpation or ultrasound mapping of the placental attachment site; determination of the incision site.
      — Atraumatic delivery of a baby.
      — Ligation of the umbilical cord.
      — In case of placenta percreta, no attempt to detach the placenta was undertaken.
      — Artery occlusion.
      — Lower segment closure with continuous suture with the placenta remaining intact.
      — In case of placenta percreta hysterectomy with dissection from adjacent tissues.
      — Suturing of the vagina.
      — Performance of the methylene-blue test to control any leakage from the bladder.
      — Deflation of balloons.
      — Haemostasis control.

— Closure of the peritoneal cavity with post-operative drainage.

d) Transfer of the patient to the radiology unit to remove catheters.

Every case was analysed in terms of blood loss. This parameter also reflected the general health condition of the patient, the necessity of transferring the patient to the intensive care unit, convalescence time, and post-operative course. Perioperative blood loss was estimated by the sum of the amount of blood in the pump, visual loss through the vagina, as well as the number of used blood-soaked mops and gauze pieces. Total blood loss during caesarean section was not determined by haemoglobin drop, as the anaesthesia progression often required massive blood transfusions to maintain proper vascular fill. As usual, there were difficulties to precisely assess the amount of blood loss during caesarean section; however, the total blood loss was estimated by the amount of required blood transfusions: packed red blood cells (PRBCs) and fresh frozen plasma (FFP), as well as the general condition of the patient after surgery, as evaluated by the need for a transfer to the intensive care unit. The criteria for transfer to the intensive care unit was vestibular-respiratory instability caused by hypovolemic shock.

The differences between the studied groups were analysed in terms of age, maternal height, maternal body weight, parity, blood group, obstetric history (number of any surgery within the uterus), concomitant diseases, course of current pregnancy, and gestational week at delivery, as well as fetal characteristics including fetal presentation, fetal body weight, and APGAR score. The health condition post-operatively was determined based on haemoglobin values in comparison to preoperative values, estimated blood loss, the number of units transfused intraoperatively, and necessity of treatment in the intensive care unit. The assessed intraoperative parameters included the time of anaesthesia, time of surgery, extent of surgery, post-operative complications, complications related to vessel occlusion, length of hospital stay.

The data were analysed for normality using the Kolmogorov-Smirnov test. Summary values are given as a mean (standard deviation from the mean) for variables with a normal distribution and median (range) for distributions other than normal. The comparison between two groups of variables with a normal distribution was conducted with the Student's t-test for independent variables; in the case of variables with a non-normal distribution, the Mann-Whitney U test was used. Two groups of categorical variables were compared with the Pearson's chi-squared test. Data were statistically significant at a value of $p<0.05$. Statistical analysis was carried out with Statistica software v. 10 (StatSoft, Tulsa, OK, USA).

RESULTS

The analysis included 29 cases of pregnant women with invasive placentation hospitalised in the 2nd Department of Gynaecology and Obstetrics Medical University in Wroclaw. Fifteen patients underwent caesarean delivery with bilateral balloon occlusion of the internal iliac arteries (study group), and 14 had caesarean delivery without a radiological procedure (control group). There were no significant differences between the two groups in terms of clinical characteristics. A comparison of the studied groups is presented in Table 1.

Two women from the study group and six from the control group delivered at term. Reasons for early delivery included bleeding — four cases; threatening preterm delivery (shortening of the cervix) – four cases; premature rupture of membranes — three cases; pregnancy-induced hypertension – one case; and HELLP syndrome — one case.

Before the caesarean section, placenta accreta spectrum was suspected in 27 patients; in two cases, this diagnosis was not expected before the surgery. In the end, placenta percreta was diagnosed in 19 patients, all of whom underwent hysterectomy. The diagnosis was confirmed both intraoperatively and histopathologically.

In the study group, following caesarean section, hysterectomy without oophorectomy was performed in 11 patients, while in 4 patients, no hysterectomy was needed. In the control group, hysterectomy without oophorectomy was performed in 8 patients. In 6 control patients with partial accretism the uterus was preserved.

During surgery, the study group required less blood transfusions than the control group ($p = 0.0176$). We administer less packed red blood cells and fresh frozen plasma. Post-operative haemoglobin was markedly but insignificantly lower in the control group ($p = 0.0519$) than in the study group. The complications were higher in the control group ($p = 0.0014$). The perioperative and post-operative period was uneventful in two cases from the control group and in 11 cases from the study group ($p = 0.0014$). In the control group, complications such as disseminated intravascular coagulation, haemorrhage, bladder damage, respiratory failure, and death were reported. Two patients required relaparotomy. In the study group, 4 patients experienced haemorrhage, haemorrhagic shock, bladder damage and post-operative wound infection. The intensive care unit transfer was higher in control group ($p = 0.0329$). Complications related to temporary balloon occlusion of the internal iliac arteries did not occur.

The duration of surgery and hospital stay did not differ between groups. The duration of anaesthesia was longer in the study group due to the need for additional time for catheter placement. Intraoperative characteristics are presented in Table 2.

Table 1. Patient characteristics

Parameter	Control group (n = 14)	Study group (n = 15)	p value
Age; years [mean (SD)]	34.7 (4.87)	34.0 (5.04)	0.9650
Height; cm [mean (SD)]	165 (3.56)	166 (5.89)	0.7752
Maternal Weight; kg [mean (SD)]	77 (10.59)	70 (11.63)	0.1376
BMI [mean (SD)]	28.35 (4.34)	25.50 (4.14)	0.0847
Gravida [median (range)]	3.5 (1–9)	2 (2–9)	0.9103
Delivery [median (range)]	2.5 (1–6)	2 (1–8)	0.9093
Gestational week at admittance [median (range)]	35 (23–39)	31 (12–38)	0.0762
Previous CSs [median (range)]	1 (0–4)	1 (0–3)	0.9074
Previous CS [n(%)] No Yes	 5 (35.71) 9 (64.29)	 1 (6.67) 14 (93.33)	0.0537
Previous vaginal deliveries [median (range)]	0 (0–4)	0 (0–4)	0.9270
Previous miscarriages [median (range)]	0 (0–5)	0 (0–3)	0.4772
Newborn body mass; g [mean (SD)]	2640 (552)	2319 (666)	0.1831
APGAR [median (range)]	8 (5–10)	9 (0–10)	0.9823
Comorbidities [n(%)] No Yes	 6 (42.86) 8 (57.14)	 6 (40) 9 (60)	0.8760
Presentation [n(%)] vertex twins pelvic transverse	 6 (42.86) 3 (21.43) 3 (21.43) 2 (14.29)	 13 (86.67 2 (13.33) 0 0	0.0514

BMI — body mass index; CS — cesarean section; SD — standard deviation

Table 2. Comparison of intraoperative data between the control and study group

Parameter	Control group (n = 14)	Study group (n = 15)	p value
Pre-operative Hb [mean (SD)]	11.76 (1.09)	11.78 (1.17)	1.0000
Post-operative Hb [mean (SD)]	6.96 (2.53)	8.75 (1.78)	0.0519
Necessity of blood transfusion [n(%)] No Yes	 0 14 (100)	 5 (33.33) 10 (66.67)	**0.0176**
Packed red blood cells [median (range)]	6 (3–21)	2 (0–10)	**0.0028**
Fresh frozen plasma (FFP) [median (range)]	4 (3–13)	1 (0–11)	**0.0104**
Platelet concentrates [median (range)]	0 (0–11)	0 (0–10)	0.4598
Estimated blood loss; ml [median (range)]	2250 (800–5000)	1700 (400–4500)	0.0686
Gestational weeks at delivery [median (range)]	36 (31–39)	35 (28–38)	0.0742
Hospital stay; days [median (range)]	29.5 (8–85)	41 (9–167)	0.2847
Duration of anesthesia; min [mean (SD)]	2:09 (1:06)	4:57 (1:22)	**0.0001**
Duration of surgery; min [mean (SD)]	1:41 (1:04)	1:58 (0:44)	0.4023
Complications [n(%)] No Yes	 2 (14.29) 12 (85.71)	 11 (73.33) 4 (26.67)	**0.0014**
Intensive care requirement [n(%)] No Yes	 7 (50) 7 (50)	 13 (86.67) 2 (13.33)	**0.0329**

Hb — haemoglobin; SD — standard deviation; significant differences are marked in bold

DISCUSSION

Our study showed that caesarean delivery with bilateral balloon occlusion of the internal iliac arteries resulted in a lower transfusion requirement and lower complication rate in comparison to caesarean section without this occlusion.

In the review of literature, many studies lead to contradictory conclusions regarding prophylactic balloon occlusion of the internal iliac arteries [17]. In a study from 2016 based on 13 cases with temporary bilateral balloon occlusion of the internal iliac arteries, the mean perioperative blood loss was 1261 mL. Over half of the patients required blood transfusion, and two of them were transferred to the intensive care unit. In the present study, the mean estimated blood loss was 1847 mL in the study group and 2757 mL in the control group. Although this difference was insignificant, the need for blood transfusion was greater in the control group versus the study group. Thus, we conclude that the advantage of prophylactic balloon occlusion of the internal iliac arteries is not only the facilitation of the removal of the uterus due to reduced perioperative bleeding, but also a decrease in numerous complications related to massive blood loss, including a reduction in the number of transfusions [18].

Similar outcomes were reported by other authors from different centres worldwide [19, 20]. There are different variants of this technique described in the literature, which are based on the occlusion of the other vessels than the uterine artery. In the case of closure of the common iliac artery, there is a need to intraoperatively monitor proper blood perfusion to the lower limbs or reduce the intraoperative time. Both factors are not favourable for those doing the operation [21]. In another study of 105 patients (57 with catheters placed in the abdominal aorta and 48 in the internal iliac artery), patients undergoing abdominal aortic occlusion experienced less blood loss, required a smaller volume of blood transfusion, and had shorter balloon insertion time and fluoroscopy time; the latter translated into a decrease in fetal radiation dose than for patients with internal iliac artery occlusion [22]. There are also papers that report high embolisation of the abdominal aorta under the origin of the renal arteries [23, 24].

However, there are published unfavourable reports concerning the application of this technique. In a study performed in an Australian medical centre that presented 52 cases of pregnant women, 27 of whom were operated on without catheters with balloons and 25 of whom had catheters, no differences were revealed in terms of estimated blood loss, post-operative drop in haemoglobin, or the number of blood transfusions. Additionally, two cases of acute thromboembolic complications related to temporary embolisation occurred [21]. In another study on the adverse consequences of the described procedure of catheterising minor pelvis vessels, the perioperative rupture of the right iliac artery took place, requiring massive transfusion and admission to the intensive care unit [25].

The complication rate of bilateral balloon occlusion of the internal iliac arteries ranges between 6 and 16%. The most significant complication with the incidence of five percent is acute ischemia of the lower limbs due to a thromboembolic event or the rupture of the vessel. Other complications include pseudoaneurysms or uterine necrosis. In our study, no complications occurred in any of the 15 patients undergoing this procedure [26, 27].

For the early prevention of placenta accreta spectrum, it is important to diagnose a scar defect after caesarean section delivery, but also to detect an improperly located gestational sac. All patients with low implantation of gestational sac and surgeries of the uterine muscle in their history, especially those who have had multiple caesarean sections should be closely monitored to detect possible symptoms of placenta accreta spectrum [6, 28].

Early detection of pathologic placentation enables proper planning and delivery timing. Caesarean section should be performed with a multidisciplinary team and sufficient blood bank supply in a tertiary referral centre what may contribute to a decrease in the complication rate and maternal mortality.

CONCLUSIONS

Temporary bilateral occlusion of the internal iliac arteries in the caesarean delivery for placenta accreta spectrum improves the quality of the surgery and the patients' general health condition. According to our study, this modality contributes to the reduction in the transfusion requirement and the decrease in the rate of complications. Although our work shows benefits of balloon occlusion of internal iliac arteries during caesarean delivery in patients with placenta accreta spectrum, further studies are essential to choose the best surgical technique in pathological implantation.

Conflict of interest

All authors declare that they have no conflicts of interest.

Acknowledgments

The study was supported by the grant from Wroclaw Medical University ST.A2602.16.037.

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VIA MEDICA

REVIEW PAPER / GYNECOLOGY

Ginekologia Polska
2021, vol. 92, no. 3, 216–219

ISSN 0017–0011, e-ISSN 2543–6767

DOI 10.5603/GP.a2020.0188

Good Samaritan Clause[1]

Kamila Mrozek, Adam Praclawski

Department of Executive Penal Law, Faculty of Law, Administration and Economics, University of Wroclaw, Poland

ABSTRACT

This paper is entirely devoted to a new legal instrument called the "Good Samaritan Clause". Its legal recognition constitutes the legislator's response to the concerns raised by the medical community, in view of the unique situation in the country, but also in the world, relating to the prevention, counteraction and suppression of COVID-19. The assumption is that this instrument is to constitute a countertype that excludes the criminal unlawfulness of the act, due to the increased risk of mistakes made by the physicians involved in providing health services during the epidemic. The paper focuses primarily on the dogmatic and legal issues, discussing the catalogue of conditions needed for the application of the instrument mentioned in the title, but it also attempts to critically evaluate the introduced solution. The idea itself of introducing a solution affecting the scope of criminal liability of physicians is good, however, it requires legislative clarification as well.

Key words: countertype; a circumstance excluding the criminal unlawfulness of an act; Good Samaritan Clause; health services; criminal liability of a physician; special circumstances

Ginekologia Polska 2021; 92, 3: 216–219

INTRODUCTORY REMARKS

The Act of 28 October 2020 on the amendment of certain acts with reference to counteraction against crisis situations connected with COVID-19 [1] in Art. 24 introduces a new and until now unknown legal institution defined as the "Good Samaritan Clause". According to the new regulations, no crime shall be committed, defined in Art. 155, Art. 156 § 2, Art. 157 § 3 or Art. 160 § 3 of the Act of 6 June 1997 — Criminal Law, by the individual who, during the announced state of epidemiological risk or state of epidemics, by means of granting health services based on the Act of 5 December 1996 on the professions of physicians and dentists, Act of 20 July 1950 on the profession of feldshers , Act of 15 July 2011 on the professions of nurses and midwives, Act of 8 September 2006 on the National Medical Rescue or the Act of 5 December 2008 on prevention and combating human infections and infectious diseases within the scope of diagnosis or treatment of COVID-19 and acting in specific circumstances, has committed a prohibited act, unless resulting from negligible lack of care required in certain circumstances.

POSITION OF THE MEDICAL SELF-GOVERNMENT

The proposal to introduce a solution affecting the scope of criminal liability with reference to physicians and other individuals performing medical professions, has first appeared in the Resolution no 71/20/P-VIII of the Supreme Medical Council of 27 May 2020 on accepting the bill of the Act on the amendment of the Act on specific solutions connected with preventing, counteracting and combating COVID-19, other infectious diseases and the thus generated crisis situations [2]. Apart from the criminal law proposal, the bill assumed implementing regulations of Acts modifying the principles of legal liability, also in the scope of civil law, and professional liability of employees of the medical services and medical care units. The epidemic state introduced on the territory of Poland on 20 March 2020 in connection with

1 A man was going down from Jerusalem to Jericho, and he fell among robbers, who stripped him and beat him and departed, leaving him half dead. Now by chance a priest was going down that road, and when he saw him, he passed by. So likewise, a Levite, when he came to the place and saw him, passed by. But a Samaritan, as he journeyed, came to where he was, and when he saw him, he had compassion. He went to him and bound up his wounds, pouring on oil and wine. Then he set him on his own animal and brought him to an inn and took care of him. And the next day he took out two denarii and gave them to the innkeeper, saying, "Take care of him, and whatever more you spend, I will repay you when I come back". Which of these three, do you think, proved to be a neighbor to the man who fell among the robbers? He said, "The one who showed him mercy". And Jesus said to him, "You go, and do likewise." Luke 10:30-37.

Corresponding author:
Kamila Mrozek
Department of Executive Penal Law, Faculty of Law, Administration and Economics, University of Wroclaw, Poland
e-mail: adw.kamila.mrozek@outlook.com

the SARS-CoV-2 infections [3] has imposed the obligation of legally sanctioning the possibility of limiting civil, criminal and professional liability in case of individuals performing medical professions for actions remaining in connection with granting medical care services within the scope of preventing, counteracting or combating COVID-19.

The bill proposed by the Supreme Medical Council (constituting an appendix to the appointed Resolution) was modeled on solutions accepted in the American law which assumed that physicians and other employees of health protection institutions who as volunteers render medical services during the state of public health risk in connection with COVID-19, shall not be liable by virtue of the federal or state law for any damages caused through action or failure during rendering medical services, except for the situation where the damage has been caused by action or failure as gross negligence (misconduct), crime or the employee was under the influence of alcohol or other abusive substances. In March 2020 the clause has been extended to all physicians and other employees of the health protection institutions rendering services within the scope of combating COVID-19.

The medical community indicated the uniqueness of the situation of individuals performing medical services during the epidemic state. It concerned not only the hazardous conditions of the medics, but mainly the necessity to face a new, not yet examined disease classification.

The lack of established, unified rules, standards of caring for patients or simply principles of acting in such circumstances excludes the possibility of objective evaluation of the physicians' proceedings in the context of reliable examination of the possible medical malpractice. Moreover, a significant problem lies in the interim course (dependable upon the gradually extended knowledge in this scope) of resolving various procedures connected with providing care to patients suspected or infected with the Coronavirus SARS-CoV-2.

These circumstances have created the grounds to come forward with a solution within the domestic law that would exclude the criminal liability of physicians and other individuals performing medical professions in the case of committing unintentional crimes against life and health defined in the special part of the criminal code, *i.e.* Art. 155, 156 § 2, 157 § 3, 160 § 3 of the Criminal Code, provided that the act has been committed subsequently to treatment performed within combating the COVID-19 epidemic. Whereas, clear focus is given to the temporary and extraordinary character of the proposed standard. It has been correctly observed that the lack of clear regulations of the subject matter may lead to unreasonable criminal liability of the physician and the remaining medical staff for unintentional crimes committed subsequently to treatment performed in good faith within combating the COVID-19 epidemic.

The medical self-government has correctly observed that the matter of criminal liability of the physician or other individual performing medical services during the epidemic state cannot be settled on the level of the individual jury evaluation during a potential criminal procedure on the medical malpractice. It is necessary to implement complex system solutions. Due to the large number (daily!) of infected individuals and those suspected of being infected, the possibility of — even if hypothetical — filing charges against physicians concerning unintentional committing of crime against life and health seems as unacceptable. In this context it cannot be forgotten that medical staff deficiency, particularly in the field of combating SARS-CoV-2, has forced the necessity to perform work incompatible with the possessed specialization. Many physicians did not have any professional experience in treating infectious diseases and directing them to combat COVID-19 was proceeded by the employer's or the governor's decision immediately enforceable. The Supreme Medical Council clearly stresses that *„the proposed system solution will allow for a reasonable shaping of the scope of criminal liability of individuals performing medical professions in extraordinary epidemic risk situation".*

GOOD SAMARITAN CLAUSE IN THE EYES OF THE LEGISLATOR

The Act of 28 October 2020 on the amendment of certain Acts referring to counteracting crisis situations connected with COVID-19, is exclusively limited to criminal law solutions, entirely disregarding the demands reported by the medical self-government to also regulate the matters of civil and professional liability. The solution accepted by the legislator has faced a definite objection within the medical environment, which expects complex support for physicians working with COVID-19, and not illusive support [4]. The current meaning of the analyzed regulation exposes medical employees to civil and professional claims. Moreover, it has not been accepted to introduce in the Art. 24 of the above-mentioned general clause in the form of "special circumstances", whereas the clause is an indeterminate phrase, granting the governing body of the proceeding a significant margin of decision. For, according to Article 24 of the Act, a condition of using the kindness assumed by the appointed regulation is not only acting within the diagnosis or combating COVID-19, but also acting "in special circumstances". It should be firmly underlined that the very fact of the epidemic state constitutes these special circumstances which should justify limiting the criminal liability of those individuals performing medical professions for actions remaining in connection with performing health care services within prevention, counteraction and combating COVID-19. For the record, it's worth mentioning that the legislator does

not indicate what should be understood under the phrase "special circumstances", nor does he give any examples.

"Health benefits" mentioned in the discussed regulations are actions serving the maintenance, rescue, rehabilitation or improvement of health and other medical actions resulting from treatment or separate regulations settling the principles of its performance [5]. In the case of the "Good Samaritan Clause" this definition is somewhat limited, because the legislator clearly indicates that the benefits must be performed according to the: the Act on the physician and dentist profession, the Act on the feldsher's profession, the Act on the nurse and midwife profession, the Act on the Public Medical Rescue and the Act on prevention and combat of infections and human infectious diseases.

The possibility of the criminal disclaimer with reference to physicians and individuals mentioned in the established regulations is basically limited to a few crimes standardized in the criminal code:

— Art. 155 Criminal Code — involuntary manslaughter,
— Art. 156 § 2 of the CC — involuntary infliction of grievous bodily injury,
— Art. 157 § 3 of the CC — involuntary infliction of medium and minor bodily injury,
and
— Art. 160 § 3 of the CC — reckless exposition to direct risk of life or grievous bodily injury.

Art. 24 of the Act of 28 October 2020 contains a criminal disclaimer — provided that additional, detailed criteria are met by - physicians, dentists, feldshers, nurses, midwives and paramedics. According to the opinion of the National Chamber of Physiotherapists the above-mentioned catalog needs to be supplemented by physiotherapists who also perform health services to patients hospitalized due to COVID-10 [6]. Similar objections have been submitted by the National Chamber of Laboratory Diagnosticians, who indicate the obligation to legally also protect this professional group. Despite the numerous demands of particular professional groups, physiotherapists and diagnosticians have not been directly included in the new regulations, which means that they will be able to refer to the "Good Samaritan Clause" only if they are directed to combat the epidemic. This means that the criminal disclaimer only concerns those cases of performing medical services within diagnosis or treatment of COVID-19, which subsequently excludes the possibility of exercising the title solution against individuals performing any other diagnostic and therapeutic actions not connected with infecting the patient with SARS-CoV-2.

The legislator excludes the possibility of applying the "Good Samaritan Clause" in case of gross negligence with reference to precautions required in the given circumstances. Similarly, as in the case of the controversial notion of "special circumstances" mentioned above, this record opens limitless possibilities of interpretation, both in the case of preparatory, as in jurisdiction proceedings. Settling the matter of possible infringement of the precaution principles should rely on an objective model. While evaluating the possible occurrence of the negative premise of applying the title institution, the individual features (personality) of the perpetrator of the crime mentioned in the Act should be considered, at the same time including the special conditions of the performed work. As an example, we could indicate the physician's fatigue, the type and nature of competence and skills, lack of time or equipment. This matter should also be examined in terms of the organization of health care which is already on the edge.

It seems that the most reliable evidence leading to settle the matter of committing a given prohibited act due to gross negligence with reference to precautions required in the given circumstances will be the court appointed expert's opinion, which does not clearly rule out the remaining measures assumed by the regulations of the criminal code. In order to disclaim the criminal liability of the physician, the conclusion of the opinion must clearly indicate that while performing medical services to the patient, the perpetrator has abode by any precaution rules required in particular circumstances.

The justification to the bill initiated by members of parliament on the amendment of certain Acts in connection with counteracting crisis situations connected with the occurrence of COVID-19 [7], it has been indicated that *„during the epidemic risk or epidemic state, criminal disclaimer should occur in case of particular acts committed by individuals performing medical professions, if the medical actions are undertaken in order to combat the COVID-19 epidemic (for e.g. when medical services are performed by individuals who in non-epidemic circumstances would not have been performing these services - thus, performing services by physicians who are in the course of completing their specializations or physicians who are experts in other fields than the possessed specialization). Criminal disclaimer is also limited, if the effect in the form of death of the deceased, grievous bodily injury, organ dysfunctions, health disorders or causing direct risk of life loss or grievous bodily injury, was the result of gross power abuse or gross non-performance of duties".*

SUMMARY

Introducing the "Good Samaritan Clause" in the Polish legislation should be thus accepted. The assumption that the institution is to create a counter type, a circumstance excluding the criminal unlawfulness of an act in connection with a greater risk of mistakes made by individuals engaged in performing medical services during the epidemic.

This solution is, thus, an answer to the numerous demands submitted by the medical environment, forced to act in extraordinary conditions, without due preparation not only professionally, but also mentally. However, in order for

the said institution to fulfill the expectations of the initiators, it still requires further refinement because the form of it, settled by the legislator, does not constitute any real legal protection for physicians and the remaining medical staff members. The provision of Art. 24 of the Act of 28 October 2020 on the amendment of certain Acts referring to counteracting crisis situations connected with COVID-19, contains not only unclear, but also arbitrary criteria which provide significant freedom of interpretation, which might be abused during the criminal proceeding. It should be underlined that this solution is temporary, and the time of its effectiveness is limited by the risk of epidemic or state of epidemic throughout the country. For this reason, it is hard to discuss the necessity of implementing system solutions which would have been permanently included in the legislation. This is, besides, the idea of the initiators of the title solution. However, according to the Swedish model of "no fault", definite action should be undertaken towards system solutions for medical problems without the necessity of being held criminally or disciplinary liable.

Moreover, it introduces the possibility of only criminal disclaimer for medical mistakes, exposing the physician to issues of disciplinary liability in cases of infringing the medical code of ethics and regulations connected with performing the physician's profession. It also leaves the possibility of bringing lawsuits connected with committing specific medical mistakes.

Conflict of interest

None.

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REVIEW PAPER / GYNECOLOGY

Ginekologia Polska
2021, vol. 92, no. 3, 220–225

ISSN 0017–0011, e-ISSN 2543–6767

DOI 10.5603/GP.a2020.0177

Providing new insights into the endometriosis-associated cancer arising in episiotomy scars

Maria João Carvalho[1, 2], Ana Sofia Pais[2–4], Ângela Rodrigues[1, 2], Ana Luísa Areia[3, 4], Margarida Figueiredo-Dias[1, 2]

[1]*Universitary Clinic of Gynecology, Faculty of Medicine, University of Coimbra, Coimbra, Portugal*
[2]*Gynecology Service, Coimbra Hospital and University Centre, Coimbra, Portugal*
[3]*Obstetric Department, Coimbra Hospital and University Centre, Coimbra, Portugal*
[4]*Faculty of Medicine, University of Coimbra, Coimbra, Portugal*

ABSTRACT

Endometriosis-associated malignancy in an episiotomy scar is rare. The predictive factors are poorly understood as are the mechanisms and pathways associated with implantation and malignant transformation.

In this study we describe the cases reported in the literature of malignancies arising in endometriosis foci of an episiotomy scar. We identified five cases described between 1990 and 2016.

These cases represent recurrence of endometriotic lesions in an episiotomy scar after previous diagnosis of endometriosis, three to twenty-five months before. Histology revealed clear cell tumours in four cases and a serous papillary carcinoma. The approach encompassed surgical removal for diagnosis and as part of the therapeutic strategy. Adjuvant treatment was performed depending on classical prognostic factors. Mechanisms of endometriosis implantation in scars include the influence of oestrogens in the healing process and activation of COX-2, aromatase and matrix metalloproteinases. Nevertheless, for malignant transformation, other pathways seem to play a role, namely inflammation, immune response and oxidative stress, induced by iron deposits due to haemorrhage.

Further studies are needed to allow the establishment of a predictive model for malignant transformation of endometriosis in episiotomy scars.

Key words: endometriosis; episiotomy; malignancy; carcinogenesis

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INTRODUCTION

Endometriosis is a chronic benign and oestrogen-dependent gynaecologic disease, with estimated frequency from 6% to 10%, among women of reproductive age [1]. Ectopic endometrium can be localized in the pelvic peritoneum, ovaries and rectovaginal septum, and infrequently in extra-pelvic structures including the diaphragm, pleura, and pericardium [1]. Although endometriosis is a benign disease, various scientific data support the notion that it represents the initial stage of a neoplastic process [2]. Furthermore, albeit a benign condition, endometriosis has the potential for malignant transformation, in less than 1%, particularly concerning ovarian implants [3]. An atypical endometriosis can be considered a transitional state from benign disease to invasive cancer [2, 4]. The first description of endometriosis in a postoperative scar was in 1903 [5]. The true aetiology is unknown, but scar endometriosis might be explained by iatrogenic transplantation of endometrial tissue to the wound edge during any surgical procedure [5, 6], with typical manifestations including an immobile lump in the scar or near it, with bulging and pain during menstruation. Accordingly, some authors reported a 0.03% to 1.08% incidence of endometriosis in abdominal surgical scar in women undergoing pelvic surgery; nevertheless, malignancy transformation is very rare [5]. Perineal endometriosis is a rare condition and usually involves the episiotomy scar (occurring in only 0.00007% of births) [7].

The risk of malignant transformation of endometriosis has been associated with malignancies of the reproductive tract, such as ovarian, cervical and endometrial cancer, and with

Corresponding author:
Maria João Carvalho
Universitary Clinic of Gynecology, Faculty of Medicine, University of Coimbra, Azinhaga de Santa Comba, 3000-354 —Coimbra, Portugal
Gynecology Service, Coimbra Hospital and University Centre, Coimbra, Portugal
e-mail: mariajoaosflcarvalho@gmail.com

other frequent malignant diseases such as breast and thyroid cancer. The influence of the hormonal environment could also explain its association with melanoma and colorectal cancer [8, 9]. Gandini et al. [8] conducted a systematic review and meta-analysis evaluating the relation between endometriosis and extra-ovarian malignancies. The authors found an increased risk of endometrial and thyroid cancer, an inverse relation with cervical cancer and no association with breast cancer [10].

The mechanisms of malignant transformation of endometriosis are not yet completely understood, and the impact of therapeutic strategies is poorly clarified. Endometriosis has various molecular similarities with invasive cancer, including inflammation, tissue invasion, angiogenesis, dysfunction of immune cells, increased local oestrogen production, apoptosis, stem cell-like dysregulation, and pro-survival features [2]. Also, several biological models have tried to explain malignant transformation of endometriosis as inflammation, oxidative stress induced by iron derived from menstrual bleeding and hyperestrogenism [2, 11, 12].

Therefore, endometriosis foci in scars are a recognized entity in clinical practice, but their accepted, though rare, malignant transformation needs a well-established approach. The aim of this study is to systematically report clinical cases of carcinoma arising in episiotomy scar endometriosis and to give an insight into the best clinical approach to these malignancies in our practice.

MATERIAL AND METHODS

We performed a search in PubMed and Embase using the combination of "endometriosis" and "AND" Boolean operators to combine with MeSH terms and text words "episiotomy", "episiotomy scar", "malignancy", "clear cell carcinoma" and "neoplasm", from January 1980 to March 2019. English abstracts were analysed, and one case was excluded as it was reported in Hungarian without access to the full text and it was not possible to contact the corresponding author. All the other corresponding authors were contacted by email to obtain further information considering the follow-up of patients and there were no responses. So, it was not possible to determine survival rates and disease-free survival for all the cases. Also, the sample size limited the statistical analyses. We describe clinical cases of malignant transformation of endometriosis in episiotomy scars, considering clinical outcomes, namely survival and prognostic factors as well as treatment options.

RESULTS

We included five patients in our review analysis, all reporting endometriosis-associated malignant transformation in an episiotomy scar [11, 13–16]. The patients' characteristics are shown in Table 1. The median age at the time of diagnosis was 45 years (range 36–50 years). Two patients were perimenopausal [13, 16], and for the remaining patients the menopausal state was not reported. No previous history of endometriosis was diagnosed.

Table 1. Characteristics of the patients with endometriosis-associated malignant transformation in an episiotomy scar

Age at diagnosis, years (median, range)	**45 (36–50)**
Interval since surgery for benign endometriosis in episiotomy scar, month (median, range)	9 (3–25)
Interval since last vaginal delivery to diagnosis of malignancy, month (median, range)	19 (15–30)
Histological type (%, n) Clear cell carcinoma Serous papillary cystadenocarcinoma	 4 1

The median time from the diagnosis of endometriosis in the episiotomy scar and the diagnosis of malignancy at the same site was 9 months (range 3 to 25 months). All patients underwent wide excision of the mass in the episiotomy scar; histology of the removed tissue revealed endometriosis. Furthermore, three patients had additional treatment options: gonadotropin-releasing hormone agonist leuprorelin acetate for 6 months [15]; danazol and laser vaporization of superficial endometriosis at pouch of Douglas by laparoscopy [13]; and medroxyprogesterone acetate injectable suspension for one year followed by mifepristone for half a year, in addition to traditional Chinese medicine [11].

All the patients presented clinical recurrence of a perineal mass after previous diagnosis of endometriosis in an episiotomy scar. The symptomatic description was a solid vaginal mass associated with cyclic perineal pain in two cases; or a painless pruritic perineal nodule with gradual increased dimensions in two other cases; and as an ulcerated lesion with bilateral lymphadenopathies in the remaining case [14].

Considering the available data, the median period from last vaginal delivery and episiotomy carcinoma was 19 months (range 15 to 30 months) [11, 13–15]. Two spontaneous vaginal deliveries and two forceps and in one case there is no data. Perineal pain was described several months after delivery in three cases, one of them associated with slow recovery of perineal wound and swelling.

The imagological studies performed included pelvic and abdominal ultrasound and/or computerized tomography and/or magnetic resonance imaging. Tumour marker analysis was carried out in two patients and results were negative, including CA 125 [13, 14].

Tumour dimensions ranged from 3 cm to 10 cm and all were submitted to biopsy. The most common histological type was clear cell carcinoma in four cases [11, 14–16]; the remaining case was a serous papillary cystadenocarcinoma, diagnosed after surgical resection, as a previous biopsy revealed endometriosis but was negative for malignancy [13]. There is no additional data regarding molecular characterization.

Table 2. Therapeutic strategies and survival described for malignancies arising in endometriosis in episiotomy scar

Case	Author	Year	Surgery	Chemotherapy	Radiotherapy	Disease-free survival	Global survival
1	Hitti et al.	1990	No	Yes	Yes	12 months	30 months
2	Todd et al.	2000	Partial vaginectomy + bilateral salpingo-oophorectomy + Hartmann's procedure	No	Neoadjuvant 19 fractions discontinued due to severe skin reaction	6 months	Unknown
3	Chene et al.	2007	Complete resection by perineal surgery	Adjuvant weekly carboplatin + interstitial application of iridium	Adjuvant 45 Gy in 5 weeks perineal area and inguinal lymph node chain discontinued at 4 weeks due to urethritis and vulvovaginal inflammation	> 10 years	Unknown
4	Kwon et al.	2008	Radical vaginectomy + wide vulvar excision with partial skin graft + total abdominal hysterectomy + pelvic lymphadenectomy + right inguinal lymphadenectomy	No	No	10 months	Unknown
5	Han et al.	2016	Radical vulvectomy with skin graft + inguinal lymphadenectomy	Neoadjuvant (1 cycle) Adjuvant (10 cycles) paclitaxel + cisplatin	No	6 months	Unknown

The treatments performed are described in Table 2. Surgery was part of the primary treatment in the majority of the cases [11, 13–15]. In the case reported by Hitti at al. [14], case 1, the patient did not accept radical surgery and was submitted to chemotherapy and radiotherapy [14]. In case 2, described by Todd et al. [16], radiotherapy was followed by radical and complete surgery that included partial vaginectomy, bilateral salpingo-oophorectomy and Hartmann's procedure, as the patient was submitted to total abdominal hysterectomy seven years before. Chene et al. [13] reported case 3, with primary surgical treatment that was radical and complete, followed by adjuvant radiotherapy of 45Gy in five weeks, followed by chemotherapy with weekly carboplatin and interstitial application of iridium. Concerning case 4, by Kwon et al. [15], surgical treatment consisted of radical vaginectomy and a wide vulvar excision with partial skin graft, total abdominal hysterectomy, pelvic lymphadenectomy and right inguinal lymphadenectomy. Concerning case 5, neoadjuvant chemotherapy was followed by surgery and chemotherapy. The surgical procedure consisted on radical vulvectomy with skin graft and inguinal lymphadenectomy, followed by chemotherapy with paclitaxel and cisplatin (1 cycle before surgery and 10 cycles after) [11]. One patient (case 1) died 30 months after the diagnosis of malignancy [14].

DISCUSSION

The most probable pathogenic mechanism for endometriosis in an episiotomy scar is a transplantation theory, which involves iatrogenic implantation of the endometrium to the surgical wound [11]. This is more commonly diagnosed in situations of vaginal delivery followed by uterine curettage [6, 17]. Indeed, this hypothesis can justify the transport of endometrial tissue to the vulva during delivery [11]. Recently, many arguments in the literature suggest a well-established causal relationship between trauma and the endometriotic lesions diagnosed in surgical scars [18]. Various traumas namely delivery, uterine curettage or episiotomy may explain atypical locations of the disease. Growth factors released in the traumatized area and the associated oestrogen production that is essential in wound healing and tissue repair, may enable the implantation and growth of endometriotic cells [18]. Activated platelets involved in the mechanisms of initial tissue repair may induce COX-2 (cyclo-oxygenase 2) production by monocytes, endothelial and stromal cells and oestrogen receptor-β expression in endometriotic stromal cells. Elevated COX-2 expression results in augmented prostaglandin E2 (PGE2) production. PGE2 activates EP2/EP4 receptors, resulting in stimulation of COX-2, aromatase and matrix metalloproteinases (MMP)-2/MMP9 expression. Increased oestradiol supports motility in ectopic endometrial cells and elevated MMP activity pro-

motes their invasiveness [19]. A possible genetic predisposition and exposure to endocrine disruptors could explain why some patients develop the disease whereas others do not, despite being exposed to the same event. A better understanding of the mechanisms favouring the onset of the disease after trauma, for example obstetric, is fundamental to establish future preventive strategies. However, in the same series, some women had pre-existing endometriosis before their gynaecological procedure, indicating that endometriosis foci in scars may originate from lymphatic or haematogenic dissemination or anomalous differentiation of extrauterine cells into endometrial cells [20]. Hormonal or immunological factors may explain the metaplastic theory.

Specific tumour markers have not yet been identified to predict malignant transformation of endometriotic extraovarian lesions [11]. The results of the five cases reported here point out the importance of a close follow-up due to the absence of specific markers for malignant transformation and unpredictable course of this disease.

The ovary is the most frequent site of endometriosis-associated malignancy, in 80% of cases and extraovarian endometriosis accounts for one quarter to one fifth of these cases [13]. The most common histological malignancies described in endometriosis-associated ovarian cancer are endometrioid and clear cell carcinoma; endometriosis was detected in 30–55% of clear cell and 30–40% of endometrioid ovarian cancers [21, 22]. In extraovarian sites, endometrioid tumours represent 69.1% to 75.9% and clear cell carcinoma 4.5% to 13.5% of the malignancies [11]. However, in abdominal surgical scars, clear cell carcinoma represented 66.7% of cases, followed by endometroid carcinoma in 14.6% [5]. These endometrioid adenocarcinomas express mainly positive oestrogen receptors, but clear cell carcinoma exhibits lower oestrogen receptor expression [2]; the development of these type of tumour is considered to be connected to oxidative stress derived from free iron from endometriomas [22]. Indeed, iron-induced oxidative stress resulting of frequent menstrual bleeding was thought to be a main pathway in the malignant transformation of the disease [1, 2]. Not only stress factors (as lactose dehydrogenase, lipid peroxidase and 8-hydroxy-2--deoxyguanosine) increase oxidative stress and consequent DNA damage [12], but also both endometriosis and cancer are linked to inflammation [2]. It has been also hypothesized that alterations in the expression of tumour suppressor genes and oncogenes happening in normal endometrial tissue originate the overgrowth of endometrial foci external to the uterine cavity [2]. Moreover, a various of genetic changes, including loss of heterozygosity (LOH), PTEN, ARID1A and p53 mutations were already described in endometriosis and also endometriosis-associated malignancies [23].

Likewise, alterations in immunological response, either cell-mediated and humoral, contribute to the pathogenesis of endometriosis and relevant alterations associated with cellular immunity originate an inadequate removal of ectopic endometrial cells from the peritoneal cavity. Considering the immunological mechanisms, either iron-induced oxidative stress, inflammation and hyperestrogenism have been advocated as important associations between endometriosis and cancer [2]. Undeniably, hyperestrogenism has been suggested as a major contributor for the development of endometrioid cancer and clear cell carcinoma [11]. The levels of oestradiol and aromatase activity inside endometriosis stimulate cyclooxygenase-2 and prostaglandin E2 production, also described as driving factors for tumour progression [12]. Furthermore, local inflammatory reactions in endometriosis originate a response that includes cytokine release [11]. The endometriosis-associated inflammatory responses are dependent on increased activated macrophages and their secreted cytokines in peritoneal fluid; this local inflammatory microenvironment will allow the growth and maintenance of endometriosis through endometrial-peritoneal adhesion, invasion, angiogenesis, and proliferation [24]. The levels of pro-inflammatory cytokines are increased in tissue/intercellular fluid of ovarian endometrioma, such as interleukin (IL)-1, IL-6, IL-8, tumour necrosis factor-α, and tumour necrosis factor-β. These mediators are involved in angiogenesis, cell proliferation and production of oxygen reactive species (superoxide; hydrogen peroxide; hydroxyl radical; hydroxyl ion; and nitric oxide) [25, 26]. These cytokines within the endometriosis microenvironment lead to the increasing synthesis of PGE2, which leads to angiogenesis, proliferation, and inhibition of apoptosis, also described in carcinogenesis [11]. The aberrant expression of fibroblast growth factor receptor-2 (FGFR2) gene has been linked to the carcinogenesis of endometriosis and has been referred to as a targeted intervention in this process [12].

Part of the mechanisms of malignant transformation were studied in endometriomas, but extragonadal endometriosis, namely rectosigmoid, colon, rectovaginal septum and pelvic peritoneum and surgical scars, point to an overlapped phenomena, as previously emphasized [23]. The presence of a transitional dysplastic region between benign endometriosis and cancer is an important histological aspect in carcinoma arising from endometriotic foci, reinforced by the fact that 36% to 42% of endometriosis-associated cancers exhibit endometrial glandular dysplasia [11].

Reported incidence of malignant transformation in surgical scars is 0.3% to 1% [13]. The rarity of the pathology stresses the difficulty in stratifying risk factors to predict the clinical progression or to establish the best treatment approaches. Moreover, these reports highlight the need to closely follow up all patients with previous removal of nodules in episiotomy scars. Routine imaging and tumour markers are still not defined and need further studies.

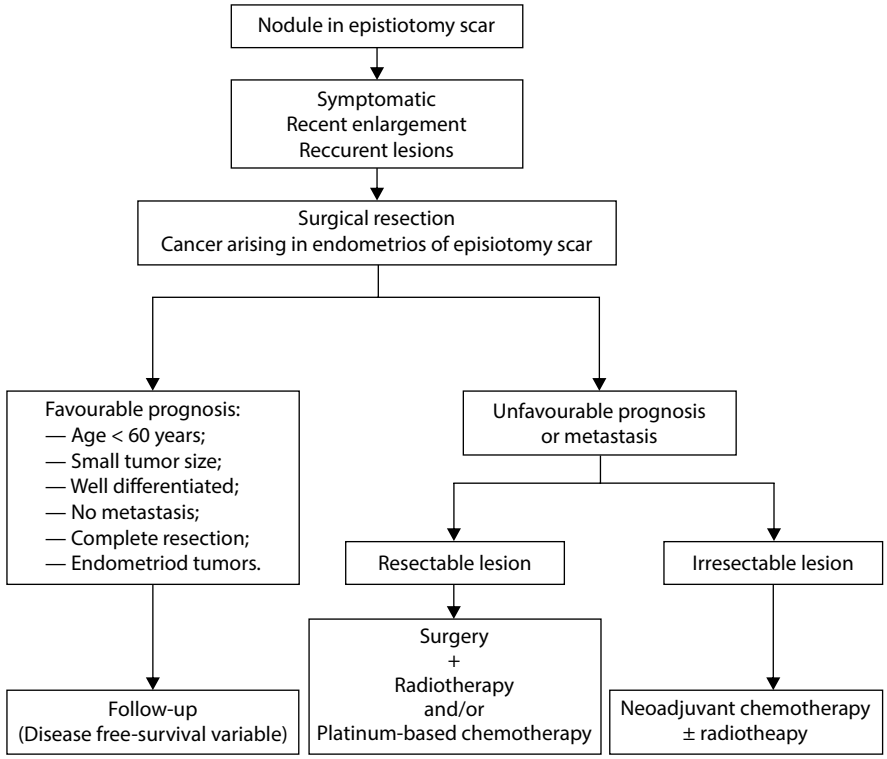

Figure 1. Proposed algorithm for diagnosis and treatment of episiotomy scar nodule

Therapeutic options were diverse, but surgical removal was mainly performed as a diagnostic and therapeutic procedure. The 5 mm free edges were defined by some authors to consider a complete excision [13]. Adjuvant treatment can be planned according to prognostic factors such as tumour size, histological differentiation, local or systemic spread, age of the patient and patient-informed decision. Nevertheless, endometrioid sub-types have better prognosis than clear cell tumours [15]. Patients with an unfavourable prognosis can be offered adjuvant treatment with radiation or platinum-derived chemotherapy [15]. Large tumours probably benefit from neoadjuvant radiotherapy to reduce size, followed by less invasive surgery due to the associated downstaging, which is probably is the best method [16].

Malignant transformation of endometriosis in an episiotomy scar is rarely reported in clinical practice. To systematize the approach of a nodule in episiotomy scar and therapeutic options of malignant lesions arising in endometriosis, we propose an algorithm described in Figure 1. Clinical suspicion should arise when a recurrent lesion is detected after endometriosis removal in an episiotomy scar. The mechanisms of transplantation in episiotomy scars have recently been highlighted, namely encompassing trauma, growth factors and hormonal influence. Also, the malignant transformation was associated with hyperestrogenism, inflammation, immunological and oxidative stress induced by iron from menstrual bleeding. The clinical approach must be individualized due to limited data and consequences for patient's quality of life.

Conflict of interest

The authors declare no conflict of interest.

Funding

The authors declare no funding.

Authors declare this manuscript has been neither published nor submitted for publication elsewhere

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VIA MEDICA

REVIEW PAPER / OBSTETRICS

Ginekologia Polska
2021, vol. 92, no. 3, 226–229

ISSN 0017–0011, e-ISSN 2543–6767

DOI 10.5603/GP.a2020.0163

Intrauterine growth retardation after laparoscopic Roux-en-Y gastric bypass — clinical presentation and literature review

Anna Rozanska-Waledziak[1], Joanna Kacperczyk-Bartnik[1], Maciej Waledziak[2], Pawel Bartnik[1], Andrzej Kwiatkowski[2], Justyna Teliga-Czajkowska[1], Krzysztof Czajkowski[1]

[1]2nd Department of Obstetrics and Gynecology, Medical University of Warsaw, Poland

[2]Department of General, Oncological, Metabolic and Thoracic Surgery, Military Institute of Medicine, Warsaw, Poland

ABSTRACT

Bariatric surgery is associated with a higher risk of intrauterine growth retardation (IUGR) and small for gestational age neonates. We present two examples of IUGR after laparoscopic Roux-en-Y gastric bypass, both associated with excessive restriction in patients caloric intake, one due to obstetrician's indications and the other resulting from patient's anxiety of weight gain in pregnancy. IUGR was observed accordingly in the 35th and 28th week of pregnancy. The first patient had an urgent cesarean section due to pathological cardiotocography tracings in the 35th week of pregnancy, with the newborn's weight of 1690g (< 1st percentile). The second patient, admitted in the 28th week with suspected IUGR, had an elective cesarean section in the 36th week, with the newborn's weight of 2095g (5th percentile). Although malabsorptive mechanisms are known to be involved in the impaired fetal growth after bariatric surgery, patients' and obstetricians' adherence to nutrition and supplementation regimen are of utmost importance. The problem of optimum daily caloric intake, vitamin and micronutrients supplementation in pregnancies after bariatric surgery is presently discussed in the literature. Optimum care and advice for bariatric patients have to be diversified as malabsorptive and restrictive operations lead to changes in metabolism, nutrition and hormonal balance.

Key words: bariatric surgery; fetal growth retardation; avitaminosis

Ginekologia Polska 2021; 92, 3: 226–229

INTRODUCTION

As the prevalence of obesity in women of reproductive age is rising every year and bariatric surgery is proven to be the mainstay of treatment, the number of women after bariatric surgical procedures experiencing pregnancy is constantly growing. In 2013 over 450,000 bariatric procedures were performed worldwide [1]. As stated by Walędziak et al. [2] observe a similar trend in Poland, with over 2000 bariatric procedures performed in 2016. The influence of bariatric surgery on the pregnancy course and perinatal outcomes has become one of the major concerns of obstetricians taking care of these patients. Nutritional deficiencies, intrauterine growth retardation (IUGR) and the risk of prematurity are only a few problems to be considered [3]. Although international recommendations about adequate nutrition and vitamin intake in pregnancy after bariatric surgery are officially accepted and widely available, there still exists an important problem of patients' and their obstetricians' adherence to the recommendations. Therefore a pregnancy in a patient who underwent a bariatric procedure should be considered high risk pregnancy.

CLINICAL PRESENTATION

Case 1

The first patient, a 32-year-old primigravida underwent laparoscopic Roux-en-Y gastric bypass (LRYGB) in November 2014. Her preoperative weight was 125 kg, with a body mass index (BMI) of 42.75 kg/m^2. The patient had a weight loss of 37kg and her BMI was 30.09 kg/m^2 before the pregnancy, reaching %EWL (excess weight loss) of 71.29%. The time-to-conception interval was two years. She had a history of chronic hypertension, treated during pregnancy

Corresponding author:
Joanna Kacperczyk-Bartnik
2nd Department of Obstetrics and Gynecology, Medical University of Warsaw, 2 Karowa St, Warsaw, Poland
e-mail: asiakacperczyk@gmail.com

with methyldopa 250 mg taken 3 times daily, with optimal control. Her gestational weight gain (GWG) was 13kg with a maximum weight of 101 kg and BMI of 34.54 kg/m^2 at the end of pregnancy. Because of elevated fasting glucose levels she was diagnosed with gestational diabetes mellitus (GDM) in the 6th week of pregnancy. She was treated only via diet, achieving normal blood glucose levels. The patient received supplementation with prenatal vitamins with additional iron sulfate 80 mg daily (orally) and folic acid 5 mg daily during the first trimester. She had a history of anemia before the pregnancy with normal levels of hemoglobin and blood count throughout pregnancy. The patient stated having been advised by her obstetrician to restrict her caloric intake throughout the pregnancy to 1200 kcal daily and having strictly followed those indications. In the 35th week of pregnancy she was admitted to hospital due to non-reassuring cardiotocography (CTG) tracings and suspected IUGR. On the day of admission the estimated fetal weight (EFW) was 1911 g. The growth retardation was of more than three weeks for the EFW. In detail: two weeks for the head circumference (HC) 299 mm — 33w1d, three weeks for the biparietal diameter (BPD 88 mm — 32w2d), four weeks for the abdominal circumference (AC) 274 mm — 31w3d. The medial cerebral artery flow peak index (MCA PI) was 0.99 (1st percentile) and umbilical artery flow peak index (UA PI) was 1.44 (96th percentile), giving the cerebral-placental ratio (CPR) of 0.69 — circular centralization.

The patient was submitted to constant fetal CTG monitoring and received one dose of 12 mg betamethasone intramuscularly. The blood glucose and blood pressure were monitored, basic blood exams were taken. Because of reduced variability and repetitive decelerations in the CTG tracings during hospitalization, the tracings were classified to be pathological and urgent cesarean section after 11 hours of hospitalization was performed. The male newborn weighed 1690g (< 1st percentile) and received 9 Apgar points on the 1st and 10 points on the 3rd, 5th and 10th minute of life.

Case 2

The second patient was a 34-year-old female in her second pregnancy, with a history of one spontaneous abortion. She underwent LRYGB in July 2009. Her weight before the operation was 137.5 kg, with a BMI of 49.3 kg/m^2. The patient had a maximum weight loss of 67.6 kg and reached a BMI of 25.06 kg/m^2, achieving %EWL 99.7%. The time-to-conception interval was seven years. Before the pregnancy her body weight was 83.7 kg, with a BMI 30.01 kg/m^2. Her weight gain during pregnancy was 4.3 kg with the maximum weight of 88 kg and BMI of 31.55 kg/m^2 at the end of pregnancy. The patient had a history of depression and a suicide attempt before pregnancy, with no medications taken during pregnancy and under care of a psychologist. She was treated for severe anemia before pregnancy with iron given parenterally. The treatment was continued during pregnancy, having resulted in normal parameters of hemoglobin and blood count. The patient also monitored her own blood pressure, with generally normal readings, without need of introducing medications. The patient had been advised about her optimum daily caloric intake in pregnancy, but she admitted having restricted herself to a maximum of 1500 calories daily due to her fear of regaining weight during pregnancy, without having informed her obstetrician about this decision. She received supplementation with prenatal vitamins. In an ultrasound examination performed in the 28th week of pregnancy IUGR was diagnosed — EFW was 862 g (26w1d). In detail: biparietal diameter for 27 weeks 4 days (69 mm), HC for 26 weeks (248 mm) and AC lower than 2nd percentile (198 mm — 24w3d). Blood flow in MCA, UA and in the left uterine artery was normal as well as placental-cerebral ratio. The left uterine artery flow was normal, whereas in the right uterine artery (RUt) flow notch was present and the peak volume index (PI) was augmented.

The patient was admitted to hospital in the 28th week of pregnancy due to suspected IUGR and abnormal flow in the right uterine artery. After admission, constant CTG was introduced and after two days of normal tracings changed to CTG six times daily, with normal tracings throughout the stay. The patient received two doses of betamethasone 12 mg intramuscularly. In repeated ultrasound examinations, the RUt PI continued to be augmented, whereas MCA PI and UA PI were normal. In the ultrasound examination performed in the 33rd week of the pregnancy, the retardation growth in EFW and AC was of three weeks. In the 34th week the patient left the hospital against medical advice. In the 36th week of pregnancy she had a cesarean section (for psychiatric indications — she was diagnosed with tocophobia) performed in another hospital. The newborn weighed 2095g (5th percentile) and had an Apgar score of 10.

SUMMARY

The problem of optimum daily caloric intake, vitamin and micronutrients supplementation in pregnancies after bariatric surgery is presently discussed in the literature. Optimum care and advice for bariatric patients have to be diversified, as malabsorptive and restrictive operations lead to different changes in metabolism, nutrition and hormonal balance. Changes in gastric pH, dumping syndrome and problems with absorption may lead to vitamin and micronutrient deficiencies. These aspects are widely presented in the literature on the subject. Although there are international recommendations considering vitamin and micronutrients in pregnancy after bariatric surgery, they are not adequately implemented and followed [3]. The novelty of

our study is presentation of two important problems considering bariatric patients' nutrition in pregnancy, up-to-date knowledge in the group of obstetricians managing these patients and patients' adherence to their doctors' indications. International recommendations are clear and univocal about adequate caloric and protein intake, micronutrient and vitamin supplementation in pregnancies after bariatric surgery and easy to be followed. However, due to symbolic presence of problem of pregnancy after bariatric surgery in our national recommendations, unfortunately the international recommendations are not generally followed. Specific recommendations should be created and introduced in our country as soon as possible to avoid situations where patients are advised by their obstetricians to keep their caloric intake in pregnancy at the level of 1200kcal daily. Additionally, we have to remember that some of the patients keep restricted diet in a fear of gaining weight. Most patients after bariatric surgery have gone through a period of hard work, diet and exercises in order to lose weight and many of them are afraid of regaining weight during pregnancy. Therefore, they restrict caloric intake in pregnancy, often against indications of their obstetricians or not informing them about their nutritional doubts, sometimes to a level which could be harmful to the fetus. The problem of direct and sincere communication between a patient after bariatric surgery and their obstetrician cannot be overemphasized. The role of a dietician nutritionist and psychologist is very important in planning the nutrition of a pregnant bariatric patient. Insufficient maternal caloric and vitamin intake may lead to retardation of the intrauterine growth of the fetus. The problem of malnutrition in pregnancy may influence the level of IUGR, bariatric surgery itself already being a risk factor.

The vast majority of studies analyzing the impact of bariatric surgery on the fetal growth retardation show an increased risk of IUGR and small for gestational age (SGA) infants [4–6]. The important question is whether there are differences in the incidence of IUGR and SGA after different types of bariatric surgery.

Chevrot et al. [7] analyzed 139 cases of women who had undergone bariatric surgery and they found a 2-fold increase in number of SGA infants. RYGB was stated to be an independent risk factor for fetal growth retardation. Unlike patients after RYGB, patients with purely restrictive surgery (mainly gastric banding) included in the study had no increase in the SGA rate. The differences in the incidence of IUGR between malabsorptive and purely restrictive surgery are also shown in other studies. Facchiano et al. [8] analyzed 42 cases of pregnancy in 36 women after bariatric surgery, 19 after laparoscopic adjustable gastric banding (LAGB) and 17 after RYGB. The mean birth weight was found to be lower in the RYGB group (2984 g) than in the LAGB group (3225 g). Sheiner et al. compared the results of 298 pregnancies after bariatric surgery with a control group and found the risk of IUGR to be 2.5 times higher after bariatric surgery than in the general population [9].

Johansson et al. [10] presented an analysis of 670 pregnancies after bariatric surgery, 98% of operations were gastric bypass. The study demonstrated that bariatric patients had a higher risk of SGA infants than obese population without a history of bariatric surgery – 15.6% vs 7.6%. Kjaer et al. [11] reviewed 339 cases of singleton deliveries in Denmark from January 2004 to December 2010 in women with prior bariatric surgery, 84.4% of whom had undergone RYGB. Mean birthweight of the children was lower (3312 g) in patients after bariatric surgery than the control group (3585 g). The risk of SGA was 2.3 higher in women after bariatric surgery than in a matched group of women with no history of bariatric surgery. An increased risk of IUGR after RYGB was also observed by Belcastro et al., who reviewed pregnancy outcomes of 44 patients who had undergone RYGB 18 to 48 months before pregnancy. They found 9 cases (20.5%) of IUGR, which was significantly higher than in the general population [12].

Contrary to those presented above, there are also studies that do not show any impact of bariatric surgery on the incidence of IUGR and SGA. Aricha-Tamir et al. [13] analyzed 144 cases of women who had paired pregnancies before and after bariatric surgery from 1988 to 2008 and found no significant differences in the SGA rate.

One of the most important questions is the influence of laparoscopic sleeve gastrectomy (LSG) on the fetal intrauterine growth. Amounting 64.6% of all bariatric procedures, LSG remains the most popular bariatric procedure both in our country and worldwide, but there are few studies analyzing its impact on the pregnancy course and neonatal outcomes. A study by Coupaye et al. [14] included 123 pregnancies after bariatric surgery, 77 after RYGB and 46 after sleeve gastrectomy (SG). They observed a comparable rate of IUGR and SGA after RYGB and SG, positively associated with protein supply and negatively with the pregnant woman's iron status. Rottenstreich et al. [15] conducted a retrospective case-control study, comparing 119 patients after LSG with obese controls. The study group had an increased risk of SGA neonates — 14.3% vs 4.2% in the control group.

To conclude, the influence of bariatric surgery on the pregnancy course and neonatal outcomes is widely discussed in the literature. Bariatric procedures reduce the incidence of obesity-related pregnancy complications, such as GDM, pregnancy-induced hypertension or large for gestational age neonates, but also have negative impact on the absorption of vitamins and micronutrients, leading to their deficiencies in pregnancy that may influence the fetal growth. Most common bariatric procedures, such as

SG and RYGB are associated with an increased risk of IUGR and SGA. Analysis of the factors influencing the fetal growth after bariatric surgery remains subject of current and future studies. Optimum supplementation and diet are crucial for a pregnant bariatric patient and such care should be provided by a specialist in nutrition. Valid knowledge of obstetricians taking care of bariatric patients, sincere contact with their patients and helping them with adherence to dietary recommendations is extremely important for the optimum pregnancy and fetal outcomes. Nevertheless, there is a strong need of implementing international recommendations about pregnancy nutrition care after bariatric surgery in our country, so that they are easily available both for pregnant patients and their obstetricians.

Conflict of interest

None.

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VIA MEDICA

RECOMMENDATIONS

Ginekologia Polska
2021, vol. 92, no. 3, 230–235

ISSN 0017–0011, e-ISSN 2543–6767

DOI 10.5603/GP.2021.0045

The Urogynecology Section of the Polish Society of Gynecologists and Obstetricians Guideline on the use of urodynamic testing in gynecological practice

Artur Rogowski[1–3], Bartosz Dybowski[4], Edyta Wlazlak[5], Wlodzimierz Baranowski[6], Tomasz Rechberger[7], Klaudia Stangel-Wojcikiewicz[8], Magdalena E. Grzybowska[9], Tomasz Kluz[10], Elzbieta Narojczyk-Swiesciak[11], Monika Szafarowska[6], Zofia Rozpendowska[5], Grzegorz Surkont[5]

[1]Department of Gynecology, „Inflancka" Specialist Hospital, Warsaw, Poland
[2]Cardinal Stefan Wyszynski University in Warsaw, Faculty of Medicine, Collegium Medicum, Warsaw, Poland
[3]Department of Obstetrics and Gynecology, Mother and Child Institute, Warsaw, Poland
[4]Department of Urology, Roefler Memorial Hospital, Pruszkow, Poland
[5]Department of Operative Gynecology and Gynecological Oncology, I Department of Gynecology and Obstetrics, Medical University of Lodz, Poland
[6]Department of Gynecology and Oncological Gynecology Military Institute of Medicine, Warsaw, Poland
[7]II Department of Gynecology, Medical University of Lublin, Poland
[8]Jagiellonian University Medical College, Department of Gynecology and Oncology, Cracow, Poland
[9]Department of Gynecology, Gynecological Oncology and Gynecological Endocrinology, Medical University of Gdansk, Poland
[10]Department of Gynecology and Obstetrics, Institute of Medical Sciences, Medical College of Rzeszow University, Rzeszow, Poland
[11]II Department of Obstetrics and Gynecology Centre of Postgraduate Medical Education Bielański Hospital, Warsaw, Poland

ABSTRACT

Objectives: The aim was to present an interdisciplinary Guideline of the Urogynecology Section of the Polish Society of Gynecologists and Obstetricians (PSGO) for the use of urodynamics (UDS) in the diagnostic process of patients with lower urinary tract symptoms (LUTS) based on the available literature, expert knowledge, and everyday practice.

Material and methods: A review of the literature concerning the use of UDS in women, including current international guidelines and earlier recommendations of the PSGO Urogynecology Section, was conducted.

Results: Urodynamic testing allows to make the urodynamic diagnosis which, nevertheless, remains to be the preliminary diagnosis. Medical history, physical examination, and detailed analysis of the previous test results (laboratory, imaging, endoscopic) need to be taken into consideration before making the final diagnosis. Urodynamic testing before surgical treatment of SUI is allowable, but the decision remains at the discretion of the physician. Urodynamic testing is not necessary before primary surgical treatment of uncomplicated SUI, but it has been demonstrated to optimize the therapeutic methods in complicated SUI. The significance of UDS in the diagnostic process of patients with overactive bladder symptoms, voiding dysfunction, and bladder outlet obstruction was discussed.

Conclusions: Urodynamic testing is a vital element of the urogynecological diagnostic process. The scope of UDS should reflect the individual needs and symptoms of each patient and be based on the current guidelines, expert knowledge and experience of the physician, indications, and eligibility, as well as additional test results of the affected patients. Due to formal and legal requirements, PSGO, in this Guideline, wishes to emphasize the need for an individualized approach to both, test performance and result interpretation.

Key words: urodynamics, stress urinary incontinence, overactive bladder, voiding dysfunction, bladder outlet obstruction, guidelines

Ginekologia Polska 2021; 92, 3: 230–235

Corresponding author:
Edyta Wlazlak
Department of Operative Gynecology and Gynecological Oncology
I Department of Gynecology and Obstetrics Medical University of Lodz
37 Wilenska St., Lodz, Poland
e-mail: edytawlazlak@gmail.com

INTRODUCTION

Urodynamics (UDS) is a collective term used to describe tests which evaluate the function of the lower urinary tract, including bladder and urethral pressure, urethral flow rate, and electromyographic measurements.

UDS includes uroflowmetry, cystometry with stress tests (cough test and Valsalva maneuver) — with or without pressure-flow test, resting and cough urethral pressure profilometry, electromyography, and video-urodynamics [1, 2]. These functional tests allow for the assessment of the bladder contractile function, urethral resistance and continence. The main indication for urodynamic testing is a specific UDS question. The choice of the urodynamic components depends on the clinical status of the patient and the experience of the physician.

Based on UDS, urodynamic diagnoses are made, which may not be equivalent to the clinical diagnosis, as they only determine the state of the urinary tract recorded in a given measurement. Importantly, any of the urodynamic tests may generate false positive and false negative results and the tests are characterized by a certain variability of observation in recognizing different conditions. Therefore, urodynamic test results should not be perceived as the final diagnosis. Data from medical history, physical examination, and earlier test results (e.g., laboratory, imaging and endoscopic), are necessary to interpret the results.

Objectives

The aim was to develop a Guideline on the use of urodynamic testing in the diagnostic process of patients with lower urinary tract symptoms (LUTS), based on the available literature reports, expert knowledge, and everyday practice.

MATERIAL AND METHODS

The literature, including current international guidelines, was reviewed for the following content: the use of UDS in the diagnostic process, patient eligibility for treatment, and the efficacy of stress urinary incontinence (SUI), overactive bladder/detrusor overactivity, voiding dysfunction, and bladder outlet obstruction therapies. Data quality, risk-to-benefit ratio, availability of the resources in Poland, and the consensus of the experts were analyzed for all guidelines. Recommendations with uncertain risk-to-benefit ratio and discrepancies between research results and expert opinions were excluded.

REVIEW OF THE LITERATURE, INCLUDING GUIDELINES

UDS in patients with SUI

The significance of UDS in the process of determining patient eligibility for the surgical treatment of SUI was evaluated in the VALUE and VUSIS I and II randomized clinical trials. The effects of surgical treatment in patients with and without pre-surgery UDS were compared [3–5]. After these results were published, the number of urodynamic tests decreased. The VALUE trial found no correlation between UDS and higher efficacy of the surgical treatment of uncomplicated SUI, as defined by the American Urogynecologic Society (AUGS) and the American College of Obstetricians and Gynecologists (ACOG). However, many experts have raised concerns about the design of these two RCTs and their subsequent interpretation. The effects were evaluated solely with questionnaires and the cough test. The surgeries were mostly performed by physicians in training, not by experts. Surgery types and eligibility criteria were not described [3]. Similar conclusions were reported after the VUSIS I trial, which had only 59 participants. In the VUSIS II trial, with 109 patients, no evidence was found of reduced efficacy of mid-urethral sling implantation in patients with SUI who had not undergone UDS before surgery. The sample size in both VUSIS trials was relatively small. Also, there were significant inter-center differences in terms of indications, planning and techniques for SUI management, so the effects of UDS on the surgical outcome varied to some extent. Notably, the VALUE trial included only women with uncomplicated SUI [4–6].

Urodynamic testing is not necessary before the primary surgical repair of uncomplicated SUI if the symptoms and normal urethral mobility were confirmed by medical history and if the cough test was positive. The following will need to be excluded: clinically significant vaginal and uterine prolapse during the Valsalva maneuver, recurrent urinary tract infections, and post-void urine retention [7–9]. According to the AUGS criteria, patients with uncomplicated SUI have a history of involuntary urine leakage on effort and coughing but no evidence of recurrent urinary tract infections, hematuria, incomplete emptying, chronic urinary retention, and absence of voiding symptoms such as hesitancy, slow stream, intermittency, and straining to void. These patients have no prior anti-incontinence surgery or extensive pelvic surgery, and no illnesses which might affect the urinary tract function, e.g., neurologic diseases. Their physical examination shows no signs of post-void residual (PVR) volume of > 100 mL or POP beyond the hymen. These patients also have normal urethral mobility and absence of urethral abnormality [7, 8, 10, 11].

Among women with SUI, uncomplicated SUI is diagnosed in 5–36% of the cases [12–15]. In the VALUE trial, 66% of the patients were excluded from the study for not meeting the eligibility criteria for uncomplicated SUI [3].

UDS in patients with UI, especially with complicated SUI, has been proven to optimize the therapeutic decision [16–21]. A multicenter trial, which included 2053 women, demonstrated that urodynamic testing led to the reevalua-

tion and change of the original UI diagnosis in 74.6% of the patients with complicated and 40% with uncomplicated SUI [18]. Management alterations based on the UDS results occurred in 62% of the patients, and the sling surgery was abandoned in 15% of the cases [18]. UDS found features of detrusor overactivity [22] and functional bladder outlet obstruction in as many as 20% of the patients with uncomplicated SUI diagnosed based on medical history [13, 19]. Voiding dysfunction, which is associated with higher risk of sling surgery failure [23], has been demonstrated in 10% of the women with uncomplicated SUI [3].

The authors of this Guideline believe that urodynamic testing is not necessary before the surgical repair of uncomplicated SUI if the findings do not affect the type of the procedure and if the probability of a successful outcome is high [6]. Urodynamic testing is allowable in all patients before surgical repair of SUI [24–26]. The decision is subjective and based either on the experience of the physician or on the formal and legal requirements. Data from the randomized trials on the possibility of omitting UDS before elective surgical repair of SUI apply only to patients with uncomplicated SUI. Pre-operative urodynamic testing may be beneficial in women with complicated SUI as it allows to determine the risk for failure of the standard surgical treatment [7, 16–19]. Patients with uncertain UI type or those with the suspicion of overflow incontinence may also benefit from UDS before surgery [24].

In various urogynecological centers, the diagnostics of the intrinsic sphincter deficiency (ISD) is performed during UDS. There are no standard diagnostic procedures for ISD. Bladder pressure at which leakage occurs (VLPP, Valsalva Leak Point Pressure) is measured during cystometry, during the Valsalva maneuver. The maximal urethral closure pressure (MUCP) is tested during urethral pressure profilometry (UPP) at rest [4, 27].

UDS in the evaluation and conservative treatment of the overactive bladder syndrome

Overactive bladder syndrome (OAB) is a symptom complex associated with the lower urinary tract, *i.e.*, urgency, frequency, nocturia and/or urgency urinary incontinence. OAB is not a separate disease entity and, as such, is not registered in the international classification of diseases. Nevertheless, the term 'overactive bladder syndrome' is commonly used by physicians in medical documentation and in the literature, in accordance with the International Continence Society (ICS) definition [28], and it is also a reimbursement criterion for certain drugs in Poland. OAB is suggestive of, but not consistent with, detrusor overactivity. The diagnosis can be made after ruling out urinary tract infections, urolithiasis and urinary tract cancers, bladder outlet obstruction, and diseases of the nervous system. Thorough medical history should be taken, and urinalysis should be performed in the diagnostic process due to urgency and frequency [29, 30]. The decision to include post-void residual volume, urine culture, or micturition diary into the evaluation should be left to the discretion of the physician. Contrary to some opinions [29, 30], the authors of this Guideline believe that an ultrasound examination, combined with the evaluation of post-void residual volume, should be incorporated into the initial diagnostic process to exclude other causes of the symptoms. However, ultrasound parameters of the bladder such as wall thickness are not useful for the diagnosis of detrusor overactivity [2]. Our recommendation is based, among others, on the following: 1) availability of ultrasound devices in gynecological and urological offices, 2) age-dependent increase in the risk for bladder tumor (mean 0.5%), 3) vesical calculi as the possible cause of such symptoms, 4) non-invasive nature of ultrasound testing [31, 32].

The role of UDS in OAB diagnosis is limited to specialist management in selected, complicated cases. Urodynamic testing is not recommended at the initial stages of OAB diagnosis [30], or as part of the qualification for pharmacological treatment due to insufficient sensitivity and specificity of the tests regarding idiopathic detrusor overactivity. Only about half of the patients with non-neurogenic detrusor overactivity diagnosed with UDS experience bothersome urinary urgency [33]. At the same time, only 50–60% of women with typical OAB symptoms present with uncontrolled detrusor contractions recorded during the filling phase of cystometry [34, 35]. Other arguments against routine UDS in patients with OAB include low inter-observer reproducibility of the result [36], and no evidence of a relationship between the prevalence or severity of detrusor overactivity symptoms and treatment effects [20, 37].

UDS may play a role in the diagnostic process after all pharmacological treatment options for OAB have been exhausted, in cases of OAB concomitant with other pelvic floor disorders for example: urinary incontinence, voiding dysfunction, pelvic organ prolapse, pain, or with inconclusive medical history and/or symptoms. It is not possible to list the conditions when urodynamic testing is indispensable. The decision to perform urodynamic tests remains subjective and may reflect the experience of the physician or may be based on the formal and legal requirements.

The role of UDS before invasive OAB treatment

UDS before BTX injections

Botulinum toxin (BTX) injection therapy has been registered and recognized as an effective management of drug resistant OAB. The main risks associated with the procedure include voiding disorders, urinary retention with the need for self-catheterization, and urinary tract infections. However, in the group of women receiving 100 IU of onabotulinum-

toxin A, these complications have been reported to be rare (≤ 5%) [38]. The diagnosis of detrusor overactivity using UDS has not been proven to be related with higher efficacy of this therapy. Therefore, patients with OAB symptoms, without detrusor contractions during the filling phase, are as likely to benefit from BTX therapy as those with confirmed overactivity [39]. Other urodynamic observations, e.g., detrusor underactivity and bladder outlet obstruction, may increase the risk for voiding dysfunction after surgery [40]. Still, it is not an indication for routine UDS before BTX therapy, also within the current clinical trial framework [41]. The Italian expert panel concluded that UDS should be obligatory in patients with neurogenic detrusor overactivity or with a suspicion of voiding dysfunction. Otherwise, urodynamic testing is not necessary. They also recommended to perform at least a single uroflowmetry with PVR volume evaluation to exclude voiding dysfunction before BTX therapy [42]. The authors of this Guideline believe that an ultrasound test, with simultaneous evaluation of the post-void residual volume, should be considered to rule out other sources of the symptoms.

UDS before sacral neuromodulation

Sacral neuromodulation (SNM) is an invasive treatment of therapy resistant detrusor overactivity, voiding dysfunction unrelated to bladder outlet obstruction, and fecal incontinence. It has also been experimentally used to treat neurogenic dysfunctions and chronic pelvic pain syndrome. Percutaneous sacral nerve stimulation, routinely performed before the final implantation, is the only predictor of therapy efficacy. No relation has been found between detrusor overactivity recorded in UDS and the efficacy of sacral neuromodulation [43]. Although in some medical centers urodynamic testing is included in the eligibility process, it is not standard management and no cases of better treatment outcomes of typical, uncomplicated, resistant to pharmacotherapy OAB after routine UDS have been reported [44]. In their statement, the ICS expert panel concluded that urodynamic testing was more justified during the eligibility process in patients with neurogenic dysfunction, comorbid SUI, or voiding dysfunction, as well as after prior procedures affecting the function of the lower urinary tract, *e.g.*, implantation of a mid-urethral sling [45].

UDS before bladder augmentation

Ileocystoplasty and other methods of bladder augmentation are highly invasive surgical procedures, with significant risk of severe complications. Their applicability in the therapy of idiopathic OAB remains marginal and is limited to extreme cases of low volume and low compliance of the bladder. Due to the risk of severe surgical complications associated with opening of the gastrointestinal tract and integrating the intestinal mucosa into the urinary tract, bladder augmentation is not the method of choice for therapy resistant OAB, despite most satisfactory functional results [46, 47]. Urodynamic testing is a vital component of the eligibility process for this form of treatment due to the need to confirm severe bladder dysfunction.

UDS in patients with bladder outlet obstruction and voiding dysfunction

The prevalence of voiding dysfunction among women has been estimated at approximately 5%, but even in that group voiding dysfunction as the dominant symptom is reported only by a small number of patients. Among patients who underwent UDS, the prevalence of impaired bladder emptying has been estimated at 6–30%, depending on the criteria. Numerous studies demonstrated bladder outlet obstruction to be an additional or unexpected urodynamic symptom in women undergoing UDS for reasons other than voiding dysfunction [2, 48, 49]. There are no strict indications for urodynamic testing in the event of obstructive symptoms. The authors of this Guideline advise to take the post-void residual volume of > 100 mL in several measurements or maximum flow rate in non-invasive uroflowmetry < 15 mL/s as an indicator of voiding dysfunction. If the cause of the obstruction remains unclear after the physical and the ultrasound tests, UDS may be helpful in confirming or excluding bladder obstruction or detrusor underactivity. Still, urodynamic testing does not allow to determine the cause of the obstruction [2, 50, 51].

Detrusor underactivity is defined as the contraction of reduced strength and/or duration, resulting in prolonged bladder emptying or failure to achieve complete bladder emptying. Like bladder outlet obstruction, the diagnosis of detrusor underactivity in women has not yet been standardized.

The following are used in the diagnostic process of detrusor underactivity:

a) video-urodynamic test,
b) pressure-flow test,
c) uroflowmetry,
d) stop-test (a modification of the pressure-flow test used to evaluate detrusor strain during isovolumetric contraction, *i.e.*, during urethral closure achieved by catheter or sphincter contraction),
e) voiding test with continuous urethral occlusion,
f) the PIP (1) parameter [projected isovolumetric pressure, PIP (1) = p det (Qmax) + Qmax],
g) extremely low detrusor pressure (*e.g.*, < 10 cm H_2O) coexisting with extremely low urinary flow rate [2, 50–52].

Urodynamic diagnosis of bladder outlet obstruction and detrusor underactivity in women is objective to some

extent, but it also depends on the physician who interprets the results, especially in borderline cases. Therefore, it is essential to analyze urodynamic results together with the physical examination and imaging test results [2, 53].

CONCLUSIONS

Urodynamic testing is an essential element of urogynecological diagnostic process. The indications for UDS as well as the scope of testing are tailored to the needs of each patient. They result from the knowledge and experience of the physician, patient symptoms and indications, additional test results, current guidelines, as well as formal and legal requirements.

The Polish Society of Gynecologists and Obstetricians issued this Guideline for the therapeutic options, with emphasis on the need for an individualized approach to urodynamic testing and result interpretation.

Conflict of interest

None.

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VIA MEDICA

RECOMMENDATIONS

Ginekologia Polska
2021, vol. 92, no. 3, 236–251

ISSN 0017–0011, e-ISSN 2543–6767

DOI 10.5603/GP.2021.0046

The Urogynecology Section of the Polish Society of Gynecologists and Obstetricians guidelines on the management of non-neurogenic overactive bladder syndrome in women

Magdalena Emilia Grzybowska[1], Tomasz Rechberger[2], Andrzej Wrobel[2], Wlodzimierz Baranowski[3], Klaudia Stangel-Wojcikiewicz[4], Artur Rogowski[5, 6, 7], Tomasz Kluz[8], Elzbieta Narojczyk-Swiesciak[9], Edyta Wlazlak[10], Bartlomiej Burzynski[11], Grzegorz Surkont[10]

[1]Department of Gynecology, Gynecological Oncology and Gynecological Endocrinology, Medical University of Gdansk, Poland
[2]II Department of Gynecology, Medical University of Lublin, Poland
[3]Department of Gynecology and Gynecological Oncology, Military Medical Institute, Warsaw, Poland
[4]Department of Gynecology and Oncology, Jagiellonian University Medical College, Cracow, Poland
[5]Department of Gynecology, „Inflancka" Specialist Hospital, Warsaw, Poland
[6]Cardinal Stefan Wyszynski University in Warsaw, Faculty of Medicine, Collegium Medicum, Warsaw, Poland
[7]Department of Obstetrics and Gynecology, Mother and Child Institute, Warsaw, Poland
[8]Department of Gynecology and Obstetrics, Institute of Medical Sciences, Medical College of Rzeszow University, Rzeszow, Poland
[9]Second Department of Obstetrics and Gynecology, The Center of Postgraduate Medical Education, Warsaw, Poland
[10]Department of Operative Gynecology and Gynecologic Oncology, I Department of Gynecology and Obstetrics, Medical University of Lodz, Poland
[11]Department of Rehabilitation, Faculty of Health Sciences in Katowice, Medical University of Silesia, Katowice — Ochojec, Poland

ABSTRACT

Objectives: The aim of the publication was to present the interdisciplinary guidelines of the Urogynecology Section of the Polish Society of Gynecologists and Obstetricians (PSGO) for the treatment of overactive bladder (OAB) syndrome based on the available literature, expert knowledge, and everyday practice.

Material and methods: A review of the literature, including current recommendations for the treatment of overactive bladder syndrome, urinary incontinence, urgency and mixed urinary incontinence, as well as the earlier recommendations of the PSGO Urogynecology Section, was conducted.

Results: Management of the patients with OAB is presented. Four lines of therapy were identified: 1) educating the patient, behavioral therapy with pelvic floor muscle training, 2) pharmacotherapy, 3) botulinum toxin injection and tibial nerve stimulation; and sacral nerve stimulation even though so far it has been used only in selected populations, 4) surgical intervention. The literature reports which provided supporting evidence and presented various aspects of the therapy were discussed. OAB pharmacotherapy-related issues which are vital in everyday clinical practice were presented.

Conclusions: A systematic review of the available guidelines and an analysis of OAB (including urgency urinary incontinence) management were conducted. The Polish Society of Gynecologists and Obstetricians issued the guidelines for the therapeutic management of OAB patients. The need for an individualized approach was emphasized.

Key words: overactive bladder; pharmacotherapy; behavioral therapy; physiotherapy; botulinum toxin; urinary incontinence

Ginekologia Polska 2021; 92, 3: 236–251

Corresponding author:
Klaudia Stangel-Wójcikiewicz
Jagiellonian University Medical College, Department of Gynecology and Oncology, 23 Kopernika St, 31–501 Cracow, Poland
e-mail: klaudia.stangel-wojcikiewicz@uj.edu.pl

INTRODUCTION

The mission of the Urogynecology Section of the Polish Society of Gynecologists and Obstetricians (PSGO) is to promote the development of urogynecology in Poland, support education, and set evidence-based standards for the management of urogynecologic diseases. The Urogynecology Section issues certificates and awards credit points. The present update of the Guidelines concerns the treatment of the overactive bladder (OAB) syndrome.

Various fields of medicine benefit from guidelines and recommendations for the management of numerous diseases issued by expert groups and associations. The aim of these guidelines is to set evidence-based standards and to present the current management of different diseases and conditions, in accordance with the global trends. Their content is based on the analysis of the available literature, having taken into consideration the specificity and resources of a given country.

The guidelines present the current management of the disease, which may be modified and altered in justifiable cases and after a detailed analysis of the clinical situation, which in turn might lead to future updates of the recommendations. Both, the patient and the treatment always require an individualized approach. Also, it is possible to apply other than recommended, and in some cases even off-label, therapies.

The available literature on the overactive bladder syndrome mostly relates to patients with mixed urinary incontinence or with urinary incontinence (UI). The authors of the present study aimed to review the up-to-date guidelines and recommendations and to analyze the management protocols for OAB patients, including cases with urgency urinary incontinence.

The present recommendations are supposed to serve as a guide to therapeutic management both, for gynecologists and other specialists. Considering the continuous advances in the field of pathophysiology and pharmacotherapy, the strategies presented herein will need to be updated in due course.

Overactive bladder is a symptom complex associated with the phase of urine storage. The International Continence Society defines OAB as a urinary urgency, typically with frequency and nocturia, with or without urinary incontinence. The diagnosis can be made after ruling out urinary tract infections, post-void urine retention, or changes such as cancer, urinary calculi or pelvic tumors modeling the bladder [1]. Pelvic organ prolapse (POP) may be the cause of OAB symptoms in the affected women. In the experience of the authors, the diagnosis of OAB should be made after excluding POP as the cause of OAB symptoms. On the other hand, numerous specialists believe that symptomatic POP should not influence the diagnosis and treatment of OAB.

A detailed diagnostic process is necessary to confirm the diagnosis of OAB before treatment. Also, other disorders, which might constitute the underlying causes for the reported symptoms, should be excluded. The following methods may be used in the diagnostic process: medical history, physical examination, urinalysis, urine culture, urine cytology, evaluation of post-void urinary retention, micturition diary, ultrasound examination, cystoscopy, urodynamic examination, and validated questionnaires to diagnose UI types, OAB severity, and health-related quality of life [2–4]. Importantly, a urodynamic examination is not necessary during the initial assessment and is not the essential condition to initiate treatment. The diagnostic process and test selection are tailored to the individual needs and symptoms of the patient. Guidelines for the diagnostic process of patients with OAB will have been presented elsewhere.

Objectives

The aim of the Urogynecology Section of the Polish Society of Gynecologists and Obstetricians (PSGO) was to develop interdisciplinary recommendations for the management of overactive bladder (OAB) syndrome, based on the available literature reports, expert knowledge, and everyday practice. The up-to-date standards, indications and expert opinions on the clinical management of OAB are presented.

MATERIAL AND METHODS

In 2005, 2006 and 2010, the panel of PSGO experts developed guidelines for the diagnosis and treatment of urogynecologic conditions. The present publication is an update of those recommendations, based on the literature reports published between 2010 and 2019, as well as the recommendations of the American Urological Association, the European Association of Urology, and the Canadian Urological Association [2–7].

The literature, including the current international recommendations for the management of overactive bladder, urinary incontinence, urgency urinary incontinence and mixed urinary incontinence, was reviewed.

Special attention has been paid to the level of evidence and degree of recommendation of the available data sources. If the literature source seemed insufficient, expert opinions and management protocols were included.

RECOMMENDATIONS

First-line treatment: behavioral therapy with pelvic floor muscle training

According to the recommendations of the American Urological Association (AUA) [2], education of the patient (resulting in active involvement in the therapy), lifestyle modifications, and various types of behavioral therapy combined with pelvic floor muscle training (PFMT),

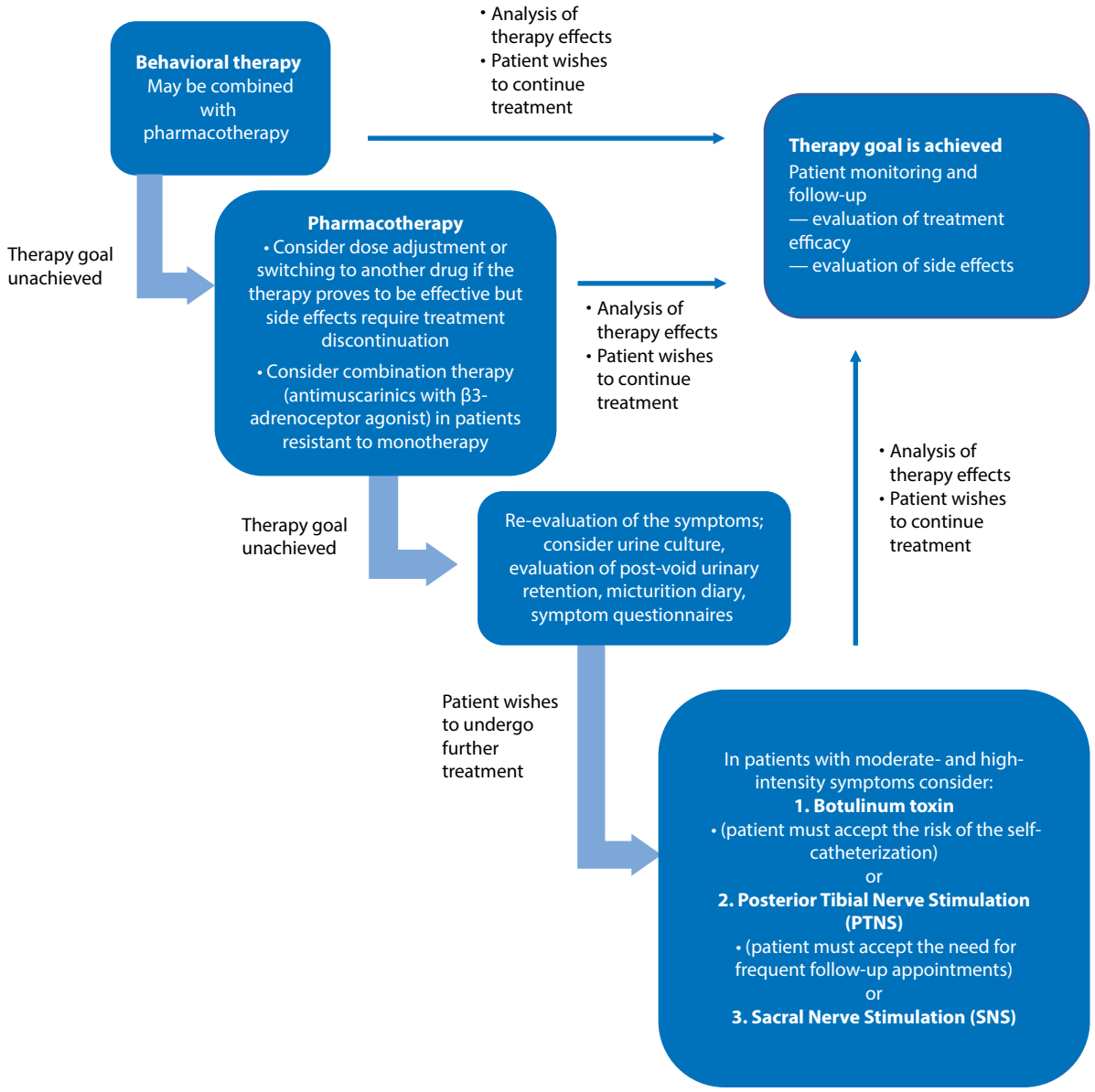

Figure 1. Management of patients with non-neurogenic overactive bladder syndrome [by M.E. Grzybowska, on the basis of Gormley EA, Lightner DJ, Burgio KL, et al. Diagnosis and Treatment of Non-Neurogenic Overactive Bladder (OAB) in Adults: an AUA/SUFU Guideline (2019). Published 2012; Amended 2014, 2019. https://www.auanet.org/guidelines/overactive-bladder-(oab)-guideline (access: 2020.01.10)]

should constitute the first-line treatment for the OAB syndrome. It is important to establish if the cognitive abilities of the patient will allow for an effective implementation of the management. From the very beginning of the therapy, the first line of treatment may be combined with pharmacotherapy, *i.e.*, the second line. In everyday practice, both lines of treatment are often used simultaneously from the start. Patient motivation is of utmost importance as it determines lifestyle changes and strict adherence to treatment regime, which directly affects the efficacy of the treatment (Fig. 1).

Behavioral therapy includes:

a) actions aimed at improving bladder function, *i.e.*, scheduled voiding at time intervals and bladder training, allowing for gradual increase of the time intervals between voids
b) control of fluid intake and reduction of caffeine intake
c) lifestyle modifications, including weight control, cessation of smoking, and bowel regularity to prevent constipation.

Pelvic floor muscle training is an example of physical therapy used to treat OAB. In certain cases, it is also advisable to use biofeedback (real-time ultrasonography feedback, EMG-biofeedback) and electrostimulation.

The choice of treatment depends on the symptoms and patient preferences. Most patients do not experience complete symptom resolution after the first line of treatment.

Second-line treatment: oral and vaginal pharmacotherapy

In everyday clinical practice, pharmacotherapy is typically initiated together with the first-line treatment as it is already applicable in the initial stages of OAB therapy.

After reviewing the available recommendations for OAB treatment, it seems prudent to follow the guidelines issued by the American Urological Association [2], with minor modifications.

1. Oral antimuscarinics or β3-adrenoceptor agonists are used as the second-line treatment.
2. If both, immediate release (IR) and extended release (ER) drugs are available, ER drugs are preferred due to lower risk for dry mouth.
3. In the event of insufficient symptom control and/or serious side effects after administering an antimuscarinic drug, the dose may be modified or another antimuscarinic drug or a β3- adrenoceptor agonist may be initiated.
4. A combination therapy (antimuscarinics combined with β3-adrenoceptor agonists) may be considered for patients who failed on antimuscarinic or β3-adrenoceptor agonist monotherapy.
5. Antimuscarinics are contraindicated in patients with narrow-angle glaucoma. Patients with glaucoma should be referred to an ophthalmologist for a consultation before anticholinergic drugs are considered.
6. Antimuscarinics should be used with caution in patients with impaired gastric emptying or history of urinary retention.
7. Adequate fluid intake, bowel management, dose modification or switching to another antimuscarinic or mirabegron should be recommended to patients with constipation who are satisfied with the effects of the OAB treatment with antimuscarinics before treatment discontinuation.
8. Adequate fluid intake, hydration of the oral cavity, dose adjustment or switching to another antimuscarinic or mirabegron should be recommended to patients with dry mouth who are satisfied with the effects of the OAB treatment with antimuscarinics before treatment discontinuation.
9. Before antimuscarinic therapy is initiated, patient use of other drugs with anticholinergic properties should be taken into consideration.
10. Mirabegron is effective and safe in older populations. Caution is advised when prescribing antimuscarinic drugs to frail patients.
11. Vaginal estrogen therapy may effectively alleviate OAB symptoms in postmenopausal women. It is recommended to combine β3-adrenoceptor agonists or antimuscarinics with estrogens in that group of patients.
12. The efficacy of pharmacotherapy may be assessed after 4–8 weeks. Then, the effects of the treatment should be evaluated, and the necessary adjustments should be introduced, if needed.
13. Patients with behavioral and pharmacologic therapy resistant OAB should be referred to a specialist for further diagnostic procedures and therapeutic options.

Third-line treatment: botulinum toxin and neuromodulation (posterior tibial nerve stimulation and sacral nerve stimulation)

Botulinum toxin

1. Patients with first- and second-line therapy resistant OAB may be offered bladder wall injection of botulinum toxin A.
2. Patients should be informed about the limited duration of drug action and the risk for both, urinary tract infections and the need for self-catheterization (it is important to ensure the patient will cooperate and be willing to perform it, if necessary). The patient is required to report for post-void residual volume evaluation after the procedure.
3. The next bladder wall injection of botulinum toxin should be performed no sooner than three months after the pervious injection.

Posterior tibial nerve stimulation (PTNS)

In some patients, posterior tibial nerve stimulation (PTNS) may be used as third-line treatment. Transcutaneous PTNS is performed by a physiotherapist using adhesive surface electrodes. Percutaneous needle PTNS, performed by a physician, consists in stimulation with a slim needle electrode. In both cases, the electrodes are placed just above the medial condyle of the ankle.

Sacral nerve stimulation (SNS)

Sacral nerve stimulation (SNS) may be offered as third-line treatment to carefully selected patient populations with severe therapy resistant OAB symptoms or those who are not eligible for second-line treatment but are willing to undergo surgery.

Fourth-line treatment

Augmentation cystoplasty or other types of urine diversion may be considered in rare and complicated cases of therapy resistant OAB [2].

Patient care

Care and monitoring should be exercised during therapy to assess patient adherence to their treatment recommen-

dations and efficacy of the therapy, or to consider other therapeutic options.

Additional therapeutic procedures

Indwelling catheters (transurethral, suprapubic, etc.) are not recommended in the management of OAB due to the unfavorable risk-to-benefit ratio, with some exceptions [2].

As for manual therapy, the following techniques may be used: myofascial relaxation of the pelvic floor muscles and the lumbar-pelvic-iliac complex, joint mobilization/manipulation of the spine and the pelvis, and nerve neuromobilization. Manual therapy allows the normalization of pelvic floor and anterolateral abdominal wall muscle tone, which affects nerve conduction within the pelvis. The literature offers limited amount of data on the matter. Based on the expert knowledge and experience of the authors of the present study, manual therapy is a useful tool in OAB therapy.

OVERVIEW OF THE RECOMMENDATIONS

First-line treatment: behavioral therapy combined with pelvic floor muscle training

Actions improving the urinary bladder function

Timed voiding (at fixed intervals) — initiated by the affected patients or their caretakers — improves urinary continence, especially in older people with cognitive impairment (LE1b — level of evidence) [3].

Bladder training, typically combined with pelvic floor muscle training, is one of the basic elements of behavioral therapy. It gradually extends the time intervals between voiding, increases the bladder volume and reduces the number of urgency urinary incontinence (UUI) episodes (LE1b). The goal of the bladder training is for the patient to adhere to a voiding schedule, with gradually delayed voiding (by 15–30 minutes/week) until the goal of a 2–3--hour interval is achieved. Bladder training is used to correct urination habits. Combined with an anticholinergic and/or β3-agonist therapy, bladder training may be a more effective way of dealing with the symptoms of frequency and nocturia than any of these therapies alone (LE1b) [3].

According to a Cochrane analysis of 23 studies and 3685 patients, symptom resolution was more frequently observed in patients receiving antimuscarinics as compared to bladder training alone (RR 0.74, 95% CI 0.61–0.91), and in patients receiving antimuscarinics in combination with bladder training than bladder training alone (RR 0.57, 95% CI 0.38–0.88) [8].

Fluid intake management

Caffeine is found in beverages such as coffee, tea and cola. **Reduced caffeine intake** may diminish the symptoms of urgency and frequency (LE2b) [3].

Modification of fluid intake, depending on the initial balance of fluid intake and output, has been advised. In a randomized controlled trial (RCT), limitation of the fluid intake by 25% reduced the symptoms of urgency, frequency and nocturia in patients with OAB [3].

Caution should be exercised when recommending fluid restriction, as this strategy is often self-initiated by the affected patients to reduce the symptoms, before seeking medical help. Minimum daily fluid intake should be approximately 1500 mL or 30 mL/kg of body weight. In order to reduce the symptoms of nocturia, patients can be advised to limit their fluid intake after 6 p.m. (or 3–4 hours before bedtime) and to redirect fluid intake to the morning and afternoon hours [4, 9].

Lifestyle modification

In RCT, an 8% **weight reduction** in obese women resulted in a 42% reduction in the episodes of UUI as compared to 26% in the control group [2, 10]. The literature offers reports which confirm that the increase in the body mass index (BMI) corresponds to the increase in the incidence of UUI. Obesity (BMI > 30 kg/m^2) is believed to be an independent risk factor for OAB [3, 11, 12].

Smoking cessation seems to be weakly correlated with symptom alleviation in patients with urinary frequency [3, 11]. Nicotine, being an irritant, is considered a risk factor for OAB symptoms in both, former and current smokers (LE3) [13].

The literature offers a considerable number of reports on higher prevalence of chronic constipation in patients with OAB [4, 14]. Charach et al., demonstrated that the **treatment of constipation** reduces the symptoms of urgency and frequency in older patients (LE4) [4, 15]. However, according to the recommendations of the European Association of Urology (EAU), no evidence supports the alleviation of OAB symptoms after reduction of constipation [3]. High-fiber diet is standard medical approach to the management of constipation [3, 4].

Pelvic floor muscle training

Pelvic floor muscle training combined with urgency suppression techniques is often based on biofeedback (real-time ultrasonography feedback, EMG-biofeedback) with electrostimulation. The patients learn how to respond to urgency, which in turn reduces its intensity and delays the need to void. Six to ten quick pelvic contractions may be performed. If done correctly, and in the absence of parasympathetic and sympathetic dysfunction, they allow the detrusor to be temporarily relaxed. The contractions must be performed at optimal times to ensure optimal benefit (LE3) [4, 16].

Summary

Although most patients do not experience complete symptom resolution after behavioral therapy, significant

Table 1. Recommendation grade for behavioral therapy [31]

Therapeutic method	Grade
Lifestyle modifications (BMI reduction, smoking cessation, adequate diet, fluid management, bowel management)	A–C
Bladder training, scheduled voiding	B

BMI — body mass index

Table 2. Recommendation grade for physiotherapy [31]

Physiotherapeutic method	Grade
Pelvic floor muscle training	A
Pelvic floor muscle training with biofeedback	B
Electrostimulation	B
Posterior tibial nerve stimulation (PTNS)	A

reduction in symptom intensity and improved quality of patient life have been reported. The absence of side effects which might accompany the pharmacotherapy in the next stages of treatment is an important benefit. Eight to twelve weeks is the optimal duration of behavioral therapy, after that time the effects of the treatment should be evaluated and modified, if necessary [2].

Promotion of healthy habits associated with the functioning of the lower urinary tract, including the bladder, should become an element of routine medical care. Lifestyle modifications and other behavioral techniques should always be discussed with the patient, not only to optimize treatment results but also to educate the patient. The grades of recommendations for behavioral and physiotherapy are presented in Tables 1 and 2.

Second-line treatment: pharmacological therapy

1. Oral medications

Pharmacotherapy of OAB aims to reduce urgency, frequency, and urgency urinary incontinence, thus improving the quality of patient life. Increased 'warning time', *i.e.*, time from the onset of the urgency to void or incontinence, is one of the most important outcomes of the drug therapy. Currently, antimuscarinic drugs and β3-adrenoceptor agonist (mirabegron) are the most used medications in OAB therapy. Combination pharmacotherapy which uses drugs with different mechanisms of action alleviates OAB symptoms more effectively as compared to monotherapy, with a comparable rate of side effects, and is recommended in patients with insufficient clinical response. An ideal medication should be safe, effective, well-tolerated, and the patients should comply with the treatment regime for the required amount of time.

The following antimuscarinic drugs are available for OAB treatment: trospium, oxybutynin, tolterodine — immediate release (IR) and extended release (ER), fesoterodine, darifenacin, and solifenacin. Their mechanisms of action and half-life are presented in Table 3. All the above- mentioned medications have a high grade (Grade A) of recommendation, though some of them are not currently available in Poland. The effects of various antimuscarinics were compared in a systematic review and the conclusions are presented below. The efficacy and side effects of the therapy were evaluated. The daily number of micturitions, urgency and leakage episodes were analyzed, as well as patient-reported subjective assessment of the treatment efficacy. Most of the available studies analyzed the treatment efficacy after a relatively short period of time — 12 weeks.

Conclusions from the Cochrane review [17]

Out of immediate release drugs, tolterodine is preferred over oxybutynin — despite similar efficacy rates — due to the lower risk for side effects, especially dry mouth. The recommended dose is 2 mg twice daily, but 1 mg may be equally effective, with a lower risk for side effects. Extended-release medications are preferred due to significantly reduced risk for mucosal dryness. Tolterodine ER should be the drug of choice compared to oxybutynin and tolterodine IR (LE1a). Fesoterodine demonstrated better effectiveness as compared to tolterodine ER but was associated with higher therapy discontinuation rates due to its adverse effects and (mainly) dry mouth. The recommended dose of solifenacin is 5 mg daily and may be increased to 10 mg daily, with elevated risk for dry mouth. Solifenacin was more effective and had lower rates of dry mouth as compared to tolterodine IR (LE1a). Solifenacin (10 mg) and tolterodine (8 mg) were more effective than their doses of 5 mg and 4 mg, respectively [4, 17].

Drug characterization

Oral medications

Oxybutynin

Oxybutynin has a mixed action. It blocks the calcium channel, and has an anticholinergic as well as a local anesthetic effect, although the latter is relevant only in case of intravesical instillation therapy. Oxybutynin is a non-selective antagonist of the muscarinic (M) receptors, with higher affinity for M1 and M3 receptor subtypes than M2. M3 receptors are in the salivary glands, which is the reason for high incidence of dry mouth reported by patients using immediate-release oxybutynin [18]. Only a small number of patients continue the treatment for longer than six months due to the side effects (dry mucous membranes, constipation, blurred vision, somnolence, etc.) [18, 19].

Oral drugs with extended release and the transdermal patches and gels are available, but not in Poland. The transdermal route allows to lower the total dose and

Table 3. Overactive bladder syndrome — drug characterization

International name	Half-life	Mechanism of action	Dosing	Grade of recommendation
Antimuscarinic drugs				
Trospium	18.3 h	Non-selective anticholinergic action	2 × 20 mg/day	A
Oxybutynin	2 h	Non-selective anticholinergic action (higher affinity for M1 and M3 than M2) blocks the calcium channel Local anesthetic effect	3 x 5 mg	A
Tolterodine	2–3 h 5-HMT (Tolterodine metabolite) 3–4 h	Non-selective anticholinergic action	2 × 1–2 mg Extended release: 1 × 2–4 mg	A
Fesoterodine	Pro-drug Metabolized in the serum to 5-HMT 7–9 h	Non-selective anticholinergic action	1 × 4–8 mg	A
Darifenacin	12 h	M3	7.5 or 15 mg/day	A
Solifenacin	45–68 h	M2, M3	1 × 5–10 mg	A
β3-adrenoceptor agonist				
Mirabegron	50 h	β3-adrenoceptor agonist	50 mg/day	A
Other				
Estrogens				C
Botulinum toxin			100 u. 200 u.	A
Resiniferatoxin, Capsaicin			Intravesical	C
Antidiuretic Desmopressin			Indicated in nocturnal polyuria	A
α-adrenergic receptor blocker			–	C

5-HMT — 5-hydroxymethyl tolterodine metabolite

leads to fewer dose-related side effects, increasing therapy continuation rates.

The drug penetrates the blood-brain barrier and may cause cognitive disorders so it should not be used in older patients (LE2b) [3].

Trospium chloride

Trospium chloride has an anticholinergic non-selective effect on the muscarinic receptors. It does not penetrate the blood-brain barrier, so it does not negatively affect the cognitive functions of the patient. Trospium chloride has a documented effect in the reduction of smooth muscle tension, among others in the urogenital and gastrointestinal tract, allowing for the relaxation of the detrusor muscle and reduction of the uncontrolled detrusor contractions [20]. Trospium efficacy has been demonstrated, both compared to the placebo and other anticholinergics. After 12 weeks of therapy (20 mg twice daily) with trospium, mean voided volume increased by 36 mL, whereas mean number of micturitions decreased by three per day and urgency leakage episodes by two per day [20, 21]. In a long-term (52 weeks) study, the efficacy of trospium was like oxybutynin, but with better overall tolerance [22].

Tolterodine

The parent drug, tolterodine, and its active metabolite, 5-hydroxymethyl tolterodine (5-HMT), are responsible for the effect. Tolterodine has low lipophilicity, which is the reason for its very limited penetration into the central nervous system and no adverse effects on the cognitive functions. It exhibits non-selective activity against the M receptor subtypes and has a higher affinity for the bladder than for the salivary glands [19]. The use of tolterodine resulted in a significantly reduced number of micturitions and urgency incontinence episodes (LE1a) in various randomized trials. After 12 weeks of therapy, symptom reduction was as follows: UUI — 80%, urgency — 78%, nocturnal frequency — 40%, and daytime frequency — 30% [23].

Fesoterodine

Fesoterodine, a non-selective anticholinergic, is a prodrug which is hydrolyzed to 5-hydroxymethyl tolterodine

after oral administration. Fesoterodine is a specific, but non-selective, oral antimuscarinic which acts as a competitive antagonist of muscarinic receptors. 5-HMT is an active metabolite, same as the metabolite formed from tolterodine. Part of 5-HMT is metabolized in the liver, but > 15% of the administered dose is eliminated unchanged with the urine. The dose-dependent clinical effect of fesoterodine has been confirmed but it was associated with increased adverse effects [24]. After 12 weeks of therapy with fesoterodine, mean daily number of micturitions decreased by 2.2, urgency episodes by 3.5, and urgency urinary incontinence episodes by almost 2, whereas mean voided volume increased by 33 mL. No statistically significant reduction in the number of nocturia episodes was observed. In comparison to tolterodine ER, fesoterodine was statistically significantly more effective in reducing the number of urgency incontinence episodes and increasing the voided volume [25]. Fesoterodine does not prolong the QT/QTc interval, either at therapeutic or higher doses [19].

Darifenacin

Darifenacin has an 11-fold higher affinity for M3 than for M2 receptor subtypes. Its inhibitory activity of bladder contraction is comparable to that of atropine, at the same time demonstrating a 5-fold lower affinity for the muscarinic receptors in the salivary glands. Darifenacin was developed as a controlled-release preparation to address the inconvenience of multiple dosing per day. It is metabolized in the liver by the P450 cytochrome, is moderately lipophilic, and has no negative impact on the cognitive functions. Darifenacin is an M3-selective receptor antagonist, however, its role in developing constipation symptoms has been increasingly reported. After a two-year follow-up, 20.9% of the patients reported constipation as compared to 7.9% in the placebo group, and 5.6% were required to use fiber supplements, stool softeners or laxatives [26]. Darifenacin does not prolong the QT/QTc interval [18]. Significant improvement in OAB symptom intensity was observed already after 6–8 days of therapy [27]. After 12 weeks of therapy with the dose of 7.5 mg and 15 mg, mean daily number of micturitions decreased by 1.6 and 1.7, urgency episodes by 2, and urgency incontinence episodes by 4.0 and 4.7, respectively. Darifenacin did not significantly impact the number of nocturia episodes [28].

Solifenacin

Solifenacin is a competitive inhibitor of the muscarinic M3 receptor and has low affinity for other M receptors (M2 and M1). Solifenacin has higher affinity for the urinary bladder than for the salivary glands. It has a long half-life, and its slow pharmacokinetics is associated with steady efficacy and reduced side effects. Solifenacin is metabolized in the liver via the cytochrome P450 system. First significant therapeutic effects may be observed as early as on day 7 of therapy, with the maximum effect after 28 days. Randomized controlled trials demonstrated the efficacy of solifenacin to be higher as compared to placebo or tolterodine. In the STAR study, after 12 weeks of therapy with 5 mg of solifenacin/day, mean daily number of micturitions decreased by 2.5, urgency episodes by 3.1, and urgency incontinence episodes by 1.5. Solifenacin at the dose of 5 mg was more effective in reducing the number of urgency and urgency incontinence episodes and was associated with lower pad use as compared to 4 mg of tolterodine ER. At the endpoint of the study, 59% of solifenacin and 49% of tolterodine ER users did not experience UUI episodes, and the difference was statistically significant [24, 29].

In the group of patients with multiple sclerosis and after spinal injuries, 10 mg of solifenacin improved the urodynamic parameters, including an increase in the maximum cystometric capacity of the bladder (by 134 mL) as compared to the placebo group (by 5 mL) [30].

Mirabegron

Mirabegron is a β3-adrenoceptor agonist. The sympathetic nervous system regulates the urine storage phase, and the β-adrenergic receptors present in the bladder mediate the relaxation of the detrusor and foster urine accumulation. There are three β receptor subtypes: β1, β2, β3. Approximately 97% of the β-adrenergic receptors in the urinary bladder are β3 receptors [31]. Stimulation of β3-adrenergic receptors increases bladder capacity without changing the micturition pressure or residual volume. In consequence, β3-adrenoceptor agonist increases bladder capacity without affecting the contraction amplitude during micturition [32]. The recommended daily dose is 50 mg, with 25 mg for patients with severe renal impairment (creatinine clearance 15–29 mL/min) or moderate liver impairment.

Four large, randomized trials demonstrated mirabegron efficacy in reducing OAB symptoms as compared to placebo. In a study by Khullar et al. [33], after 12 weeks of therapy with 50 mg of mirabegron, mean daily number of micturitions decreased by 1.9, episodes of urinary incontinence by 1.6, and of urgency by 2.3, while mean voided volume increased by 24 mL. The incidence of treatment-related adverse events (hypertension, urinary tract infection, headache, nasopharyngitis) was similar in the mirabegron and the placebo groups. Additional analysis revealed a similar efficacy of mirabegron as far as the number of incontinence episodes and micturitions was concerned, both in OAB patients with no history of antimuscarinic therapy (treatment naïve) and those who had discontinued prior antimuscarinic therapy [34]. The SYNERGY I and II studies confirmed higher efficacy of the combination therapy (solifenacin and mirabegron) as

compared to the monotherapy. The combination therapy additionally decreased mean daily number of micturitions by 0.1–0.5 and of incontinence episodes by 0.4–0.5, and increased mean voided volume by another 13–16 mL per micturition [35].

Antidepressants

Imipramine is an antidepressant used in the treatment of OAB but is currently unavailable in Poland [36]. It exerts a complex pharmacological impact through its antimuscarinic activity as well as serotonin and noradrenaline reuptake blocking properties. Imipramine has an indirect α-adrenergic effect, thus promoting detrusor relaxation and causing an increase in the intraurethral pressure [37].

Duloxetine is a norepinephrine and serotonin reuptake inhibitor, and weakly inhibits dopamine reuptake. Duloxetine increases the activity of the urethral sphincters in the urine storage phase [19]. The Onuf nucleus is a distinct group of motor neurons, located in anterior horns of the spinal cord in the sacral segment, and is the origin of the pudendal nerve. Through the pudendal nerve, the Onuf nucleus innervates the urethral striated muscles. Noradrenaline and serotonin potentiate the glutaminergic stimulation of the motor neurons, increasing striated muscle contraction [19].

Most research so far has focused on the use of duloxetine to treat stress urinary incontinence, but few reports concerned its beneficial effect in OAB therapy. Duloxetine reduces the daily number of micturitions and urgency episodes and improves the quality of patient life, while mean voided volume remains unchanged (LE4). The efficacy of duloxetine therapy has been confirmed in patients with detrusor overactivity and mixed urinary incontinence. In light of its efficacy in treating depression, duloxetine may present a therapeutic option for patients with depression and concomitant OAB symptoms (off-label use, the drug is not registered for urinary incontinence in Poland) [36].

Management of nocturia with concurrent overactive bladder

Desmopressin (DDAVP, deamino-D-arginine vasopressin) is a synthetic analogue of vasopressin and exhibits antidiuretic activity through vasopressin V2 receptors, affecting water reabsorption in the renal tubules. Desmopressin is used in the treatment of nocturia caused by nocturnal polyuria [3]. The recommended daily dose is 25 μg for women (50 μg for men) of desmopressin lyophilizate, administered sublingually, one hour before bedtime. Food may reduce drug strength and effect duration. Some studies support the efficacy of desmopressin for treating nocturia in patients with OAB. A randomized trial compared the use of combination therapy (25 μg of desmopressin and 4 mg of tolterodine ER) versus tolterodine monotherapy. After 12 weeks of therapy, a significant difference in the nocturnal urine volume and prolonged time between the initial sleep point and the first episode of nocturia were observed in the desmopressin group of patients treated for OAB and nocturnal polyuria.

Administration of desmopressin may be considered in patients affected by nocturia with concurrent OAB to reduce the number and volume of nocturnal micturitions [38].

Therapy continuation

Numerous studies demonstrated low continuation rates of antimuscarinic therapy, mainly due to patient-reported lack of results and adverse effects. Wagg et al. [39], reported the following results for therapy continuation after 12 months: 35% — solifenacin, 28% — tolterodine ER, 26% — trospium, 24% — tolterodine IR, 22% — oxybutynin IR, and 17% — darifenacin [39]. However, after 24 months, the rates of therapy continuation ranged from 6 to 12% [40]. According to the literature, mirabegron has a significantly longer time to therapy discontinuation as compared to antimuscarinics. After 12 months of therapy, 38% of the patients continued mirabegron. Mean time to mirabegron and tolterodine ER discontinuation was 169 and 56 days, respectively. Factors promoting therapy discontinuation in OAB patients included: younger age (< 60 years), insufficient information about the purpose of treatment, exceedingly high expectations about the therapy effects, reluctance to use chronic pharmacotherapy, or significant alleviation of OAB symptoms [19].

Cardiovascular effects

Drug selection for OAB therapy needs to include the possible effect of chronic pharmacotherapy on the cardiovascular system [41]. The safety profile of antimuscarinics has been confirmed by numerous studies. Unfortunately, the risk for developing drug-induced cardiac events and symptoms such as increased heart rate (HR), prolonged QT interval, and polymorphic ventricular tachycardia is a cause for some concern [42]. The M2 receptors are predominant muscarinic receptor subtypes expressed in the heart and they play an important role in the maintenance of the heart rate and cardiac output. M2 receptor blockade in the sinus node, the heart's natural pacemaker, increases the pulse and decreases other parameters of the vagal tone, *e.g.*, return to resting heart rate after exertion and baroreceptor reflex response [42].

Darifenacin selectivity for M3 receptors is suggestive of a minor effect on the cardiovascular system. Olshansky et al., evaluated the effects of a seven-day treatment regimen with 15 mg/day of darifenacin, 4 mg/day of tolterodine and placebo in healthy participants. Tolterodine was found to significantly increase the heart rate as compared to darifenacin and placebo, while darifenacin did not affect the heart rate as compared to placebo. The maximum increase in HR for tolter-

odine occurred at times of maximum plasma concentration and was approximately 4 bpm [43]. Fesoterodine was also found to cause a dose-related increase in HR. Mean change in HR for 4 and 8 mg of fesoterodine and placebo was 3, 4 and 1 bpm, respectively [44]. As for oxybutynin, no increase in HR as compared to placebo was observed [45].

Solifenacin did not cause an increase in mean HR or mean blood pressure [46]. Trospium therapy may be associated with dose-related increase in HR. Mean increase in HR after trospium was 9 bpm for the 20 mg dose and 18 bpm for the 100 mg dose. The increase in HR was noted after 4-8 hours and disappeared 12 hours after administration. No significant effect on the blood pressure was detected, regardless of the dose [19]. In conclusion, darifenacin, solifenacin, and oxybutynin show no significant effect on HR [47].

In a study with placebo, mirabegron increased HR by 1–2 bpm [48]. A pooled analysis of clinical trial data found no proof of increased risk for cardiovascular adverse events for mirabegron or antimuscarinic therapy as compared to placebo. Cardiovascular adverse events were related to the pre-existing conditions of the patients, not the OAB pharmacotherapy. **No correlation between OAB treatment and increased risk for adverse cardiac events was demonstrated** [49]. In the SYNERGY study, which analyzed combination therapy with mirabegron and solifenacin, no statistically significant increase in resting blood pressure was observed [50]. The analysis of the safety profile for the combination therapy with mirabegron and solifenacin revealed comparable rates of adverse cardiovascular events for both, combination and monotherapy [50].

QT-interval prolongation and its consequences result from inhibition of the cardiac hERG potassium channel [42]. Among antimuscarinics, darifenacin, fesoterodine and trospium chloride do not affect the QT/QTc interval [19, 42, 51]. Solifenacin may prolong the QT interval but not to a clinically relevant degree (10 mg — by 2 milliseconds, 30 mg — three times the maximum therapeutic dose — by 8 milliseconds) [19]. The effect of tolterodine on the QT interval correlates with its plasma concentration. Tolterodine blocks hERG channels with high affinity but produces little QT prolongation clinically [42]. Data on the possible QT effects in patients using oxybutynin are limited [19, 42, 52]. Studies on mirabegron monotherapy found no effect on the QT/QTc interval, either in the study group or in the combination therapy with solifenacin or placebo [50]. Imipramine has a negative effect on the cardiovascular system; it prolongs the QTc interval and has a potent antiarrhythmic action [19].

Polypharmacy and metabolism

Polypharmacy (> 5 drugs) is a common phenomenon in the older populations. Drug interactions frequently involve the P450 cytochrome hepatic isoenzymes. Tolterodine, darifenacin, solifenacin, oxybutynin, and mirabegron are metabolized by the P450 cytochrome system. Consequently, susceptibility to altered drug metabolism in case of drug interactions of medications based on hepatic metabolism is increased. Trospium is eliminated unchanged through the kidneys [19].

Anticholinergic burden

Anticholinergic burden should be considered when treating patients who use polypharmacy. Numerous drugs from other groups have an additional anticholinergic activity (antimuscarinics together with antidepressants and antihistamines constitute > 90% of medications with anticholinergic properties prescribed to patients). The additive effect of the drugs can be expressed as higher number of adverse effects (dry mouth, constipation, blurred vision, cognitive impairment) and lower effectiveness. The anticholinergic effect of the drugs is dose-dependent [53]. Various scales are used to assess the overall anticholinergic effect of the drugs [54]. The list of selected drugs with high and low anticholinergic potential is presented in Table 4 [55].

Pharmacotherapy in older patients

Mirabegron is effective and safe in older populations (LE1b). Antimuscarinics are equally effective in older patients and other age groups (LE1b). Over time, the impact of anticholinergic drugs on the cognitive functions increases with drug accumulation (LE2b). Oxybutynin may worsen cognitive functions in older patients, so it is not recommended for people over the age of 65 years (LE2b). In short-term studies, solifenacin, darifenacin, fesoterodine, and trospium were not found to cause cognitive dysfunction in older patients. Long-term antimuscarinic therapy should be used with caution in older patients, especially those at risk for developing cognitive impairment [2, 3].

2. Vaginal estrogens

The role of estrogens in OAB therapy remains ambiguous and they are not included in most international guidelines. Patients with estrogen deficiency have been confirmed to be at an increased risk for OAB [56]. In rat models after ovariectomy, a significant reduction in voided volume and an increase in micturition frequency were observed, and the administration of exogenous estrogen reversed these changes [57].

A systematic review of 11 randomized trials demonstrated the efficacy of estrogens versus placebo in reducing the number of frequency, nocturia, urgency, and incontinence episodes, and increasing bladder volume and bladder volume at the first sensation. These results pertained to local therapy (vaginal and intravesical). Systemic therapy was effective only in reducing the number of incontinence episodes and increasing the bladder volume at the first sensation, while at the same time intensifying the symptoms of nocturia [58].

Table 4. Anticholinergic drugs and their anticholinergic potential [54, 55]

Drug	anticholinergic potential: 1 — low 2 — high
Psychotropic drugs (N)	
Amitriptyline	2
Carbamazepine	1
Citalopram	1
Diazepam	1
Fentanyl	1
Fluoxetine	1
Clozapine	2
Quetiapine	1
Lithium	1
Mirtazapine	1
Olanzapine	1
Paroxetine	1
Promazine	1
Risperidone	1
Trazodone	1
Drugs which affect the digestive and metabolic system (A)	
Domperidone	1
Hyoscine	2
Loperamide	1
Ranitidine	1
Drugs which affect the respiratory system and antiallergic drugs (R)	
Cetirizine	1
Fexofenadine	1
Codeine	1
Loratadine	1
Theophylline	1
Drugs which affect the musculoskeletal system (M)	
Baclofen	1
Tizanidine	2
Drugs which affect the urogenital system (G)	
Darifenacin	2
Oxybutynin	2
Tolterodine	2
Drugs which affect the cardiovascular system (C)	
Digoxin	1

The results of studies which compared the use of antimuscarinic drugs in combination with intravaginal estrogen versus antimuscarinic monotherapy remain conflicting. Tseng et al., demonstrated significant improvement in frequency, voided volume, and quality of life among women who received tolterodine and vaginal conjugated equine estrogen treatment as compared to tolterodine monotherapy. Symptoms of nocturia, urgency and UUI after treatment improved as compared to baseline, but the combination therapy was not superior [59]. Serati et al. [60], analyzed a group of women with detrusor overactivity confirmed by urodynamic tests and showed no synergistic effect of 4 mg of tolterodine ER and estriol cream in OAB therapy. Jiang et al., showed that solifenacin efficacy in reducing OAB symptoms was identical in combination with vaginal estradiol and without estrogens. However, the addition of estradiol significantly improved patient-reported subjective impressions and quality of life [61].

THIRD-LINE TREATMENT: BOTULINUM TOXIN AND NEUROMODULATION (POSTERIOR TIBIAL NERVE STIMULATION AND SACRAL NERVE STIMULATION)

Botulinum toxin

1. Patients with OAB resistant to first- and second-line therapy may be offered onabotulinumtoxin A (100 U) bladder wall injections [3].
2. Patients should be informed about the limited duration of action of the drug, the risk of urinary tract infection and the possibility of self-catheterization (make sure the patient will be cooperative). The patient is required to return for post-void residual evaluation [3].
3. The next injection should not be performed within three months. In clinical trials, the median duration of the effect was 166 days (approx. 24 weeks) [3, 62].

Onabotulinumtoxin A belongs to the A group of toxins. It is a neurotoxin which binds permanently to the neuromuscular junction, paralyzes neuromuscular conduction by fragmenting the synaptosomal-associated protein 25 (SNAP-25) and inhibiting the release of acetylcholine from the presynaptic terminal.

Onabotulinumtoxin A is used in idiopathic detrusor overactivity (IDO) at the dose of 100 U dissolved in 10 mL of saline and injected into 20 points of the bladder wall above the bladder trigone (0.5 mL per injection site). Different types of type A botulinum toxin are currently available on the market, including those not registered for OAB treatment (abobotulinumtoxin A and incobotulinumtoxin A). Considerable attention should be paid to the registered indications of the drugs, especially in the absence of dose equivalence for these preparations [3].

In a randomized trial after 12 weeks of follow-up, onabotulinum significantly reduced all OAB symptoms as compared to the placebo group, decreased the daily number of UUI episodes (–2.95 vs –1.03; $p < 0.001$), and positively affected the quality of patient life (positive response to treatment was reported by 62.8% of the patients as compared to 26.8% in the placebo group) [63]. UUI episodes were not

reported by 22.9% of the patients in the onabotulinum group and 6.5% in the placebo group [62].

In a study comparing onabotulinum with antimuscarinics after 6 months of follow-up, both methods proved to be associated with a similar reduction in the frequency of UUI episodes (3.3 vs 3.4, respectively). However, complete resolution of UUI symptoms occurred in 27% of the patients in the onabotulinum group and only 13% in the antimuscarinic group (p = 0.003). The onabotulinum group had significantly lower probability of dry mouth (31% vs 46%, respectively), but higher probability of urine retention (5% vs 0%, respectively in the first 2 months of therapy) and urinary tract infections (33% vs 13%, respectively). The treatment effect was maintained in 38% of the patients after 12 months of onabotulinum therapy (LE1b) [3, 64].

In case of neurogenic detrusor overactivity (NDO), the recommended dose of onabotulinum is 200 U (30 intra-detrusor muscle injections at the dose of 1 mL per site), in which case median duration of the drug effect is 256–295 days according to phase III studies [65].

Other bladder injection protocols

The concept of preventing vesicoureteral reflux is the main reason behind injecting the area above the trigone. However, several studies investigated other locations for bladder onabotulinum injections [19].

The studies which compared various sites of bladder injections did not demonstrate any increase either in post-void urine retention, or the rates of patients requiring self-catheterization, or the vesicoureteral reflux in cases when the injections were performed into the trigone [19]. In one study among patients with idiopathic detrusor overactivity (IDO), three types of injection sites were compared: body of the bladder (100U); body of the bladder (75U) and the trigone (25U); as well as the fundus (50U) and the trigone (50U). The success rate at three months of follow-up was 70% for the body of the bladder, 74% for the body and trigone, and 73% for the fundus and trigone. No statistically significant differences were found in success rates, number of urgency and UUI episodes, or long-term measures among the three subgroups. The incidence of adverse events was similar in the three groups. No vesicoureteral reflux was detected in any of the patients [66].

In contrast, a meta-analysis of eight studies and 419 patients with NDO and IDO revealed that trigone injections were more effective and were not associated with higher complication rate as compared to trigone-sparing injections. Injection depth did not affect the efficacy or safety of onabotulinumtoxin A [67].

The most common side effects of onabotulinumtoxin are related to the urinary tract. At 12 weeks of follow-up, uncomplicated UTI were found in 15.5% of the patients in the onabotulinumtoxin group and in 5.9% in the placebo group. Additionally, symptoms of dysuria (12.2%), bacteriuria (5%) and urinary retention (5.4%) were reported. An increase in post-void residual (PVR) of ≥ 200 mL as compared to baseline was observed in 8.7% of the patients. No significant increase in PVR was observed in the placebo group. The rate of patients who required self-catheterization at any time during the first treatment cycle was 6.1% as compared to 0% in the placebo group [68].

Posterior tibial nerve stimulation (PTNS)

Percutaneous tibial nerve stimulation (PTNS) may be used as third-line treatment in some patients [3].

The tibial nerve is a peripheral nerve, with sensory and motor fibers. It originates from the L4–S3 spinal nerve roots, which are also responsible for the sensory and motor innervation of the urinary bladder and the pelvic floor. The PTNS effect is believed to be related to the retrograde stimulation of the sacral nerve plexus. The treatment typically consists in 12 weekly sessions, 30 min each, after which maintenance therapy sessions are recommended. The stimulation is performed percutaneously using a slim 34-Gauge needle inserted just above the medial condyle of the ankle (P-PTNS) [3].

PTNS is effective in treating therapy resistant OAB. It demonstrates significantly higher efficacy as compared to placebo, without serious side effects, and comparable efficacy to antimuscarinic therapy (LE1b). According to various meta-analyses, PTNS shows 37–100% effectiveness and decreases the number of frequency, urgency, UUI and nocturia episodes [69]. Stimulation with transcutaneous electrodes (T-PTNS), whose effectiveness in reducing daytime frequency is comparable to P-PTNS, is also an available treatment modality (LE1b) [70].

P-PTNS maintenance therapy, performed approximately once a month, proved to be effective in maintaining the treatment effect for up to three years of follow-up (LE1b) [3]. It can also be conducted with adhesive skin surface electrodes (T-PTNS) in a weekly three-session regimen (30 min/session), (LE1b) [71].

In OAB patients, a physiotherapist may use vaginal, transrectal and transcutaneous electrostimulation (paraspinal electrostimulation of the micturition centers, non-invasive electrostimulation of the tibial or peroneal nerves). Based on the available sources, it is challenging to determine the sufficient number of sessions. Also, there is no consensus on the duration of one series of the electrostimulation. The authors of the present study recommend that the electrostimulation parameters be adjusted individually, taking into consideration the condition of the patient and symptom severity [72, 73].

Sacral nerve stimulation (SNS)

SNS may be suggested as the third-line treatment to carefully selected populations of patients with severe therapy resistant OAB or those not eligible for second-line treatment and willing to undergo surgery [2]. In Poland, only a handful of procedures have been performed so far so the experience is limited. The efficacy of SNS is higher if juxtaposed with the option of continuing unsuccessful conservative treatment to treat UUI (LE1b) [3].

The efficacy of SNS was demonstrated in patients with therapy resistant UUI. At six months of follow-up, 50% of the patients after SNS implantation showed over 90% improvement as far as UUI symptoms were concerned as compared to 1.6% in the group with continuous pharmacotherapy (LE1b) [74].

In a prospective randomized study in patients resistant to therapy with at least one antimuscarinic drug, at six months of follow-up 86% of the patients in the SNS group reported improved or very much improved OAB symptoms as compared to 44% in the antimuscarinic group ($p < 0.001$). The therapeutic success rate for SNS was 85% at 12 months and 82% at five years of follow-up. Therapeutic success was defined as at least 50% improvement in UUI episodes or at least 50% improvement in the daily number of micturitions, or a return to the normal daily number of micturitions (< 8 per day). At five years of follow-up, mean daily number of UI episodes decreased by 2.0 ± 2.2 as compared to baseline ($p < 0.0001$), and complete continence was achieved in 45% of the patients. Mean daily reduction in the number of micturitions was 5.4 ± 4.3 ($p < 0.0001$). At 12 months of follow-up, the most common device-related adverse events included 'undesirable' change in stimulation in 12%, implant site pain in 7%, and implant site infection in 3% of the patients. The cumulative five-year rate of lead-related adverse events which required reoperation after complete implantation was 22.4%. Ineffectiveness of the therapeutic product was observed in 13% of the patients. At five years of follow-up, the rate of patients with device removal was 19.1% (LE1b) [75].

In a ROSETTA study, which compared SNS with injections of 200 U of onabotulinum at six months of follow-up, patients in the onabotulinum group had higher reduction in the mean daily number of UUI episodes as compared to the SNS group (–3.9 vs –3.3 episodes/day; $p = 0.01$). They also reported significantly greater improvement in the Overactive Bladder Questionnaire SF, which evaluates symptom bother, and a higher level of satisfaction with the treatment. Urinary tract infections were significantly more frequent in patients from the onabotulinum group (35% vs 11%, $p < 0.001$) as well as the need for self-catheterization (8% at 1 month, 4% at 3 months, and 2% at 6 months of follow-up). The need for device revisions and removals was found in 3% of the patients. The small but significant difference in subjective and objective indices of therapy efficacy reported in that study gave rise to a heated debate about the clinical significance of the obtained results [76]. Based on that, the consensus in the European recommendations is that SNS efficacy is not superior to injection therapy with 200 units of onabotulinum at six months of follow-up (LE1b) [3].

Although SNS constitutes the third-line treatment, along with PTNS and onabotulinum, it should be treated as a higher-risk and more invasive method. Therefore, it is recommended to patients who are resistant to other methods of treatment [4].

In addition to OAB therapy, SNS is also effective in treating painful bladder syndrome, interstitial cystitis, urine retention not induced by bladder outlet obstruction, and fecal incontinence [69].

SNS and magnetic resonance imaging

SNS is a relative contraindication for magnetic resonance imaging (MRI). The magnetic field generates electric currents in the neuroelectrodes, which heats the electrodes *in vivo* and *in vitro*, and may cause nerve damage. Device removal is recommended if elective MRI is required. In newer devices, it is possible to perform a head examination under highly specified conditions [69].

SUMMARY

Before treatment commencement, it is necessary to conduct an adequate and thorough diagnostic process. If the therapy proves ineffective, the patient needs to be referred to a specialist. In selected situations, a multidisciplinary team consultation may be recommended.

Pharmacotherapy remains the gold standard in OAB treatment and should not be delayed. However, the limitations and side effects of pharmacotherapy are the reasons why the search for new solutions continues. Animal studies are conducted to find new drugs to treat the OAB syndrome [19, 36, 77–80]. Preclinical studies lead to the development of new drugs, which may in time find applications in clinical practice [16, 77].

Conflict of interest

None.

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CLINICAL VIGNETTE

Ginekologia Polska
2021, vol. 92, no. 3, 252–253

ISSN 0017–0011, e-ISSN 2543–6767

DOI 10.5603/GP.a2020.0156

Pregnant 30-year-old with idiopathic pulmonary arterial hypertension

Karol Glowacki[1], Marek Grabka[1], Jaroslaw Myszor[1], Tomasz Maciejewski[2], Andrzej Witek[3], Ewa Kucewicz-Czech[2], Katarzyna Mizia-Stec[1]

[1]1st Department of Cardiology, Medical University of Silesia in Katowice, Poland

[2]Department of Anaesthesiology and Intensive Therapy with Cardiac Supervision, Medical University of Silesia in Katowice, Poland

[3]Department of Obstetrics and Gynecology, School of Medicine in Katowice, Medical University of Silesia in Katowice, Poland

Key words: pulmonary arterial hypertension; pregnancy; right heart failure

Ginekologia Polska 2021; 92, 3: 252–253

A 30-year-old woman was hospitalized for the first time due to resting dyspnea. At the time of admission she was in the WHO IV class, with lowered arterial blood saturation and echocardiographic features of right ventricle overload. A right heart catheterization (RHC) revealed severe reactive pulmonary arterial hypertension (PAH). Treatment with sildenafil and diltiazem led a reduction of symptoms associated with the WHO II class. The patient was advised to avoid pregnancy. Two months later we noted a significant clinical improvement, but the blood test showed elevated beta-hCG. The risk of pregnancy related complications in PAH patients was discussed, and therapeutic options were proposed, including those related to termination of the pregnancy. The patient's decision was to maintain the treatment and the pregnancy was not terminated.

During the thirty weeks of gestation the patient did not present any symptoms and the course of pregnancy was not complicated. In the 31st week, rapid clinical deterioration occurred. She was urgently admitted to the hospital with severe resting dyspnoea, tachycardia, blood pressure 90/70 mmHg and oxygen saturation of 90–92%. Transthoracic echocardiography (TTE) showed signs of severe right heart pressure overload. We planned for possible escalation of therapy with permanent intravenous epoprostenol infusion, but we had to expect for epoprostenol delivery and due to the patient's critical and life-threatening condition, emergency inhalations of iloprost was administered. RHC was performed trying to avoid excessively exposing the fetus with X-rays. The severe non-reactive PAH was confirmed. On the 3rd day of hospitalization, the patient developed a respiratory tract infection, due to the negative result of the influenza screening test. Eempirical antibiotic therapy was introduced, but the patient's condition continued to deteriorate — leukocytosis and heart rate increased, O2 saturation and blood pressure dropped. Immediately, an urgent specialist consultation was carried out, attended by a cardiologist, cardio-anesthesiologist, neonatologist and gynecologists. The state of the fetus was regarded as a stable, so the decision was made to start an intravenous infusion of epoprostenol and then to perform a Caesarean section. Within three hours of the epoprostenol infusion, the patient had moderate bleeding from the genital tract. Placental ablation or epoprostenol-induced platelets inhibition were suspected, so the patient was immediately transferred to the Cardiac Surgery Department, where a gynecologists performed a caesarean section.

The patient gave birth to a boy (weight: 2110 g, Apgar score: 2/3/5/7 points).

After the procedure, the mother was in critical condition: cardiogenic and septic shock, tachycardia, severe acidosis. In addition, suprasystemic pressure in the pulmonary artery was noted. She required mechanical ventilation with 100% oxygen, intensive antibiotic therapy (meropenem, linezolid), as well as forcing diuresis. To maintain cardiovascular function, it was necessary to use an infusion of inotropes (adrenaline, noradrenaline, milrinone) and PAH-specific wide-range therapy. Stabilization of the circulatory system was obtained, but without a noticeable improvement in the patient's condition. In addition, restrictions were encountered in the escalation of the epoprostenol infusion due to thrombocytopenia and the features of a hemorrhagic diathesis manifested by respiratory bleeding. Increasing respiratory failure and haemodynamic instability necessitated the emergency use of arteriovenous extracorporeal membrane oxygenation (ECMO). Mechanical support allowed to reduce the

Corresponding author:
Karol Glowacki
1st Department of Cardiology, Medical University of Silesia in Katowice, Poland
e-mail: glowacki47@gmail.com

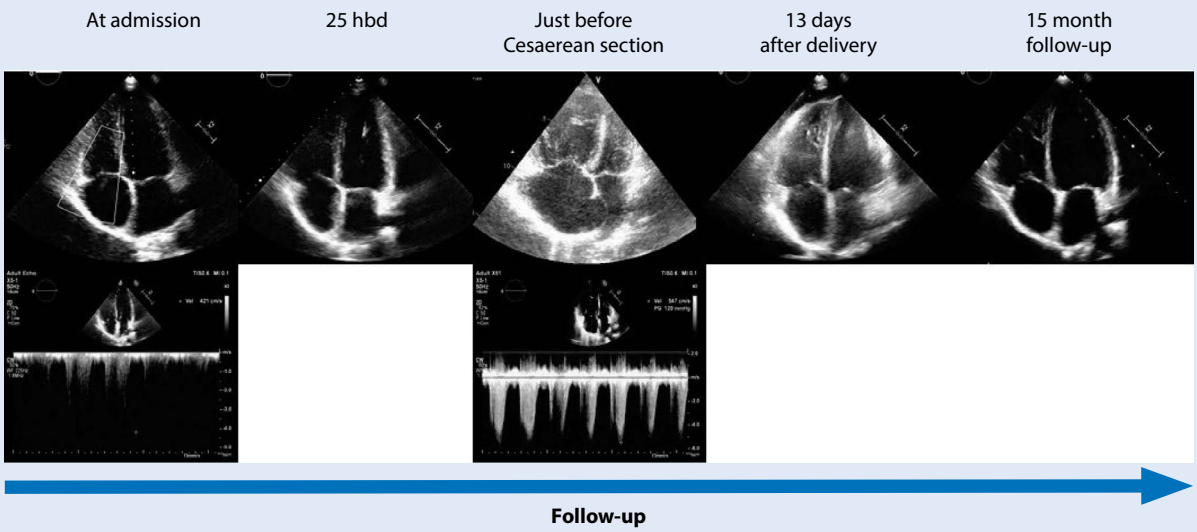

Figure 1. Transthoracic echocardiography — 4-Chamber views in different points of clinical follow-up

infusions of inotropes. Despite subsequent platelet substitution, the patient had another hemorrhagic complication, she required urgent laparotomy due to massive bleeding into the peritoneal cavity, and 3 days later relaparotomy was necessary because the bleeding returned. On the 7th day of its use, after adding levosimendan to therapy, it was decided to remove ECMO due to persistent bleeding. After 18 days post delivery, the patient returned to our ward, where pharmacotherapy consisted mainly of escalation of the infusion of epoprostenol. Ultimately, the escalation of therapy brought the expected clinical effect. In further treatment, a Hickman tunneled catheter was inserted into the left subclavian vein and a portable pump was used for intravenous epoprostenol administration.

At discharge it was recommended she use two methods of preventing pregnancy.

During the last hospitalization 15 months after delivery, the patient was in the WHO class I. She achieved treatment goals for PAH therapy on epoprostenol, macitentan, sildenafil and diltiazem treatment.

CONCLUSIONS

Current ESC guidelines [1, 2] advise against pregnancy in the presence of PAH as well as recommending pregnancy termination. Reactive form of PAH is related to less severe risk of pregnancy complications.

Initially, reactive iPAH was diagnosed in our patient. The patient responded well to diltiazem and sildenafil and the course of the first and second trimester of pregnancy was uncomplicated.

The dramatic course of the last pregnancy period was present. The final positive outcome resulted via the implementation of large amounts of inotropes, extracorporeal oxygenation and targeted treatment of PAH.

Regardless of the initial diagnosis of reactive iPAH, the patient necessitates the use of complex treatment to achieve the goals for PAH therapy.

In our opinion, the course of pregnancy in patients with reactive PAH may be unexpected, even dramatic, particularly in the third trimester of the pregnancy. In our opinion, it needs a coordinated multidisciplinary approach and may likely influence the long-term treatment and prognosis of the patient.

Conflict of interest

None.

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CLINICAL VIGNETTE

Ginekologia Polska
2021, vol. 92, no. 3, 254–255

ISSN 0017–0011, e-ISSN 2543–6767

DOI: 10.5603/GP.a2020.0157

Uterine haematoma — a complication after delayed management of caesarean scar pregnancy

Anna Stepniak, Tomasz Paszkowski, Piotr Czuczwar

3rd Chair and Department of Gynecology, Medical University in Lublin, Poland

Ginekologia Polska 2021; 92, 3: 254–255

Caesarean scar pregnancy (CSP) is a type of ectopic pregnancy implanted into the defect in the myometrium at the hysterotomy site from a previous caesarean delivery [1]. Untreated CSP may be associated with life-threatening complications, such as placenta praevia or accreta, uterine rupture and haemorrhage [2, 3]. Therefore, an early diagnosis is crucial to decrease maternal morbidity and mortality. There is no universal treatment option for CSP and data about the complications of treatment are scarce [4, 5]. Selective uterine artery chemoembolization with intra-arterial methotrexate (MTX) infusion followed by suction curettage is one of the treatment options for CSP and is considered as a safe method. We report a case of a complication after this treatment.

A 35-year-old patient, two CSs in history, at 8 weeks of gestation was admitted to the hospital with suspected CSP. On transvaginal ultrasound (TVUS) two gestational sacs (GS), implanted in the anterior wall of cervicoisthmic area in the caesarean scar were visualized. In the first GS a single embryo with foetal heart rate was observed, while the second GS had no embryonic structures (Fig. 1). On Colour Doppler examination a high vascular pattern was present around both GSs. The patient was informed about the recognition and possible life-threatening complications of CSP. Nevertheless, she wanted to preserve and continue the pregnancy. After two weeks the patient changed her decision and was qualified for selective uterine artery chemoembolization with intra-arterial MTX infusion followed by suction curettage. TVUS followed by magnetic resonance imaging revealed very thin myometrium in the caesarean scar site and a high risk of bladder infiltration (Fig. 2). The treatment, however, went with no complications and the patient was discharged in good condition (Fig. 3). Abnormal uterine bleeding occurred three months afterwards and a haematoma (max diameter 50 mm) in the area of evacuated CSP was found during TVUS (Fig. 4). The patient was scheduled for dilatation and curettage (D&C). After D&C the symptoms did not disappear and the haematoma reformed. The decision was made to perform vascular embolization and suction curettage to stop the bleeding. The result was satisfying and the patient was discharged without any further complications.

It is important to stress that, although selective uterine artery chemoembolization with intra-arterial MTX infusion followed by suction curettage is considered to be a safe procedure, complications may occur. In this case, the factors that could possibly

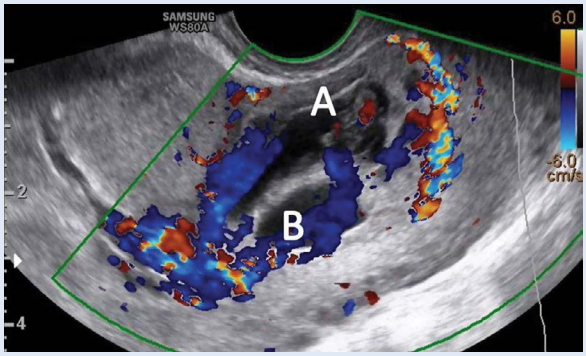

Figure 1. Transvaginal ultrasound revealed two gestational sacs at caesarean section scar site, the first (A) with a single embryo with foetal heart rate and the second (B) without embryonic structures, both with high peripheral vascularity shown on colour Doppler

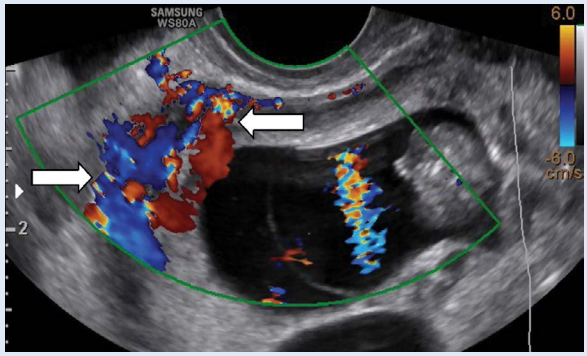

Figure 2. After two weeks thinning of the myometrium in the anterior uterine wall was seen on transvaginal ultrasound and there was a suspicion of bladder infiltration.

Corresponding author:
Anna Stepniak
3rd Chair and Department of Gynecology, Medical University in Lublin, 8 Jaczewskiego St, 20–954 Lublin, Poland
e-mail: aanna.stepniak@gmail.com

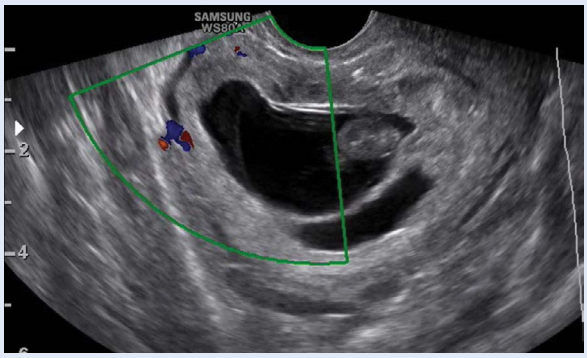

Figure 3. After selective uterine artery chemoembolization with intra-arterial methotrexate infusion no foetal heart rate and a low vascular pattern were observed

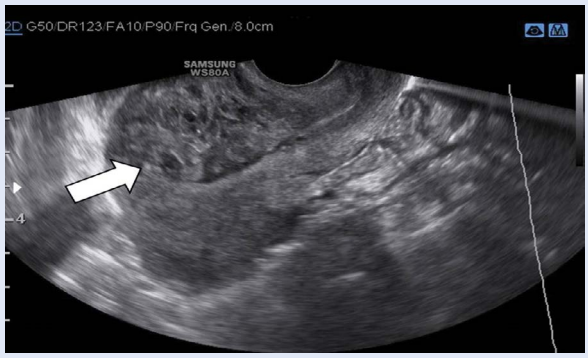

Figure 4. Haematoma in the uterus at the site of previous caesarean scar pregnancy 3 months after chemoembolization

have contributed to the formation of a haematoma were: delayed intervention, multiple pregnancy and high vascularity of gestational sacs. Early recognition and treatment of CSP are essential for successful management.

Conflict of interest

None.

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