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

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: Pain and postoperative nausea and vomiting are among the most unpleasant sensations experienced after surgery. Patients after gynaecological surgery are at higher risk for both complications. Former methods of pain management based mainly on opioid administration were much less safe, especially for elderly patients. In addition, they generated an even greater increase of postoperative nausea and vomiting.
Multimodal therapies in anesthesiology are currently being used more and more often. These include both multimodal postoperative pain management and multimodal prophylaxis of postoperative nausea and vomiting.
The aim of the study was to assess the benefits of the methods used for gynaecological patients in the immediate postanesthetic period.

Material and methods: The research material is an analysis of medical documentation of 150 patients from the gynaecology clinic who underwent surgical procedures of categories III and IV from October 2018 and until January 2019, carried out in one of the clinical hospitals in Szczecin at the Anesthesiology and Intensive Care Clinic. Patients were divided into 3 groups:

1. Patients who received multimodal analgesia using non-opioid and opioid analgesics.
2. Patients who received multimodal analgesia using non-opioid and opioid analgesics and adjuvants.
3. Patients who received multimodal analgesia using non-opioid and opioid analgesics and central blockade.

Results: The highest age was in the third group at 57.48 years of age, 50.86 in the second group, and 47.8 in the first group. Healthy patients classified as ASA 1 accounted for 14% of group I, 18% of group II and 10% of group III. Patients with severe systemic disease (ASA 3) constituted 30% of group III 18%, of group II and 8% of group I. Upon leaving the operating room, as many as 80% of the patients from groups II and III did not feel any pain. In group I was 52%. When entering the recovery room, 26% of the patients in group I, 10% in group III, and 8% in group II rated their pain as higher than 5. The most used antiemetic medication in the studied facility was ondansetron. In group II it was given to 36 (72%) patients, in group III to 23 (46%) patients, and 13 (26%) patients in group I. In the postanaesthetic care unit, 9 (18%) patients in group III, 6 (12%) patients in group I, and 3 (6%) patients in group II received ondansetron. Metoclopramide was given only to patients in group III — one intraoperatively, and the other in the recovery room.

Conclusions: Multimodal analgesia is effective in pain treatment. The use of PONV prevention is used for gynaecological patients. The analysis of the surgical records facilitated the recognition of patient needs.

Key words: pain; multimodal analgesia; PONV; surgical gynaecology; direct anaesthesia supervision

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INTRODUCTION

Gynaecology is the discipline of medical science dealing with the diagnosis and treatment of diseases of the female genital organs. It is a field of medicine where surgical procedures are a frequent element of diagnostics and therapy.

Therapeutic success in surgical gynaecology is conditioned by many factors, from the surgeon's skills and experience, to comprehensive postoperative care. The work of the nurse in a post-anaesthetic care unit is currently particularly challenging starting from diagnosing early postoperative complications and ensuring patient safety, through participation in pain treat-

Corresponding author:
Katarzyna Plagens-Rotman
Hipolit Cegielski State University of Applied Sciences, 38 Stefana Wyszyńskiego St, 62-200 Gniezno, Poland
phone: 61 4242942, e-mail: plagens.rotman@gmail.com

ment, postoperative nausea and vomiting, and unintentional perioperative hypothermia. In order to provide comprehensive patient care, the anaesthesia nurse should know and understand the course of the anaesthesia, as well as the impact of specific procedures and techniques on the human body, as these elements affect the level of postoperative risk and determine and facilitate the recognition of patient needs.

The aim of the study was to assess the effectiveness of multimodal analgesia on pain and vomiting in the immediate postoperative period. The second part of the study presents theeffects 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 at one of the clinical hospitals in Szczecin. The Directorate's consent to use the medical records was obtained before the material was collected. 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. Originally, the data collected concerned 193 patients. After a preliminary analysis, the patients who had undergone category II surgical procedures were excluded from the study. The remaining 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. Group I was also a control group.

For statistical analysis, Excel 2019, the Shapiro-Wilk test, Mann-Whitney-Wilcoxon test and Boschloo tests were applied, using the R environment for statistical computing.

RESULTS

The average age of the patients differed in each group. The highest age was in the third group at 57.48 years of age, 50.86 years in the second group, and 47.8 years in the first group (Fig. 1).

The lowest average body weight was found for group III at 65.88 kg. It was highest for group II at 71.9 kg, and for group I at 70.4 kg. Due to the administration of many medications, such as opioids, the body weight values were divided into three intervals: up to 50 kg, from 50 to 70 kg, and over 70 kg (Fig. 2).

Healthy patients classified as ASA 1 accounted for 14% of group I, 18% of group II and 10% of group III. Patients with severe systemic disease (ASA 3) constituted 30% of group III 18%, of group II and 8% of group I (Fig. 3).

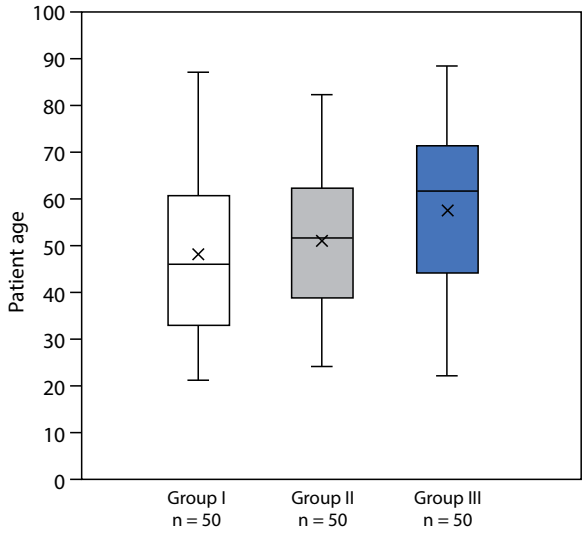

Figure 1. The distribution of patient age in particular groups

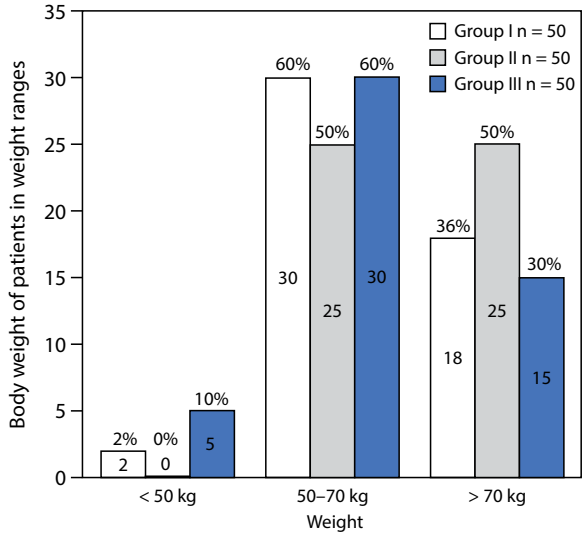

Figure 2. Body weight of patients from particular groups in weight ranges

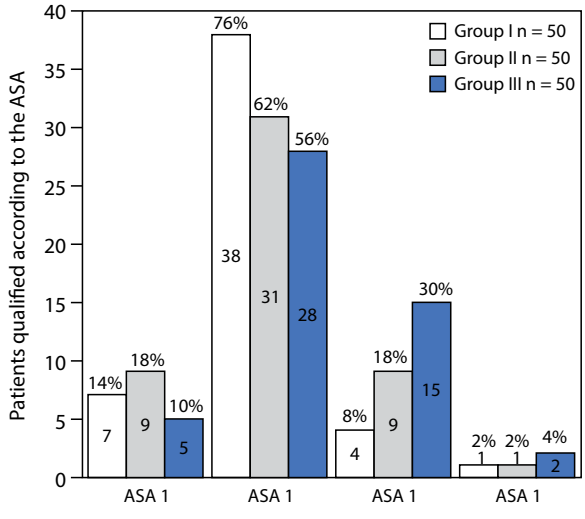

Figure 3. Patients qualified to the ASA scale

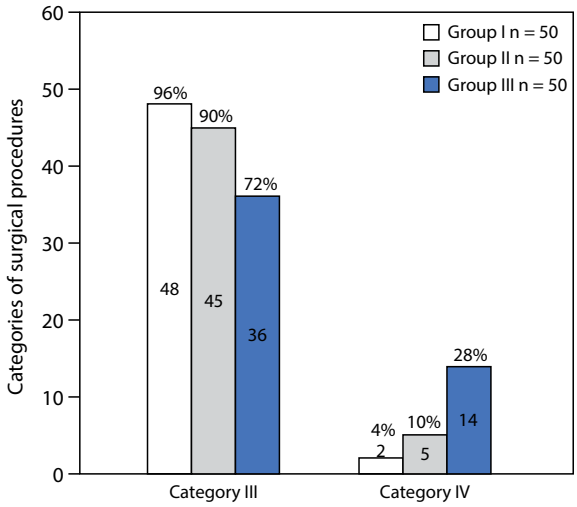

Figure 4. Categories of surgical procedures by the degree of damage

The length of the procedures was divided into four intervals: up to 1 hour, between 1–2 hours, between 2–4 hours, and over 4 hours. There were 7 (14%) procedures lasting up to 1 hour in group I, 10 (20%) in group II, and 3 (6%) in group III. More than half of the procedures lasted from one to two hours in groups I and II, which is 28 (56%) in group I and 26 (52%) in group II, and much less in group III — 16 (32%). The greatest number of procedures lasting from two to four hours were in group III — 22% (44%). In other groups their number was comparable — 12 (24%) in group I and 13 (26%) in group II. There were significantly more procedures lasting over 4 hours in group III — 18%, compared to group II — 2% and group I — 6%. Category III surgical procedures, associated with extensive tissue damage, were predominant in each group, 96% in group I, 90% in group II, and 72% in group III. Analogically, the greatest number of procedures associated with extensive tissue damage, *i.e.* category IV, was observed in group III — 28%, while in the remaining groups they constituted no more than 10%.

Category III surgical procedures, associated with extensive tissue damage, constituted 96% in group I, 90% in group II, and 72% in group III. Analogically, the largest number of procedures associated with extensive tissue damage, category IV, was in group III — 28%, while in the remaining groups they constituted no more than 10% (Fig 4).

The intraoperative doses of opioids administered during anaesthesia are presented in Table 1. If analgesia administered intraoperatively was insufficient, it was continued

Table 1. Intraoperative medications administered during anaesthesia

Doses of opioids administered during anaesthesia					
		GI (n = 50)	GII (n = 50)	GIII (n = 50)	
Fentanyl in mg					
Dose of fentanyl in mg	lack	0	0	3 (6%)	
	0.05–0.1	4 (8%)	11 (22%)	24 (48%)	
	0.1–0.2	8 (16 %)	1 (2%)	18 (36%)	
	0.2–0.3	28 (56%)	27 (54%)	3 (6%)	
	0.3–0.4	9 (18%)	11 (22%)	2 (4%)	
	0.4–0.5	1 (2%)	0	0	
Oxycodone in mg					
Dose of oxycodone in mg	lack	36 (72%)	29 (58%)	46 (92%)	
	0–2	1 (2%)	3 (6%)	3 (6%)	
	2–4	6 (12%)	11 (22%)	1 (2%)	
	4–6	7 (14%)	6 (12%)	0	
	6–8	0	1 (2%)	0	
	8–10	0	0	0	
Morphine in mg					
Dose of morphine in mg	lack	46 (92%)	46 (92%)	48 (96%)	
	0–2	0	0	0	
	2–4	2 (4%)	1 (2%)	1 (2%)	
	4–6	2 (4%)	2 (4%)	0	
	6–8	0	0	0	
	8–10	0	1 (2%)	1 (2%)	

Table 2. Doses of opioids given in the recovery room to patients with low postoperative pain rated as 0–4 on the NRS scale

Doses of opioids administered during anaesthesia					
		G I (n = 50)	GII (n = 50)	GIII (n = 50)	p
Fentanyl in mg					
Oxycodone in mg					
Dose of oxycodone in mg	lack	20 (40%)	23 (46%)	33 (66%)	G1 0.00207 GII 0.000635 GIII 0.0000219
	0–2	3 (6%)	1 (2%)	2 (4%)	
	2–4	4 (8%)	11 (22%)	6 (12%)	
	4–6	11 (22%)	11 (22%)	6 (12%)	
	6–8	10 (20%)	3 (6%)	2 (4%)	
	8–10	1 (2%)	0	0	
Morphine in mg					
Dose of morphine in mg	lack	46 (92%)	46 (92%)	41 (82%)	G1 vs G2 0.3661352 G1 vs GIII 0.00009917 GII vs GIII 0.00000194219
	0–2	1 (2%)	0	1 (2%)	
	2–4	3 (6%)	1 (2%)	2 (4%)	
	4–6	0	2 (4%)	2 (4%)	
	6–8	0	0	4 (8%)	
	8–10	0	0	0	

in the postanaesthetic care unit. In group I, 20 patients (40%), in group II — 23 patients (46%), and in group III — 33 (66%) did not require oxycodone. Since the continuation of analgesic treatment is associated with increased doses of opioids, the doses of morphine and oxycodone given in the operating room and the postanaesthetic care unit were added together. In groups I and II, the number of patients not requiring oxycodone was similar — 16 (32%) in group I and 14 (28%) in group II, while in group III it was more than twice as high — 33 (66%) patients (Tab. 2).

Since the length of the patients' stay in the postanaesthetic care unit varied, pain intensity on awakening and the maximum level of pain recorded in the recovery room were compared. When leaving the recovery room, none of the women rated their pain as higher than 2, according to the NRS scale.

On leaving the operating room, as many as 80% of the patients from groups II and III did not feel any pain. In group I it was 52% (Fig. 5 and 7). When entering the recovery room, 26% of the patients in group I, 10% in group III, and 8% in group II rated their pain as higher than 5 (p = 0.06153).

In the recovery room paracetamol was administered to 7 patients in group III, 2 patients in group I, and 1 patient in group II. After leaving the operating room, 18% of the patients in group III, 10% in group I, and 8% in group II received metamizole. The detailed distribution of administered medications is presented in Figure 6.

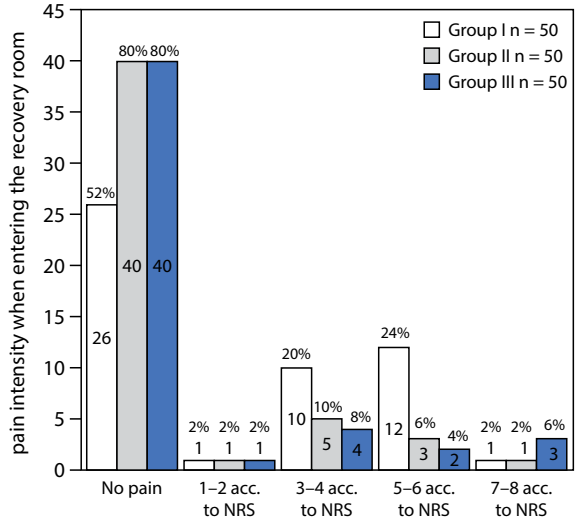

Figure 5. Pain intensity on awakening

Other anesthetic drugs given during anesthesia

The most used antiemetic medication in the studied facility was ondansetron. In group II it was given to 36 (72%), in group III to 23 (46%), and in group I to 13 (26%) patients. In the postanaesthetic care unit, 9 (18%) patients in group III, 6 (12%) patients in group I, and 3 (6%) patients in group II received ondansetron (Fig. 8 and 9). Metoclopramide was

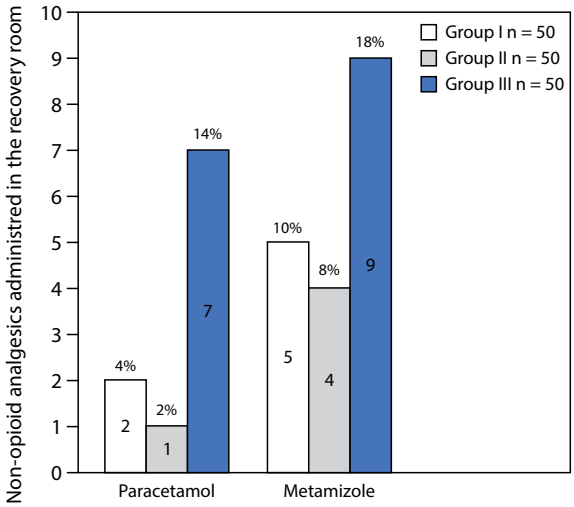

Figure 6. Non-opioid analgesics administered in the post-anaesthetic care unit

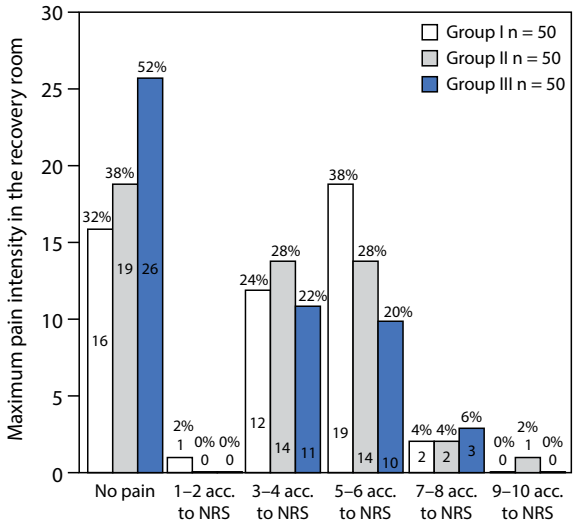

Figure 7. Maximum pain intensity in the recovery room (NRS scale)

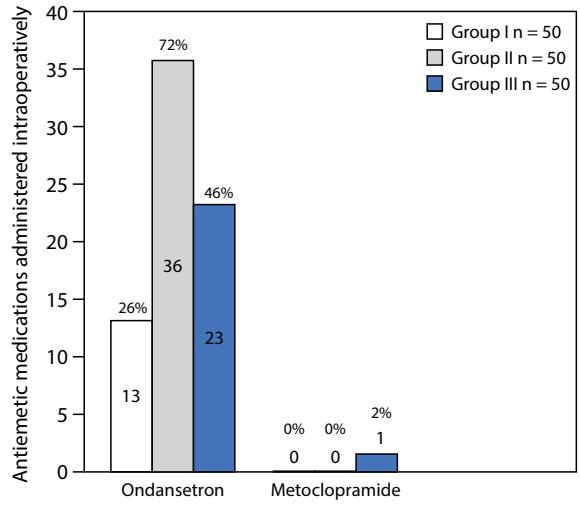

Figure 8. Antiemetic medications administered intraoperatively

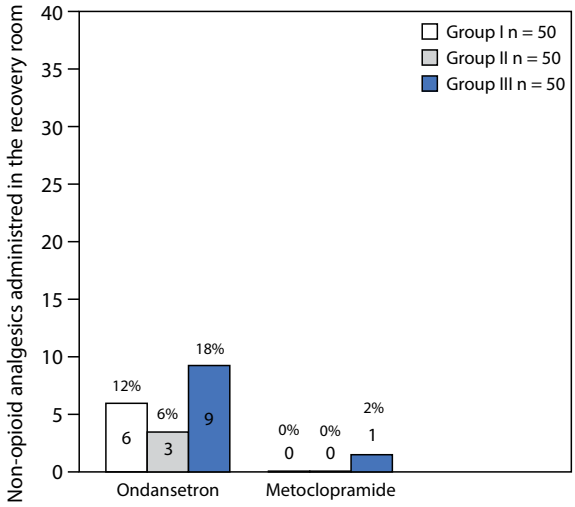

Figure 9. Antiemetic medications the recovery room

given only to patients in group III — one intraoperatively, and the other in the recovery room (p = 0.03503).

DISCUSSION

The ERAS protocol, first outlined by Danish surgeon Henrik Kehlet in the 1990s, assumes that the development of postoperative 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 postoperative 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.

The results of the conducted analysis varied greatly between the groups. One differentiating factor was the age of the patients. In each group, the age of the patients ranged from 20 to more than 80 years, yet in group III more than half of the patients were older than 60 years of age. This relates to surgical risk, as in group III 34% of the patients were classified as ASA 3 and 4. This is three times more than in group I, where such patients accounted for 10%. The length of the surgical procedure also varied greatly in the groups. In groups I and II, the highest number of procedures lasting up to two hours — about 70–72% was recorded. In group III, it is the exact opposite. 62% of surgeries lasted over two hours. This also translates into the category of damage. Category IV procedures, with extensive tissue damage, concerned 28% of the patients from group III, 10% of the patients from group II, and 4% of the patients from group I. The conducted analysis confirms that older patients were in a worse physical

condition. According to the Central Statistical Office (GUS) in Poland, 88.3% of people aged 80 years or over and 77.1% of people aged 70 years complain about chronic diseases [1]. This translates into higher surgical risk and extensive surgical procedures, mainly due to oncological reasons.

Analysis of the doses of fentanyl during surgery shows that the doses in group III where neuraxial anaesthesia was applied were different than in groups I and II. A single bolus administration (1–3 μg/kg) is short acting, *i.e.* 0.1–0.2 mg usually works for less than an hour. At high doses (> 20 μg/kg), however, the end of action depends on slow elimination processes and fentanyl becomes a long-acting drug [2]. Additionally, in elderly people, the dose is reduced with age: from 65 to 74 years of age by 20%, from 75 to 85 years of age by 50%, over 85 years of age by 60% [3]. The analysis of the medical charts showed that in group III 90% of the patients received a dose of fentanyl not greater than 0.2 mg. In groups I and II, 76% of the patients received a dose higher than 0.2 mg with relatively shorter surgical procedures.

During surgical procedures other opioids were also administered in advance in the studied groups: oxycodone and morphine. Oxycodone was administered to 28% of the patients in group I, 42% in group II, and 8% in group III. 8% of the patients in groups I and II, and 4% of the patients in group III received morphine. In the post-anaesthetic care unit, oxycodone was administered to 60% of the patients in group I, 54% in group II, and 34% in group III. In the recovery room, morphine was administered to 18% of the patients in group I, and to 8% from groups II and III. When analysing the data, it can be concluded that oxycodone was used much more freely than morphine. This is justified in the case of oxycodone, as compared to other opioids the adverse effects, particularly symptoms from the central nervous system, nausea and vomiting, are much less frequent [4, 5], the lessening of which is important, especially in gynaecological patients. Moreover, oxycodone is more effective than morphine in the treatment of visceral pain. It also has a slightly different tolerance profile — smaller blood pressure drops and a lesser sedative effect than morphine, which is beneficial especially in obese patients [6]. Besides, the analysis showed that in groups without neuraxial anaesthesia, the use of opioids was more frequent, and the doses were higher. The statistical analysis showed, similarly to fentanyl, that the distribution of morphine and oxycodone doses were different among patients rating their pain no higher than 4 on the NRS scale. The concentration of values at zero was greatest in group III, where the largest number of patients where neuraxial anaesthesia was applied did not require opioids in the recovery room. The analgesic efficacy of neuraxial anaesthesia is greatly beneficial in terms of reducing opioid doses, especially in older people.

Pain management through the use of neuraxial anaesthesia is recommended by the Section of Regional Anaesthesia and Pain Therapy of the Polish Society of Anaesthesiology and Intensive Therapy, the Polish Society of Regional Anaesthesia and Pain Therapy, the Polish Association for the Study of Pain and the National Consultant in Anaesthesiology and Intensive Therapy from 2018, where neuraxial anaesthesia is recommended in postoperative analgesia after open chest and abdomen procedures, particularly in patients at risk of cardiac and pulmonary complications, or prolonged intestinal atonia with the risk of obstruction [7, 8].

Metamizole and paracetamol are standard painkillers used in accordance with the recommendations for treatment of postoperative pain, as well as with the WHO analgesic ladder. The analysis showed that paracetamol was used in the perioperative period for 96% of the patients in group I, 90% in group II, and 82% in group III. Metamizole was administered to 90% of the patients from group II, and 76% of the patients from groups I and III.

Metamizole is an extraordinarily strong analgesic and antipyretic medication that has been used worldwide for 98 years. Its efficacy was confirmed in the German university centre in Ulm, where randomised double-blind trials were conducted in which patients after abdominal surgery, mainly laparoscopic cholecystectomies, were given 1 g of metamizole or a placebo every six hours. In the control group, analgesia with buprenorphine was applied. Parallel administration of metamizole reduced the use of opioid to 1/3 of the control group dose [9].

Paracetamol, like metamizole, has both analgesic and antipyretic effects. Because of its intravenous form, it can be used in patients after surgical procedures. Fijałkowska A. et al. confirms the usefulness of paracetamol after gynaecological, particularly laparoscopic procedures. After laparotomy, administration of paracetamol requires multimodal management for the first 12 postoperative hours [10].

In multimodal pain therapy, positive effects are also achieved by associating paracetamol and metamizole with opioids. Administration of paracetamol with morphine results in an additional analgesic effect. Such a combination allows a reduction in dose of both analgesics, yet the dose of paracetamol necessary to achieve the satisfactory analgesic effect remains high [11].

The treatment of postoperative pain is multidimensional and should be as effective as possible with the minimal possible side effects. The conducted analysis shows that the highest effectiveness was achieved in group III. More than 50% of the patients did not feel pain in the recovery room. For groups II and I the number was over 30%. Maximum pain levels recorded in the recovery room of 1 to 4 on the NRS scale were reported by over 20% of the patients. A minimum pain level of 5 or higher was rat-

ed by 40% of the patients in group I, 34% in group II, and 26% in group III. To enable the patients to leave the recovery room with a reported pain level no higher than 2, opioids were most commonly used. The doses of morphine or oxycodone per kg body weight were compared. The results show different dosing distributions for groups I and II, as well as for groups I and III. The concentration of values at zero was the highest in group III, which means that most patients from this group did not require the administration of opioids.

Prevention of postoperative vomiting and nausea is another essential component of quality comprehensive perioperative care. Propofol, recommended for the induction of anaesthesia to prevent PONV, was used for all patients in groups I and II. In group III, 6% received etomidate as a result of their cardiovascular diseases, and 10% did not require propofol as the standard anaesthesia was sufficient. Halogen-containing anaesthetics were used in all patients under general anaesthesia — this risk factor was not reduced. Nitrous oxide was not used.

In multimodal therapies, doses of opioids are minimised by the use different types of analgesics. Neostigmine was given to 62% of the patients in groups I and II, and 38% of the patients in group III. Sugammadex is not routinely used due to its high price and was administered to less than 20% of the patients in groups I and II, and 10% of the patients in group III. As far as PONV-preventing medications are concerned, dexamethasone was used only in group II, in which coanalgesics were added to the multimodal analgesia methods for 88% of those patients. Ondansetron was most frequently used in group II — 72% of the patients received it intraoperatively. In group III, it was given to 46% of the patients, and in group I — 26%. Postoperative nausea and vomiting occurred in less than 20% of the patients in all groups, in just 4% of the patients in group II, 12% in group I, and 16% in group III.

The relationship between the administration of antiemetic medications (dexamethasone and ondansetron) to PONV was studied. The results confirm the efficacy of the intraoperative use of dexamethasone and ondansetron for PONV prevention and are consistent with Paxton et al. who studied 118 patients after gynaecological laparoscopy, comparing the prophylactic effects of ondansetron, DHBP and metoclopramide. Ondansetron was most effective in the first 4 hours after surgery [12]. Similar results were obtained by Świątkowski et al. in a study of 126 patients in four randomly selected groups. The control group consisted of patients that did not receive the studied medications. Ondansetron (4 mg), dehydrobenzperidol (DHBP) (75 mg kg–1) or metoclopramide (0.4 mg kg–1) were administered intravenously immediately after the induction of general anaesthesia. Ondansetron and DHBP caused a statistically significant increase in the number of PONV-free patients and a decrease in intensity and frequency of PONV symptoms in the first 6 hours after surgery, compared to the control group. No significant differences in prophylactic efficacy of either medication were observed [13].

The effectiveness of dexamethasone in PONV prevention has been confirmed in many scientific studies. De Oliveira GS Jr. et al. [14], in an updated meta-analysis of randomised controlled trials, confirm that a dose of dexamethasone from 4 to 5 mg has a similar clinical effect in PONV prevention as a dose from 8 to 10 mg, irrespective of whether the medication is used individually or in combination therapy.

RESULTS

1. Multimodal analgesia is effective in pain treatment.
2. The use of PONV prevention is used for gynaecological patients.
3. The analysis of the surgical records facilitated the recognition of patient needs.

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Analysis of background parenchymal enhancement (BPE) on contrast enhanced spectral mammography compared with magnetic resonance imaging

Elzbieta Luczynska[1], Marta Pawlak[2], Tomasz Piegza[2], Tadeusz J. Popiela[3], Sylwia Heinze[2], Sonia Dyczek[4], Wojciech Rudnicki[5]

[1]*University of Rzeszow, Faculty of Medicine, Rzeszow, Poland*
[2]*Maria Sklodowska-Curie National Research Institute of Oncology in Cracow, Poland*
[3]*Chair of Radiology, Jagiellonian University Medical College, Cracow, Poland*
[4]*University Hospital in Cracow, Poland*
[5]*Jagiellonian University Medical College, Cracow, Poland*

ABSTRACT

Objectives: With the growing number of new breast cancer cases in women, new methods of imaging arise. Contrast enhanced spectral mammography (CESM) and magnetic resonance imaging (MRI) are comparable methods regarding sensitivity. The aim of this study is to check if analysis of background parenchymal enhancement on CESM can improve its usefulness.

Material and methods: A total of 64 patients with breast lesions found previously on ultrasound or mammography underwent MRI and CESM within less than one month. On MRI the contrast enhancement kinetics and visual BPE were evaluated. On CESM the enhancement of lesions was noted as well as a quantitative level of BPH. The gathered data was analysed in terms of patterns and relations.

Results: A total of 66 lesions were identified both on MRI and CESM, including 11 (17%) benign and 55 (83%) malignant lesions. Among malignant lesions 13 (20%) were assessed as intraductal and 42 (64%) as infiltrating carcinomas. The study showed correlation between the level of enhancement on CESM and the type of kinetic curve on MRI and lesion enhancement on CESM as well as confirmed the fact that the BPE is a destimulant in both methods of imaging.

Conclusions: Evaluation of BPE level on CESM can help reading radiologists to define a lesion as malignant with higher probability than based only on the qualitative lesion enhancement level.

Key words: breast cancer; mri; cesm; diagnostic imaging; breast; cancer; mammography

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INTRODUCTION

Nowadays, breast cancer is the most frequent type of cancer in women in the European Union countries (29.2% of all cancers) [1]. Early detection of cancer significantly increases the chance for cure [2]. Therefore, at the time of fast developing technology, basic imaging methods such as ultrasonography and mammography were complemented by MRI (magnetic resonance imaging) and more recently by CESM (contrast enhanced spectral mammography), accepted by FDA in 2011.

Both methods are stated to have comparable sensitivity and specificity described in numerous studies, which enables more diagnostic possibilities in a bigger number of patients. Above examinations can be applied interchangeably in cases when the patients report contraindications to any of them [3–5]. This fact emphasises the need of exploring all the aspects of every new method, including CESM.

Breast parenchymal enhancement (BPE) is a feature routinely evaluated on MRI [6]. MRI reports include one of four BPE values measured qualitatively: minimal, mild, moderate, marked and symmetry of enhancement in both breasts. A correlation between BPE on MRI and breast cancer risk was found. The stronger the enhancement, the higher the risk [7]. What is more, lesion evaluation on the background of strongly marked BPE is much more difficult for a radiologist describing the findings.

Similarity of this imaging method to CESM leads to the assumption that this parameter should be also measurable

Corresponding author:
Wojciech Rudnicki
The University Hospital in Krakow, 36 Kopernika St, 31–501 Cracow, Poland
e-mail: wrudnicki@cmuj.pl

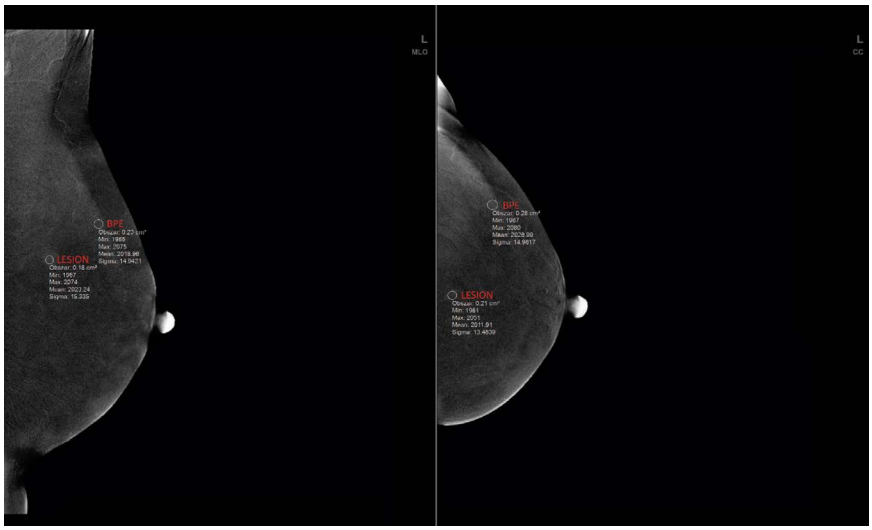

Figure 1. Measurement of BPE value and lesion enhancement using an ellipse shaped Region of Interest (ROI) on contrast enhanced spectral mammography (CESM) from Figure 2

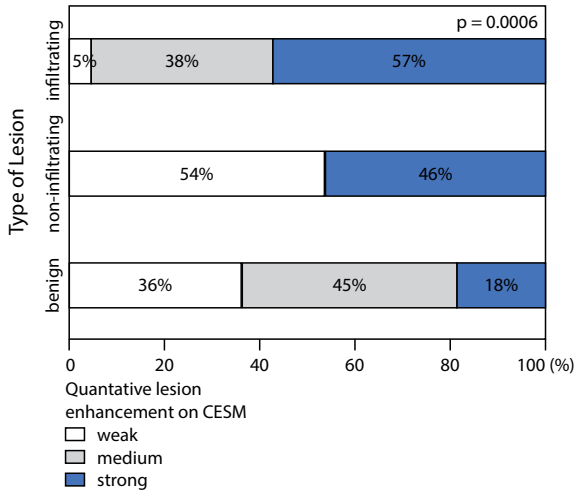

Figure 2. Relation between qualitative lesion enhancement on contrast enhanced spectral mammography (CESM) and histopathological result

on CESM. So far, the studies analysed BPE only in terms of finding if its value can determine the risk of breast cancer [8, 9]. The outcomes of these analyses indicate that the parameter should be taken into consideration in the final assessment of examination. Up to now BPE on CESM has not been compared to BPE on MRI in the same patients. The aim of our study is to determine the usefulness of BPE evaluation on CESM. We also checked if it allows radiologists to assess lesions and exclude the probability of neoplastic process with greater certainty.

This study was performed in compliance with the Declaration of Helsinki and it received the approval of the Ethical Committee at the Regional Medical Chamber (acceptance No. OIL/KBL/17/2018).

MATERIAL AND METHODS

Both examinations, CESM and MRI were performed on 84 patients in 2018. Patients suspicious of multifocality and multicentricity or in case of other diagnostic doubts such as heterogeneous or dense breast anatomy underwent CESM examination. MRI examination followed CESM if the diagnostic problem was still present or if histopathologic verification was necessary for lesions visible only after contrast administration. Within the observed group the enhancement visible on CESM was not confirmed on MRI in 5 cases. Another 6 patients were referred to chemotherapy due to extension of the disease process and receptor status and 7 patients underwent surgical procedure in another Oncology Clinic. As a result, the analysis comprises 64 patients who underwent breast CESM and MRI.

For CESM a protocol routinely used in the department was applied with GE Senographe Essential machine. Contrast medium administration was performed with an automatic syringe Optivantage DH. Dose of contrast media (iopromide a 370 mg/mL) was calculated following the formula 1.5 mL/kg of body weight. Patients without any known contradictions were given a bolus of contrast with a rate of 3 mL/s followed by a chaser of NaCl 0.9% solution. At that moment, a timer was started and after 2 minutes the first image acquisition was performed. A total of 4 exposures were performed in the following order: craniocaudal (CC) of the breast with smaller probability of cancer based on preliminary diagnostic imaging, CC of the more suspicious breast, mediolateral oblique (MLO) of first breast and then MLO of the second breast.

Lesion enhancement was evaluated on subtraction images and described qualitatively as weak, medium or strong as well as qualitatively using the Region of Interest (ROI) tool.

ROI is a part of the used SenoIris software and gives information of the minimum, maximum and average pixel brightness distribution within the shape of our choosing (oval was used in this study). Since there are only 2 time-points of contrast kinetics measured, there is no possibility to assess a kinetic curve like in breast MRI.

BPE on CESM was measured with the ROI with an oval shape in the most homogenous part of parenchyma both in CC and MLO views of the breast with the suspicious lesion (Fig. 1). Afterwards, the values were divided into 4 equal ranges and described as minimal, mild, moderate and marked to adapt the scale to the one used in MRI (ACR BI-RADS standards for reporting).

In order to compare BPE on CESM and MRI qualitative assessment was performed based on enhancement values measured with ROI. For every patient mean BPE was calculated for CC and MLO views. The obtained results ranged from 2000.7 to 2067.1. As a next step, the enhancement values were divided into four scopes, following the BI-RADS standards for BPE evaluation on MRI: minimal ranging from 2000.7–2017.3, mild — 2017.4–2033.9, moderate — 2034.0––2050.5, marked — 2050.6–2067.1.

MRI examination was performed using Siemens Avanto 1,5T machine. Patients without any known contradictions were qualified for the examination. There was a strict time requirement of menstrual cycle for the patients to be scheduled for the examination – the day of the procedure was within 5–12 day of the cycle. If the patient underwent hysterectomy, they had their progesterone level evaluated before the exam. Only patients with the progesterone level within follicular phase of the menstrual cycle were qualified for the study. The protocol used included T1WI, T2WI — with and without Fat Suppression (FATSAT), Diffusion Weighted Images (DWI), and dynamic T1-weighted 3D sequence after contrast media administration. Contrast medium (gadobutrolum a 0.60472 g/mL) was injected using Optistar Elite automatic syringe. The amount of contrast was calculated according to 0.1 mL/kg of body weight formula.

Lesion kinetic curve assessment was performed afterwards using Siemens syngo® software and described as persistent, plateau or wash-out.

Histopathological examination

All lesions were histopathologically verified. Following biopsy, methods were used to obtain lesion samples: core-needle biopsy, vacuum assisted breast biopsy, stereotactic biopsy guided on MG/MRI or lumpectomy. Standard hematoxylin and eosin staining was followed by histopathological examination by pathologists experienced in breast diseases.

Histopathological examination confirmed the presence of one focal lesion in all 66 patients on both CESM and MRI. Among all diagnosed lesions 55 (83%) were malignant including 42 (64%) infiltrating lesions, and 13 (20%) non-infiltrating lesions. The remaining 11 (17%) lesions were benign.

Statistical methods

Statistica software and following statistical methods were used for calculations:

- chi-squared dependence test to compare lesion enhancement on CESM and its histopathological character; BPE parameter assessment both on CESM and MRI in terms of its histopathological type; assess the influence of BPE on MRI on enhancement curve type on MRI
- ROC analysis to check if quantitative lesion enhancement on CESM and lesion enhancement curve type on MRI depends on histologically determined cancer stage
- Kruskal-Wallis test ANOVA to assess the relation between ratio of quantitative BPE value on CESM to quantitative lesion CESM enhancement and qualitative lesion enhancement on CESM; assess the relation between qualitative BPE on CESM and BPE on MRI; compare the quantitative BP enhancement indicator on CESM and quantitative lesion enhancement on CESM to BPE on MRI
- Mann-Whitney U test to compare the quantitative BP enhancement indicator on CESM and quantitative lesion enhancement on CESM to lesion enhancement curve on MRI

RESULTS

CESM qualitative enhancement of the lesion

Based on CESM results, weak enhancement was determined for 12 (18%) lesions, medium for 21 (32%), and strong for 33 (50%). Strong enhancement was more frequent among malignant lesions than benign (56% vs 18%). This relation was statistically significant (proportion test p=0.02). However, the number of benign cases classified with strong enhancement was only two. The relation between lesion type (malignant and benign) and enhancement level was not statistically significant (chi-squared dependence test p = 0.054).

Lesion enhancement level depends on lesion type only if the classification of the lesions is extremely specific, *i.e.* infiltrating and non-infiltrating benign lesions (chi-squared dependence test p = 0.0006). The higher the level of malignancy, the more often the enhancement visible on CESM was described as strong. Consequently, the more benign the lesion was, the more often the enhancement was described as weak on CESM. This is shown in Figure 2.

There was also a significant difference between median value of quantitative lesion enhancement on CESM and histopathological result (U Manna-Whitney test p = 0.03) and lesion type (Kruskal-Wallis test p = 0.05). Figure 3 shows that there has been a gradual increase in the median value of lesion enhancement on CESM with rising the degree of

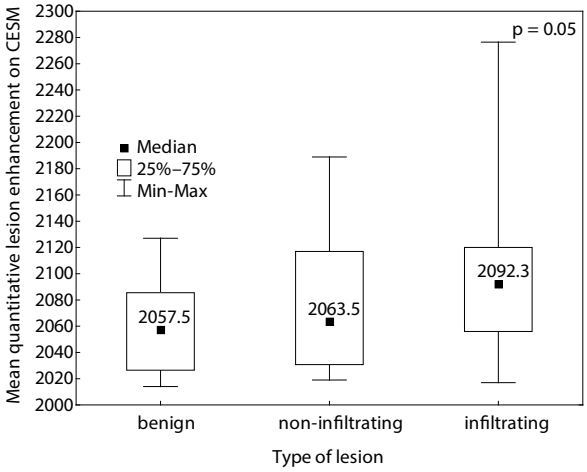

Figure 3. Relation between qualitative lesion enhancement on contrast enhanced spectral mammography (CESM) and histopathological result

Table 1. AUC, p and threshold values for calculation of lesion enhancement and BPE

Parameter on CESM	AUC	p	Treshold value
Qualitative lesion enhancement	0.711	0.0110	Strong
Quantitive lesion enhancement	0.712	0.0077	2091.5
BPE quantitive*	0.582	0.3398	2018.86
BPE qualitive*	0.569	0.4191	minimum
Ratio/indicator*	0.746	0.0004	97.3

* destimulant; AUC — area under curve; CESM — contrast enhanced spectral mammography; BPE — background parenchymal enhancement

malignancy of the lesion. Therefore, the result for comparison of qualitative and quantitative lesion enhancement on CESM with lesion type is comparable.

As a next step quantitative BPE value on CESM was compared. In the analysed material, median value of BPE on CESM was 2030.11 — minimum 2000.7, maximum 2067.1. BPE value was neither related to the type of lesion nor to its malignancy as shown in Figure 4A and 4B.

The enhancement values on CESM were analysed with ROC to determine whether the lesions could be described as malignant on their basis and what range of values would be adequate. Based on quantitative and qualitative enhancement it was possible to determine the lesion's malignancy ($p < 0.01$ AUC). The malignancy can be determined based on percentage ratio of BPE value on CESM to lesion CESM enhancement ($p = 0.0004$). The described ratio/indicator is incredibly useful in differentiating between benign and malignant lesions — AUC [(area under curve) is the biggest, p is the lowest and the estimated sensitivity, specificity and accuracy based on threshold value are the highest. This ratio/indicator is a distimulant, which means that the lower its value, the higher the malignancy of the lesion. The results of analysis showed that for values smaller or equal 97.3% lesions can be described as malignant. All values are shown in Table 1.

The results show that the variable is a destimulant, which means that the lower its value, the higher the malignancy of the lesion. Further step involved determining whether quantitative lesion enhancement value on CESM depends on qualitative BPE on CESM. This relation is presented in Figure 5.

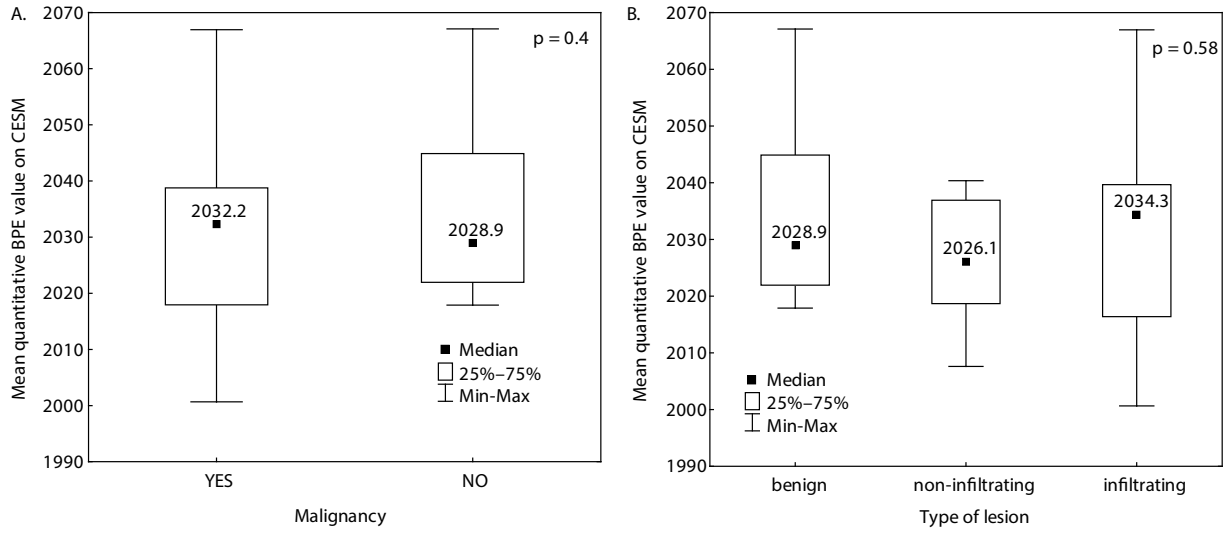

Figure 4. Relation between mean quantitative background parenchymal enhancement (BPE) value on contrast enhanced spectral mammography (CESM) and malignancy (**A**) and type of lesion (**B**)

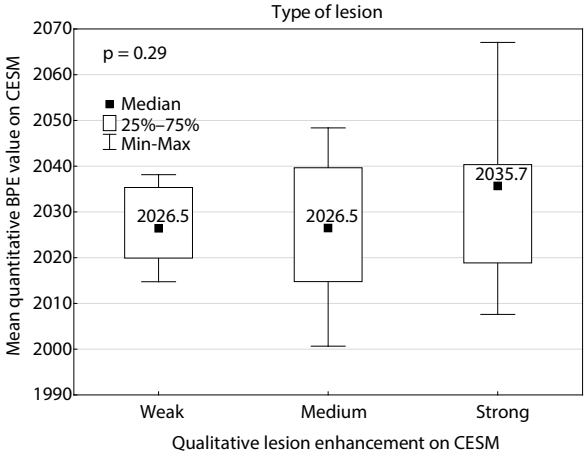

Figure 5. Relation between mean quantitative background parenchymal enhancement (BPE) value on contrast enhanced spectral mammography (CESM) and qualitative lesion enhancement on CESM

There is a strong correlation between BPE qualitative enhancement on CESM and lesion qualitative enhancement on CESM ratio and qualitative enhancement (Kruskal Wallis test ANOVA $p < 0.001$). The smaller the share - the ratio value — the stronger enhancement on CESM. Additionally, the rank correlation between mean enhancement on CESM and mean BPE enhancement was evaluated ($p = 0.01$). Correlation coefficient was 0.31.

MRI qualitative BPE and lesion enhancement

BPE was determined as minimum on MRI in 16 (24%) cases, mild in 33 (50%) cases, moderate in 13 (19%) cases and marked in 4 (6%) cases. Both BPE on CESM and BPE on MRI do not reveal malignancy of the detected lesion neither imply the particular type of lesion (chi-squared dependence test $p = 0.93$ and 0.99 respectively). Taking p into account, enhancement and lesion type are not related to parenchymal enhancement.

It was analysed to which extent curve type on MRI and level of BP enhancement could be applied to determine lesion malignancy. Based on the curve type on MRI it is possible to decide if the lesion is malignant (ROC analysis $p < 0.001$), *i.e.* reference level type III (wash-out). Parenchymal enhancement level on MRI, similarly to BPE on CESM does not allow to determine malignancy ($p = 0.69$). This variable is also destimulant. This is shown in Table 2.

Material analysis revealed a lack of correlation between curve type on MRI and BPE on MRI (chi-squared dependence test $p = 0.68$). Type II of kinetic curve in lesion was seen in patients with PBE on MR described as: minimal in 31%, mild in 50%, moderate in 15%, marked in 4% of total cases. Type III was seen in lesion with BPE described as: minimal in 20%, mild in 50% moderate in 23%, marked in 7% of cases.

It was also proved that mean qualitative BPE on CESM is not related to BPE level on MRI (Kruskal Wallis test ANOVA $p = 0.06$). Figure 6 shows the values.

Table 2. AUC parameter, p and threshold value for calculations of MRI kinetic curve and BPE in MRI

Parameter	AUC	p	Treshold value
Qualitative enhancement	0.864	0.0000	Type III
Quantitative enhancement	0.538	0.6861	moderate

AUC — area under curve

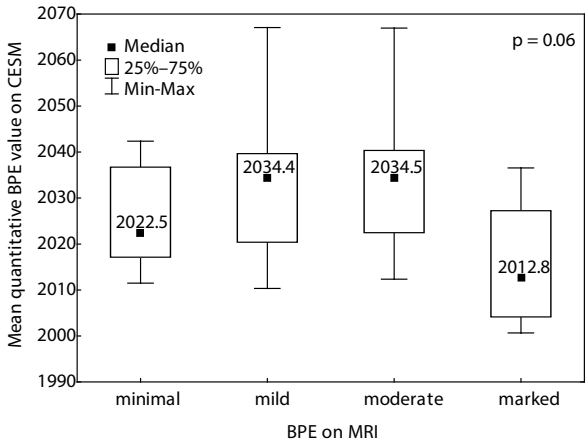

Figure 6. Relation between mean quantitative background parenchymal enhancement (BPE) value on contrast enhanced spectral mammography (CESM) and BPE on magnetic resonance imaging (MRI)

Comparison of BPE on CESM to mean enhancement ratio with the results of MRI examination shows that the ratio depends on curve type on MRI (U Mann-Whitney test $p = 0.0004$). The ratio is lower for lesions with determined curve type III on MRI but is not related to BPE level on MRI (Kruskal-Wallis test ANOVA $p = 0.63$). Figure 7a and 7b show the relations.

The analysis also revealed a lack of relation between qualitative BPE on MRI and CESM. The assessments of both methods were concordant in only 20 cases (30%) — *i.e.* that many cases were evaluated the same on both methods of examination. It is worth noting, that none of the cases determined as marked on CESM was determined as marked on MRI. The cases described as marked on MRI were characterised by the lowest BPE value.

DISCUSSION

The study revealed that analysis of BPE on CESM brings tangible results. It appeared that this feature is a destimulant both on MRI and CESM. It can be said that it creates noise which deteriorates the visibility of lesions in breast imaging examinations. Therefore, the assessment of this parameter allows reading radiologists to determine breast cancer probability with greater accuracy.

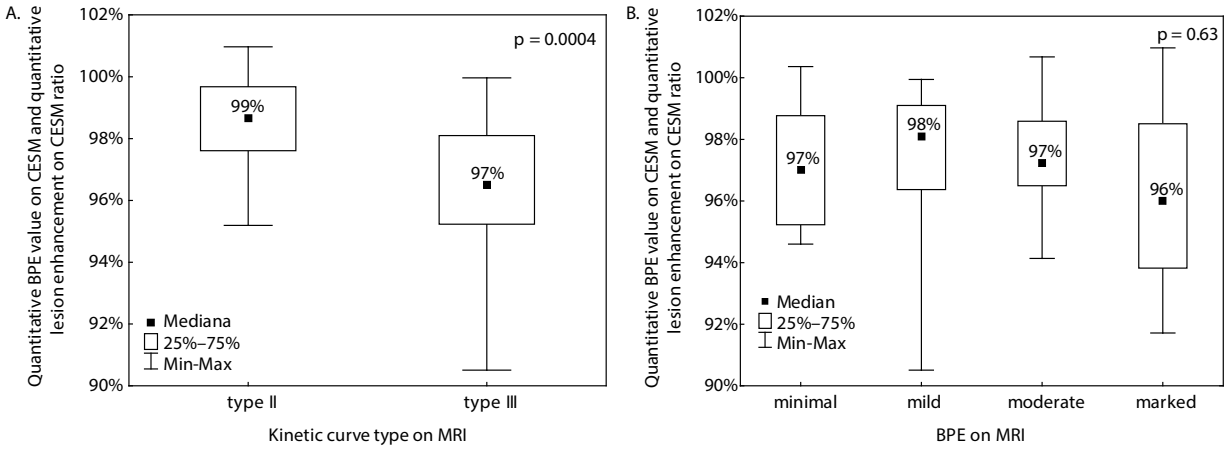

Figure 7. Relation between quantitative background parenchymal enhancement (BPE) value on contrast enhanced spectral mammography (CESM) and quantitative lesion enhancement on CESM ratio and lesion enhancement curve type II and III on magnetic resonance imaging (MRI) (**A**) BPE on MRI (**B**)

Our findings are not consistent with the results of previous study [10], where BPE did not affect lesion detection efficacy on CESM. It is important to emphasise that in our study quantitative BP and lesions enhancement were evaluated for the first time, which could have influenced the discrepancy between the results. This issue requires further analysis.

Since mammography examination is two-dimensional, BPE is not reproduced on CESM in the same way as on MRI. That is the reason why quantitative assessment brings advantages and increases repeatability.

As a limitation of our study we should mention a lack of data on the menstruation cycle day of the patients admitted for CESM and carefully selected date of MRI examination. However, it results from the studies [3, 11] that the menstrual cycle does not influence BPE on CESM significantly and it does not fluctuate during the cycle. Another limitation is a small group of analysed patients. It stems from a retrospective form of conducted analysis and limited number of patients who underwent both examinations due to clinical indications before treatment.

CONCLUSIONS

Our study suggests that evaluation of BPE level on CESM can help radiologists to define a lesion as malignant with higher probability than based only on the qualitative lesion enhancement level and should be evaluated for each patient.

Conflicts of interest

The Authors declare that no conflicts of interest exist in terms of publication of this article.

Authors' contributions

E.L. developed and researched the concept, collected and performed the data analysis and edited the text. T.P and M.P. collected the data. S.H., T.J.P., S.D. contributed to the final version of the manuscript. W.R. edited text and supervised the study.

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Emotional disorders, marital adaptation and the moderating role of social support for couples under treatment for infertility

Diana Antonia Iordachescu[1], Corina Gica[2, 3], Elena Otilia Vladislav[1], Anca Maria Panaitescu[2, 3], Gheorghe Peltecu[2, 3], Mirona Elena Furtuna[3], Nicolae Gica[2, 3]

[1]*Faculty of Psychology and Educational Sciences, University of Bucharest, Romania*

[2]*Department of Obstetrics and Gynecology, "Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania*

[3]*Filantropia Clinical Hospital, Bucharest, Romania*

ABSTRACT

Objectives: Over the last few years, the impact of infertility on the psychological well-being of couples has been well recognised. Men and women with infertility experience stress, anxiety and depression and their relationship might be under pressure.

Material and methods: We conducted a non-experimental correlational descriptive study where transversal analysis using questionnaires and quantitative data was performed for 76 couples with diagnosed infertility under the care of various reproductive medicine clinics in Romania between 2018 to 2019. Participants were asked to fill, via internet or in person, a set of tests including data on socio-demographic and infertility characteristics along with five psychological tests: The Fertility Problem Inventory (FPI), State-Trait Anxiety Inventory, Beck's Depression Inventory (BDI), Dyadic Adjustment Scale and Interpersonal Support Evaluation List-12. The aim of the study was to explore how couples with infertility respond and adapt to this diagnosis and to assess the relationship between emotional disorders, marital adjustment and social support.

Results: Mean age of females was 34.2 and of males 36.7 and 38.2% of the couples were experiencing infertility for > 6 years. Women had worse scores on infertility-related distress (FPI) ($t = -4.35$, $p = 0.01$), on the BDI depression scale ($t = -5.43$, $p = 0.01$) and on anxiety scales ($t = -5.48$, $p = 0.01$). Participants with a longer duration of infertility scored significantly higher on infertility-related distress than those with more recent difficulties. Marital adjustment scores correlated negatively with emotional disorders. Both appraisal social support and belonging support moderated the relationship between state-anxiety and marital adjustment.

Conclusions: Infertility carries a significant psychological burden for the couple and the longer its duration, the higher the distress level. Women seem to be more vulnerable to its psychological consequences. Marital adjustment correlates negatively with the degree of emotional disorders. In couples with high levels of social support, the relationship between state-anxiety and marital adjustment was negatively correlated.

Key words: infertility; emotional disorder; marital adaptation; social support

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INTRODUCTION

Over the past few years, the impact of infertility on the psychological well-being of couples has been recognized and documented by researchers. There is no doubt that infertility is a complex and difficult experience for many couples. Data shows that there is a significant association between infertility and loss of self-esteem, guilt, frustration, anxiety, depression, and marital problems (particularly sexual problems) [1]. Among the emotional disorders of infertile couples, stress, depression and anxiety are predominant aspects. Infertile women are more likely to experience negative emotions rather than their male partners [2]. Infertility in women may be associated with diagnoses as endometriosis or ovarian tumors that carry their own burden on the patients' anxiety levels, and this affects the quality of life [3, 4]. To make things even more complicated, there is evidence that anxiety and depression further reduce the couple's ability to conceive a child [5]. Zhou et al. showed that for couples undergoing in vitro fertilization (IVF) treatment that experience higher level of stress, documented

Corresponding author:
Corina Gica
Department of Obstetrics and Gynecology, "Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania; Filantropia Clinical Hospital, Bucharest, Romania
e-mail: mat.corina@gmail.com

by increased levels of salivary alpha-amylase, women have a higher risk of pregnancy failure and men have lower sperm density, motility and viability [5, 6].

Depression is a common condition associated with infertility. Advanced maternal age, over 30 years, time of infertility, low education level and low social support represent the main risk factors for depression [7]. Thus, depression affects 34–54% of women and 23–32% of their male partners diagnosed with infertility [8]. Taking into consideration that, despite the good prognosis and the availability of treatment options for depression, it's been observed that the more likely is she to give up after a single treatment procedure, due to emotional imbalances [9].

Infertility can have major effects on a couple's life, including marital satisfaction, as well as having a remarkable role in family life and well-being [10]. A satisfying marital relationship is a significant predictor of general happiness and well-being, while poor quality of marital relationships is associated with many family and community problems [11, 12]. Taking these into account, infertility may be a turning point in a couple's life, leading to potential conflicts [13], and in some cases, even divorce [14, 15].

While most psychosocial studies have focused on investigating risk factors in infertile couples [16], there have been several studies that looked into the protective factors, such as the positive impact of social support and social interactions in men and women who face infertility [17]. Social support plays a key role in how an individual adapts when it comes to a present difficulty. It is generally perceived as an act of availability, which requires confidentiality and care [18]. Despite the stressful experience, those with significant social support will suffer less from the potentially harmful effects of that stressful event, thus facilitating adaptation [17].

There is a significant negative relationship between social support and stress associated with infertility [8]. Social support is one of the mechanisms of resilience against the challenges of infertility. This condition has an important role in reducing the negative effects of this medical problem and in improving self-control, increasing self-confidence and quality of life [19].

The aim of this study was to investigate how Romanian couples respond and adapt to infertility. We also assessed the associations between emotional disorders, marital adjustment and social support.

MATERIALS AND METHODS

Design

The current study was a non-experimental, quantitative with transversal analysis and data obtained with the use of questionnaires. It was designed as a descriptive, correlational study in which various hypothesis were tested.

Procedures and participants

The study was conducted between August 2018 and November 2019 and was approved by the Research Ethics Committee of the University of Bucharest. Couples under infertility treatment in various Romanian clinics were approached and asked for voluntary participation. Before completing the questionnaires, couples received information leaflets regarding the purpose of the study, data collection and storage methods. Couples signed an informed consent form. The research ethics principles were respected: the confidentiality of data and anonymity of the participants. The instruments used and work procedures were noninvasive and did not put the couples in any stressful or frustrating situations. Questionnaires were individually filled out, given directly or via the internet.

Instruments

Couples were asked to complete a general form including data on socio-demographic characteristics (age, marital status, level of education) and infertility related information (duration, infertility type, treatment, number of fertilizations, previous pregnancies, biological or adopted children). Furthermore, they completed the following scales:

a) The Fertility Problem Inventory (FPI) [20]. This is a widely used instrument to measure infertility-related stress and infertility-related beliefs; it includes 46 items and its score ranges from 46 to 276. The scale assesses five dimensions: social concern, sexual concern, relationship concern, rejection of childfree lifestyle and need of parenthood. The higher the score, the higher the infertility stress. For this study, Cronbach's alpha coefficients range from 0.70 to 0.84.

b) State-Trait Anxiety Inventory Form Y (STAI-Form Y) [21]. The STAI is a 40-item scale that uses a four-point Likert scale ranging from almost never to almost always. The STAI-S assesses the intensity of the current anxious feeling at that moment and the STAI-T indicates how the couples generally feel. The STAI has been adapted to Romania and has been found to have satisfactory psychometric properties. For this study, the Cronbach's alpha coefficient were 0.95-for STAI-S and, 0.89 for STAI-T.

c) Beck's Depression Inventory II (BDI-II) [22]. The BDI is a self-report rating inventory that consists of 21 items and measures different areas of depression symptomatology during the past few weeks. Each question consists of four possible responses ranging in intensity. BDI scoring ranges from 0 to 63 with a higher total score indicating more severe depressive symptoms. For this study, the Cronbach's alpha coefficient was 0.91.

d) Dyadic Adjustment Scale (DAS) [23]. DAS is used for evaluating marital satisfaction. DAS is a 32 items self-report

evaluation instrument that can be completed by one or both partners, and has four subscales: Dyadic consensus (13 items), Affective expression (5 items), Dyadic cohesion (4 items) and Dyadic satisfaction (10 items). This instrument has been validated and standardized in Romania. The Cronbach's alpha reliability analysis was applied to measure internal consistency: for this study it was α = 0.93. Also, Cronbach's alpha was applied for every subscale, ranging from α = 0.67 to α = 0.91.

e) Interpersonal Support Evaluation List-12 (ISEL-12) measures perceived social support [24]. The ISEL-12 can be scored by summing the items to create an overall social support score; three subscale scores representing appraisal, belonging, and tangible social support have also been proposed. For present study, Cronbach's alpha ranges from 0.63 to 0.77. IBM SPSS Statistics for Windows, version 25 was used as the data processing and analysis program [25]. All statistical tests with a p value < 0.05 were considered statistically significant.

RESULTS

Sample characteristics

The research sample consisted of 76 couples (n = 152 participants) with fertility problems. Table 1 describes the demographic and fertility characteristics of the infertile couples. Six participants (3.9%) consider that they have an excellent state of health, 47 participants (30.9%) very good, 88 participants (57.9%) considered that they have a good state of health, and 11 participants (7.2%) state that their state of health is reasonable.

Table 1. Demographic and fertility characteristics of the infertile couples (n = 152)

Age, years [mean]	76 couples n = 152	
	Female: m = 34.25 (SD = 0.489)	Male: m = 36.76 (SD = 0.511)
Education		
Elementary school	2%	
High school	9.2%	
Post-secondary school	5.3%	
Without bachelor's degree	5.9%	
Bachelor's degree	35.5%	
Postgraduate degree	42.1%	
Marital status		
Married	86.8%	
Live with a partner	13.2%	
Duration of infertility		
1–2 years	27%	
2–5 years	34.9%	
More than 6 years	38.2%	
FIV treatment		
Not yet	31.6%	
One treatment	27.6%	
Multiple treatment	40.8%	

Regarding the type of infertility, in 43 couples (56.5%) the infertility was classified as primary, and in 33 couples (43.5%) as secondary. Out of the couples with secondary infertility, 14 have one child, 6 have two children, and one couple had three children.

Some of the couples underwent certain medical or surgical interventions aiming to get pregnant. Seventeen patients (11.2%) had a surgical intervention for obstructed fallopian tubes, 22 patients (14.5%) required other medical intervention.

The Fertility Problem Inventory (FPI), State-Trait Anxiety Inventory (STAI) and Beck's Depression Inventory (BDI).

With the use of the T test for independent samples, there were statistically significant differences between women and men in the overall scores of FPI (t = –4.35, p = 0.01, the overall BDI depression scale (t = –5.43, p = 0.01) and on anxiety scale (t = –5.48, p = 0.01). Also, there were significant differences between the women and men, in terms of the subscales of the FPI test: "Social concern" (t = –4.74, p = 0.01), "Sexual concern" (t = –3.20, p = 0.02), "Relationship concern" (t = –2.49, p = 0.01), and "Need of parenthood" (t = –2.89, p = 0.01).

The size of the d-Cohen effect was calculated and showed the magnitude of the difference between the two groups. Thus, for both the distress scale and the depression and anxiety scales, the effect size parameters indicated medium and high effects (ranging from 0.40 to 0.89). Following the results, it can be stated that the differences are statistically and practically significant, so that women have higher scores on the scales of distress, anxiety and depression compared to men.

The results of the unifactorial variance analysis with ANOVA for FPI indicated that there were significant differences in infertility-related stress between couples experiencing different infertility time intervals [F (2,149) = 4.36, p = 0.014] (Tab. 2).

Bonferroni-type post-hoc analysis to reduce the risk of detecting false-positive results due to multiple analysis identified significant differences in the infertility distress score between couples experiencing a relatively short duration of infertility (1–2 years) and those who faced a relatively long duration of 3–5 years (difference between averages 0.05, p = 0.014, confidence interval of differences between

Table 2. Variance analysis between independent variable (duration of infertility) and psychopathology scales (n = 152)

Overall score of infertility-related distress (FPI)					
	Sum of Squares	Df	Mean Square	F	Sig.
Between Groups	0.074	2	0.037	4.358	.014
Within Groups	1.259	149	0.008		
Total	1.332	151			

Df — degree of freedom; F — Anova test; Sig — statistical significance

Table 3. Differences in the score on marital adjustment between couples depending on the cause of infertility

ANOVA						
		Sum of Squares	Df	Mean Square	F	Sig.
DAS-Affective expression	Between Groups	0.128	3	0.043	3.452	0.018
	Within Groups	1.825	148	0.012		
	Total	1.952	151			
	Within Groups	0.619	148	0.004		
	Total	0.631	151			

Df — degree of freedom; F — Anova test; Sig — statistical significance

Table 4. Post-hoc analysis regarding the differences between couples in cases of female infertility when compared to couples with male infertility

Bonferroni							
Dependent Variable	(I) Cause	(J) Cause	Mean Difference (I-J)	Std. Error	Sig.	95% Confidence Interval	
						Lower Bound	Upper Bound
DAS-Affective expression	Female	Male	0.06827*	0.02448	0.036	0.0028	0.1337
		Both	0.05543	0.02266	0.094	–0.0052	0.1160
		Unexplained	0.01377	0.02955	1.000	–0.0653	0.0928

Sig — statistical significance

averages of level 95% –0.101– –0.008). Therefore, couples experiencing a longer duration of infertility scored significantly higher on infertility-related distress than those with more recent difficulties.

Regarding the scores on the stress, depression and anxiety tests, statistical analysis revealed that there were no differences in the cause of infertility between the women and men participating in the study.

Dyadic Adjustment Scale (DAS)

We used the Pearson Correlation standard test for testing the correlation between marital adjustment and emotional disorders.

We found that the first subscale of DAS, "Couple consensus" correlated negatively with the overall score of infertility-related distress ($r = 0.310$, $p < 0.01$), with depression ($r = 0.228$, $p < 0.01$), with state-anxiety ($r = 0.378$, $p < 0.01$) and with trait-anxiety ($r = 0.287$, $p < 0.01$). The second subscale, "Couple satisfaction" correlated negatively with the overall score of infertility-related distress ($r = 0.359$, $p < 0.01$), with depression ($r = 0.298$, $p < 0.01$), with state-anxiety ($r = 0.406$, $p < 0.01$) and with trait-anxiety ($r = 0.382$, $p < 0.01$). The third subscale, "Affective expression" correlated negatively with the overall score of infertility-related distress ($r = 0.267$, $p < 0.01$), with depression ($r = 0.301$, $p < 0.01$), with state-anxiety ($r = 0.417$, $p < 0.01$) and with trait-anxiety ($r = 0.341$, $p < 0.01$). The finale subscale, "Couple cohesion" correlated negatively with depression ($r = 0.235$, $p < 0.01$), with state-anxiety ($r = 0.181$, $p < 0.05$) and with trait-anxiety ($r = 0.195$, $p < 0.05$). The overall scale of marital adjustment correlated negatively with the overall score of infertility-related distress ($r = 0.330$, $p < 0.01$), with depression ($r = 0.307$, $p < 0.01$), with state-anxiety ($r = 0.411$, $p < 0.01$) and with trait-anxiety ($r = 0.357$, $p < 0.01$).

As for the marital adaptation, there were differences between couples depending on the cause of infertility, but only regarding the subscale "Affective expression" (Tab. 3).

Post-hoc analysis demonstrated that there were significant differences between couples with female infertility when compared to couples with male infertility. Therefore, couples in which the woman faces infertility had a higher affective expression of marital adjustment compared to those in which the man was infertile (Tab. 4).

Interpersonal Support Evaluation List-12 (ISEL-12)

A series of models of moderation on the relationship between marital adjustment and emotional disorders by social support were tested. State-anxiety (independent variable) and social support (appraisal, belonging, and tangible-moderating variables) were standardized in z-scores, generating the interaction variable by multiplying them. Only two models were significant, namely moderators: appraisal social support and belonging support, in moderating the relationship between state-anxiety and marital adjustment.

For the first model, a hierarchical regression was performed compared to marital adjustment, with appraisal social support and state-anxiety in block 1, and the interaction variable in block 2. The R2 change value for the model with the interaction was 0.026, statistically significant [$F(1,148) = 24.42$; $p = 0.018$].

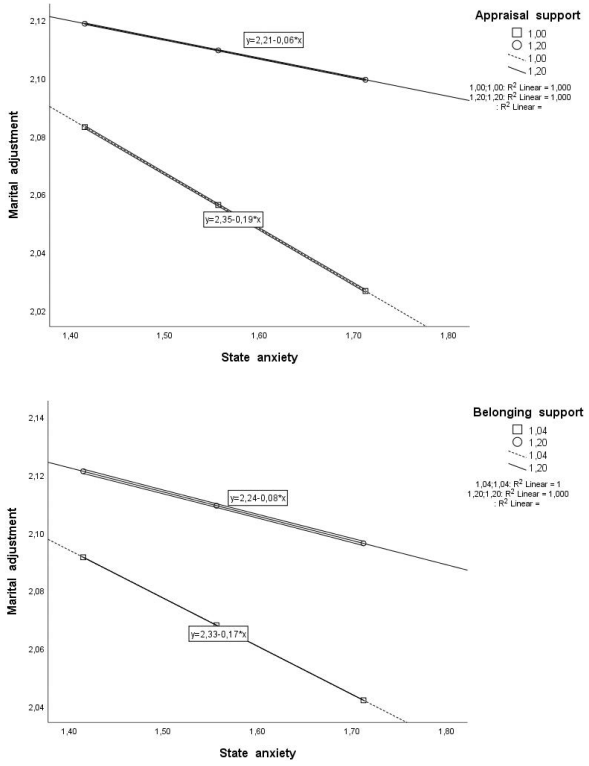

Figure 1. Appraisal (**A**) and Belonging (**B**) support attenuate the relationship between state-anxiety and marital adjustment

For the second model, the R2 change value for the interaction between state-anxiety and belonging support was 0.020, statistically significant [F (1,148) = 26.06; p = 0.034]. These results indicate that both appraisal social support and belonging support moderated the relationship between state-anxiety and marital adjustment.

In order to find out the manifestation of the moderation effect, the level of anxiety was analyzed in relation with the upper and lower values of the social support, as well as the scatter-plot graphs (Fig. 1A and B). Thus, the moderation effect for both models tested was manifested by diminishing the relationship between state-anxiety and marital adjustment when social support had higher values.

DISCUSSION

The present study aimed to highlight how couples adapt to the diagnosis of infertility, exploring the relationship between emotional disorders, marital adjustment and social support. Infertility is a predominant problem in today's society, but especially among those who postpone conception for later age. In the present study, the mean age in women was 34.25 years while the mean maternal age in the Romanian general population in the same geographical area was found to be 28 years [26]. The scientific literature increasingly states that the less risky maternal age range in terms of obtaining a pregnancy is 20–30 years, but on the other hand, today's couples perceive the idea that they should postpone conception after 30 years old [27].

Our results show that, for infertile couples, stress, depression and anxiety are more common among women than men. This has also been reported in several previous studies [21, 28]. One of the characteristics of infertile couples is that women are necessarily more deeply involved in treatment procedures and it is expected that they will be more affected by the process.

In general, women, when compared to men, reported higher levels of emotional difficulties during all stages of infertility [29]. The possible explanation for this could be the fact that women often feel guilty when a couple is infertile, and this can lead to social stigma. Therefore, women are more vulnerable than men to the negative psychological impact of infertility.

Infertility seems to have implications on the marital relationship as well. There are differences between partners regarding marital adjustment, consensus and satisfaction in the couple. In this study we hypothesised that marital adjustment is negatively correlated with emotional distress and when marital adjustment is high, emotional distress is low. One possible explanation is that the longer the time of infertility, the stronger the couple's relationship has the potential to become. Most respondents in this study stated that life without children brought them closer and strengthened their relationship. This has also been reported in the study of Schmidt et al. where the authors proposed that infertility may have certain marital benefits [30]. However, the same hypothesis may mean that emotional disorders increase when marital adjustment is low. Psychological pressure on men and women to have children can reduce intimacy and sexual satisfaction. Thus, infertility, through the impact on marital satisfaction or through the dysfunction of marital relations, can lead directly or indirectly to the failure of fertilization [31].

Infertility has also been associated with marital problems, conflicts and has serious implications for the mental and social well-being of the involving parts. Infertile couples have certain psychological disorders, including lack of marital satisfaction, lack of sexual satisfaction, loss of partner trust, decreased libido and dysphoric emotions [32, 33]. This can be problematic because the marital relationship is considered to be the most important source of support in the context of infertility treatment.

The results in our study show that social support is a significant factor in managing infertility and these results are compatible witht those of previous studies [34]. We therefore proposed a theory whereby social support acts as a protective factor which moderates/attenuates the relationship between emotional disorders and marital adjustment (Fig. 1). If a woman is unable to fulfill her role in

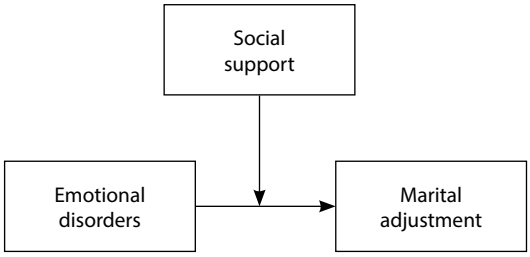

Figure 2. Moderation model — social support as moderator in the relationship between emotional disorders and marital adjustment

a traditional collective culture, in which maintaining marital status and giving birth to a child are landmarks of family life, she may suffer rejection, isolation and emotional abuse. On the contrary, if a woman is well supported by her family and especially her partner, then she is less succeptible to develop mental health issues or depression.

The present study contributes to the existing knowledge regarding emotional disorders and marital adaptation in infertile couples, having both theoretical and practical implications. It is well known that the experience of infertility affects the lives of both partners, and the failure of this common purpose in life affects the way they perceive themselves as a partners. Thus, the results of our study may support a clinician's decision to actively involve both partners in the diagnosis and treatment process, in accordance with the European Society of Human Reproduction and Embryology guidelines to meet the needs of both partners when the couple undergoes stressful treatment in medically assisted human reproduction technology [35].

The present study has several strengths that should be considered, including: (1) the concomitent evaluation of both symptoms of stress, with a specific instrument, and anxiety and depression; (2) assessment of marital relationship and social support; (3) the inclusion of both women and men facing fertility problems; (4) the examination of the aforementioned constructs according to certain demographic and clinical characteristics, such as the level of education, socio-economic status and type of infertility (primary or secondary); (5) the evaluation was carried out in several cities of Romania, which allowed the generalization of the results, unlike other studies that include participants from a single clinic.

The main limitation of this study is that because couples were volunteers and there were no available data for couples who refused to take part, we could not determine whether the analyzed sample may differ to some extent from the general infertile population. Another limitation is the cross-sectional design of the study. For this reason, no causal inferences can be made about the relationships between variables. In addition, the group of participants was not tested longitudinally to possibly estimate changes in time. Future controlled or longitudinal studies will help clarify these relationships. The general aim should be the development of assessment tools specific to infertility issues, as this study and many other in the literature use mainly general tools [36].

Although the sample size is relatively small, the results allow formulation of solid conclusions and future directions. Appropriate intervention strategies to support couples facing infertility should be developed and implemented. In our study, all couples underwent medical treatment for their fertility problem, but only three couples in the entire sample received psychological counselling to manage the emotions associated with conception difficulties, although psychological interventions plays an important role in the treatment of infertility, relieving the emotional symptoms that are felt by couples [37].

Despite the above listed limitations, this paper contributes to the existing knowledge on emotional disorders, marital relationship and social support associated with infertility especially in Romanian couples. The results of the study are expected to contribute to the development of educational programs on the importance of married life and sexual health in the treatment of infertile couples, as well as appropriate methods of therapeutic intervention. Organizing support groups for infertile couples and developing psychotherapeutic/psychoeducational intervention programs that focus on developing strategies to deal with emotional disorders can have positive effects on their lives.

Further research for the factors associated with marital satisfaction in infertile couples could help find a way to help couples maintain their interest in treatments and increase their chances of success by planning effective interventions. Other psychological variables (for both partners), such as: quality of life related to the experience of infertility, attachment style, difficulties for infertile people, but also their relationship with health care providers in specialized fertility clinics should be looked into.

CONCLUSIONS

In conclusion, infertility carries a significant psychological burden for couples and the longer its duration, the higher the distress level. Women seem to be more vulnerable to the psychological consequences of infertility compared to men. In the couples undergoing infertility treatment, marital adjustment correlates negatively with the degree of emotional disorders. The better the marital adjustment, the lower the levels of stress, depression and anxiety. Social support is often a neglected component in managing infertility. In couples where social support had higher values, the relationship between state-anxiety and marital adjustment was negatively correlated.

Conflict of interest

None.

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Evaluation of inflammatuar response in hysterectomies: a retrospective study in Kocaeli, Turkey

Mehmet Özsürmeli, Ünal Türkay, Bahar Salıcı, Mehmet Salıcı, Karanfil Nisan Bölge, Hasan Terzi

Derince Research and Education Hospital, Department of Obstetrics and Gynecology, Kocaeli, Turkey

ABSTRACT

Objectives: The authors aimed to detect the inflammatory marker changes in laparoscopic hysterectomy (LH) and abdominal hysterectomy (AH) and to determine whether oophorectomy affected the results.

Material and methods: The patients who underwent LH and AH with or without oophorectomy between 2018 and 2019 were identified as two groups. The records of patients were reviewed retrospectively. Preoperative and postoperative in the first 24 hours hematocrit (HCT), hemoglobin (HB), white blood cell (WBC), platelet-lymphocyte ratio (PLR), and neutrophil-lymphocyte ratio (NLR) values were compared.

Results: WBC, NLR, and PLR were statistically increased, and HB and HCT were decreased in all groups in the postoperative period. However, all changes were more prominent in the AH group than in the LH group. In other words, in the postoperative period, there were fewer changes in the inflammatory markers WBC, NLR, and NLR in the LH group. Oophorectomy did not affect these results.

Conclusions: LH, as in other laparoscopic operations, was associated with lower inflammatory response. The addition of oophorectomy did not increase inflammation in either AH or LH. Clinical Trials registration number is NCT04184765.

Key words: hysterectomies; inflammation mediators; lymphocyte activation; neutrophil activation; platelet activation

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INTRODUCTION

Surgery suppresses postoperative inflammatory response [1–3]. Systemic leukocytic alterations, such as leukocytosis, neutrophilia, and lymphopenia, occur in response to operations because of the effects of various hormones and cytokines [4, 5]. Laparoscopic surgery should cause less immune impairment, as it is associated with less tissue damage than abdominal surgery is [6–8]. The measurement of leukocytic changes, including neutrophil (NLR) and platelet-lymphocyte (PLR) ratios could be a useful method for assessing the postoperative inflammatory response.

Although the role of systemic leukocytic changes in the inflammatory response is uncertain, white blood cell (WBC), neutrophil, platelet, and lymphocyte counts as well as NLR and PLR have been well studied in many diseases, such as diabetes, coronary artery disease, ulcerative colitis, surgeries, and various cancers [8–12]. Reich et al. first described laparoscopic hysterectomy [13]. However, there is not enough information in the literature about how these values change in laparoscopic hysterectomies (LH) with or without oophorectomy, which is frequently used in gynecological practice. Moreover, oophorectomy may change the inflammatory response by altering cytokines and the microenvironment. Animal studies showed that oophorectomy led to changes in inflammatory response and neutrophil count [14, 15].

In the present study, we aimed to investigate the value of alterations in WBC, NLR, and PLR in patients with and without oophorectomy for LH or abdominal hysterectomy (AH).

Although NLR and PLR levels, as preoperative and postoperative markers, have been the subject of many studies, to the best of our knowledge, this study is the first to evaluate their association with LH and AH with or without oophorectomy.

Objectives

Laparoscopic hysterectomy revealed less postoperative inflammation than abdominal hysterectomy. The addition

Corresponding author:
Mehmet Özsürmeli
Derince Research and Education Hospital, Department of Obstetrics and Gynecology, Kocaeli, Turkey
Phone: 05079427497
e-mail: ozsurmeli@gmail.com

of oophorectomy did not change this result. To the best of our knowledge, this study is the first to evaluate their association with LH and AH with or without oophorectomy.

MATERIAL AND METHODS

This study was conducted in the reference obstetrics and gynecology clinic. Informed consent was obtained from each patient in our hospital. The patients who underwent LH and AH with or without oophorectomy between 2018 and 2019 were identified as two groups. The records of patients were reviewed retrospectively. Preoperative and postoperative in the first 24 hours hematocrit (HCT), hemoglobin (HB), WBC, PLR, and NLR values were compared.

We determine the type of surgery according to the clinical condition of the patient, the gynecological examination, and the patient's request. In cases where there is no clinical suspicion, oophorectomy is performed according to the patients' wishes. In benign cases, the preferred type of hysterectomy is type 1 extra facial hysterectomy. We usually perform total laparoscopic hysterectomy, so the vaginal cuff is sutured laparoscopically.

Patients with chronic diseases, the presence of active infection, corticosteroid use, acetylsalicylic acid, and anticoagulant use were not included in the study. Bladder and bowel injuries, blood transfusion requirements, wound infection and hematoma, postoperative respiratory system complications were evaluated as surgical complications. Patients whose data could not be accessed were excluded.

Blood tests

Maternal venous blood samples were taken into hemogram tubes. The calibrations of the device were completed and analyzed using the Pentra DF Nexus Hematology System® (Horiba Healthcare, Japan). PLR and NLR were calculated by dividing platelet and neutrophil counts, respectively, by the lymphocyte count.

Statistical analysis

The Number Cruncher Statistical System (NCSS) 2007 (Kaysville, Utah, USA) was used for the statistical analysis. The normal distribution of the quantitative data was tested using the Shapiro–Wilk test and graphical analysis. The Student's t-test and the Mann–Whitney U test were used to compare the normal and the non-normal distributed quantitative variables, respectively. The paired sample t-test was used for the preoperative and postoperative comparisons of the variables with normal distribution. The Wilcoxon signed-rank test was used for the preoperative and postoperative comparisons of the variables with normal distribution. Pearson's chi-square test and Fisher's exact test were used to compare the qualitative data. Statistical significance was accepted at $p < 0.05$.

RESULTS

Hysterectomy was performed in 234 patients, 92 of which were abdominal and 142 were laparoscopic. Nine patients in the first group and eight patients in the second group did not meet our inclusion criteria. Three patients in the first group and two patients in the second group were excluded from the study because they could not be contacted. Finally, data on 80 patients in the AH group and 132 patients in the LH group were evaluated. Oophorectomy was added to 16 patients in the AH group and 23 patients in the LH group.

The demographic features and inflammatory markers are shown in Tables 1 and 2. Preoperative and postoperative changes in NLR and PLR between the oophorectomy group and the non-oophorectomy group are shown in Table 3. The average age is lower in the AH group. Except this, there were no significant differences between the groups in terms of the demographic data. The most common indication in the LH group was uterine descensus, whereas the most common indication in the AH group was fibroids. Although no difference in complications was observed, the length of hospital stay was lower in the LH group. Regardless of the procedure, WBC, NLR, and PLR were statistically increased, and HB and HCT were decreased in all groups in the postoperative period. However, all changes were more prominent in the AH group. In other words, in the postoperative period, the inflammatory markers WBC, NLR, and NLR changed less in the LH group. Oophorectomy did not affect these results.

DISCUSSION

The main findings of our study are as follows:

1. The preoperative and postoperative HB and HCT values did not change significantly in both the AH and the LH groups; however, the NLR and PLR values changed significantly. Moreover, the changes were more prominent in the AH group. This result was not surprising because it was consistent with the literature. The inflammatory response was also less in the LH group, where less tissue damage was expected.
2. In both the AH and the LH groups, oophorectomy did not change these results. The inflammatory responses in the laparoscopy and the open surgery have been evaluated in many previous studies, which showed that the immune response was suppressed by adjusting the cytokines level and cellular components of the immune system after open surgery [16–18]. Less tissue trauma in laparoscopic surgery may be associated with the lower response to systemic inflammation [19]. In many previous studies, the total leukocyte count was increased after open surgery, but it did not increase after laparoscopic surgery [20, 21]. The potential advantages of laparoscopy over laparotomy include shorter op-

Table 1. Evaluation of descriptive characteristics by type of operation

	Abdominal hysterectomy (n = 80)	Laparoscopic hysterectomy (n = 132)	p value
Age [years]	46.91 ± 5.26	50.63 ± 8.06	[a]0.001**
Gravida	2.94 ± 2.00	3.40 ± 1.63	[a]0.067
Systemic disease	7 (8.8)	23 (17.4)	[b]0.079
Number of previous operations	26 (32.5)	44 (33.3)	[b]0.900
Indication			
Dysfunctional uterine bleeding	15 (18.8)	31 (23.5)	**[b]0.418**
Symptomatic fibroids	52 (65.0)	30 (22.7)	[b]0.001**
Postmenopausal bleeding	3 (3.8)	8 (6.1)	[c]0.292
Adnexal mass	7 (8.8)	16 (12.1)	[b]0.444
Desensus uteri	1 (1.3)	22 (16.7)	[b]0.001**
Endometrial hyperplasia	2 (2.5)	21 (15.9)	[b]0.002**
Mole pregnancy	0 (0)	1 (0.8)	[c]1.000
Cervical intraepithelial hyperplasia	0 (0)	3 (2.3)	[c]0.292
Patients without oophorectomy	64 (80.0)	109 (82.6)	[a]0.639
Complications	3 (3.8)	8 (6.1)	[c]0.540
Duration of hospital stay [days]	2.58 ± 0.90	2.28 ± 0.68	[d]0.002**

[a]Student t Test; [b]Pearson χ^2 Test; [c]Fisher's Exact Test; [d]Mann-Whitney U Test; **Indicates statistical significance; Data are expressed as number (%) or mean ± standard deviation

Table 2. Evaluation of WBC, HGB, HCT, PLT, and NLR measurements by operation type

	Abdominal hysterectomy (n = 80)	Laparoscopic hysterectomy (n = 132)	p value
Preop WBC [$\times 10^3/mm^3$]	6.63 ± 1.96	6.95 ± 1.94	[a]0.254
Postop WBC [$\times 10^3/mm^3$]	11.17 ± 371	9.80 ± 2.97	[a]0.004**
[c]p-value	0.001**	0.001**	
Difference (Postop-Preop)	4.54 ± 3.40	2.85 ± 2.70	[a]0.001**
Preop HB [g/dL]	12.23 ± 1.73	12.45 ± 1.40	[a]0.341
Postop HB [g/dL]	10.66 ± 1.46	10.65 ± 1.32	[a]0.942
[c]p value	0.001**	0.001**	
Difference (Postop-Preop)	–1.57 ± 1.00	–1.80 ± 0.79	[a]0.080
Preop HCT	37.07 ± 4.44	37.57 ± 3.40	[a]0.387
Postop HCT	32.93 ± 3.98	32.62 ± 3.28	[a]0.531
[d]p-value	0.001**	0.001**	
Difference (Postop-Preop)	–4.14 ± 3.02	–4.96 ± 2.30	[a]0.027*
Preop PLR	9.36 ± 5.37	9.86 ± 5.57	[b]0.291
Postop PLR	23.65 ± 16.84	17.24 ± 10.25	[b]0.007**
[d]p-value	0.001**	0.001**	
Difference (Postop-Preop)	14.29 ± 15.28	7.38 ± 10.73	[b]0.001**
Preop NLR	2.72 ± 5.20	2.16 ± 1.60	[b]0.838
Postop NLR	8.67 ± 8.38	6.41 ± 6.35	[b]0.005**
[f]p-value	0.001**	0.001**	
Difference (Postop-Preop)	5.96 ± 9.64	4.25 ± 6.45	[b]0.002**

[a]Student's t-Test; [b]Mann–Whitney U Test; [c]Paired Samples t-Test; [d]Wilcoxon Signed-Rank Test; *p < 0.05; **p < 0.01; Data are expressed as mean ± standard deviation; HB — hemoglobin; HCT — hematocrit; NLR — neutrophil-lymphocyte ratio; PLR — platelet-lymphocyte ratio; Postop — postoperative value; Preop — preoperative value; WBC — white blood cell

Table 3. Evaluation of PLR and NLR measurements according to oophorectomy in the AH and LH groups

	Oophorectomy (+)	Oophorectomy (–)	[a]p
AH (n = 80)	n = 16	n = 64	
PLR difference (Postop-Preop)	16.93 ± 12.35	13.62 ± 15.95	0.163
NLR difference (Postop-Preop)	6.94 ± 4.60	5.71 ± 10.55	0.207
LH (n = 132)	n = 23	n = 109	
PLR difference (Postop-Preop)	10.46 ± 14.37	6.73 ± 9.75	0.575
NLR difference (Postop-Preop)	4.92 ± 5.72	4.11 ± 6.61	0.789

[a]Mann–Whitney U Test; Data are expressed as mean ± standard deviation; AH — abdominal hysterectomy; LH — laparoscopic hysterectomy; NLR — neutrophil-lymphocyte ratio; PLR — platelet-lymphocyte ratio; Postop — postoperative value; Preop — preoperative value

eration time, smaller surgical scarring, faster recovery time, fewer adhesions, and lower cost [22, 23]. The lower systemic inflammatory response may be the reason for the advantages of laparoscopy [2].

It is reasonable to assume that there is a lower inflammation response in LH. However, no previous study has investigated the response to inflammation in LH. Although NLR and PLR have been studied in many diseases, such as various cancers, inflammatory diseases, and preeclampsia, they have not been evaluated in LH. Our study groups consisted of patients who did not have any disease, did not use medication, and underwent hysterectomy for benign reasons. Therefore, it was crucial to demonstrate WBC, NLR, and PLR changes in these patients.

Animal studies have shown that oophorectomy changed the leukocyte count by altering the cytokine response. Souza et al. reported an increased neutrophil count in the bronchoalveolar lavage fluid in ovariectomized mice [14]. To the best of our knowledge, no similar human study has been conducted. In the present study, the authors found that removal of the ovaries did not affect the changesin inflammatory markers after surgery.

NLR and PLR measurement, unlike other immune mediators such as interleukins, are inexpensive and simple tests in routine practice. Changes in total leukocyte counts (*e.g.*, neutrophilia, lymphopenia, and increased NLR) have been shown to increase mortality and morbidity in cancer patients, cardiovascular diseases, and chronic renal disease [9, 12, 24, 25]. We believe that these values are predictors of postoperative morbidity and mortality. Because morbidity was low in both groups, no difference was found in this respect. It could also be expected that the energy modality used in LH would affect inflammation. Bipolar energy was used in all patients in both groups.

The limitations of our study include its retrospective design. Patients whose data could not be accessed were excluded from the study. Moreover, the number of cases was too small to compare morbidity. Another important point is that in the present study, the LHs were performed by experienced gynecologists, each of whom had more than five years' of experience in this surgical procedure. However, the AH were performed by less experienced gynecologists. This difference in surgical experience could have biased the results of our study. However, the strength of this study is that it is the first in the literature to evaluate the inflammation marker in LH and determine whether oophorectomy affected the results.

CONCLUSIONS

Laparoscopic hysterectomy revealed less postoperative inflammation than AH. This result is demonstrated by inexpensive and straightforward tests in daily practice. The addition of oophorectomy does not increase inflammation in either AH or LH.

Conflict of interest

The authors report no declarations of interest.

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Fetal growth trajectory in type 1 pregestational diabetes (PGDM) — an ultrasound study

Lukasz Adamczak*[1], Daniel Boron*[1], Pawel Gutaj[1], Grzegorz H. Breborowicz[2], Jerzy Moczko[3], Ewa Wender-Ozegowska[1]

[1]Department of Reproduction, Chair of Obstertics, Gynecology and Gynecological Oncology, Poznan University of Medical Sciences, Poland

[2]Department of Gynecological Oncology, Chair of Obstertics, Gynecology and Gynecological Oncology, Poznan, Poland

[3]Department of Computer Science and Statistics, Poznan University of Medical Sciences, Poland

**equal contribution*

ABSTRACT

Objectives: Growth disorders are frequent in diabetic pregnancies. However, they are difficult to predict and capture early during pregnancy. These newborns are at risk of obesity, diabetes, and cardiovascular disease. While developing, fetal growth abnormalities are typically progressive. Therefore, capturing the earliest moment when they emerge is essential to guide subsequent obstetric management.

Material and methods: We aimed to analyze fetal ultrasound growth trajectories in type 1 diabetics. Moreover, we aimed to establish time points when first ultrasound manifestations of fetal growth abnormalities appear and to identify factors that affect fetal growth in women with diabetes.

We collected clinical and ultrasound data from 200 patients with PGDM managed in the third-referential centre for diabetes in pregnancy. During every visit, patients underwent an ultrasound examination according to a standard protocol giving 1072 ultrasound scan's records. Every ultrasound consisted of fetal weight estimation, according to the Hadlock 3 formula. Retrospectively patients were divided into three groups depending on neonatal weight. In the group of 200 patients, 60 (30%) delivered LGA and 9 (4.5%) SGA newborns.

Results: Fetal growth trajectories show different patterns among fetuses with growth abnormalities in women with type 1 diabetes. The moment, when fetal growth curves diverge, seems to take place in the second trimester, just after the 23rd week of gestation.

Conclusions: It suggests that fetal growth abnormalities in type 1 diabetes may have its roots much earlier than expected. In the first trimester, there were differences in LDL-cholesterol, total cholesterol, triglyceride levels and in insulin requirements between AGA, SGA and LGA subgroups.

Key words: fetal growth; pregestational diabetes; ultrasound; type 1 diabetes mellitus

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INTRODUCTION

Pregnancy in diabetic patients increases the risk of developing maternal and fetal complications. Pregestational diabetes mellitus (PGDM) complicates about 0.2–0.3% of pregnancies, depending on the studied population [1]. Patients with diabetes are much more likely to develop obstetric complications such as pregnancy-induced hypertension, preeclampsia and polyhydramnios. Premature births, operational deliveries, perinatal infections are also much more common in that group of patients [2–4]. Acute carbohydrate disturbances may pose a direct threat to the life of the pregnant woman and fetus.

Among fetal complications we can distinguish congenital malformations, neonatal hypoglycemia and in particular excessive growth of the fetus (LGA, large for gestational age), which is often the cause of perinatal injuries [5]. Depending on the type of diabetes this complication concerns 15% to even 50% of pregnant women with type 1 diabetes [6].

Fetuses of mothers with pregestational diabetes mellitus are particularly vulnerable to complications during pregnancy and the percentage of pregnancies complicated by excessive growth continues to increase despite improved diabetes management [1].

Corresponding author:
Lukasz Adamczak
Department of Reproduction, Chair of Obstertics, Gynecology and Gynecological Oncology, Poznan University of Medical Sciences, 33 Polna St, Poznan, Poland
e-mail: lukasz.dyzury@gmail.com

Fetal overgrowth is challenging to predict and capture early during pregnancy. It affects mainly children exposed in utero to maternal hyperglycemia, followed with fetal hyperinsulinemia. Moreover, studies are suggesting the involvement of other factors including maternal lipids, adipokines and excessive weight gain [7]. These newborns are also at risk of obesity, diabetes and cardiovascular disease later in life [8, 9]. Most of the fetal complications are irreversible, so capturing the earliest moment when growth disorders occur to prevent this process is essential.

Due to the still inaccurate ultrasound diagnostics and severe consequences for the neonatal health that result from undetected fetal overgrowth, special attention should be placed on the best obstetric and diagnostics procedures for diabetic pregnant women to prevent them.

Our work aimed to assess the incidence of disturbances in the fetal growth in the studied group of patients with pre-existing type 1 diabetes and to analyze the ultrasound growth charts of fetuses from the examined group of pregnant women to indicate the period of pregnancy in which they begin. The next goal is to identify factors that significantly affect fetal growth in pregnant women with diabetes.

Spotting of this moment and identifying factors influencing the fetal growth disturbances would possibly allow identifying a group of women particularly predisposed to these complications.

MATERIAL AND METHODS

In line with the Polish standards of medical care each woman with pregestational diabetes was admitted to our department the tertiary reference centre for pregnant diabetic women from central-west Poland, as soon as her primary care gynaecologist confirmed the pregnancy.

We collected data from 200 pregnancies with pregestational type 1 diabetes mellitus (PGDM1) that we admitted in the first trimester to our department in 2015–2018. Patients were regularly admitted in the clinic in every trimester to assess health status, metabolic control, and to supervise the fetal development. During every visit, each patient underwent an ultrasound examination by an experienced sonographer according to a standard protocol. In the study, based on biparietal diameter (BPD), head circumference (HC), abdominal circumference (AC) and femur length (FL) measurements, fetal weight was estimated according to the Hadlock 3 formula, which is considered to be the most accurate estimation of fetal weight in diabetic pregnancies [2].

We analyzed data of diabetic, singleton pregnancies we retrospectively retrieved from our department's database. All women conceived naturally. Analyzed patients were admitted to our department at least once before the 12th week of pregnancy, according to the last menstrual period (LMP). Gestational age was confirmed or corrected in the first trimester of pregnancy with the measurement with transvaginal ultrasound. Each pregnant woman with type 1 diabetes admitted to the department we thoroughly interviewed during the first antenatal visit. Only patients admitted in the first trimester were taken into the study.

Patients were all Caucasian and received standard pregnancy care for patients with diabetes, as recommended by the Polish Diabetes Association and Polish Gynaecological Society. As target we took a fasting glucose level of 3.9–5 mmol/L (70–90 mg/dL), 1-hour postprandial glucose below 7.8 mmol/L (140 mg/dL), and glycated haemoglobin (HbA1c) below 6.5 % (48 mmol/L) in the first trimester of pregnancy and next trimesters below 6.0% (42 mmol/L) [4].

At the first antenatal visit we recorded the following maternal parameters: maternal age, duration and class of diabetes according to White, pre-pregnancy body mass index (BMI), the concentration of haemoglobin A1c (HbA1c), presence of vascular complications (hypertension, proteinuria, and retinopathy) and pregnancy planning.

All women were on intensive insulin therapy using either multiple daily injections (MDI) or continuous subcutaneous insulin infusion (CSII).

Exclusion criteria from this paper were multiple pregnancies, miscarriage, preeclampsia and delivery before completed the 34th week of gestation or delivery in another hospital.

We collected anthropometric, clinical and laboratory data during three planned hospital admissions, according to our protocol: in the first trimester (< 12th week of gestation), in mid-pregnancy (20th–24th weeks of pregnancy) and before delivery (34th–39th weeks of gestation).

The term large-for-gestational-age we used for fetuses or newborns with estimated weight above the 90th percentile or more than two standard deviations from the mean for the gestational age. Small for gestational age refers to fetuses or neonates that were born with weight below the 10th centile or more than two standard deviations from the mean for the gestational age adjusted to World Health Organization definitions [5].

Blood samples were taken for analysis after overnight, in the fasting state and immediately transported to the central laboratory of the Gynaecologic Obstetrical University Hospital in Poznan. HbA1c level in the whole blood was determined using the turbid metric inhibition immunoassay, Tina-quant Haemoglobin A1c II test in a Cobas c311 analyzer (Roche Diagnostics, Basel, Switzerland). The normal range for this test is 4.8–6.0% (29–42 mmol/mol) for a non-pregnant population. The total serum cholesterol, high density lipoprotein (HDL)-cholesterol and triglyceride (TG) levels were determined with Roche Diagnostics reagents (Cholesterol CHODPAP, HDL-C plus and Triglycerides GPO-PAP, respectively) on a Cobas c501 analyzer.

Table 1. Characteristic of studied groups

	AGA n = 131	LGA n = 60	SGA n = 9	p*
Diabetes duration [years] (SD)	10.8 (7.7)	11.2 (7.5)	9.2 (6.1)	1
Mean age of DM diagnosis [years] (SD)	19.3 (9.1)	17.2 (8.5)	18.5 (8.7)	0.9
Body weight before pregnancy [kg] (SD)	73.1 (18.2)	70 (17.4)	90.2 (14.4)	0.09
Weight gain during pregnancy [kg] (SD)	11.9 (5.7)[1]	14.7 (4.7)[1]	11.7 (4.9)	0.5
Weight gain in 1st trimester [kg] (SD)	1.1 (2.2)	0.8 (3.1)	1.4 (1.8)	0.4
Weight gain in 2nd trimester [kg] (SD)	4.7 (3.7)	5.7 (3.8)	3.4 (3.1)	0.7
Weight gain in 3rd trimester [kg] (SD)	5.5 (4.3)	7.0 (5.1)	5.3 (2.6)	0.7

*Kruskal-Walis and ANOVA tests comparing three study groups; [1]comparing two groups AGA vs LGA with Mann-Whitney test ($p < 0.05$); SD — standard deviation; SGA — small for gestational age; AGA— appropiate for gestational age; GA— gestational age

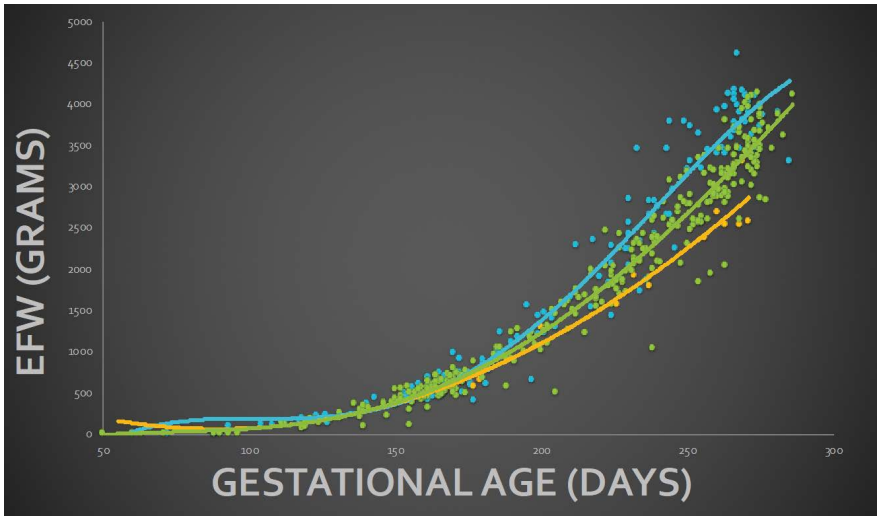

Figure 1. Estimated fetal weight in ultrasound according to the final weight of the newborns — three groups: SGA (yellow), AGA (green), LGA (blue) SGA — small for gestational age; AGA — appropiate for gestational age; LGA — large for gestational age

The following formula we used to calculate the level of low-density lipoprotein (LDL) [LDL-cholesterol = total cholesterol – HDL-cholesterol – (TG/5)]. Total cholesterol (CHOL), LDL-cholesterol (LDL-CH), HDL-cholesterol (HDL-CH), and triglycerides (TG) levels were measured with the appropriate Roche Diagnostics reagents (cholesterol CHOD-PAP, HDL-C plus and triglycerides GPO-PAPrespectively) on Hitachi 912 analyzer. Reference values for CHOLis 3.9–7.2 mmol/L, TG is 0.46–1.71 mmol/L, for LDL-CH is 4.1 mmol/L and for HDL-CH < 1.29 mmol/L for women.

We performed statistical analysis using PQstat program. The Shapiro-Wilik test we used for testing the normality of data distribution. We used the ANOVA test to check the significance of the difference between three groups, if data fitted normal distribution. Results are as the mean ± standard deviation (SD). Comparisons of non-normally distributed data are using the Kruskal-Walis test with conclusions expressed as the median and interquartile range (IQR). Parameters that shown significant differences in ANOVA and Kruskal-Walis tests were further analyzed with post-hoc analysis with appropriately Fisher LSD and Dunn Bonferroni tests to find the differences between the subgroups.

RESULTS

In our 200 of PGDM1 group, sixty (30%) patients gave birth to children meeting LGA criteria, and nine (4.5%) newborns were small for gestational age. The birth weight of the remaining newborns (n = 131, 65.5%) was appropriate for the gestational age (AGA). Maternal parameters related to the bodyweight of the newborn divided into three groups (LGA, AGA, and SGA), are presented in the Table 1.

The Figure 1 shows fetal growth charts in these three subgroups of patients (AGA, SGA, LGA). We present subsequent ultrasound examinations on a scatter plot with a superimposed trend line, which maps the trajectory of fetal growth in selected groups.

Data has shown that both estimated fetal weight and abdominal circumference start to differ between our three

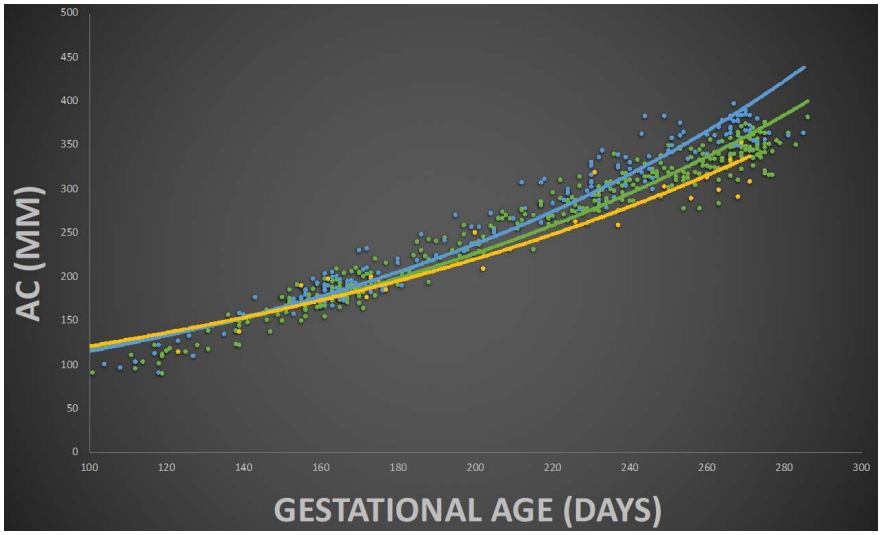

Figure 2. Abdominal circumference (AC) in ultrasound according to the final weight of the newborns — three groups: SGA (yellow), AGA (green), LGA (blue) SGA — small for gestational age; AGA — appropiate for gestational age; LGA — large for gestational age

groups around the 23rd week (161 days). Similar results were presented by other authors [10]. Abdominal circumference is a measurement that varies the most the fetuses with growth disorders, as well as with excessive as with too small fetal growth. In our diabetic group we observed differences in abdominal circumference, especially in the LGA fetuses in the third trimester (Fig. 2).

In the next part of our study we analyzed the metabolic parameters of the patients to show which of them had a significant impact on the development of excessive fetal growth. Our results have shown, that there was no difference in any of the studied parameters between patients who delivered LGA and AGA newborns and all of them met the target criteria of glycemic control. The percentage of HbA1c, which reflects the mean glycemia was not significantly different between the LGA and AGA group. SGA patients had higher HbA1c levels in the first trimester, but this difference was not significant (Tab. 2). In none of the trimesters HbA1c concentrations were statistically different between LGA, SGA, and AGA patients.

Also the concentration of the maternal lipids concentrations (HD-L, LDL-, total cholesterol and triglycerides) analyzed in each of the three trimesters did not differ significantly between diabetic patients with excessive and with proper fetal growth. We found somewhat surprising differences between the SGA and the AGA groups. SGA patients had a substantially higher level of the total cholesterol, LDL-cholesterol and triglycerides in the first trimester ($p < 0.05$). They also needed more insulin in the first and second trimester to maintain euglycemia ($p = 0.05$). Interesting differences we found in weight gain during pregnancy ($p < 0.05$) Women who delivered LGA neonates presented higher weight gain during pregnancy than AGA group.

For the analysis of the effectiveness of fetal weight prediction before delivery we qualified 87 patients whose ultrasound was performed up to seven days before childbirth. We predicted in 69 (79%) a weight as being appropriate for gestational age. After birth this diagnosis was confirmed in 59 (68%) newborns. Eight newborns (9%) turned out to be LGA, while two belonged to the SGA group. Predicting LGA based on EFW was less sensitive than based on abdominal circumference. Our results revealed that AC measurements had higher accuracy in LGA detecting and lower negative predictive value, which is crucial to avoid perinatal injuries in diabetic pregnancies (Tab. 4, 5)

DISCUSSION

Pregestational diabetes may lead to many maternal complications during pregnancy but especially coincides with the development of adverse neonatal outcomes. One of the most common complications is excessive fetal growth, which can be associated with fetal fetopathy including metabolic disturbances and the risk of shoulder dystocia [4].

There is no one specific formula for fetal weight estimation in small for gestational age fetuses as well as in big babies. Coombs et al. [11] compared 31 formulas in their study and did not show significant superiority of individual methods. Many authors have proved that Hadlock's formula is the best for estimating the weight of hypotrophic fetuses, as well as the macrosomic babies. Therefore we decided to use it for our measurements [12].

Excessive fetal growth increases the risk of cesarean section and traumatic delivery [5]. To predict and avoid these complications precise estimating of fetal weight in ultrasound is necessary. Also very important is to find the moment when fetal overgrowth is starting, because then

Table 2. Laboratory parameters of studied groups.

	AGA n = 131	LGA n = 60	SGA n = 9	p*
HbA1c 1st trimester [%] (SD)	6.9 (1.6)	6.5 (1.1)	7.1 (1.8)	0.2
HbA1c 2nd trimester [%] (SD)	5.7 (0.7)	6.8 (8.1)	5.3 (0.8)	0.5
HbA1c 3rd trimester [%] (SD)	6.0 (0.7)	5.9 (0.8)	6.1 (1.4)	0.9
HDL 1st trimester [mg/dL] (SD)	68.6 (17.1)	70.3 (17.5)	60.7 (22.3)	0.5
HDL 2nd trimester [mg/dL] (SD)	85.1 (19.0)	89.0 (19.6)	73.9 (9.6)	0.2
HDL 3rd trimester [mg/dL] (SD)	76.8 (19.2)	79.4 (20.3)	71.4 (22.1)	0.7
LDL 1st trimester [mg/dL] (SD)	85.3 (24.1)[1]	79.1 (20.6)[6]	100.5 (35.4)[1.6]	**0.01**
LDL 2nd trimester [mg/dL] (SD)	127.4 (96.8)	120.1 (35.1)	124.4 (34.6)	0.9
LDL 3rd trimester [mg/dL] (SD)	146.5 (54.0)	140.7 (42.3)	148.6 (29.6)	0.8
Total cholesterol 1st trimester [mg/dL] (SD)	170.1 (27.4)[2]	163.3 (25.1)[7]	186.7 (39.8)[2.7]	**0.01**
Total cholesterol 2nd trimester [mg/dL] (SD)	230.1 (41.2)	233.7 (51.2)	248.4 (39.4)	0.7
Total cholesterol 3rd trimester [mg/dL] (SD)	269.3 (67.5)	296.0 (231.1)	260.5 (46.6)	0.9
TG 1st trimester [mg/dL] (SD)	83.1 (44.4)	69.8 (29.5)[5]	127.6 (68.0)[5]	**0.01**
TG 2nd trimester [mg/dL] (SD)	148.5 (70.0)	142.3 (52.3)	194.1 (56.8)	0.3
TG 3rd trimester [mg/dL] (SD)	248.8 (89.6)	219.4 (93.2)	258.9 (86.9)	0.2
Hypertensionn (%)	25 (19.2)	10 (16.7)	2 (22.2)	0.7
Proteinuria 1st trimester n (%)	13 (12.3)	8 (17.4)	0	0.4
Proteinuria 2nd trimester n (%)	12 (18.1)	3 (10.7)	0	0.4
Presence of proteinuria 3rd trimester n (%)	15 (6.6)	8 (38.1)	1 (20)	0.9
Insulin intake 1st trimester [IU] (SD)	38.0 (17.4)[3]	30.0 (17.4)[3.8]	48.6 (25.7)[8]	**0.01**
Insulin intake 2nd trimester [IU] (SD)	42.0 (18.5)[4.9]	37.1 (19.5)	68.0 (33.7)[4.9]	**0.01**
Insulin intake 3rd trimester [IU] (SD)	34.3 (18.1)	30.4 (15.1)	38.8 (23.5)	0.4
Insulin intake per kg I trimester [IU/kg] (SD)	0.49 (0.28)	0.53 (0.22)	0.51 (0.35)	0.5

*Kruskal-Walis and ANOVA tests comparing three study groups; [1, 2, 3, 4, 6, 7, 8, 9] POST-HOC statistically significant difference $p < 0.05$. Fisher LSD test; [5]POST-HOC statistically significant difference $p < 0.05$. Dunn Bonferroni test; SD — standard deviation; SGA — small for gestational age; AGA — appropiate for gestational age; GA — gestational age; HDL — high density lipoprotein; LDL — low-density lipoprotein; TG — triglyceride

we have the possible chance to intensify the metabolic and maternal weight gain control.

In our study we tried to determine the week of pregnancy when excessive fetal weight gain begins. In daily clinical practise we observe that children who are macrosomic after delivery, start their excessive weight gain around the 26th–28th weeks of pregnancy. Determining the growth trajectories for fetuses with AGA, LGA and SGA in our studied groups we noticed the tendency to diverge curves distinctly earlier, *i.e.* from 24–25 weeks of pregnancy. In our study, we estimated the moment when fetal growth impairment begins among patients with pregestational diabetes. However statistical analyzes have not confirmed this. They have shown that based on the available data we are not able to determine the exact moment when the excessive growth of the fetus or its restriction begins. We speculate that our studied group, however well treated with proper metabolic control is quite heterogeneous and it might impair the precision of this finding. Patients differ in duration of the disease, weight gain during pregnancy, total insulin doses, presence of vascular and renal complications and this complexity of the diabetic disease potentially causes a different moment of the beginning of fetal growth disturbances.

The proper on time detection of this process might give in impulse for better glycemic and weight gain control, which in some studies confirmed the suppressing of fetal overgrowth [13]. Our observations might constitute a motivation for searching for better indicators of growth impairment in the early stages of pregnancy. From all measured metabolic parameters in our studied group only maternal weight gain during pregnancy differed significantly the groups with LGA and AGA newborns. It shows that higher energy intake determines not only maternal weight gain but also affects fetal weight. In the SGA group patients were heavier at the beginning of pregnancy, had significantly higher triglycerides in I and II trimester and insulin intake during the second trimester. Surprisingly only two patients from that group presented hypertension during pregnancy.

Table 3. Ultrasound measurements in analyzed groups

	AGA Mean (SD) n = 131	LGA Mean (SD) n = 60	SGA Mean (SD) n = 9	p*
BPD (22–24 week) mm (SD)	55.1 (3.4)	55.8 (3.3)	53.2 (5.7)	0.8
HC (22–24 week) mm (SD)	203.4 (11.3)	208.3 (11.2)	190.3 (23.4)	0.3
AC (22–24 week) mm (SD)	178.1 (12.9)	184.2 (11.9)[1]	165.5 (20.6)1	**0.03**
FL (22–24 week) mm (SD)	39.1 (2.9)	40.2 (3.2)	34.5 (8.3)	0.6
BPD (29–31 week) mm (SD)	78.2 (6.2)	79.4 (8.5)	0	0.7
HC (29–31 week) mm (SD)	273.1 (41)	261.1 (58.8)	0	0.5
AC (29–31 week) mm (SD)	256.8 (39.2)	256.2 (58)	0	1
FL (29–31 week) mm (SD)	60.7 (10)	62 (14.5)	0	0.8
BPD (36–38 week) mm (SD)	85.6 (2.9)[2]	92.7 (4.1)[2,5]	87.5 (0.2)[5]	**0.0004**
HC (36–38 week) mm (SD)	323.1 (8.8)[3]	335.6 (12.7)[3,6]	320.5 (8.4)[6]	**0.00001**
AC (36–38 week) mm (SD)	325.7 (20)[4,8]	350.7 (16.5)[4,7]	302.7 (11)[7,8]	**< 0.000001**
FL (36–38 week) mm (SD)	70 (3.5)	72.2 (2.7)	53.5 (35.7)	0.1

- Kruskal-Walis and ANOVA tests comparing three study groups

[1,3,4,6,7,8]- POST- HOC statistically significant difference p<0,05. Fisher LSD test.

[2,5]- POST- HOC statistically significant difference p<0,05. Dunn Bonferroni test.

SD — standard deviation; SGA — small for gestational age; AGA — appropiate for gestational age; GA — gestational age; BPD — biparietal diameter; HC — gead circumference; AC — abdominal circumference; FL — femur lenght

Table 4. Prediction of the occurrence of large for gestational age based on EFW

	born LGA	born AGA	sum
predicted LGA	12	1	13
predicted AGA	8	59	67
sum	20	60	80
sensitivity		60.00%	
specifity		98.33%	
Positive predictive value		92.31%	
Negative predictive value		88%	

LGA — large for gestational age; AGA — appropiate for gestational age

Table 5. Prediction of the occurrence of large for gestational age based on AC

	born LGA	born AGA	sum
predicted AC ≥ 90 percentile	16	3	19
predicted AC < 90 percentile	4	57	61
sum	20	60	80
sensitivity		80.00%	
specifity		95.00%	
Positive predictive value		84.00%	
Negative predictive value		93.00%	

LGA — large for gestational age; AGA — appropiate for gestational age; AC — abdominal circumference

Still, as we know parameters mentioned above belong to the group of metabolites that predispose to changes in placental vessels and could cause insufficient placental circulation resulting in growth restriction.

Our results confirmed that in women with suspicion of LGA we may estimate it more precisely, using abdominal circumference calculation, than using the estimated fetal weight. Abdominal circumference above the 90th-centile has higher negative predictive value in detecting LGA than the estimation of fetal weight, which allows the obstetrician to plan the route of delivery with higher accuracy. Our results are not in concordance with Blue, who observed that after the 24th week of gestation AC measurement has no advantage in the LGA risk assessment in fetuses with estimated overgrowth [14]. Caradeux has not confirmed the effectiveness of longitudinal growth assessment as a better method to detect excessive growth compared to standard biometric measurements [15]. In our opinion although fetal weight estimation is still imperfect there is no better way, as longitudinal observations to diagnose hypertrophy among fetuses. It is in line with Ben-Haroush [16].

Accurate estimation of fetal weight is fundamental both to predict the occurrence of complications and also involves the choice of delivery method. In the study of Phillips et al. the effectiveness of ultrasound performed two weeks before delivery in predicting macrosomia was only 33% [17]. Their study shows how unpredictable can be the weight of the fetus and how dynamically it changes, especially in the last weeks of pregnancy, in which we decide about the method of delivery. Ben-Haroush in his review concludes that based on the available methods we are not able to determine the birth weight of fetuses accurately in women with diabetes [16]. His observation makes the choice of delivery more challenging and therefore increasing the risk of shoulder dystocia. In our study we estimated the risk of macrosomia using known risk factors. We took into consideration prior history of macrosomia, maternal pre-pregnancy weight, weight gain during pregnancy, multiparity, fetal sex (male), gestational age (40 weeks), maternal birth weight, and maternal height and obesity [17]. We confirmed that the total maternal weight gain in a relatively well-controlled diabetic group predisposes significantly to fetal overgrowth.

The main goal of our study was to indicate the moment when growth disorders begin to develop. Schaefer-Graf et al. revealed that the following factors were leading in the late second and early third trimesters, genetic and patient's history turned out to be the most significant factors influencing fetal growth. In the late third-trimester maternal hyperglycemia has the most significant influence on the macrosomia [18]. In our group of patients the maternal weight gain throughout pregnancy was the only statistically significant factor that correlated with macrosomia.

We assume that it is the matter of vital importance not to stop looking for new parameters to diagnose both excessive growth and growth restriction as soon as possible during pregnancy. Especially in the group of patients with the disease predisposing to these complications like with pregestational diabetes. Our results confirmed that in patients with an efficient metabolic control the next steps should be done. Strict weight gain control during pregnancy, planning the pregnancy by reducing the body weight and treatment of hypertriglyceridemia before pregnancy might let to avoid impaired fetal growth. Maybe further studies will find some vascular complications in early pregnancy, putting such patients to a group of the high risk of developing growth restriction.

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Barley malt-based composition as a galactagogue — a randomized, controlled trial in preterm mothers

Aleksandra Wesolowska[1], Bronislawa Pietrzak[2], Bozena Kociszewska-Najman[3], Miroslaw Wielgos[2], Krzysztof Czajkowski[4], Ewa Wietrak[5], Katarzyna Karzel[6], Maria K. Borszewska-Kornacka[7]

[1]Laboratory of Human Milk and Lactation Research at Regional Human Milk Bank in Holy Family Hospital, Medical University of Warsaw, Department of Neonatology, Warsaw, Poland

[2]1st Department of Obstetrics and Gynecology,Faculty of Medicine, Medical University of Warsaw, Poland

[3]Department of Neonatology , Faculty of Health Sciences, Medical University of Warsaw, Poland

[4]2nd Department of Obstetrics and Gynecology, Warsaw Medical University, Warsaw, Poland

[5]R&D Nutropharma Llc, Warsaw, Poland

[6]University of Warsaw, Faculty of Psychology, Warsaw, Poland

[7]Department of Neonatology and Intensive Care Unit, Faculty of Medicine, Medical University of Warsaw, Poland

ABSTRACT

Objectives: Delayed or insufficient breast milk production, as well as low milk supply, is still a challenging problem to overcome, particularly in the case of preterm delivery. Herbal galactagogues might be a good way to increase milk supply, however, there is a lack of clinical studies confirming their efficacy and safety.

The aim of this study was to verify the safety and effectiveness as a galactagogue of the unique galactagogue composition based on barley malt with β -glucan and lemon balm.

Material and methods: The study included 117 mothers of preterm infants randomly divided into the Galactagogue Group given galactagogue and the Placebo Group. A complete data set was obtained for 80 participants, divided equally between two groups.

Volume of milk expressed by mothers during the first two weeks after delivery was the primary outcome and safety of the product was the secondary outcome.

Results: Volume of milk recorded on participants' last visit in the Galactagogue Group was significantly higher than in the Placebo Group (95 mL vs 62.5 mL, p = 0.049). The total expressed milk volume during the study was 4209 ± 335 mL in the Placebo Group vs 6036 ± 498 mL (p = 0.003) in the Galactagogue Group.

Conclusions: Supplementation with unique Galactagogue composition was safe and increased milk output which allowed achieving target minimal volume of 500 mL per day in first week of lactation in preterm mothers.

Key words: barley malt; galactagogue; insufficient milk supply; preterm baby; human milk

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INTRODUCTION

Lactogenesis in humans is a very complicated process. It depends not only on reproductive and metabolic hormones but is self-regulated through the autocrine-paracrine mechanism. Additionally, both physical and emotional factors are involved in successful onset of milk production [1–4]. The fall of progesterone after delivery, followed by increase in prolactin (PRL) levels triggers the beginning of lactogenesis II, a period of copious milk secretion. However, there is no direct correlation between baseline PRL levels and volume of expressed milk [5]. Milk volume depends mostly on frequency and duration of breastfeeding/pumping throughout early lactation period [5].

Delayed or insufficient breast milk production, as well as low milk supply, is still a challenging problem to overcome, particularly in the case of preterm delivery [6–8] which results in lower basal PRL levels compared with mothers who give birth at term [9]. The other non-physiological causes of

Corresponding author:
Aleksandra Wesolowska
Laboratory of Human Milk and Lactation Research at Regional Human Milk Bank in Holy Family Hospital, Medical University of Warsaw, Department of Neonatology, 63a Zwirki i Wigury St, 02–091 Warsaw, Poland
e-mail: aleksandra.wesolowska@wum.edu.pl

lactational failure are complex and include separation from the newborn after delivery, poor maternal psychological well-being and health after an unexpected delivery [10–13].

For vulnerable preterm infants, a mother's own milk is more a medicine than nutrition. The mother's milk intake is increasingly recognized as a key variable associated with positive clinical outcomes in preterm infants [14–16]. Therefore, it is reasonable to seek new, natural substances which act as a galactagogues) initiating and augmenting the secretion of mother's milk [17]. Unfortunately, earlier studies with herbal based galactagogues have not been well-designed because of a lack of randomization, controls or blinding and with poor evidence regarding the efficacy and safety [18–20]. A good candidate for natural and safe galactagogue may be ß-glucan present in barley malt.

Barley malt is produced from the malting process where grains are allowed to germinate and then quickly dried. As a result of malting, bioactive components including those that potentially increase milk supply, are released from barley grain [21]. In fact, non-alcoholic beer is used traditionally by mothers in many cultures during lactation to increase milk supply although its prolactogenic mechanism has not been fully clarified with a clinical study [22, 23].

Studies based on animal models suggests that a polysaccharide such as *β*-glucan found in barley enables milk production by prolactin dependent mechanisms after intravenous injection [24, 25]. An observational study was conducted in group of 128 mothers with insufficient milk supply who consumed barley malt-based product for 14 days [26]. Certified lactation consultants evaluated time of effective sucking and other factors responsible for a successful lactation. Regular breast milk swallowing was elongated in 91% of babies and the amount of milk pumped by mothers increased more than twice [26]. Therefore, the beneficial effect of the formulation based on barley malt with β -glucan and lemon balm (Galactogogue) was investigated further in the group of mothers who gave birth prematurely and were vulnerable to lactation failure.

Objectives

The aim of this double-blind, randomized, placebo controlled study was to investigate efficacy in increasing milk production and safety of use of unique galactagogue composition.

MATERIAL AND METHODS

Settings and Participants

This study was conducted at two NICUs associated with the Medical University of Warsaw between April 2014 and October 2015 with approval of the Ethics Committee in the Medical University of Warsaw (number KB 40/2014). The target population consisted of women above 18 years old who delivered infants < 37 weeks gestation (gestational age confirmed according to the last menstrual period) and gave written informed consent to participate in the study.

Participants were eligible for the study if they were available to be enrolled within two days following birth, declaredelectric breast pump use (at least 6 times a day, including night) and agreed on filling up the lactation diary which allowed to monitor the increase in expressed milk volume through the progress of establishing and maintaining lactation. Women were considered ineligible if they were diagnosed with hypothyroidism or either type 1 or 2 diabetes before pregnancy and were receiving treatment. Moreover, participants already participating in another clinical trial were excluded.

This RCT was retrospectively registered on ClinicalTrials.gov on November 14th, 2017 under the identification number NCT03341481.

Study Design

This clinical trial was double-blind, randomized, and placebo-controlled, conducted according to the Good Clinical Practice, including monitoring by a qualified Clinical Research Associate. One Hundred Seventeen mothers who gave birth prematurely were enrolled in the study within 48 hours postpartum and were randomly assigned to the two study groups (Placebo Group or Galactagogue Group). The concealed allocation sequence was generated by central randomization using a computer software program. Femaltiker® a proprietary, commercially available product produced by Nutropharma Llc., was used as the galactagogue in the Galactagogue Group. Femaltiker® containing composition was notified at the Polish Chief Sanitary Inspectorate as food for special medical purposes. Femaltiker formula consists of powdered lemon balm leaves (Melissa officinalis L.); barley malt (Hordeum vulgare Linn) enriched with 70% barley-glucan. Other inactive ingredients included sucrose and natural caramel flavoring. The composition is protected by patent nr. 229569, therefore the exact amount of each component was not disclosed. The placebo was produced as a blend of sucrose, apple fiber and natural aroma caramel and was in the same package as Femaltker®. The products were indistinguishable by color, taste and texture. Each subject received 28 packages to take twice daily for 14 days during the study. Participants were asked to return the empty packages during their check-up for compliance monitoring. Participants and medical staff were blinded to which package contained the active product until the end of the trial.

According to the study scheme mothers had to have undergone three hospital visits during the first two weeks postpartum. The first visit occurred as soon as possible, following delivery but no later than on the second day (± 1 day) post-delivery. The second visit occurred at the end of the first week of lactation at day six and the third visit was

on day 14 (± 2 days) postpartum. Mothers were instructed to pump their breasts every four hours (six times per day for 10–15 minutes per breast) using a standardized electric breast pump. A Symphony® PLUS™ Breast Pump, Medela, Switzerland was used in the hospital and a Lactina Electric® PLUS™ Medela, Switzerland was available for home use.

Primary and secondary outcomes

The primary outcome was the total volume of milk expressed by participants from the second to the 14th postnatal day. Secondary outcome was the safety of the intervention.

Data collection

Clinical data of mothers and infants at delivery and throughout study duration were collected including maternal and infant demographics, prior breastfeeding experience, colostrum expression after delivery and ability to latch onto the breast.

Milk production data

Participants recorded daily lactation information during the study including exact volume of milk in mL expressed at each expression session, the exact time of each milk expression session, the total milk expression time per day, the total amount of milk expressed per day, and the longest interval between expression sessions in a standardized lactation diary. Information concerning self-estimation of the onset of lactogenesis stage II was provided by participants marking the applicable answer in the lactation diary (feeling of full/empty breasts, swollen, painful, tender). The lactation diary and lactation equipment including Medela's 150 mL disposable bottles were provided to participants at the study enrollment.

Daily volume of milk produced was confirmed by the medical staff by summation of all recorded milk volumes during a 24-hour period prior each of hospital visits. Furthermore, the amount of milk expressed in a single session during each hospital visit on days 2 (+/1 day), 6, 14 (+/2 days) postpartum was measured using Medela's 150 mL disposable bottles by the lactation consultant.

Safety data

Possible side effects of the intervention were monitored at each visit by a member of the clinical team. It included skin examination and collecting information from subjects concerning digestive symptoms such as nausea, a bad taste in the mouth, and pain. If side effects occurred, they were assessed by completing a rating scale of adverse symptoms intensity (mild, moderate, severe).

Data analysis and statistical tests

Data analysis included only those subjects who completed the study per protocol.

Study sample was calculated based on previous research. It was assumed that the standard deviation (SD) of the mean milk production in the second week of lactation is approximately 160 mL/day [27]. Therefore, we expected a SD of total breast milk volume of about 2500 mL within the first 14 days postpartum. Under further assumptions of statistical significance level of $p < 0.5$ and power of 0.8, we calculated that with a sample size of 40 participants per group it would be possible to assess (using standard t-test) a difference between study groups of size 1585 mL as statistically significant. A full data set was obtained for 80 participants, divided equally between the two study groups. The data was imported into SPSS for Windows for further analysis.

Student t-test for independent sample was used to analyze demographic variables including mother's age at the time of delivery, duration of pregnancy (in multiple pregnancies), infant gestational age and birth weight. They were compared using 95% confidence intervals for means with standard error (SE).

Moreover, maternal factors related to pregnancy and postnatal care were compared using $\chi 2$ testing. Student t-test was used to compare lactation stimulation parameters as total volume of expressed milk, total time of expressing, number of expression sessions between groups. There were showed using 95% confidence intervals for means with SE. Difference in daily volume of milk in the following days was presented using 95% confidence intervals for means with SE. Volume of milk from day 4 to 11 depending on the study group was analyzed by variance analysis (ANOVA). The daily volume of expressed milk was only analyzed for the time in which all 80 subjects participated in the study (to the 11th day postpartum) and the volume of expressed milk was measurable in mL (volume ≥ 1 mL from 4th day postpartum).

Additionally, covariance analysis (ANCOVA) was performed with Placebo Group vs Galactagogue Group as grouping variable and number of the sessions during the day as a covariant.

A p-value of $< .05$ was considered statistically significant, $p <. 01$ was considered highly significant.

RESULTS

One hundred seventeen mothers of preterm infants were randomized with 59 allocated to the placebo and 58 to the Galactagogue group. Four participants from each group did not receive the intervention. Reasons for not receiving the intervention, loss to follow-up and exclusion from analysis are listed on Figure 1. Complete data was obtained for 40 participants in each arm.

There was no statistically significant difference between participants in terms of demographic characteristics. In addition, there were no statistically significant differ-

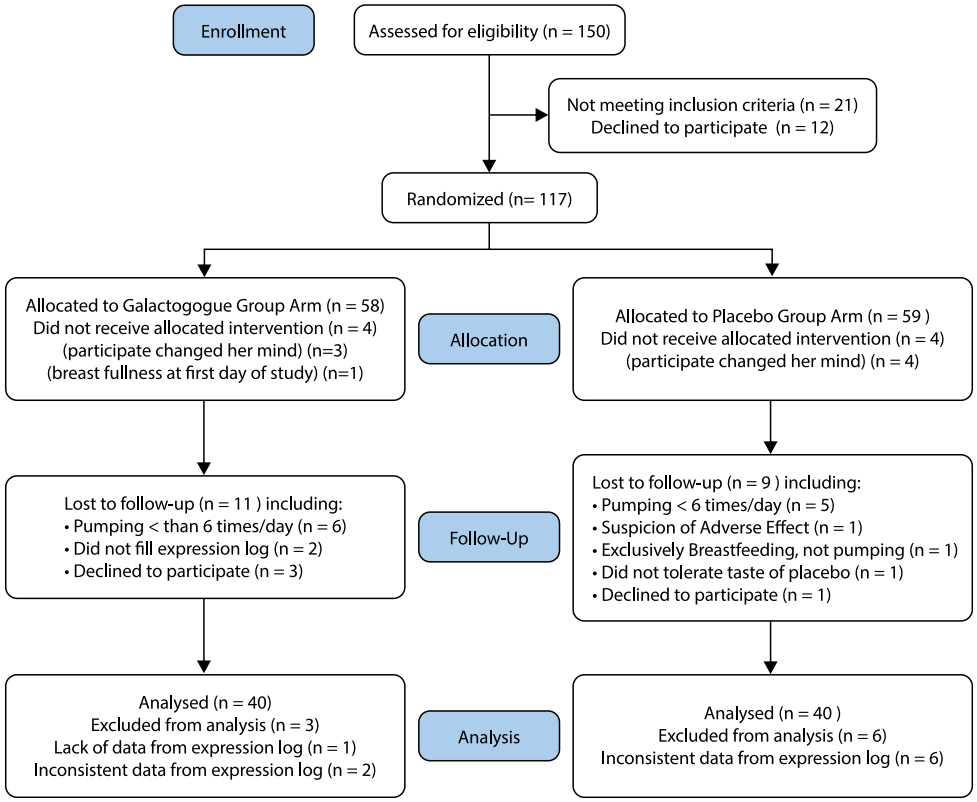

Figure 1. Flow Chart of Study; The blue boxes show the progress through the phases of a parallel randomized trial of two groups: Galactagogue and Placebo. Numbers in white boxes (n) show the subjects excluded, withdrawn from the study, patients that dropped off and number of subjects taken for analysis

Table 1. Mothers (n = 80) and infants (n = 114) characteristics at randomization

Mothers	Placebo group (n = 40)		Galactagogue group (n = 40)		t	p
	M ± SE	95% CI	M ± SE	95% CI		
Age [years]	31.6 ± 0.8	30.0–33.1	30.9 ± 0.8	29.3–32.5	0.63	0.53
Pregnancy week at birth	31.5 ± 0.4	30.6–32.4	31.5 ± 0.5	30.4–32.8	0.00	1.00
Infants	**Placebo Group (n = 56)**		**Galactagogue Group (n = 58)**		**t**	**p**
	M ± SE	**95% CI**	**M ± SE**	**95% CI**		
Birth weight	1719 ± 100	1553–1885	1745 ± 92	1589–1900	0.19	0.85
Gestational age [weeks]	31.4 ± 0.4	30.7–32.2	31.8 ± 0.5	31.0–32.7	0.60	0.55

Demographics of participants in analyzed sample n (80) of mothers and infants n (114); The difference with p value < 0.05 is considered statistically significant; M — mean; SE — standard error; CI —confidence interval

ences in their infant's birth weight or gestational age (Tab. 1). Finally, there was no significant difference in pregnancy and postnatal care in both groups. Participants were mostly primiparas that gave singleton birth through caesarian section with no previous breastfeeding experience (data not shown). Colostrum expression was possible in 39 women (97.5%) from Placebo Group and 37 women (92.5%) in the Galactagogue Group ($\chi 2 = 1.05$; $p = 0.30$). Due to premature birth a low number of neonates were able to latch on instantly 5 (12.5%) in the Placebo Group and 7 (17.5%) in the Galactagogue Group; $\chi 2 = 0.32$; $p = 0.53$).

Milk production data

Volume of milk expressed during the three hospital visits is presented as the median with 95% CI in Figure 2. Volume expressed during the third visit (day 14) was statistically significantly higher in mothers who received Galactagogue compared to the Placebo Group (62.5 mL vs 95 mL; $Z = 2.40$, $p = 0.01$, with Bonferrroni correction $p = 0.049$).

Total volume of milk recorded in the lactation diaries over the entire study from day 2 to 14 was statistically significantly higher in the group receiving Galactagogue (6036 mL ± 498 vs 4209 mL ± 335; $p = 0.003$). There were

no differences in the total expression time (p = 0.68) and number of milk expression sessions (p = 0.27) between the study groups (Tab. 2). Despite the exemptions from the protocol regarding the interval between follow-up visits in case of four participants, the mean period of participation in the study did not differ between groups (p = 0.40) (Tab. 2).

Comparison of the average daily volume of milk expressed revealed that the Galactagogue Group expressed statistically more milk already on day seven of the study (p = 0.01). The Placebo Group failed to reach 500 mL of expressed milk per day throughout whole study period (Fig. 3, Tab. 3).

A statistically significant effect of the group was found on daily volume of milk (F = 5.91, p = 0.017). The daily volume of milk was statistically significantly higher in the Galactagogue Group throughout the study period in comparison to the Placebo Group. Only on 4 day (p = 0.13) and 6 day (p = 0.05) of the study the results failed to show statistical significance (Tab. 3).

The analysis with a number of milk expressing sessions during particular day as a covariant has shown differences in daily milk volume between the study groups. In the Galactagogue Group on days from 7 to 11 of the study there was statistically significantly (p < 0.05 for group factor) higher milk production in comparison to the Placebo Group (Tab. 4). On Days 9 and 10 the daily number of sessions had shown significant influence on the milk production in the study groups (p = 0.009 and p = 0.04, respectively). This factor (daily number of sessions) has been included in the results and despite it the experimental group still obtained higher results for milk volume than the Placebo Group (Tab. 4).

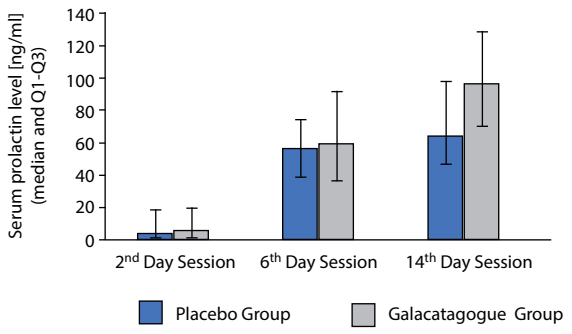

Figure 2. The volume of expressed mother's milk recorded at the hospital visit; The median milk volume expressed by women in the study groups (blue — placebo group, dark grey — galactagogue group) in the subsequent three measurement sessions at the hospital visit. The error bars represent 95% CI. The asterisks indicate result that differ statistically significantly with p-value < 0.05

Safety data

During the verbal assessment of intervention safety, two affirmative answers were noted in the placebo group, one was qualified as a serious side effect (SAE) not related to the product taken. Reported dryness of the skin was assumed to be related to iatrogenic hyperchloremia caused by administrated intravenous fluids and the participant was withdrawn from the study. There were no side effects reported in the group receiving Galactagogue. The product was well tolerated and consumed as a drink by a majority of the participants. One subject in the Placebo group reported the compound tasted bad and was withdrawn from the study.

DISCUSSION

This study suggests that Galactagogue which is composed of barley malt, β-glucan and lemon balm can serve as a galactagogue in mothers of preterm infants who struggle with insufficient milk production. Our study revealed that dietary intervention supplementation with food for special medical purposes Femaltiker® during the first two weeks of lactation increased milk volume in mothers of premature infants. Compared to the Placebo Group, mothers who received the Galactagogue composition produced 34% more milk during session on day 14 of lactation. Data obtained from the lactation diaries were consistent with data obtained by lactation consultations at the hospital. The Galactagogue Group produced 30% more milk during the whole study period that was taken into the consideration for statistical analyses (from day 2 to 14 of the study).

Table 2. Total volume of expressed milk, total time of expressing and total number of expression sessions, duration of the study (n = 80)

	Placebo group (n = 40)		Galactagogue group (n = 40)		t	p
	M ± SE	95% CI	M ± SE	95% CI		
The volume of expressed breastmilk [mL]	4209 ± 335	3531–4886	6036 ± 498	5029–7043	3.04	0.003
Total expression time [min]	2211 ± 114	1980–2442	2280 ± 123	2031–2530	0.41	0.68
Number of expression sessions [n]	82 ± 2	78–86	85 ± 2	81–90	1.11	0.27
Duration of the study [days]	12 ± 0.2	11.3–12.2	12±0.2	11.6–12.3	0.84	0.40

Indicators related to stimulation of lactation for analyzed sample (n = 80); The difference with p value < 0.05 is considered statistically significant; M — mean; SE — standard error; CI —confidence interval

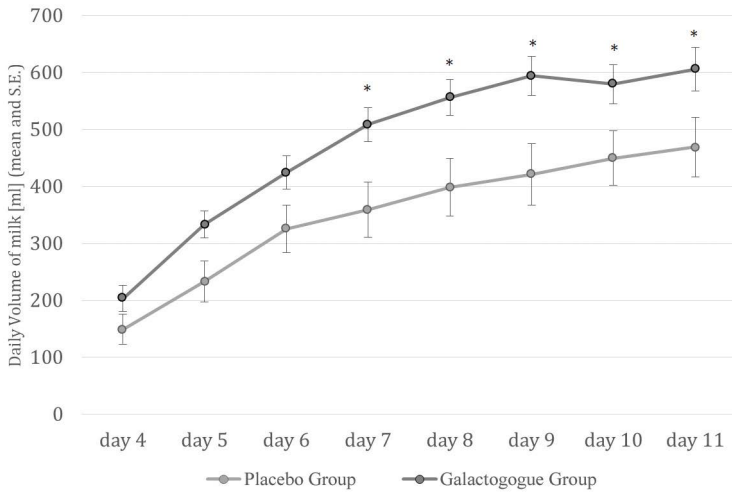

Figure 3. The average daily volume of mother's milk expressed by participants in the course of study; Mean milk volume expressed from day 4 to 11 in the Galactagogue Group (dark grey line) and the Placebo Group (light grey line). The error bars represent Standard Error (SE), The asterisks indicate result that differ statistically significantly with p-value < 0.05

Increases in milk volume were not associated with maternal factors, postnatal care, or lactation practices recognized as supportive to milk supply in mothers of preterm infants.

Perceived and real insufficient milk supply is the most common reason for formula introduction in the early neonatal period [28, 29]. It is especially harmful for preterm infants for whom mother's milk is crucial for their development and health [30, 31]. Unfortunately, mothers of preterm infants are at high risk of breastfeeding difficulties and the reasons for this are complex [32]. Often, regular milk expression, family support and medical advice including lactation consultation fail to resolve the problem [10, 15, 33] and maternal treatment to increase milk supply may be important. It is noteworthy that in Poland drugs such as domperidone and metoclopramide, that have proven efficacy in increasing milk production are not authorized for this indication, therefore their use is treated as off- label use [17] and is rather marginal. Other popular herbal galactagogues such as fenugreek and silymarin from milk thistle (*Silybum marianum*) does not have strong and consistent scientific evidence in milk increase [17]. Fenugreek should be used with caution due to its unclear safety profile and very mild effect on milk production in studies with likely a placebo effect [17, 34].

One of the first randomized controlled trial (RCT) aimed to evaluate the efficacy of silymarin in mothers of preterm infants did not show statistically significant differences in milk production. When the formulation was improved by adding components to increase absorption, lactogenic effects were observed in the first month of lactation which continued over the first 3 months [35, 36]. The total average milk volume observed in both groups by Zecca et al. [35], (4136 ± 4093 mL in the placebo vs 6523 ± 5298 mL in the experimental, $p < 0.02$) was comparable to our study (4208.8 ± 335.04 mL, in the Placebo Group vs 6035.9 ± 497.80 in Galactagogue Group , $p = 0.0033$). However, in our study the result spread between the patients was less by order of magnitude and intervention time was two times shorter (30 days of supplementation versus 14 days).

It is noteworthy that mothers in the experimental group in our study achieved an average daily expressed volume of milk of more than 500 mL/d on day seven in comparison to the Placebo Group where this amount of milk was not achieved even at the last day of the study (Fig. 3, Tab. 3). As was shown earlier milk volume in the early stage of lactation is a predictor of successful milk production after very preterm birth [11, 37]. Evidence indicates that the first 14 days is a critical period for coming into the volume. Milk supply greater than 500 mL/d is a predictor of infants receiving maternal milk at discharge [33, 38].

To reflect the demands of a breastfed term baby recommendation for expression frequency is 8–12 times per day including during the night [39, 40, 41]. However, this frequency is not always achieved which may affect the quantity of milk produced [42]. Our study revealed that the overall mean number of daily expression sessions was seven times per day. Because expression frequency can impact milk production, daily volume of milk from day 7 to 11 were controlled for number of expression sessions in consecutive days by covariance analysis. Even though differences in milk expression frequency were observed between groups in selected study days (days 9 and 10), the daily volume of milk in the Galactagogue Group was still statistically significantly higher from day 7 to day 11 in comparison to the Placebo Group (Tab. 4).

Barley malt-based product was mentioned as a lactation stimulant and included as a part of lactation consultation scheme in case of insufficient milk supply [43]. The Expert's

Table 3. Daily volume of milk in consecutive days

Day	Mean nr. of sessions		Volume of milk: Placebo Group (n = 40)	Volume of milk: Galactagogue Group (n = 40)	Contrast estimates p	ANOVA [1]Group [2]Day [3]Interaction
4th	7	M ± SE	149.3 ± 23.5	203.4 ± 26.7	0.13	
		95% CI	101.6–196.9	149.3–257.5		
5th	7	M ± SE	233.4 ± 23.5	333.3 ± 35.9	0.02	$F^1 = 5.91$ $p^1 = 0.017$
		95% CI	185.9–280.9	260.8–405.9		
6th	7	M ± SE	325.9 ± 28.8	424.6 ± 41.8	0.05	
		95% CI	267.7–384.2	340.1–606.2		
7th	7	M ± SE	359.5 ± 29.7	508.6 ± 48.2	0.01	$F^2 = 135.83$ $p^2 < 0.0001$
		95% CI	299.4–419.6	411.0–606.2		
8th	7	M ± SE	398.9 ± 32.0	556.4 ± 50.6	0.01	
		95% CI	334.2–463.6	454.0–658.9		
9th	7	M ± SE	421.4 ± 34.1	594.3 ± 54.0	0.008	$F^3 = 3.12$ $P^3 = 0.0031$
		95% CI	352.5–490.4	485.0–703.6		
10th	8	M ± SE	449.7 ± 34.4	579.5 ± 48.0	0.03	
		95% CI	380.1–519.4	482.6–676.9		
11th	7	M ± SE	469.2 ± 37.9	605.8 ± 52.4	0.03	
		95% CI	392.5–545.8	499.8–711.8		

M — mean; SE — standard error; CI —confidence interval; The daily volume of milk and number of expression sessions in consecutive days from 4 to 11 was indicated as a M with SE and 95% CI. The difference with p value < 0.05 is considered statistically significant

Group recommendations of the Dietary Guidelines for lactating women put barley malt product use as an example of good dietary praxis supporting lactation process in women [44]. Authors emphasized that barley malt and its active constituent - β-glucan are safe for use. Although allergy to barley is rare, individuals suffering from celiac disease should eliminate barley from their diet because it contains gluten. In our study safety data were collected and we showed that consumption of Femaltiker® which contains Galactagogue composition of barley malt with β-glucan and lemon balm did not cause any adverse reactions in mothers throughout study period.

CONCLUSIONS

Galactagogue composition, based on barley malt is safe and increases milk production in mothers of preterm infants.

We conclude that unique patented galactagogue formula can be safely administered in the first two weeks of lactation but the effect of the intervention on maintaining milk supply needs to be evaluated in the future studies.

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The effects of a physical exercise program on fetal well-being and intrauterine safety

Beata Makaruk[1], Rafal Iciek[2], Andrzej Zalewski[3], Anna Galczak-Kondraciuk[4], Weronika Grantham[1]

[1]Department of Sport for All, Faculty of Physical Education and Health in Biala Podlaska, Jozef Pilsudski University of Physical Education, Warsaw, Poland

[2]Department of Obstetrics and Women's Diseases, Karol Marcinkowski University of Medical Sciences, Poznan, Poland

[3]Andrzej Zalewski's Specialist Practice, Biala Podlaska, Poland

[4]Department of Health Promotion, Faculty of Physical Education and Health in Biala Podlaska, Jozef Pilsudski University of Physical Education, Warsaw, Poland

ABSTRACT

Objectives: The aim of this study was to evaluate the effects of a supervised physical exercise program on fetal well-being and intrauterine safety. Physical activity is recommended for healthy pregnant women. However, constant evaluation of fetal condition and development is recommended to ensure the safety of the exercise program.

Material and methods: Randomized control trial study design. Sixty-six healthy pregnant women (age 24–35) with singleton gestation were randomly assigned to either an exercise group (EG, n = 34) or a non-active control group (CG, n = 32). The exercise program included 81 sessions (moderate intensity, 3 times per week, 50–60 min/session from weeks 13 to weeks 40/41 of pregnancy). Fetal well-being was assessed in weeks 32 and 37 of pregnancy. The cerebroplacental ratio (CPR) was calculated to evaluate the safety of the exercise program for the fetus.

Results: The differences in the CPR ratio measurements between EG and CG groups in week 37 ($p < 0.05$) were observed. The increase in the CPR ratio was also shown in week 37 of pregnancy in comparison to week 32 ($p < 0.01$). Moreover, maternal heart rate was significantly lower in the exercise group as measured at 37 weeks ($p < 0.05$).

Conclusions: The results of this study confirm that regular and supervised exercise program throughout pregnancy does not affect fetal well-being and is safe for the fetus. Additionally, regular physical activity improves maternal physical fitness and cardiac efficiency which might aid at preparing pregnant women for natural labor.

Key words: pregnancy; physical activity; regular exercise program; fetal safety; cerebroplacental ratio

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INTRODUCTION

Pregnancy is a period in a woman's life when intense changes in her body occur. This requires continuous surveillance of both maternal and fetal well-being. Constant evaluation of uterine blood flows allows for the assessment of fetal health, development, and intrauterine safety [1]. The surveillance of fetal well-being is maintained through a detailed evaluation of blood flow velocity waveforms during noninvasive Doppler ultrasound examinations [2]. It is usually carried out throughout pregnancy, beginning from the end of the first trimester [3].

To determine fetal well-being or distress more accurately, cerebroplacental ratio (CPR) is used. CPR is defined as the ratio of middle cerebral artery pulsatility index (MCA-PI) and the umbilical artery pulsatility index (UA-PI) [3]. CPR ratio is considered as a better indicator of hemodynamic changes and the cardiac output redistribution in the fetus, than the MCA-PI and UA-PI measurements alone [4]. CPR ratio is predictive for fetal health even in cases where the vascular resistance of the umbilical circulation seems to be normal [4]. CPR ratio below 1.04 might be symptomatic of centralization of fetal circulation, known as the brain-sparing effect, in which the blood is redistributed to the organs potentially most vulnerable to hypoxia, namely fetal central nervous system, heart, and adrenal glands [3, 5]. CPR is also considered as more accurate at indicating the potential fetal hypoxia (as compared to the MCA-PI and UA-PI measurements alone) and generally correlates with

Corresponding author:
Weronika Grantham
Department of Sport for All, Faculty of Physical Education and Health in Biala Podlaska, Jozef Pilsudski University of Physical Education, Warsaw, Poland
e-mail: weronika.grantham@awf.edu.pl

potential perinatal risks. Moreover, it is indicative of a slight increase in placental resistance and a slight reduction in fetal cerebral resistance [3]. In routine clinical care, CPR is potentially the most indicative parameter of fetal intrauterine growth restriction (IUGR) or small-for-gestational-age fetuses (SGA) [6].

Fetal well-being may be associated with numerous lifestyle interventions. One of those interventions is physical exercise adapted specifically for pregnant women [1]. A training program should be individually designed and supervised by a qualified exercise specialist [1, 7]. According to American College of Obstetricians and Gynecologists (ACOG) guidelines [1], the recommendation for pregnant women is to engage in physical activity for at least 20––30 mins/day with moderate intensity, on most (if not all) days of the week. However, ACOG emphasizes the lack of unequivocal data in the literature presenting the influence of regular exercise programs on fetal well-being, to assess the redistribution of oxygen, carbon dioxide, and nutrients through the placenta [1].

Several studies considered the influence of physical exercise on fetal well-being based upon a single bout of dynamic, submaximal exercise (usually cycle ergometer) [8–11]. The evaluation of individually advised regular exercise programs during pregnancy and their influence on maternal and fetal well-being in literature is still scarce [12–15]. To determine its safety, current and future research evaluating regular physical activity throughout pregnancy should include a multidimensional approach, examining intensity, duration, and type of exercises used as well as their influence on maternal and fetal blood flow measurements.

Objectives

The aim of this study was to evaluate the effects of a supervised and specifically designed complete physical exercise program on fetal well-being and intrauterine safety.

MATERIAL AND METHODS

Participants

Eighty women with uncomplicated pregnancies were enrolled in this randomized controlled trial. Out of those, fourteen resigned because of personal reasons, before the start of the exercise program. Sixty-six healthy pregnant women (age 24–35 years), with no contraindications to exercise [1], and no clinical signs of IUGR or genetic defects, assessed at 11–14 weeks gestation [2], were finally included in this study. After providing informed written consent, eligible participants were randomly assigned to either the exercise group (EG, n = 34, mean age 27.55 ± 1.70) or non-active control group (CG, n = 32 mean age 27.55 ± 1.70). Women in the EG group, after the initial prenatal Doppler examination at weeks 11–14 [2], took part in an exercise program entitled 'Conscious 9 months'. The exercise program was initiated at 13 weeks gestation and continued until 40–41 weeks gestation. The CG group consisted of randomly assigned 32 healthy pregnant women. All participants also received routine prenatal care throughout pregnancy and were instructed not to participate in any other exercise programs. This study protocol was approved by the Bioethical Committee at the District Medical Chamber in Lublin, Poland. All the women were informed about the aims of the study and that they may discontinue the program at any time. Demographic characteristics of all the participant are presented in Table 1.

Table 1. Characteristics of both the exercise and the control groups

Groups	EG (34)	CG (32)
Maternal age, y	27.18 ± 1.72	27.55 ± 1.70
Maternal BMI kg/m^2	21.5 ± 0.5	23.4 ± 1.23
Maternal body weight before birth [kg]	73.5 ± 3.8	78.9 ± 9.6
Week of delivery	39.8 ± 0.4	38.7 ± 1.6
Type of delivery N*/C*	32/2	18/16
Birthweight, g	3487 ± 315	3468 ± 425
Apgar Score (0–10)	9.94 ± 0.348	8.84 ± 1.04

EG — exercise group; CG — non-active control group; *N — normal delivery; *C — Cesarean delivery

Exercise program

The exercise program included three 50–60 minutes training sessions per week (Monday, Wednesday, Friday). A total of 81 sessions were conducted. Adherence to the program in the EG was exceedingly high, with thirty-two out of thirty-four participants taking part in 100% of the training sessions. The remaining two participants missed only 1 (98.8%) and 2 sessions (97.5%) respectively. Hence, the overall adherence to the exercise program was 99.9%.

Program intensity was moderate, with heart rate (HR) consistent between 100–145 beats per minute (individually advised). Women's HR was monitored during the training sessions, using HR monitor Polar M400, with a range of 15–240 bpm.

All training sessions included a warm-up (100––125 HRmin), core exercises (125–145 HRmin) and a cool down period (90–110 HRmin), which are described in detail in Table 2. Overall, all the sessions included breathing and relaxation techniques, antithrombotic exercises, strengthening exercises, stretching, pilates elements, and pelvic floor exercises.

To ensure maximum safety for both the mother and her fetus, all training sessions included 4–6 participants only, supervised by a qualified prenatal physical activity specialist (who was also the author of the program). Additionally, support from prenatal specialists, such as an obstetrician, a midwife, and a physiotherapist, was available to women at all times.

Table 2. An example session of the 'Conscious 9 months' exercise program

	EXERCISES	NOTES
Preparatory part *Warm-up 10–12 mins*	Sitting on the ball: — finding the correct position — spine mobility exercises — short sequence: marching, step touch, side lunge, forward lunge	Exercise ball of the right size Bare feet Both sides
Dynamic stretching y 2–3 mins (8–12 repetitions)	Forward lunge: dynamic leg stretching From sitting on a ball (wide-legged): — lunge side stretches — spine rolls (up and down)	Gentle stretching — both sides
Main part *20–25 mins* *(repetitions: individually advised, suggested 6–12)* *(repetitions: individually advised, suggested 6–12)*	Strengthening exercises on the ball (various positions): In sitting: — squats and arm circles — marching with spine rolls — wide-legged sit: 'crushing' the ball — sitting with legs in front: lifting one foot at a time and holding In lying on the back: — lifting the hips — lifting the hips and heels In lying on the side: — kneeling: opening and closing the chest (thoracic spine mobilization) with breathing coordination On hands and knees: — lifting the legs — press-ups — lifting the arms, arm circles	Strengthening exercises for main muscle groups, intertwined with breathing exercises and exercises for spine mobility Maintaining breath awareness As a variation: introducing balancing element Both sides in all asymmetrical exercises
Finishing part *Stretching and relaxation* *12–15 mins* *(6–8 repetitions)*	Sitting on the knees, transitioning to kneeling Kneeling with one leg straight: hip flexors stretching Wide-legged seated forward bend Cross-legged seated forward bend and opening the arms backward — chest opening Relaxation Lying supine on a medium soft ball, next to a wall, feet together, knees open	Both sides in asymmetrical exercise During relaxation, blankets or cushions under the knees Relaxing music In relaxation, the participants are covered with blankets

Fetal well-being

Fetal well-being assessment included blood flow velocity measurement obtained by a VOLUSON 730 EXPERT color Doppler ultrasound system. Prenatal examinations were carried out in weeks 11–14 of gestation [2]. Fetal Doppler examinations were performed in both groups in weeks 32 and 37 and included the assessment of the pulsatility index (PI) in the middle cerebral artery (MCA) and in the umbilical artery (UA). This allowed for completion of a quantitative analysis of fetal blood flow velocities and resistance, as well as calculation of the CPR.

In the method used, the speed of blood flow is characterized by several indicators which express the level of pulsation of the curve of blood flow. Those indicators are based on the maximum Doppler wave shift of the blood flow in one cycle of a heartbeat. They express maximum speed in the systolic and diastolic phases of a heartbeat.

Doppler examinations were carried out according to the recommendations of the Fetal Medicine Foundation (FMF) [16] and the International Society of Ultrasound in Obstetrics and Gynecology (ISUOG) [17].

Additionally, fetal heart rate (FHR) and resistance index (RI) were measured.

Statistical analysis

The data are presented as group mean values ± standard deviation (SD). The data were tested for normality of distribution using the Shapiro-Wilk test. A two-way (group x time) repeated measurement ANOVA with Tukey post-hoc adjustments was used to compare the changes in the dependent variables inside the groups over the intervention period. Statistical significance was set at $p < 0.05$. Statistica vs 13.1 program was used for all calculations.

RESULTS

Mean ± SD values were measured in 32 and 37 weeks (Tab. 3). A significant interaction was observed as follows: group (EG, CG) x time (32 and 37 weeks), CPR ($F_{1,66} = 7.05$;

Table 3. CPR values (mean ± SD) in the exercise group and the non-active control group

Group	CPR 32 week	CPR 37 week
EG	1.78 ± 0.34	2.08 ± 0.52*^
CG	1.80 ± 0,33	1.71 ± 0.66

CG — control group; CPR — cerebroplacental ratio; EG — exercise group; *statistical difference between the EG and CG ($p < 0.05$); ^statistically different from the value at week 32 ($p < 0.01$)

Table 4. MCA PI values (mean ± SD) in the exercise group and the non-active control group

Group	MCA PI Week 32	MCA PI Week 37
EG	1.86 ± 0,27	1.63 ± 0.34*^
CG	1.91 ± 0,27	1.42 ± 0.37

CG — control group; EG — exercise group; *statistical difference between the EG and CG ($p < 0.05$); ^statistically different from the value at week 32 ($p < 0.01$)

Table 5. MCA RI values (mean ± SD) in in the exercise group and the non-active control group

Groups	MCA RI Week 32	MCA RI Week 37
EG	0.83 ± 0.05	0.79 ± 0.08*^
CG	0.84 ± 0.05	0.74 ± 0.10

CG — control group; EG — exercise group; *statistical difference between the EG and CG ($p < 0.05$); ^statistically different value from the value at week 32 ($p < 0.05$)

Table 6. UMBA PI values (mean ± SD) in the exercise group and the non-active control group

Groups	UMBA PI Week 32	UMBA PI Week 37
EG	1.05 ± 0.18	0.79 ± 0.09
CG	1.10 ± 0.18	0.88 ± 0.23

CG — control group; EG — exercise group

Table 7. UMBA RI values (mean ± SD) in the exercise group and the non-active control group

Groups	UMBA RI Week 32	UMBA RI Week 37
EG	0.64 ± 0.08	0.57 ± 0.07
CG	0.68 ± 0.08	0.59 ± 0.11

CG — control group; EG — exercise group

Table 8. HR values (mean ± SD) in the exercise group and the non-active control group

Groups	FHR Week 32	FHR Week 37
EG	138.33 ± 8.51	136.45 ± 6.86*^
CG	142.57 ± 6.27	147.43 ± 7.35

CG — control group; EG — exercise group; FHR — fetal heart rate; *statistical difference between the EG and CG ($p < 0.05$); ^statistically different value from the value at week 32 ($p < 0.05$)

$p < 0.01$, $\eta p2 = 0.097$), $\eta p2 = 0.097$. The CPR cerebroplacental ratio difference was statistically significant between EG and CG groups at 37 weeks ($p < 0.5$). Moreover, CPR increased in week 37 as compared to week 32.

Moreover, a significant interaction was observed between groups (EG, CG) x time (32 and 37 weeks), MCA PI ($F1,66 = 5.60$; $p < 0.05$, $\eta p2 = 0.078$). The MCA PI parameter difference was statistically significant between EG and CG groups at 37 weeks ($p < 0.05$), which can be seen in Table 4.

There was also another significant interaction observed as follows: group (EG, CG) x time (32 and 37 weeks), MCA RI ($F1,66 = 6.52$; $p < 0.05$, $\eta p2 = 0.089$). The MCA RI parameter difference was statistically significant between EG and CG groups at 37 weeks ($p < 0.05$), which can be seen in Table 5.

Furthermore, there was no significant interaction between groups (EG, CG) x time (32 and 37 weeks), in UA-PI ($F1,66 = 0.86$; $p > 0.05$, $\eta p2 = 0.012$). The UA-PI parameter difference was not statistically significant between EG and CG groups at 32 and 37 weeks ($p > 0.05$), which can be seen in Table 6.

There was also no significant interaction between groups (EG, CG) x time (32 and 37 weeks), in UA-RI ($F1,66 = 1.33$; $p > 0.05$, $\eta p2 = 0.019$). The UA-RI parameter difference was not statistically significant between EG and CG groups at 32 and 37 weeks ($p > 0.05$), which can be seen in Table 7.

In addition, a significant interaction was observed as follows: group (EG, CG) x time (32 and 37 weeks), maternal HR ($F1,66 = 7.34$; $p < 0.05$, $\eta p2 = 0.100$). The HR parameter difference was statistically significant between EG and CG groups at 37 weeks ($p < 0.05$), which can be seen in Table 8.

DISCUSSION

The aim of this study was to evaluate the effects of a regular complete physical exercise program in the course of pregnancy on fetal well-being and intrauterine safety. To assess fetal well-being and safety, Doppler examinations were used, allowing for non-invasive evaluation of fetal hemodynamic changes and the degree of flow resistance [6, 18–21].

The results of this study present that during 27 weeks of this experiment, neither fetal hypoxia, growth retardation, placental exchange nor amniotic fluid volume abnormalities were observed in any of the fetuses, which is consistent with previous research [22–24]. The results of this trial are in accordance with the results of other studies, presenting that regular moderate physical activity program in pregnancy is not posing any health risks neither to the mother nor to the fetus [1, 12–15].

The results confirm no adverse influence of physical exercise on fetal well-being both in weeks 32 and 37. In week 32 the CPR ratio was within its normal range in both groups,

which indicates that maternal physical exertion as part of the exercise program had no effect on the fetus. Similarly, in week 37, the CPR ratio was also within norms, showing no adverse effect on fetal health. Importantly, CPR is seen to be a more effective parameter of fetal hemodynamic changes, as well as the cardiac output and blood flow redistribution of the fetus, than the MCA-PI and UA-PI measurements alone [4]. Several other studies assessed fetal well-being based upon the above-mentioned parameters alone, which defines the vascular resistance in the progress of blood flow, measuring this flow in the tested vessel [11, 25–27], which is not as accurate.

In this field, some studies are based on surveys and questionnaires in which pregnant women evaluate their physical activity subjectively [14, 28, 29]. Clearly, this method has clinical limitations. Moreover, the choice of exercises (their intensity, duration, and type) to determine physical activity's influence on a woman's body, still remains to be examined in further studies [11, 30]. Little data is available on physical activity in the course of pregnancy.

Barakat et al. [12] suggested that more research is needed on specifically designed regular exercise programs, including exercise guidelines and safety.

Fetal well-being assessment for this study included blood flow velocity measurements obtained by a color Doppler ultrasound system. UA and MCA were examined. The analysis of blood flow was based on the shape of the Doppler wave shift and the assessment of the PI in the MCA and in the UA.

The results show there was a slight decrease in both the MCA-PI and MCA-RI parameters, which are normal physiological mechanisms in an uncomplicated pregnancy. Hence, in both groups in weeks 32 and 37, this decrease was comparable and within a normal range.

The exercise program did not significantly influence fetal umbilical artery flow parameters. In weeks 32 and 37, the PI and RI parameters did not differ significantly or clinically in both exercise and control groups. Additionally, the dynamics of PI and RI decrease was comparable in both groups and was within normal range with the progression of pregnancy.

All of those further confirm that the exercise program did not adversely affect the fetus, as examined by Doppler ultrasound.

Additionally, the described regular exercise program had a positive effect on maternal HR in week 37. HR was significantly lower in the exercise group, which is not in line with the current research [31–35]. This result can indicate general improvement of maternal physical fitness and cardiac efficiency. It might also serve as an important factor in preparation for normal labor.

The innovation of this study, next to the use of CPR ratio, lies also in the intervention used. The exercise program was complete and rounded, included various elements, not generally available to pregnant women in routine care. Moreover, the program was individually designed, aimed at preparing women towards labor and led by an experienced prenatal exercise specialist, who continually communicated with medical personnel, ensuring maximum safety for both mother and fetus. This also had its impact on ensuring an exceedingly high adherence of the participants to the exercise program.

CONCLUSIONS

The results of the current experiment confirm that the specifically designed regular exercise program 'Conscious 9 months' (taking into consideration specific types, intensities, and duration parameters) does not pose a risk to fetal well-being and is safe for the fetus.

Additionally, the program described positively affected maternal HR in the exercise group, indicating potentially improved maternal physical fitness and cardiac efficiency, which may significantly influence normal labor.

Conflicts of interest

The authors declare that they have no competing interests, financial or otherwise.

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Effect of re-approximation of the rectus muscles on diastasis recti abdominis at cesarean section — a prospective cross-sectional study

Ersin Çintesun[1], Feyza Nur İncesu Çintesun[2], Meltem Aydoğdu[1], Denizhan Bayramoğlu[1], Çetin Çelik[1]

[1]Department of Obstetrics and Gynecology, Selcuk University Medicine Faculty, Selçuklu, Konya, Turkey
[2]Konya Research and Training Hospital, Meram, Konya, Turkey

ABSTRACT

Objectives: Caesarean section (CS) is one of the most frequently performed surgical procedures in the world and Turkey. In this study, we aimed to investigate the relationship between re-approximation of the rectus muscles during CS and the severity of diastasis recti abdominis in the first postoperative month. To investigate the relationship between re-approximation of the rectus muscles during CS and the severity of diastasis recti abdominis in the first postoperative month.

Material and methods: The study was designed as a prospective cross-sectional study. Patients were divided into two groups: parietal peritoneum closure only (Group 1), and closure of the parietal peritoneum and re-approximation of rectus muscle (Group 2). The distance between the rectus muscles and the thickest rectus muscle thickness were measured one month after CS from three anatomic regions using superficial ultrasonography by the same blinded physician. The anatomic regions were described as xiphoid, 3 cm above the umbilicus, and 2 cm below the umbilicus. The relation of the measurements between the groups was evaluated.

Results: There was a total of 128 patients, 64 in Group 1 and 64 in Group 2. There were no statistical differences between the groups in terms of the distance between rectus muscles and the thickness of rectus muscle at the described anatomic regions ($p > 0.05$).

Conclusion: Re-approximation of rectus muscles has no effect on the prevention of diastasis recti, which is an important cosmetic problem.

Key words: cesarean section; diastasis recti abdominis; parietal peritoneum; umbilicus

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INTRODUCTION

Caesarean section (CS) is an important intervention that provides safe delivery for both mother and baby. CS, defined as the delivery of the foetus through an abdominal and uterine incision, is one of the most frequently performed surgical procedures in the world and Turkey [1–3]. As with most surgical procedures, CS does not have a standard technique. There are many different techniques depending on surgeon preference from the skin to the uterus step. The effort to compare different procedures of CS and find a standard surgical technique has been ongoing for a long time [4–6]. The outcomes of the closure of peritoneum and re-approximation of the rectus muscles have been studied in the literature [7]. In some studies, early parameters such as analgesia dose, postoperative pain, infection, fever, endometritis, and length of hospital stay were investigated, but long-term complications such as diastasis recti abdominis (DRA) have not yet been investigated [7–10]. DRA is defined as the right and left rectus abdominal muscles being abnormally separated from each other at the level of the linea alba. There is no clear cut-off value associated with the inter-rectus distance used in the diagnosis of DRA [11, 12]. DRA can be caused by elevated intra-abdominal pressure, such as pregnancy and obesity. During pregnancy, DRA occurs physiologically and in some patients, it may reduce after birth, whereas in other patients, it either progresses or stays the same. Advanced age, multiparity, cesarean section history, high weight gain – especially after birth – and ethnicity have been defined as risk factors for DRA [13, 14]. There are many qualitative classification methods for DRA. In these classification methods, the width is taken at three reference points (xiphoid, 3 cm above the umbilicus, and 2 cm below

Corresponding author:
Ersin Çintesun
Selçuk Üniversitesi Tıp Fakültesi, Selçuklu/KONYA, 42075, Turkey
e-mail: ersincintesun@gmail.com

the umblicus) [12, 15], and other classifications take into account myofacial deformity [16]. In addition, studies have shown that the inter-rectus distance of women in postpartum is significantly higher than in nulliparous women up to 12 months after birth [17]. The relationship between rectus abdominis re-approximation, which is a step in CS surgery, and DRA after birth has not been investigated previously.

In this study, we aimed to investigate the relation between re-approximation of the rectus muscles during CS with DRA in the first postoperative month.

MATERIAL AND METHODS

The study was designed as a prospective cross-sectional study between June 2019 to August 2020 in patients who underwent CS at Selcuk University Hospital. This study was conducted on patients who had a standard CS in our clinic and who were eligible for the study. The patients were divided into two groups according to the closure of the anterior abdominal wall.

Each patient was assigned to one of these two groups: Group 1: parietal peritoneum closure only. Group 2: closure of the parietal peritoneum and re-approximation of the rectus muscle.

Patients with a known skeletal, muscular or systemic disease, patients with preterm pregnancies, very weak patients [body mass index (BMI) < 18 kg/m^2], overweight patients (BMI > 30 kg/m^2), multiple pregnancies, multigravid patients, patients with previous abdominal surgery or rectus abdominis muscle surgery, and patients outside the age range of 18–35 years were excluded from the study.

Sixty-four patients who underwent primary CS for various reasons were enrolled in the study. Approval from the institutional local ethics committee was obtained and each patient gave signed informed consent for their participation in the study (Reg. No. 2019/022). The physician performing the ultrasonographic measurement was blinded.

Inter-rectus distance was measured in the first postoperative month. The distance between rectus muscles and the thickest rectus muscle thickness were measured from three anatomic regions using superficial ultrasonography by the same blinded physician. The anatomic regions were described as xiphoid, 3 cm above the umbilicus, and 2 cm below the umbilicus. The relation of measurements between the groups was evaluated (Fig. 1).

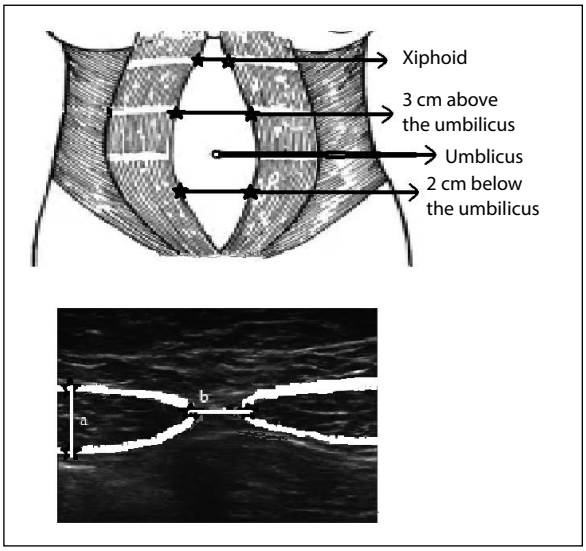

Figure 1. Schematic drawing of the anterior abdominal wall reference points and ultrasonographic measurement of inter-rectus distance and rectus thickness

Surgical procedure

In our clinic, CS is performed as described below as standard except for the rectus and peritoneum steps. Most CS are performed under regional anesthesia. All women have a Pfannenstiel-type transverse incision. The subcutaneous tissue layer is dissected using the fingers and then a small transverse incision is made medially with a scalpel and extended laterally using scissors in the fascial layer. Rectus muscles are separated bluntly. The peritoneum is opened with the forefinger. A bladder flap is formed, and a low transverse incision is made in the uterus. The uterine incision is closed using a single-layer continuous locked suture with a Vicryl 1.0 suture (Ethicon Johnson & Johnson, USA). The abdominal cavity is cleaned from amniotic fluid and blood. The parietal peritoneum is closed using a continuous Vicryl 2.0 suture (Ethicon Johnson & Johnson, USA). The re-approximation of the rectus muscle in our clinic varies according to the preference of the surgeon. The rectus muscles were re-approximated using three loose vertical midline interrupted sutures with Vicryl 2.0 sutures (Ethicon Johnson & Johnson, USA). Sutures are placed about 1 cm from the edge of the incision and 1 cm apart, without excessive tension. Subcutaneous fat is closed when the tissue was thicker than 2 cm. The skin is reapproximated using a continuous subcuticular suture with 2.0 polypropylene (Ethicon Johnson & Johnson, USA). All operative procedures are performed by the same surgeon.

Statistical analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS) version 21.0 software (IBM Corp., Armonk, NY, USA). The distribution of variables was tested for normality using histograms and the Shapiro-Wilk W-test. Parametric continuous data are presented as means ± standard deviation, nonparametric continuous data are presented as medians (min–max), and categorical variables are expressed as numbers (percentages). Data

Table 1. Characteristics of the 84 Postpartum Primiparous Women

		Group 1 n = 64	Group 2 n = 64	P
Age (years)		28.2 ± 5.5	26.9 ± 4.7	0.164
BMI		22.9 ± 3.0	22.5 ± 2.8	0.478
Gestational week		38 (37–41)	38 (37–39)	0.310
Fetal weight		3190 ± 499	3085 ± 432	0.203
Fetal sex	Female	25 (39.7%)	38 (60.3%)	0.022
	Male	39 (59.6%)	26 (41.2%)	

The data was calculated as n (%), mean (± standard deviation) and median (minimum–maximum). BMI — Body mass index; MP — Malpresentation; HT — Hypertension in pregnancy; FD — Fetal distress

Table 2. Comparison of ultrasonographic measurements of inter-rectus distances at the level of linea alba

	Group 1 n = 64	Group 2 n = 64	P
Width at xiphoid	2.1 ± 0.77	2.2 ± 0.62	0.167
Thickness at xiphoid	0.80 ± 0.24	0.84 ± 0.18	0.334
Width 3 cm above umbilicus	2.41 ± 0.83	2.67 ± 0.67	0.056
Thickness 3 cm above umbilicus	0.69 ± 0.20	0.75 ± 0.21	0.099
Width 2 cm below umbilicus	2.16 ± 0.82	2.33 ± 0.61	0.210
Thickness 2 cm below umbilicus	0.83 ± 0.42	0.79 ± 0.17	0.478

The data was calculated as mean (± standard deviation)

were analyzed using Student's t-test, Pearson's Chi-square test, Fisher's exact test, and the Mann-Whitney U test. $p < 0.05$ was considered statistically significant.

The sample size for the research, calculations were made using G*Power 3.1.9.2 computer software [18]. The sample size was calculated using a fixed-effects single factor design of the t-test (independent sample t-test). Assuming $\alpha = \%5$, power $(1-\beta) = \%80$, and an effect size $(d) = 0.50$, a sample size of 64 cases in each arm was found to be required. One hundred twenty-eight patients were enrolled in each arm of the study protocol.

RESULTS

The demographic and ultrasonographic measurements of the patients are summarized in Table 1 and Table 2. There was a total of 128 patients, 64 in Group 1 and 64 in Group 2. All patients had CS under spinal anesthesia. Age, gestational week, fetal sex, and fetal birth weight were similar between the groups ($p > .05$). The most frequent caesarean indication was malpresentation in both groups.

There were no statistically significant differences between the groups in terms of the distance between the rectus muscles and thickness of the rectus muscle at the described levels of xiphoid, umbilicus 3 cm above, and umbilicus 2 cm below ($p > .05$).

DISCUSSION

CS is as one of the most frequently performed surgical procedures in the world, and the primary CS numbers have increased globally in recent times. There are many reasons for this stiuation: advanced maternal age, nulliparity, increased obesity, fear of pain during vaginal birth, concerns of genital changes after vaginal birth, idea of a more suitable method for both mother and healthcare professionals, and fear of legal issues due to delivery complications. Although it is one of the most common surgeries, there is no standard procedure for the whole operation, the search for a standard procedure continues. DRA is an important cosmetic problem that is frequently seen during pregnancy, in multiparous women, and after cesarean surgery [11, 14, 17]. Due to the risk for persisting of DRA in the postpartum period, it is important to take steps to prevent it during CS, especially at the rectus abdominis re-approxiamation step. In the literature, it has not been investigated whether there is a relationship between DRA and surgery interventions such as CS. Re-approximation of the rectus muscle can be considered as a reasonable intervention during CS in order to prevent DRA that increases as cesarean number increases. In our study it was found that the re-approximation of the rectus muscles during CS had no effect on DRA with ultrasonography performed in the first postoperative month.

There are studies on the re-approximation of the rectus muscles during CS. Although short-term effects are mostly investigated in the literature, there are also studies investigating long-term results such as adhesions [10, 19] Lylel et al. [10] found that rectus muscle re-approximation increased immediate postoperative pain without differences in surgical time, surgical complications, or maternal satisfaction, and Omran et al. [19] found that rectus muscle re-approximation among women undergoing primary CS was associated with a significant increase in postoperative pain and analgesic requirements. In general, many physicians believe that re-approximation of the rectus muscles causes postoperative pain [20].

In our study, we investigated whether there was a relation between DRA – a condition that occurs physiologically during pregnancy and disappears after some time, but it persists in some women and causes cosmetic problems – and rectus muscle approximation in CS. For this reason, the distance between the rectus muscles in patients who had undergone primary CS was evaluated one month after the operation. In our study, the inter-rectus distances at all three anatomic regions were similar between the groups ($p > .05$).

DRA is a condition defined as an enlargement of the distance between the rectus muscles and occurs in the vast majority of pregnant patients. In a study conducted by Hsia et al. [21], the distance between the rectus muscles of women at 36 gestational weeks and at 12 gestational weeks was measured and the difference was observed to be 300–400%. In another study, 84 healthy primiparous patients were followed up in terms of DRA for 35 gestational weeks and in postpartum periods from three different anatomic regions. In this study, the limit value for DRA was accepted as 16 mm at 2 cm below the umbilicus and all patients were diagnosed as having DRA at 35 weeks of gestation. However, this rate decreased to 35–39% in the ultrasonography examined at the 6th postoperative month [22]. There is no clear consensus on DR distance. Some authors accept a direct 2 cm limit; however, DR distances have been found differently in some studies [11, 12, 23]. In some symptom-based studies, DRA symptoms were found to be at the margins of less than 2 cm [23]. In our study, we measured and compared direct distances because there was no clear cut-off value for DRA.

It has been shown that DRA is not just a cosmetic problem, it can also cause some clinical problems such as low back and pelvic girdle pain, urinary and anal incontinence, and pelvic organ prolapse [24–26]. However, there are conflicting results in the literature. A study by Spitznagle et al. [24] found that patients with DRA had at least one pelvic floor dysfunction, and there was a relationship between DRA and stress urinary incontinence, fecal incontinence, and pelvic organ prolapse. In a study by Parker et al. [25], it was found that abdominopelvic pain was significantly greater in women with DRA. In a systematic review of Benjamin et al. [26] on 2242 patients, no significant relationship was found between DRA and lumbopelvic pain, health-related quality of life, and incontinence.

The limitations of the study include the low sample size of patients, we only took primigravid patients; the inter-rectus distance is unknown during pregnancy; and some variables such as the exercise and muscle strength history of patients were not investigated. However, the strength of the study is the investigation of the relation between a frequent surgical procedure and a common clinical condition that has never been investigated before.

Reapproximation of rectus muscles has no effect on the prevention of DRA. However, there is a need for randomized controlled trials with large patient numbers where all variables are kept under control.

Conflict of interest

The authors declare that we have no conflicts of interest.

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Is there a role of prophylactic bilateral internal iliac artery ligation on reducing the bleeding during cesarean hysterectomy in patients with placenta percreta? A retrospective cohort study

Seyhun Sucu[1], Hüseyin Çağlayan Özcan[1], Özge Kömürcü Karuserci[1], Çağdaş Demiroğlu[2], Neslihan Bayramoğlu Tepe[1], Muhammed Hanifi Bademkıran[3]

[1]Deparment of Obstetrics and Gynecology, Gaziantep Univercity, Medical Medicine, Turkey
[2]SANKO University, Gaziantep Gazi Muhtarpaşa Bulvarı, Gaziantep, Turkey
[3]Department of Obstetrics and Gynecology, Health Science University, Gazi Yasargil Education and Research Hospital, Diyarbakır, Turkey

ABSTRACT

Objectives: Our study aims to evaluate the effect of bilateral prophylactic internal iliac artery ligation (IIAL) on bleeding in patients with placenta percreta who undergo cesarean hysterectomy (CH) with the use of blunt dissection technique.

Material and methods: This retrospective cohort study included 96 patients with placenta percreta who underwent planned CH with using the blunt dissection technique to allow better vesico-uterine dissection at the gynecology and obstetrics unit of a university hospital between the years 2017–2019. We carried out bilateral IIAL before CH in the study group (group 1) while we performed only CH in the control group (group 2).

Results: Group 1 and Group 2 consisted of 50 and 46 patients; respectively. There was no statistical difference between the two groups as regards to the mean estimated blood loss, the mean transfused blood products, the mean operation time, and the number of complications. In total, 24 patients (25%) had complications with the finding that the most common one was bladder injury (16/96, 16,66%).

Conclusions: Routine bilateral prophylactic IIAL before CH in placenta percreta cases does not have a beneficial effect on decreasing the amount of bleeding and the amount blood transfusion

Key words: blunt dissection technique; cesarean hysterectomy; internal iliac artery ligation; placenta percreta

Ginekologia Polska 2021; 92, 2: 137–142

INTRODUCTION

Placenta percreta is an abnormal invasion of the chorionic villi in all uterine layers and sometimes throughout the bladder and rectum [1]. Approximately 5% of adhesive placental disorders are related to placenta percreta [2]. Despite modern imaging techniques and new surgical methods, placenta percreta remains an important cause of life-threatening condition [3]. Although a hysterectomy is the most preferred surgical procedure [4], bilateral internal iliac artery ligation (IIAL) technique has been performed as a life-saving modality to decrease haemorrhage in obstetrical and pelvic surgeries when other commonly used surgical methods fail [5, 6]. There are only a few studies about using bilateral IIAL during abnormally invasive placenta [7, 8] and only placenta percreta surgery [9] which are mostly designed with a limited number of patients. Blunt dissection technique with index finger is a new surgical method to reduce bleeding in the vesico-uterine pouch and to avoid bladder injury during CH in patients with placenta percreta that invades posterior bladder wall [10].

Our study aims to evaluate the effect of bilateral prophylactic IIAL on bleeding in patients with placenta percreta who undergo CH with the use of blunt dissection technique.

MATERIAL AND METHODS

This retrospective cohort study included 96 patients with placenta percreta who underwent CH at the gynaecology and obstetrics unit of a university hospital between the years 2017–2019. A consent form was obtained from the patients before operations and an approval form was received

Corresponding author:
Çağdaş Demiroğlu
SANKO University, Gaziantep Gazi Muhtarpaşa Bulvarı, 27000 Gaziantep, Turkey
e-mail: cagdasdemiroglu@gmail.com

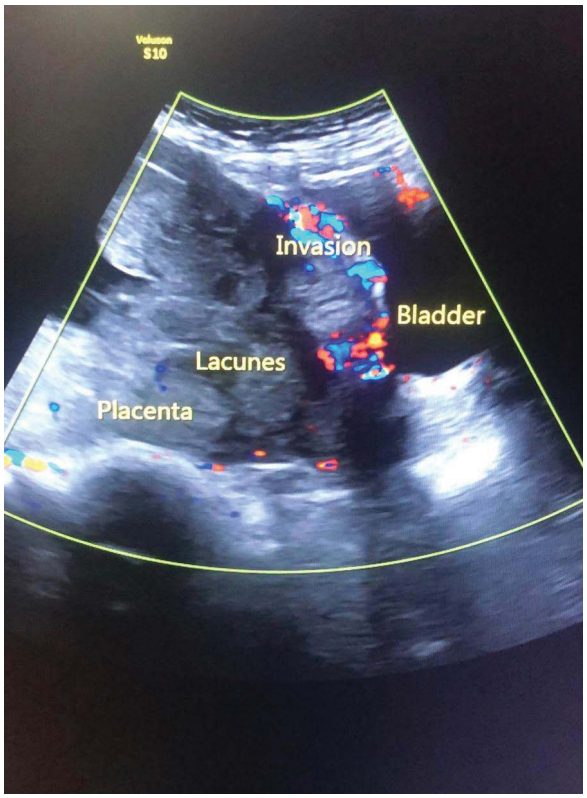

Figure 1. Doppler Ultrasonographic image of placenta percreta

from the University's Ethics Committee (Ethics Approval Number: 2019/44). We diagnosed the patients via grayscale and doppler ultrasonography (USG). Either placental lacunar zone or ambiguous vesico-uterine myometrial borderline in grayscale USG and increased vascularity between placental tissue and bladder in doppler USG were considered ultrasonographic diagnostic criteria (Fig. 1). All patients underwent planned CH with using the blunt dissection technique at various gestational weeks ranging from 34 to 37 weeks. After delivering the fetus via vertical uterine fundal incision, we filled the bladder with 300 cc saline to better determine the vascularised vesicouterine line and to provide less bleeding in all patients. Blunt dissection method was applied for all patients to make vesico-uterine dissection easier. In the first step of this method, aberrant veins between the low uterine segment and the bladder were skeletonized. In the second step, the bladder was bluntly dissected from the cervix up to the distal cervical point by using the index finger (Fig. 2). Finally, a total hysterectomy was performed. We utilized prophylactic bilateral IIAL by tying the internal iliac artery at 3 cm distal point of common iliac artery bifurcation with 2–0 silk sutures before CH in Group 1 patients (Fig. 3) and performed only CH in Group 2 patients. The same experienced surgical team who had expertise in placenta percreta surgery and were familiar with retroperitoneal anatomy. Patients with hematologic disorders, history of using anticoagulant drugs and undergoing emergency CH were excluded from the study.

Post-operative complications were handled through a multi-disciplinary approach, which included a vascular surgeon and a urologist. We repaired bladder injuries by continued suturing with absorbable synthetic monofilament suture *(Monosyn®* 3/0, B-Braun) 3/0 in the mucosa and by interrupted suturing with 2–0 polyglactin 910 *(Vicryl®*; Ethicon) in the serosa and muscular layer. Neocystostomy was employed in only one patient with the ureteral injury. Internal iliac vein injuries were repaired with 5–0 polypropylene suture (*PROLENE®;* Ethicon). We estimated the blood loss by analyzing the sum of aspirated liquid (blood minus intraoperative saline usage) to the collectors, plus, the weight difference between blood-soaked surgical compress and gauze sponges from the dry ones. The final diagnosis of patients was confirmed by histopathological findings.

Statistical Analysis

Shapiro-Wilk test was used to understand whether numerical variables were distributed normally. The data that were normally distributed between the groups were analysed through student's t-test while non-normally distributed data were compared via Mann–Whitney U test. Chi-square test was used to analyse the relations between categorical variables. For statistical analyses SPSS 22.0 Windows version was used and a p-value under 0.05 was considered significant.

RESULTS

In the present study, Group 1 and Group 2 consisted of 50 and 46 patients; respectively. The mean age of the patients in the study was 32.03 ± 4.96 (range: 19–44 years). The mean body mass index (kg/m^2) was 27.34 ± 2.35 (range: 22––33). The mean parity, gravidity and gestational age (weeks) were 3.09 ± 1.44 (range: 1–8), 4.65 ± 1.80 (range: 2–11), and 35.7 ± 1.08 (range: 34–37); respectively. The comparison of maternal demographic data was shown in Table 1. There was no statistical difference between the two groups concerning age, BMI, parity, previous caesarean section, and gestational age but there was significant difference between the two groups concerning gravidity (5.04 ± 1.95 vs 4.22 ± 1.53, p = 0.024). The mean intraoperative estimated blood loss was 1005.73 ± 518.34 mL (range: 400–3000). The mean amounts of transfused erythrocyte suspension and fresh frozen plasma were 2.47 ± 2.01 units (range: 0–8) and 2.17 ± 1.83 units (range: 0–8); respectively. The mean time of operation was 98.65 ± 31.23 (range: 50–200) minutes. The mean duration of hospitalization was 4.41 ± 2.15 (range: 2–16) days. The comparative data related to preoperative, intraoperative, and postoperative findings were listed in Table 2. There was no statistical difference between

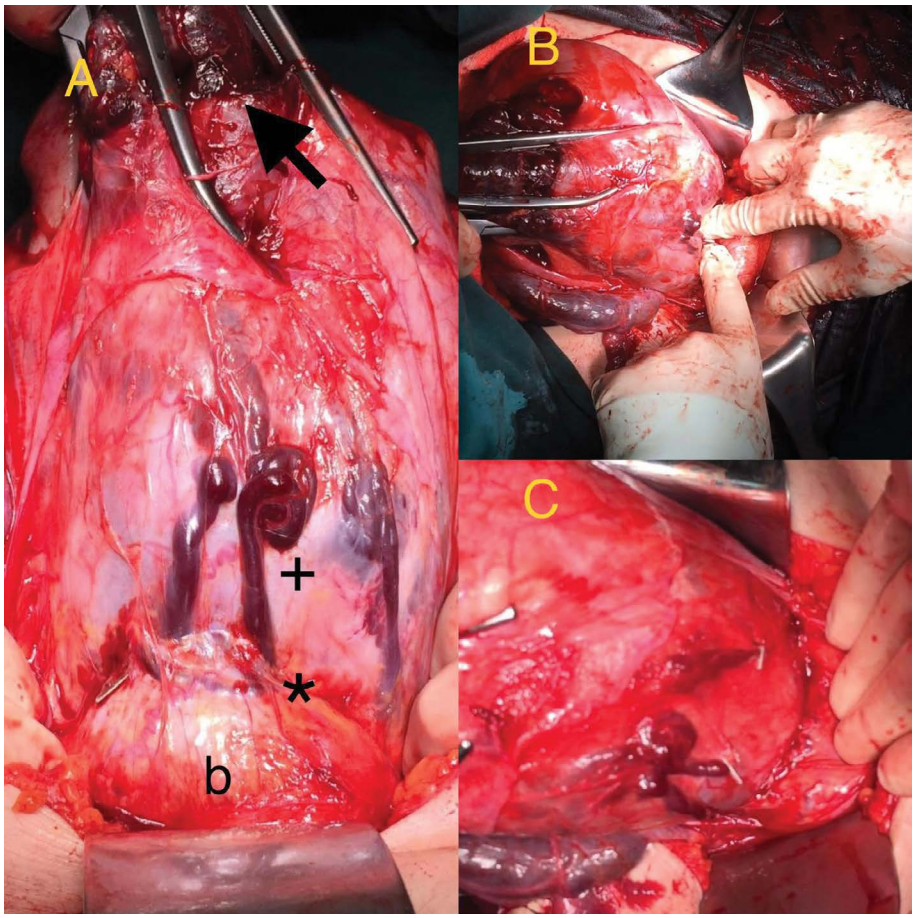

Figure 2. Utilizing blunt dissection technique; **A.** Asterisk indicates vascularised vesicouterine line. Plus sign indicates lower uterine segment; b indicates filled bladder with 300 mL saline, Arrow indicates lower part of fundal vertical incision; **B.** Vesicouetrine dissection with index fingers; **C.** Dissected bladder from lower uterine segment

the two groups as regards to all parameters which were listed in Table 2. The mean birth weight of neonates was 2732.40 ± 320.30 (range: 2000–3500) grams. The mean Apgar scores at 1st and 5th minutes were 7.10 ± 1.17 (range: 3–9) and 8.41 ± 0.88 (range: 6–10); respectively. In total, 24 patients (25%) had complications with the finding that the most common one was bladder injury (16/96, 16.66%). The complication data concerning preoperative, intraoperative and postoperative data were shown in Table 3.

DISCUSSION

In recent years, the prevalence of patients with placenta percreta has been increasing gradually both in Turkey and throughout the world. It becomes a significant complication since it might threaten mothers' health by causing massive bleeding. In this respect, it is crucial to examine whether prophylactic IIAL might be useful in decreasing massive bleeding during placenta percreta surgery.

Our study found that using prophylactic IIAL has no statistically significant role in reducing the mean blood loss and the mean transfused blood products in placenta percreta patients before CH with the use of blunt dissection technique. These findings are compatible with those of former studies that examine utilizing prophylactic bilateral IIAL before CH in patients with abnormally invasive placenta [7, 8] and only placenta percreta [9]. Kuhn et al. retrospectively found that bilateral IIAL in patients with placenta percreta undergoing CH did not significantly decrease the amount of blood loss in 11 patients when compared to 26 patients without bilateral IIAL [9]. The most recent prospective randomized study, which compared 29 patients with prophylactic IIAL before CH and 28 patients with only CH, suggested that this procedure has no significant impact on reducing intraoperative blood loss [7].

To the best of our knowledge, this study is the most comprehensive regarding the impact of utilizing prophylactic bilateral IIAL before CH on decreasing the amount of bleeding in patients with placenta percreta.

Bilateral IIAL has a beneficial impact on decreasing postpartum haemorrhage ranging from 40% to 100% in the literature [11]. The surgeons' ability and experience play a crucial role. The surgeon has to know retroperitoneal anatomy

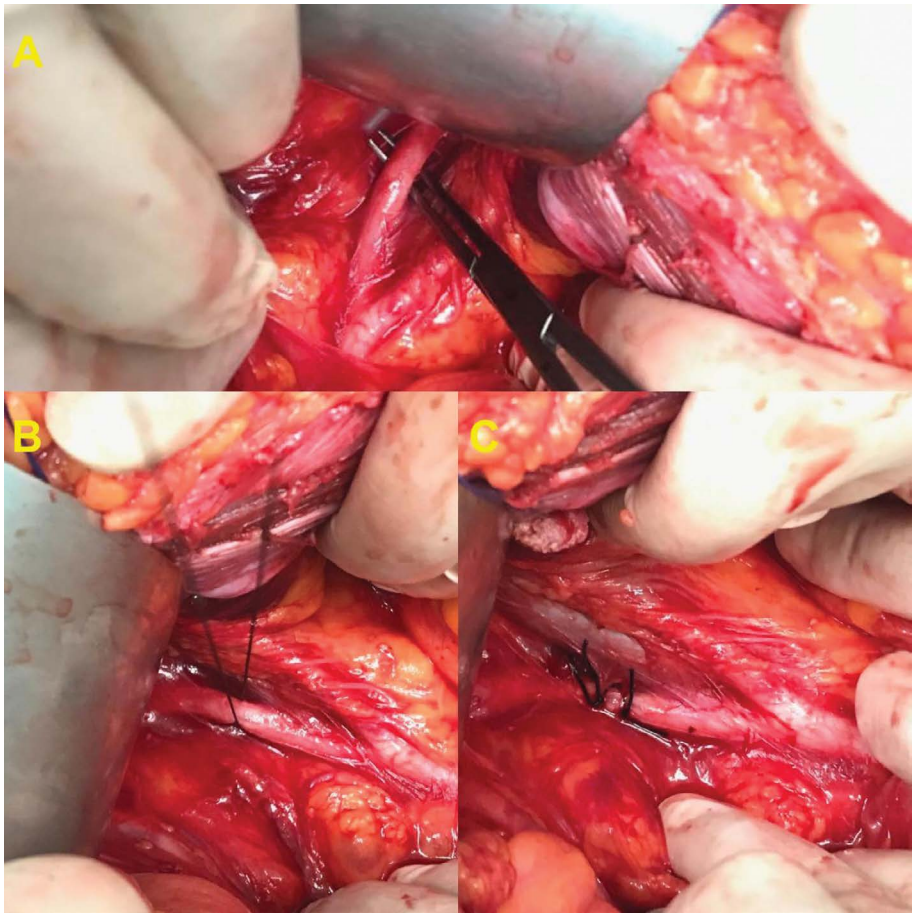

Figure 3. Intraoperative image of internal iliac artery (IIA) ligation; **A.** Dissection of IIAs sub-region with Wright surgical clamp; **B.** Holding IIA with 2–0 silk suture; **C.** Ligation of IIAL from two different points 0.5 cm apart at 3 cm distal point of common iliac artery bifurcation

Table 1. Comparison of demographical and obstetrical data

	GROUP 1 (n = 50)	GROUP 2 (n = 46)	p
Age [years] †	32.03 ± 4.96	31.17 ± 4.5	0.105
BMI [kg/m^2] †	27.53 ± 2.68	27.14 ± 1.95	0.421
Gravidity †	5.04 ± 1.95	4.22 ± 1.53	0.024*
Parity †	3.36 ± 1.63	2.8 ± 1.15	0.103
Gestational age [weeks] †	35.54 ± 1.2	35.87 ± 0.91	0.149
Previous cesarean delivery †	2.72 ± 1.01	2.5 ± 0.84	0.281

† mean ± SD; BMI — body mass index; *p < 0.05 value is significant

and must be familiar with potential complications including hypogastric vein injury, ureteral laceration or ligation, external iliac artery ligation, and peripheral nerve injuries [12]. The strengths of our study are the extensive sample size and having experienced surgeons both in retroperitoneal and placenta percreta surgery.

Internal iliac artery balloon occlusion can be used as an alternative to IIAL. However, this procedure is rarely employed only in health centres where experienced interventional radiologists can be found [13]. Moreover, performing an arterial catheter leads to chaotic complications including arterial pseudoaneurysms, acute lower extremity ischemia, reperfusion injury, and even arterial rupture [14–19]. The studies related to internal iliac artery balloon occlusion could not demonstrate any significant decrease in blood loss results [14, 20].

Although the bilateral IIAL procedure decreases the amount of bleeding in women's genital system, it cannot eliminate it [21]. Some studies stated that collateral circulation between internal and external iliac arteries contributes to extensive bleeding [22, 23]. Several studies demonstrated that intra-operative mean blood loss is less than the mean value reported in the literature by temporarily occluding common iliac arteries or aorta through the femoral artery [13, 24, 25]. Therefore, these procedures may have a promising potential on decreasing the amount of bleeding.

The main limitation of our study is designing in a retrospective manner. Another limitation may be the overestimation of complications due to the high referral rate to our third-degree hospital, which has the biggest obstetrical

Table 2. Comparison of preoperative, intraoperative and postoperative data

	GROUP 1 (n: 50)	GROUP 2 (n: 46)	p
Preoperative Hb [g/dL] †	11.43 ± 1.35	11.51 ± 1.11	0.738
Postoperative Hb [g/dlL] †	10.39 ± 1.35	9.9 ± 1.17	0.064
Intraoperative EBL [mL] †	993 ± 493.43	1019.57 ± 549.29	0.862
Intraoperative units of RBCs transfused †	2.14 ± 1.79	2.82 ± 2.18	0.102
Intraoperative units of FFP transfused †	1.88 ± 1.56	2.47 ± 2.05	0.151
Intraoperative fibrinogens [1 gr/flacon] †	0.2 ± 0.57	0.3 ± 0.73	0.587
Maternal ICU admission ‡	7 (14%)	10 (21.7%)	0.321
Operation time [minutes] †	101.4 ± 29.95	95.65 ± 32.64	0.190
Duration of hospitalization [days] †	4.26 ± 2.11	4.57 ± 2.21	0.473
The number of complication ‡	12 (24%)	12 (26.1%)	0.814

† mean ± SD; ‡ n (%); EBL — estimated blood loss; g/dL — gram/decilitre; ICU — intensive care unit; RBCs — red blood cells, FFP — fresh frozen plasma; Hb — haemoglobin; *p < 0.05 value is significant

Table 3. Complications data

Complications	Group 1 (n: 50)	Group 2 (n: 46)
İntraoperative		
Bladder injury ‡	9 (18%)	7 (15.2%)
Urethral injury ‡	0	1 (2.17%)
Internal iliac vein injury ‡	2 (4%)	0
Internal iliac artery injury ‡	1 (2%)	0
Postoperative		
Pelvic hematoma leading to re-laparotomy ‡	1 (2%)	2 (4.34%)
Ileus‡	0	1 (2.17%)

‡ n (%)

capacity in the southeast region of Turkey. The complications were classified as intra-operative (bladder injury, ureteral injury and vascular injury) and post-operative (ileus and post-operative hematoma) in our study.

Bladder injury was the most common complication

Bladder injury is more common in patients that have a hysterectomy due to placental invasion than those patients that have an elective hysterectomy because of various gynaecological reasons [26, 27]. In literature, the incidence of genitourinary injuries related to abnormally placental invasion is up to 29% [26, 28]. Nieto-Calvache et al. [29] demonstrated that the incidence of bladder injury in patients with abnormal placental invasion is 23%. However, this incidence was lower in our study when compared to the above-mentioned studies (16/96, %16,6). We attribute the low rate of bladder injury to the use of blunt dissection technique in all patients.

CONCLUSIONS

In conclusion, routine bilateral prophylactic IIAL before CH in placenta percreta cases does not have beneficial effect on decreasing the amount of bleeding and the amount of blood transfusion. Further prospective studies with more extended sample size are needed for more accurate outcomes.

Conflicts of interest

We declare that there are no conflicts of interest in connection with this article.

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Radical hysterectomy and its importance in the concept of cervical cancer treatment

Kamila Kazmierczak, Blazej Nowakowski

Surgical, Oncology and Endoscopic Gynecology Department, The Greater Poland Center Cancer, Poznan, Poland

ABSTRACT

The role and place of a radical hysterectomy in the concept of cervical cancer treatment, despite over one hundred years of its traditional use, still excites controversy.

To fully understand the value of the surgical treatment, it is worth analysing and understanding the evolutionary path of the radical hysterectomy and the changes that have occurred in this method over the years. This knowledge will allow for a better understanding as to why the choice of therapy between surgery and radiochemotherapy in the early and locally advanced stages of cervical cancer still raise doubts.

Both the introduced changes in the scope of surgery and the use of multi-module treatment - surgery with subsequent radiation therapy did not significantly improve the results of cancer treatment, but significantly increased the prevalence of side effects and therapy complications.

As cervical cancer most often affects relatively young women, the number of potential years of life after treatment is high. Over 30% of women in Poland with cervical cancer are in the 45–49 years-old age group. From the perspective of these data, obtaining a high therapeutic index, which is defined as the ratio of the number of healed patients to complications and side effects of treatment significantly reducing the quality of life, is very important in the therapy process.

Regardless of the classical radical surgery, which has evolved over many years, a new concept of radical hysterectomy based on tissue morphogenesis, called total mesometrial resection (TMMR) with therapeutic Lymph Node Dissection (tLND) with no adjuvant radiotherapy, has recently been proposed.

Based on the ontogenetic research and the study of cancerous tumour development, the concept of TMMR was first introduced by M. Höckel in 2001. In the research conducted by the author, encouraging results of the treatment of stages IB1, IB2, IIA1 and IIA2, and selected cases of stage IIB [according to 2009 International Federation of Gynecology and Obstetrics (FIGO)] cervical cancer were obtained.

Key words: cervical cancer, radical hysterectomy, total mesometrial resection

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INTRODUCTION

Surgical treatment of cervical cancer in accordance with the recommendations of the National Comprehensive Cancer Network (NCCN) and other leading scientific societies in the field of gynaecologic oncology covers the stage of disease progression from IA to IIA according to the classification of the International Federation of Gynaecology and Obstetrics (FIGO 2018). In the updated FIGO 2018 classification, stage IB has been divided into three groups according to tumour size: < 2cm; 2–4 cm: > 4 cm. In stage IA, the horizontal diameter is no longer used, only the depth of invasion is measured. No changes were made in stage II, except for the possibility of using imaging diagnostics techniques and/or pathological assessment to assess the size and extent of the tumour. [1–3].

The standard type of surgery performed in the treatment of stage IB-IIA cervical cancer according to FIGO 2018 is a radical hysterectomy with pelvic lymphadenectomy.

The concept of a radical hysterectomy was created at the turn of the 19th and 20th centuries.

In over 100 years of surgical development, the introduced modifications have allowed significant progress in reducing side effects, but both these modifications and classification changes have not had a positive effect on improving the oncological outcomes that are not sat-

Corresponding author:
Kamila Kazmierczak
Surgical, Oncology and Endoscopic Gynecology Department, The Greater Poland Center Cancer, 15 Garbary St, 61-866, Poznan, Poland
e-mail: kamilka35@icloud.com

isfactory in early and particularly locally advanced stages of cervical cancer.

The first systematised work describing in detail the method based on 500 surgery cases was published in 1912 by E. Wertheim [4]. At the very start of the author's work they pointed out that in order to achieve good results in the treatment of cervical cancer, the development of an appropriate surgical technique is of great importance.

Over the years, the technique of radical hysterectomy has undergone further modifications.

An important element of this development was the introduction of a systematic lymphadenectomy to the surgery protocol proposed and conducted by J.W. Meigs [5].

In Meigs' original surgery, the intraoperative exclusion criterion was the assessment of lymph nodes of the aortic bifurcation region (by palpation or histopathological examination in cases of macroscopically unsuspected nodes). In the absence of metastases, a full surgery including pelvic lymph nodes was performed in this region. In the former years, only enlarged-suspected pelvic lymph nodes were removed [4]. The Wertheim-Meigs radical surgery has become the standard treatment since the 1950s and the next half century.

Further modifications to a radical hysterectomy were intended to demarcate and possibly reduce its radical nature in cases of less advanced disease. These concepts were aimed at reducing possible complications associated with surgery and introduced so-called tailoring.

Piver et al. [6], published a paper in which they introduced five classes of extended hysterectomy depending on the extent of a parametrial resection.

The classification of Piver et al., has been used for many subsequent years. However, a prospective study conducted by Landoni et al., demonstrated that there were no differences in the oncological outcomes between class II and III according to Piver, but only an increase in the percentage and severity of side effects when using class III (the extent of class III surgery according to Piver corresponded to the Wertheim-Meigs operation) [7].

At the same time, over the years, a significant progress has been made in tissue preparation techniques and a deeper understanding of pelvic anatomy for radical surgery. A new approach to anatomy, considering the topography of vasculature and innervation of the pelvic organs, has been described [8].

Consequently, a new technique of radical surgery was introduced, saving the vegetative innervation, which has a significant impact on the functions of the large intestine, urinary bladder and vagina. The exact description and information of the importance of this technique can be found in a Japanese work by S. Fujii from 2007 [9].

S. Fujii originated from the school of Okabayashi H. in Kyoto, Japan, who, as early as the 1920s, was one of the world's pioneers of radical hysterectomy in that part of the world and drew attention to the possibility and need to save innervation [10].

The classification of Piver et al., did not include the principles of saving vegetative innervation proposed mainly by Japanese surgeons and adopted in European surgery [8, 9, 11–13]. In addition, other types of treatment, including the ultra-radical hysterectomy and fertility-saving surgery developed by French surgeons that were also not included in the Piver classification, were introduced [14–17].

Finally, the Piver classification only concerned open surgery and did not include the development of laparoscopic techniques and vaginal surgery. In this situation, the Piver classification ceased to be valid and was replaced by a new one introduced by Querleu and Morrow, which has been used as the most common one until now [18].

All the mentioned modifications of radical surgery were mainly associated with the concept of tailoring its radical nature and reducing universally understood side effects, but did not improve oncological effectiveness, which is still not satisfactory.

The Wertheim-Meigs radical surgery with its modifications is based on the so-called utero-centric model of anatomy described more empirically than in accordance with the biological process of human embryonic development. In the oncological aspect, it is based on the theory of accidental non-directed and uncontrolled development of a cancerous tumour. As a result of these assumptions, radical surgery should remove the organ/tumour along with a wide margin of surrounding tissues to achieve oncological effectiveness.

To a certain extent, contrary to the concept described above, another method of surgical treatment of cervical cancer was proposed by M. Höckel [19] in 2001 under the name of total mesometrial resection (TMMR).

The interesting and at the same time distinctive aspect in TMMR is an innovative approach to the anatomy of the pelvic organs and a fresh look at the resulting local and regional tumour development [20–22].

The TMMR idea is based on 3 concepts:

1. Description of embryologically defined pelvic anatomy.
2. Research on the development of a cancerous tumour that does not spread accidentally and during an initial phase of progression, only occupies tissues belonging to the embryological compartment in which it arose.
3. Development of a surgery that aims at the resection of the embryological compartment, from which a given organ, in this case the cervix, arose as a potential area at risk of the recurrence of the disease, taking into account the microscopic and molecular non-detectable aspects before and during surgery [23].

An essential and equally important element of this surgery is therapeutic lymph node dissection (tLND) [24].

Lymph nodes are one of the most important risk factors for a regional recurrence. From the perspective of the compartmental concept, all lymphatic tissue within the Mullerian compartment should be removed.

As a result of the analyses of embryological development carried out by the author of the method, the autonomic nervous system does not belong to the compartment from which the uterus originates, and therefore TMMR surgery is a nerve sparing surgery. According to the concept of this method all tissues belonging to the Mullerian compartment, which has its clear and described boundaries, should be removed. However, there is no need for extensive removal of tissues that do not belong to the compartment, although they may be in the vicinity of the cancerous tumour [25].

In the analysis of their research work, the author suggests the possibility of improving oncological outcomes based on the tissues potentially exposed to tumour development are completely removed. In a single-centre prospective study conducted by the author on a group of over 500 patients, encouragingly good results were obtained for patients treated with TMMR with tLND suffering from stage IB-IIB cancer according to FIGO 2009 (In the TMMR study, it was impossible to retrospectively adapt the current 2018 FIGO staging due to differences in diagnostic methods).

This study demonstrates that TMMR with tLND without adjuvant radiotherapy in stages IB1, IB2, IIA1 and IIA2 provides results comparable to those obtained by traditional surgery with postoperative radio/radiochemotherapy. The results for stage IIB treated with the TMMR or EMMR (extended mesometrial resection) method correspond to the oncological outcomes achieved using the latest radiotherapy techniques. An exceptionally low percentage of side effects was also observed: 21% of second grade and 3% of third grade ones according to Franco-Italian glossary. In a retrospective single-centre trial, complete or extended mesometrial resection with therapeutic nodectomy based on cervical cancer ontogenesis has good therapeutic outcomes. However, the results need to be ultimately confirmed in prospective multicentre studies [26].

It should be noted that according to the TMMR concept described above, patients do not require adjuvant radiation therapy and none of these patients received such treatment. It is assumed that surgical treatment applies to patients in whom the disease has not exceeded the compartment (up to FIGO 2009 stage IIB), which, when removed completely, leaves no room for adjuvant irradiation [26–28].

Of course, this management applies only to patients involved in the TMMR study, as it does not meet the current standards of adjuvant treatment.

According to the current standard, in the case of postoperative presence of unfavourable risk factors (positive resection margins, involvement of the parametrium, size of the primary tumour>3cm, involvement of the vascular spaces of the cervix, low histological differentiation, positive lymph nodes, exceeding the nodal capsule, invasion of the uterine muscle, histological type — glandular or anaplastic cancer, deep cervical stromal infiltration, uterine muscle infiltration, incomplete histopathological report), patients in stage I (FIGO 2018 staging) undergo adjuvant radio/radiochemotherapy and those in clinical stage IIB are treated with radiochemotherapy [31].

In the TMMR study, adjuvant chemotherapy was given only to patients with two or more metastatic lymph nodes in the postoperative specimen [26].

Similar studies were performed for the treatment of colorectal cancer in terms of oncological outcomes with the introduction of total mesorectal excision (TME). As a result of the application of TME, the 5-year survival rate increased from 45–50% to 75%, the number of local recurrences decreased from 30% to 5–8%, and the percentage of sphincter-sparing surgery increased by 20%. Thanks to TME it was possible to withdraw from adjuvant treatment in cases of colorectal cancers of stage T3N0M0 [29].

SUMMARY

The concept of treatment using the TMMR method seems interesting and inspiring, however, the question is whether it will be possible to introduce it more widely, because it is a type of surgery constituting a major challenge to a surgeon.

In over 100 years of surgery development, the introduced modifications have allowed significant progress in reducing side effects, but both these modifications and classification changes have not had a positive effect on improving oncological outcomes that are not satisfactory in early and particularly locally advanced stages of cervical cancer.

Assuming that the method of TMMR with tLND proves efficient in multi-centre studies (the study No. NCT01819077 is currently underway), it is the only one that proposes to improve oncological outcomes and, interestingly, despite its radical nature, it results in improved outcomes in terms of side effects, considering that is a nerve sparring surgery and patients are not subjected to multi-module treatment.

An important problem in the traditional approach to a radical hysterectomy is that up to 50% of patients are qualified for adjuvant radio/radiochemotherapy, which does not improve the oncological effectiveness as compared to the methods used separately, and significantly increases the number of side effects [30].

If no improvement in terms of the oncological outcomes for independent surgery is achieved, it seems very reasonable to limit surgical treatment to very early lesions (up to stage IB1 according to FIGO 2018 without suspected pelvic lymph node metastases in pre- and intraoperative tests).

This is in line with current recommendations of leading scientific societies and is highly understandable, because the excessively frequent qualification of patients for multi-module treatment seems the least beneficial.

In this context, classification and sparing techniques of the classical radical hysterectomy are of lesser importance. The case would be simple and patients with large tumours or suspected lymph node metastases should qualify for radiochemotherapy, however the results of such treatment are not satisfactory, and at the same time it also often concerns relatively young women to whom late complications of radiation therapy pose a serious threat.

A detailed description of the surgery protocol for TMMR with tLND, its subsequent modifications and treatment outcomes for individual stages of cervical cancer is not included here, because it is available and has been already reported by the author, while the present study is focused on the general concept of surgical oncology treatment of cervical cancer [24].

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REVIEW PAPER / OBSTETRICS

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Peripartum cardiomyopathy — a cardiovascular disease in pregnancy and puerperium. The actual state of knowledge, challenges, and perspectives

Karolina E. Kryczka, Marcin Demkow, Zofia Dzielinska

Department of Coronary and Structural Heart Diseases, National Institute of Cardiology, Warsaw, Poland

ABSTRACT

Peripartum cardiomyopathy (PPCM) is an idiopathic, multifactor cause of heart failure occurring at the end of pregnancy or in the first months after delivery. Although the prevalence of the disease is increasing, the awareness of both physicians and patients is rather low. Symptoms of PPCM are unspecific, making a prompt diagnosis even more difficult. In severe functional insufficiency and dilatation of the left ventricle, the recovery rate is particularly low. Therefore, the later PPCM is diagnosed, the more severe heart failure, and the worse the patient's outcome.

Despite the increasing frequency of PPCM, the exact pathophysiology and predictors of outcome are still not well determined. Therapeutic management in patients with PPCM remains a challenge, requiring a multidisciplinary approach.

At the base of the disease lies dysfunction of microcirculation with 16-kDa prolactin as the main trigger of this state. Therefore, adding bromocriptine to standard heart failure pharmacotherapy may be particularly beneficial.

In this review, we present the current state of knowledge and diagnostic and management recommendations and perspectives.

Key words: peripartum cardiomyopathy, pregnancy, bromocriptine

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INTRODUCTION

In most European counties, including Poland, there is a lack of epidemiological data on the prevalence of cardiac diseases in pregnancy and associated complications. Data from Great Britain indicate that cardiac diseases, especially those unrecognised previously, are the leading cause of death in pregnant women [1].

Although it is rare, peripartum cardiomyopathy (PPCM) comprises a significant cause of heart failure in pregnancy and puerperium [2].

Approximately 50% of patients with PPCM recover left ventricle's function. However, in the other 50% of young women at child-bearing age, the left ventricle (LV) impairment either persists or progresses to severe heart failure [2].

The aetiology of the disease is multifactorial and includes an inflammatory response to unbalanced oxidative stress, overproduction of inflammatory agents, and cathepsin D — an enzyme that induces proteolysis of full-length 23-kDa prolactin (PRL) with the generation of shorter 16-kDa fragment of PRL [3]. 16-kDa PRL induces endothelial and cardiomyocytic dysfunction, apoptosis, and it suppresses angiogenesis [3].

There is a lack of PPCM-specific treatments. However, bromocriptine — by suppressing PRL excretion from the pituitary gland — diminishes the substrate for 16-kDa PRL formation [4].

Overall management of PPCM, especially in the acute heart failure stage, requires an intensive, multifactor approach [5].

PPCM DEFINITION AND DIAGNOSIS

PPCM is an idiopathic cardiomyopathy with a reduced left ventricular ejection fraction (LVEF) < 45% with or without LV enlargement, occurring in previously healthy women at the end of pregnancy or in first months after delivery [1, 2]. No strict timeframes for the diagnosis of PPCM have been defined. However, PPCM onset is the most frequent in the first month postpartum (44%) and at delivery (23%). In pregnancy, PPCM was diagnosed in 6% of patients. The remaining 27% of women were diagnosed up to six months

Corresponding author:
Karolina E. Kryczka
Department of Coronary and Structural Heart Diseases, National Institute of Cardiology, 42 Alpejska St, 04–628 Warsaw, Poland
e-mail: kkryczka@ikard.pl

Table 1. Diagnosis of peripartum cardiomyopathy (PPCM)

PPCM symptoms	Signs of left and right heart failure	Diseases to exclude
Fatigue Decreased exercise tolerance Dyspnoea Cough Orthopnoea Palpitations Chest pain Peripheral oedema Abdominal discomfort (congestion of the liver)	Rales Jugular venous distension Gallop rhythm Ascites Peripheral oedema Low blood pressure in cardiac decompensation Peripartum hypercoagulation Haemoptysis due to pulmonary embolism Neurologic symptoms due to an acute cerebrovascular event	Heart failure exacerbation of previously undiagnosed dilated cardiomyopathy Pre-existing valve disease or congenital heart disease Myocarditis Pulmonary embolism/ amniotic liquid embolism Myocardial infarction Preeclampsia or sepsis

postpartum [6]. New onsets of PPCM thereafter are rare. However, primary mild, undiagnosed symptoms may aggravate after six months postpartum.

Awareness about the disease is rather low, and PPCM continues to be a late-recognised disease. It is especially important to diagnose PPCM at an early stage when chances for recovery are the highest [7]. Data shows that approximately 60% of PPCM patients seek a gynaecologist's advice before diagnosis by a cardiologist. Unfortunately, only 10% of these women are directly referred for cardiological consultation [7].

PPCM remains a challenge to diagnose because some signs and symptoms that occur during pregnancy and postpartum (e.g. exercise intolerance, leg oedema) may mask heart failure (Tab. 1). Moreover, there is no specific diagnostic test for PPCM. To confirm the diagnosis, other possible causes of heart failure must be excluded (Tab. 1) [8].

Therefore, it is essential to not leave women with peripartum dyspnoea without the diagnosis, as untreated PPCM may lead to further progression of heart failure and hemodynamic instability. To rule out or confirm the cardiac aetiology of dyspnoea, it is advisable to perform a simple examination and the following tests:

— 12-lead electrocardiography (ECG),
— B-type natriuretic peptide (BNP)/N-terminal pro-B-type natriuretic peptide (NT-proBNP) serum level,
— Echocardiography (Fig. 1) [2].

In case the patient is diagnosed with PPCM, strict follow-up is crucial. Even in women who present with mild symptoms, persisting LV insufficiency may be observed many months after delivery or may progress [9].

PREVALENCE AND RISK FACTORS

An accurate rate of the prevalence of PPCM worldwide has not yet been established. The highest prevalence was reported in Haiti at 1:299, and in South Africa at 1:1000. In Caucasians, the prevalence has increased in recent years from 1:1923 in 2004 to 1:1316 in 2011 [10, 11]. The latest EURObservational Research Registry on PPCM included 739 patients from 49 countries worldwide [12, 13]. Among them, 207 patients from 24 European countries constituted

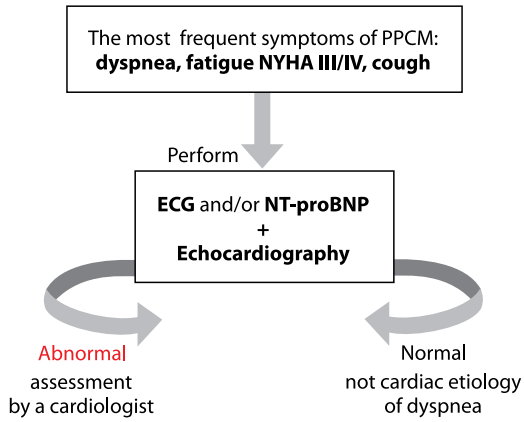

Figure 1. Diagnosis of peripartum cardiomyopathy (PPCM)

27% of all women enrolled. There were also 16 women from Poland recruited, the majority of whom (nine patients) were enrolled in the National Institute of Cardiology in Warsaw. Poland was in fourth place, regarding the number of patients recruited, after Great Britain, Germany, and Macedonia. These data show that PPCM occurs globally, and it is a matter of awareness of the disease that influences the diagnosis rate.

Therefore, it is important to recognise the risk factors of PPCM, which include advanced or early maternal age (> 30 or < 18 years, multiparity, twin pregnancies, hypertension, pre-eclampsia, prolonged use of beta-agonists, family history, a previous incidence of PPC, ethnicity, smoking [2, 14].

Observations made in the United States indicate that the mean age of women with PPCM has increased from 30.3 to 30.8 years. This data was found to be associated with a higher rate of comorbidities, such as hypertension, diabetes, dyslipidaemia, smoking, anaemia, obstructive pulmonary disease, hypothyroidism, chronic renal insufficiency, and atrial fibrillation [11].

AETIOLOGY

The aetiology of PPCM is not fully understood. In literature, there are plenty of possible pathophysiological mechanisms analysed. The main risk factors include inflammatory cytokines (INF-gamma, TNF-alpha, interleukin-6), apoptosis

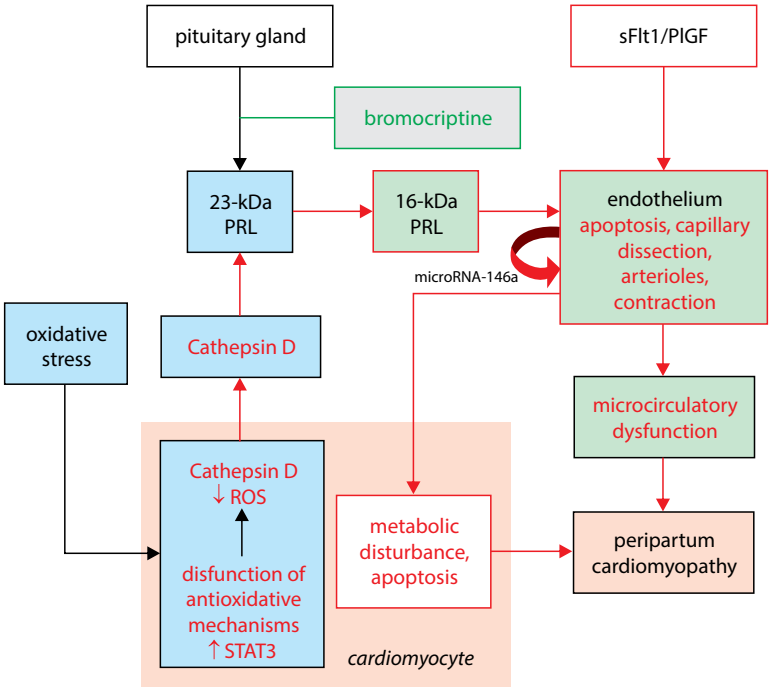

Figure 2. 16-kDa prolactin-dependent pathophysiological path in peripartum cardiomyopathy

(Fas/Apo-1), ox-LDL, and autoimmunological mechanisms including pregnancy-related autoimmunological disturbances (e.g. anti-actin antibodies), and the 16-kDa fragment of PRL [15–17].

Dysfunction of microvasculature and angiogenic imbalance seem to be the fundamental points that may be influenced by the vast majority of the pathophysiological risk factors of PPCM mentioned above. The dysfunction of microcirculation is directly resultant from endothelial dysfunction and the apoptosis of endothelial cells leading to the closure of capillary vessels by apoptotic bodies [18].

These changes, not present in dilated cardiomyopathy, are accompanied by the presence of preadipocytes, which may take part in neoangiogenesis by differentiating into endothelial cells [18]. Furthermore, an increased level of placental growth factor (PlGF) and a decreased level of soluble Fms-like tyrosine kinase (sFlt-1), resulting in a decreased sFlt-1/PlGF ratio, were found in PPCM patients after delivery [19]. These findings indicate the need for further exploration of the endothelial function in PPCM.

16-KDA FRAGMENT OF PRL

One of the main mechanisms proven to lead to endothelial dysfunction, and afterward to PPCM, is a depletion of signal transducers and activators of transcription-3 (STAT3), which protects against oxidative stress and apoptosis [3]. In the case of the depletion of STAT3, cathepsin D is activated. This enzyme cleaves a 16-kDa chain from the intact 23-kDa PRL. The shorter chain, via NF-kB path, increases synthesis of microRNA-146a in endothelial cells. MicroRNA-146a inhibits migration, proliferation of endothelial cells, and angiogenesis. It also may trigger apoptosis leading to cardiomyocyte damage (Fig. 2) [3, 20].

GENETIC PREDISPOSITION

Cases of PPCM have also been described in families with a history of dilated cardiomyopathies [21]. These findings suggest a genetic predisposition to PPCM, with mutations in the titin gene being the most frequent [21]. Recently, we have reported that the interaction of biological factors such as a high PRL levels, ventricular arrhythmias, and autoimmune disorders could modify genetic predisposition. Additionally, we have noticed that a number of coexisting risk factors may also play a role [22].

PROGNOSTIC FACTORS OF ADVERSE CARDIAC EVENTS IN PPCM

PPCM presentation, response to treatment, and outcome may vary significantly between patients.

Although it is a potentially reversible cardiomyopathy, with about a 50% rate of recovery, LVEF impairment persists or progresses to a life-threatening condition in the second half of patients [2].

The mortality rate remains high and varies in different populations, from 1.36% (in-hospital mortality) to 30% in 47-month observation [2, 16].

The first six-month data from the EURObservational Research Registry on PPCM indicated that the total death rate

was 6%, and the reported rehospitalization rate was 10% [13]. The main reported causes of death were progressive heart failure, sudden deaths, arrhythmias (including VT and VF), and embolisation [12, 13].

Although the prevalence of PPCM is increasing, exact predictors of outcome are not well defined. Among them, the baseline LVEF < 30% and LV end-diastolic diameter > 60 mm was found to be associated with a low recovery and high mortality rate [14, 23]. Additional right ventricle impairment also worsens the patient's prognosis [2]. Moreover, patients with PPCM who had not improved their cardiac function by a six-month follow-up had higher baseline NT-proBNP levels [17].

Recent studies on CMRI revealed that early signs of fibrosis assessed by T1 and T2 mapping, especially increased extracellular volume (ECV), are associated with a low rate of recoveries in long-term follow-up [24]. Also, elevated markers of fibrosis in PPCM were shown to be associated with poor LVEF recovery [25].

PPCM MANAGEMENT

According to data from the World Health Organisation, PPCM in pregnancy puts a patient at a significantly increased (19–27%) or extremely high (> 40%) risk of severe morbidity and mortality depending on LVEF (class III 30%–45% or IV LVEF < 30%) [16]. This data indicates that a patient with PPCM should be managed at an expert centre for pregnancy and cardiac diseases. As PPCM is a complex phenomenon, multidisciplinary care including different specialists, such as cardiologists, obstetricians, and clinical geneticists, is obligatory for a satisfactory outcome [5, 16].

The treatment of PPCM should meet the heart failure guidelines and be adjusted if the patient is still pregnant, as in that period some medications are contraindicated [5, 26, 27]. Heart failure therapy in pregnancy mainly consists of diuretics, vasodilators (hydralazine, nitroglycerine), and beta-blockers [5, 27].

After delivery, treatment according to the BOARD (bromocriptine, oral heart failure therapy, anticoagulation, relaxants, and diuretics) concept is recommended [28].

According to the European Society of Cardiology's guidelines on heart diseases in pregnancy, bromocriptine should be considered (Class IIb) as an addition to beta-blockers and an angiotensin-converting enzyme inhibitor (ACE-I) or angiotensin receptor blocker (ARB) [16]. Different schemes of bromocriptine treatment have been proposed according to the severity of heart failure (Tab. 2).

Bromocriptine inhibits the release of PRL from the pituitary gland. This action leads to a decrease in the amount of substrate for 16-kDa PRL formation during imbalanced oxidative stress (Fig. 2).

One randomised trial on bromocriptine therapy with a control group has been conducted so far [4]. In this study, a significant benefit from the use of bromocriptine has been observed in a group of 20 women with PPCM [4]. The dosage of bromocriptine proposed in the study was 2.5 mg twice daily for two weeks, followed by 2.5 mg daily for four weeks.

Prolonged treatment with bromocriptine, up to eight weeks, was found to enhance LVEF recovery, especially in patients with severe LVEF impairment < 30% [29].

It is worth noting that a placebo-controlled study on bromocriptine in PPCM is being conducted (ClinicalTrials.gov identifier: NCT02590601) [30].

The most beneficial bromocriptine treatment duration is yet to be established. However, such a prolonged treatment guided by serum PRL levels may be particularly beneficial [22]. Nevertheless, bromocriptine may evoke hypertension and increase hypercoagulation in the already increased hypercoagulative state associated with pregnancy and puerperium [2].

Recently, it was observed that plasminogen activator inhibitor-1 (PAI-1) is increased in patients with PPCM and plausibly possess a pathophysiological function in triggering endothelial dysfunction, cardiomyocyte injury, and myocardial fibrosis [31].

Treatment with low-molecular-weight heparin (LMWH) during bromocriptine administration is recommended after previous risk–benefit assessment [28, 29].

In the case of hemodynamic instability, treatment with inotropic agents should be introduced. As dopamine and dobutamine may increase heart failure associated with PPCM, levosimendan is the inotropic drug of choice, although its administration may be limited by hypotension [5].

As cardiac function can normalise within months in a significant number of PPCM patients, the decision to refer the patient for cardiac transplantation should not be made too early. A more recent study reports worse cardiac transplantation results, including higher rejection rates and higher mortality in women transplanted due to PPCM as compared to other patients [32].

Similarly, before any decision about the implantation of a cardioverter-defibrillator (ICD), individual clinical status (i.e. dyspnoea, history of syncope, arrhythmias) and other prognostic factors — not only LVEF — need to be evaluated. If available, a wearable cardioverter-defibrillator (WCD) should be considered in patients with LVEF under 35% for six months [5, 11].

Key PPCM treatment issues are summarised in Table 2.

If treated efficiently, LVEF improvement is most often observed in the first 6–12 months after delivery [2, 33]. However, some patients present late recoveries over 12 months [33]. The pharmacological treatment of heart failure may be gradually decreased after six months of maintaining

Table 2. PPCM management

PPCM treatment	
Antepartum	**Postpartum**
Drugs with foetal toxicity should be avoided e.g. ACE-I, ARB, MRA	Standard heart failure guidelines management BOARD: bromocriptine + beta-blockers + ACE-I/ARB + LMWH + relaxants (vasodilators) + diuretics • MRA, Ivabradine, verapamil with sacubitril (Entresto) in a later stage, if appropriate
Diuretics (furosemide) Risk of hypovolemia, hypoperfusion of uterus and oligohydramnios Vasodilators Hydralazine, nitrates • decreased vascular resistance • increased cardiac output and stroke volume • The risk of: • tachycardia, headache • angina (hydralazine) • increased uterus contractility (hydralazine)	Bromocriptine May be considered to stop lactation and enhance LV recovery (IIb) [15]: • in a patient with severe LV impairment LVEF < 25% or in cardiogenic shock: • 2x2.5 mg for 2 weeks, then 1x2.5 mg for following 4 weeks • in uncomplicated patients consider 2.5 mg once daily for at least 7 days • risk-benefit assessment (bromocriptine may increase hypercoagulation and evoke hypertension)
Beta-blockers (except labetalol) Risk of: • lower foetal birth weight, IUGR, and bradycardia in a foetus • hypertonia of the uterus Monitoring of the foetus is necessary	Statins In case of hypercholesterolemia (except patients in acute heart failure stage)
• Anticoagulation with heparin in patients with LVEF ≤ 35% or treated with bromocriptine in at least a prophylactic dose (if no contraindication exists)	
Severe PPCM course	
NYHA class III/IV, HR > 130/min or < 45/min Saturation < 90%, systolic blood pressure < 90 mm Hg Lactates > 2 mmoL/L, oliguria, cold skin, deteriorated mental state	
Oxygenation, preload optimisation hospitalisation in an intensive care unit	
Antepartum	**Postpartum**
Maturation of the foetus's lungs > 23 Hbd + 5 days (glucocorticosteroids 24 h before Caesarean section if possible)	Bromocriptine 2 × 2.5 mg (up to 10–20 mg daily, according to serum prolactin levels, until normal values are reached)
In the case of cardiogenic shock, consideration of levosimendan (0.1 µg/kg/min for 24 h) instead of catecholamines. Early transfer to an experienced centre Early evaluation of mechanical circulatory support according to the centre's experience	
1. Optimised HF-therapy (as above) 2. No response: digoxin, IABP/ECMO 3. Caesarean section	1. Optimised HF-therapy (as above) 2. No response: IABP/ECMO, LVAD, BiVAD (bridge to recovery or transplant)
Consideration of WCD in early prevention of sudden cardiac death (if accessible) or ICD (in late prevention of sudden cardiac death) in patients with LVEF ≤ 35%	

ACE-I — angiotensin-converting enzyme inhibitors; ARB — angiotensin receptors blockers, BiVAD — biventricular assist device; IABP — intraaortic balloon pump; ECMO — arterio-venous extracorporeal membrane oxygenation; ICD — implantable cardioverter-defibrillator; IUGR — intrauterine growth retardation; LMWH — low-molecular-weight heparin; LVAD — left ventricle assist device; MRA — mineralocorticoids receptor antagonists; WCD — wearable cardioverter-defibrillator

LVEF > 50%. However, drugs cannot be discontinued in all patients who have recovered.

It is important to remember that if LVEF does not increase above 50%, the risk of heart failure relapse in the next pregnancy as high as 56% with a mortality rate of 12% [34]. On the other hand, in case of subsequent pregnancies of PPCM patients, prophylactic bromocriptine administration directly after delivery with standard HF therapy improved outcomes [34].

Co-morbidities

The patient with PPCM needs to have a strict ambulatory follow-up performed in case she develops other conditions such as postpartum thyroiditis — the most frequent autoimmune disorder after delivery that may also affect the course of PPCM [22, 35].

SUMMARY

PPCM remains a significant cause of heart failure in pregnancy and postpartum. Undiagnosed PPCM may rapidly progresses into a life-threatening condition. The primary diagnosis of pregnancy/puerperium-associated dyspnoea should include ECG, NT-proBNP, and echocardiography. Strict ambulatory monitoring during treatment is essential in case of the development of other cardiac and extracardiac conditions. It would be advisable to conduct a Polish PPCM

Registry, as there is no data related to PPCM prevalence, course, or outcome available for the country. Moreover, such a registry may be the impetus for studies that may identify new pathophysiological pathways active in PPCM aetiology. These may lead to the discovery of new therapeutic agents that improve patients' survival.

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VIA MEDICA

RECOMMENDATIONS

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Recommendations for the prevention and treatment of postpartum depression

Monika Dominiak[1], Anna Z. Antosik-Wojcinska[2], Marta Baron[3], Pawel Mierzejewski[1], Lukasz Swiecicki[3]

[1]*Department of Pharmacology, Institute of Psychiatry and Neurology in Warsaw, Poland*
[2]*Department of Psychiatry, Medical University of Warsaw, Poland*
[3]*Department of Affective Disorders, II Psychiatric Clinic, Institute of Psychiatry and Neurology in Warsaw, Poland*

ABSTRACT

Epidemiological data clearly indicate that depression is becoming an increasingly important health and social problem today. According to the World Health Organization (WHO), depression currently affects 350 million people worldwide and is considered the second most common cause of disability in Europe after ischemic heart disease. It is estimated that this health problem may affect as many as five million people in Poland. The gap between the reported number of patients treated and the prevalence of depression, highlights the scale of unmet needs. With the limited availability of specialists in psychiatric care, the most appropriate measures seem to be those aimed at increasing the competence of doctors of other specialties in the diagnosis and treatment of depression. Early detection and treatment results in faster remission, reduces relapses and mortality.

The recommendations concerning prevention of depression were commissioned by the Polish Ministry of Health as a part of the Depression Prevention Program for 2016–2020. The Program has developed recommendations addressed to specialists in various fields of medicine, other than psychiatry, focusing on three risk groups: children and adolescents, women in the perinatal period and the elderly. These recommendations focus on the management of suspected postpartum depression and provide specific guidelines for medical staff having contact with pregnant and postpartum women (gynecologists, midwives, pediatricians).

Key words: postpartum depression; postnatal depression; perinatal depression; prevention of depression; recommendation

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INTRODUCTION

Postpartum depression [also called pure postpartum depression, postnatal depression, post baby depression (PPD)] affects 10–15% of women. Adapting to the role of a parent may be a great challenge for a woman, and the postnatal period is often associated with various challenges and health problems. This may trigger new disorders, as well as exacerbate existing ones. It is a moderate to severe disorder that usually occurs up to four weeks after childbirth. The episode of postpartum depression usually lasts between 3–9 months but can last longer if is untreated - the symptoms may persist for one year after childbirth [1].

Epidemiology

According to a report by the World Health Organization (WHO) [2], 80% of women may experience a complex of emotional difficulties after childbirth, the so-called "baby blues". The prevalence of postpartum depression is estimated at 7–19% [3, 4]. The results of the meta-analysis indicate that the prevalence of depressive disorders in women in the postnatal period is about 13% [5], which makes it the most common postnatal complication [3]. However, researchers emphasize, that the disease remains under-diagnosed and its actual occurrence is much higher [6–8].

The risk of relapse depends on the individual history of the disease. Women who have experienced an episode of postnatal depression for the first time, have an almost doubled risk of developing depression in subsequent pregnancies [9]. Beginning of depression within 6–8 weeks after childbirth, the higher severity of depressive symptoms, presence of psychotic, hypomanic or manic symptoms suggest, that the risk of recurrence of PPD in these patients may be higher as compared to general population.

Symptoms of postpartum depression

The axial symptoms of postpartum depression are persistent sadness and fatigue combined with anxiety concerning the development and health of the child. In the course

Corresponding author:
Anna Z. Antosik-Wojcinska
Department of Psychiatry, Medical University of Warsaw, 7 Nowowiejska St, 00-665 Warsaw, Poland
email: antosikwojcinska@gmail.com

of the illness intrusive thoughts (mainly related to hurting the baby), sleep disorders, lack of appetite, lack of energy, problems with concentration, feeling guilty and suicidal thoughts occur also quite often [10]. Anxiety, excessive and inadequate care about one's own health and baby's health are also often observed.

Recognition of postpartum depression

The current two major classification systems, Diagnostic and Statistical Manual of Mental Disorders V (DSM-V) [11] and International Classification of Diseases-10 (ICD-10) [12], do not consider postpartum depression as a separate diagnosis. According to the ICD-10, to recognize postpartum depression, the patient should meet the criteria for a depressive episode and the time criterion - the beginning of the episode up to 6 weeks after childbirth. The DSM-V classification is similarly precise, the difference concerns the beginning of the episode of depression - up to four weeks after delivery. However, some reports indicate that the disorder may develop up to one year after birth [13].

The criteria for recognizing depression are presented in Table 1.

In severe depression, it is necessary to identify at least two basic symptoms and two additional symptoms. In depressive disorders that do not meet the criteria for severe depression, there is usually only one symptom from the list of basic symptoms.

Baby blues

Postpartum depression should be differentiated from so-called baby blues syndrome (postpartum blues), which occurs in most mothers. Characteristic symptoms include moderately decreased mood, irritability and combined emotional lability with fear and tearfulness, feeling overwhelmed by new responsibilities, hypersensitivity to stimuli, feeling of exhaustion, problems with concentration of attention [14]. Baby blues usually appear between 1–14 days after childbirth, reaching a maximum between 3–7 days, *i.e.* in the period with the greatest hormonal changes. This condition should cease to exist up to three months after childbirth. These symptoms do not impair the mother's ability to normal functioning.. It does not require psychiatric treatment, but rather the support for mother, to ensure her safety and help in her daily activities. Sometimes intense and persistent baby blues can develop into postpartum depression [15].

Table 1. Criteria for diagnosing a depressive episode according to ICD-10

Basic symptoms	Additional symptoms
Decreased mood	Weakening of concentration and attention
Loss of interest and ability to rejoice	Low self-esteem and little self-confidence
Reduction of energy leading to increased fatigue and reduced activity	Feeling guilty and of little value (even in mild episodes)
	Pessimistic, black vision of the future
	Suicidal thoughts and deeds
	Sleep disorders
	Reduced appetite

Note: In order to make a diagnosis, it is necessary to state that the disorder persists for a period of at least 2 weeks, although it may be shorter when the symptoms reach very high intensity and increase quickly.

Postnatal psychosis

Postpartum depression also requires differentiation from psychosis, which usually manifests itself before the third week after the childbirth. The incidence of this disorder is estimated at 0.1–0.2%. Among risk factors are mental disorders in the family or in the woman's past life, first childbirth, caesarean section, death of a child in the perinatal period, single motherhood, social isolation. Symptoms usually include sleep disorders, agitation, anxiety, psychotic symptoms (hallucinations, delusions) associated with the child, suicidal thoughts or obsessive thoughts of harming the baby. If postnatal psychosis is suspected, an urgent referral to psychiatric treatment is recommended.

Postpartum depression risk factors

Similarly, to other mental disorders, there is no single cause of PPD. Although, biological factors seem to play a role, and environmental factors are often needed to trigger the illness [16]. This is also supported by the fact, that convincing empirical evidence on the impact of sole biological agents (including genetic, epigenetic, reproductive hormones changes or immune system variations) are still lacking, despite a strong theoretical rationale for its impact [17]. Thus, numerous factors may play a role and PPD is considered as a complex, multifactorial disorder. The identified factors that may foster its development can be grouped into several categories [14, 15,17–22]:

- Biological factors: genetic loading (depression or other mental disorders in the family)
- Clinical factors: previous occurrence of depression during pregnancy (women who have had depression during pregnancy are five times more likely to develop postpartum depression [23]), previous history of depression not related to pregnancy, anxiety during pregnancy, prolonged baby blues
- Obstetric and infant related factors: pregnancy or delivery related complications, stress related to childcare, difficult child temperament
- Psychological factors: recent stressful life events

- Social factors: lack of social support, marriage problems, lack of support from the partner
- Socioeconomic status: lack of employment, mother's difficult financial situation

Problems related to postpartum depression

Despite numerous evidence of the effectiveness of the treatment of postpartum depression [24, 25], the disorder is still very often unrecognized. There are at least several reasons for this. The postnatal period is very specific in woman's life and may involve various obstacles to access the treatment. The first obstacle is that women who are breastfeeding may be reluctant to take up drug treatment because of the concerns of the possible impact of drugs on the baby [26]. Secondly, new mothers absorbed by their newborn baby may not have time to undertake psychotherapy [27]. Besides, instead of planning long sessions with the psychotherapist, they may want to sleep, eat a meal in peace or just rest a moment [27]. A completely different matter is also a lack of general knowledge in society about this issue and stigma related to mental disorders. All the above make it difficult for women to perceive their mental state as an illness and to motivate them to seek help. Finally, new mothers may be particularly over-sensitive about how they are perceived [28]. Fear of the stigma of being a "bad mother" can serve as a major barrier in seeking specialist help. As a result, depressed women may refuse to accept help or even deny the diagnosis of depression. Interestingly, although postpartum depression is a condition experienced by woman regardless of cultural identity and beliefs [29], these issues often significantly affect (positively or negatively) the perception of this disorder and result in seeking a professional help. In particular, a reluctance of women from minority ethnic groups to ask for help is noticeable [30]. Because of these unique barriers, the prevention of postpartum depression, instead of treatment, seems to be particularly important.

Since there is no single etiological pathway leading to the development of postpartum depression, methods of its prevention include various activities. However, it appears that in terms of prevention there are also various barriers that hinder its wider application. Some studies also point to the important role of education in birthing schools. This intervention is practiced in Poland, but it seems insufficiently. Such intervention makes women and their partners aware of the problem and helps them to overcome their resistance to seek specialist help [31]. However, regardless of insufficient education in birthing schools, it seems that medical staff involved in the perinatal care are also quite very often not able to recognize postpartum depression. There is a shortage of postgraduate education concerning mental health during pregnancy and postpartum period leading to insufficient knowledge among medical staff and under-diagnosis. In addition, a lack of unified approach to screening for depression results in a lack of relevant skills among professionals involved in perinatal care. There are also no national guidelines for the prevention, treatment and further management of a patient with PPD. Moreover, there is a lack of properly, centrally organized perinatal mental health service and no guidelines concerning referral to psychiatric services. Furthermore, the access to psychiatric/psychological consultation at public clinics financed by National Health Fund is problematic in Poland, and the waiting period is exceedingly long in the majority of facilities. The possibility of receiving proper and prompt support is limited also for many other reasons (*e.g.* for financial reasons, barriers to service provision, availability of a specialist). All these factors ultimately lead to the fact that a woman in need of help is unlikely to receive such help. In summary, there is a lack of adequate support for new mothers and this is particularly noticeable in the context of their mental well-being. According to a meta-synthesis of studies aiming at exploration of new mothers' needs, women want to feel 'cared for' during the postnatal period, to be recognised as individuals and have access to a good quality care with flexibility in recognition of their personal and cultural contexts [32].

Impact of postpartum depression on child development and family life

Untreated depression can lead to long-term changes in many areas of family life. It not only results in a direct deterioration of a woman's mental health, but can also be reflected in marriages, the development of the child, as well as translate into subsequent decisions related to procreation.

The mother's mental state directly translates into the child's health and development. Studies confirm delayed speech development in children, delayed psychomotor development [33–35], as well as incorrect formation of the mother-child bond [36].Various mental problems in children can persist up to the age of 4–8 years [37–39]. However, the research confirms that the effective treatment and the relief of depressive symptoms in the mother directly translates into improvement of the child's mental state, development and behavior [40]. That is why it is so important to accurately diagnose and treat it early [41].

The other research has also shown that women with depressive symptoms are less likely to attend gynecological check-ups after childbirth, as well as pediatric visits and vaccinations [42]. Mothers are also often unaware that their experience exceeds the norm of mental state after childbirth. That is why it is so important to include all the health professionals that may come into contact with a woman in the perinatal period (general practitioner, pediatrician, gy-

necologist, midwife in a gynecological hospital, community midwife) in the postnatal care [1].

The aim of this recommendation was to determine the principles of prevention, screening, treatment and management with postpartum depression for medical staff treating woman in the perinatal period.

REVIEW OF GUIDELINES FOR THE PREVENTION, SCREENING AND TREATMENT OF POSTPARTUM DEPRESSION DEVELOPED IN VARIOUS COUNTRIES WORLDWIDE

In order to analyze the available recommendations for prevention, screening and treatment of patients with postnatal depression, a selection of available guidelines developed worldwide was performed. The guidelines were evaluated in accordance with Appraisal of guidelines for research and evaluations (AGREE II instrument) [43]. The recommendations were compiled based on the chosen guidelines (Tab. 2 and 3).

Guidelines for the prevention and screening for postpartum depression

One of the most recognised guidelines for the prevention of depression is the Australian Beyond Blue Program (www.beyondblue.org.au), a national initiative to raise public awareness of early responses to depressive behavior. This program has also developed recommendations for the prevention of and dealing with postpartum depression (Beyond Blue Clinical Practice Guidelines for Depression and Related Disorders — Anxiety, Bipolar Disorder and Puerperal Psychosis - in the Perinatal Period. A Guideline for Primary Care Health Professionals. Melbourne: beyondblue; 2011) [49]. The most comprehensive recommendations, covering many issues related to perinatal depression, are contained in the Beyond Blue initiative and also the document developed by the National Institute for Health and Care Excellence (NICE, 2014) [48]. The Scottish Intercollegiate Guidelines Network (SIGN) [15] are also extremely detailed, focusing mainly on the mental health of the mother as well as prevention and treatment of mental disorders. A summary of conclusions from the most important recommendations is presented in Table 2.

In clinical settings, identification of women with risk factors during pregnancy allows for early intervention and prevention of episodes of PPD. Early screening during pregnancy allows not only to identify women at risk who do not show symptoms, but also those who already show subclinical symptoms of depression.

Table 2. Key recommendations for prevention and screening for postnatal depression (PPD)

Organization	Recommendation
U.S. Preventive Services Task Force (USPSTF), 2016 [44]	Recommends routine screening of adult populations and pregnant and postpartum women. At the same time, it indicates the need to provide the examined person with access to further care and coordinated treatment.
American Psychiatric Association (APA), 2010 [10] American College of Obstetricians and Gynecologists (ACOG), 2007 [45]	Recommends a routine screening for PPD during a follow-up gynecological visit 4–6 weeks after childbirth. The patient during pregnancy should be educated about possible complications associated with PPD. Patients with baby blues symptoms require special monitoring and evaluation of depressive symptoms.
American Academy of Pediatrics Bright Futures (AAP), 2010 [46]	The role of the pediatrician as the key to ensuring health for the whole family, the mother's mental problems directly affect the child's development. The guidelines recommend that pediatricians should routinely assess the presence of depression in women who come to visit with their children.
American College of Nurse-Midwives, 2003 [47]	As a routine part of the care of a patient during pregnancy and after childbirth, it is recommended to screen for PPD.
National Institute for Health and Care Excellence (NICE), 2014 [48]	Recommends routine assessment for depressive symptoms in every woman in the perinatal period using standardized screening tools. This examination should be performed at least twice (at the first visit during pregnancy and during the first year after birth). NICE recommends a set of two initial "Whooley questions". If a woman answers positively to any of the two questions, or is at risk of mental illness, or if her clinical history indicates depression, a full assessment of her mental condition using EPDS or PHQ-9 screening tools or referral for further treatment (family doctor or specialist psychiatrist) is recommended. It also recommends asking woman about the history of alcohol and drug addictions.
Scottish Intercollegiate Guidelines Network (SIGN), 2012 [15]	Recommends a minimum of three assessments (during the first visit in pregnancy, 4–6 weeks and 3–4 months after the childbirth). In addition, it is advisable to add an interview for affective disorders, and in the case of a positive interview, a screening for depression at each visit. Same as NICE, SIGN recommends a set of two initial questions for screening and, if further evaluation is needed, use the EPDS scale.
Beyondblue, Guideline for Primary Care Health Professionals, 2011 [49]	Recommends using the EPDS questionnaire to examine all pregnant and postpartum women for depression as part of an assessment for the occurrence of depressive and anxiety symptoms. Screening should be performed between 6 and 12 weeks after childbirth during the follow-up visit. A score of 13 or more may be interpreted as postpartum depression.

Table 3. The most important recommendations regarding treatment and further management with woman with postpartum depression (PPD)

Organization	Recommendations
American Psychiatric Association (APA), 2010 [10]	Recommended non-pharmacological interventions include CBT and interpersonal therapy. The risk of potential exposure of the child to the drug should be taken into account when deciding whether to use pharmacological treatment during breast-feeding.
National Institute for Health and Care Excellence (NICE), 2014 [48]	Recommends a stepwise approach to treatment model (does not apply to women with a severe disease episode, which should be immediately referred to specialist psychiatric care). Mild to moderate PPD can be successfully treated at the level of primary care. NICE also emphasizes that a comprehensive appointment and treatment plan should be prepared for women with already diagnosed mental illness.
Scottish Intercollegiate Guidelines Network (SIGN), 2012 [15]	CBT therapy should be considered in women with mild to moderate PPD. Both SSRIs and tricyclic antidepressants may be recommended for the treatment of moderate to severe episodes of postpartum depression, after careful assessment of the risk to the breast-fed child.
Beyondblue, Guideline for Primary Care Health Professionals, 2011 [49]	Recommended non-pharmacological interventions include: psychological support, CBT therapy, interpersonal therapy and psychodynamic therapy. When deciding whether to use pharmacological treatment during breastfeeding, the risks arising from the child's potential exposure to the drug should be taken into account.

To assess the severity of postpartum depression, specialist screening tools are used, *e.g.* Edinburgh Postnatal Depression Scale (EPDS) [50], Postpartum Depression Predictors Inventory (PDPI), Antepartum Questionnaire (APQ), Postpartum Checklist or Bromley Postnatal Depression Scale (BPDS). In each case, however, the assessment of the patient's mood should be supplemented by an interview covering psychological and social aspects. A especially sensitive and widely investigated test to detect postpartum depression is EPDS [51]. It is a self-assessment questionnaire consisting of ten short questions relating to symptoms such as: anhedonia, sense of guilt, anxiety, panic attacks, exhaustion, sleep disorders, sadness, tearfulness and suicidal thoughts. The authors of the questionnaire indicate a score of 12/13 points as a borderline, indicating the occurrence of postpartum depression symptoms. An additional advantage is the possibility to draw attention to a particularly important issue — suicidal thoughts, when a woman highly appreciates the presence of suicidal thoughts, even when the overall EPDS score is low. Studies confirm that most women and medical professionals accept screening with EPDS. It is also stressed that the completed EPDS questionnaire enables and facilitates discussion about the feelings and woman's mental condition. A Polish version of this questionnaire is also available [52]. The positive predictive value of the EPDS questionnaire is estimated at 70% [50] and even 90% [53]. It has already been successfully used in Polish studies evaluating the occurrence of postnatal depression, which demonstrated its high reliability (alpha-Cronbach coefficient — 0.90) [54]. Interestingly, an intervention in the form of screening with the EPDS carried out six weeks after childbirth during a midwife's home visit, proved to be effective in reducing the risk of PPD [55].

Beyond Blue recommends using EPDS to screen all pregnant and postpartum women for depression as a part of an overall assessment of depression and anxiety.

The US Preventive Services Task Force (USPSTF, 2016) [44] has recently updated its recommendations and recommends a routine screening for depression of pregnant and postpartum women. The UK National Institute for Health and Care Excellence (NICE), on the other hand, recommends a routine assessment of depressive symptoms in every woman in the perinatal period using a set of two initial "Whooley questions":

- Have you had feelings of sadness, depression or hopelessness in the last month?
- Have you experienced reduced interest or reduced pleasure in doing activities in the last month?

The differences between the cited recommendations concern in particular the time and frequency of follow-up visits during which screening for depression is carried out. This is partly due to differences in the organization of health care for women in perinatal period in different countries. For example, in Australia, women report to their GP, obstetrician or pediatrician six weeks after the childbirth. In the UK, on the other hand, midwives play an essential role in maternity care, including home visits after childbirth.

Guidelines for treatment and further management with woman with postpartum depression

The treatment of depressive disorders in women in the perinatal period is a major medical challenge. Such decision must include consideration of the balance of the risks associated with fetal exposure to the drug, potential negative effects of untreated depression and benefits related to the relief of depression. Untreated depression during pregnancy is not only associated with poor nutrition and worse prenatal care, but also with a greater risk of smoking and abuse of psychoactive substances by a pregnant woman, as well as with significant suffering for women experienc-

ing decreased mood, dissatisfaction with parenthood and a sense of parenthood guilt. In extreme cases, they may even attempt suicide or infanticide. Therefore, treatment is necessary to improve the functioning of both the depressed women and her family.

Many pregnant women prefer psychological rather than pharmacological intervention. The main reasons include: the fear of potential side effects of antidepressants on the developing fetus or newborn during lactation, putting baby's health over own's health, general concerns about the effectiveness of medicines and fear of drug addiction. Recommendations for the treatment of mild to moderate depression in pregnancy, based on the results of meta-analyses, indicate the effectiveness of cognitive-behavioral (CBT) or interpersonal (IPT) therapy, both in individual and group form. Psychotherapy is recommended as a first-line treatment that should be applied before pharmacotherapy.

Considering the established efficacy of SSRIs in the treatment of major depression beyond the perinatal period, drugs such as citalopram, escitalopram and sertraline are suggested in pregnancy - based on their effectiveness and safety — as a second-line treatment, a combination therapy with SSRI and CBT or IPT may also be considered. All drugs from the SSRI group , except of paroxetine, are included in group C, while paroxetine belongs to group D. However, it should be emphasized that the use of antidepressants is associated with a higher risk of spontaneous miscarriages and preterm birth [56],withdrawal syndromes (occurring in 30% of newborn) , *i.e.* tremor, increased muscle tension, sleep disorders or loud crying [57, 58]. However, these symptoms usually resolve spontaneously and do not require any specific treatment. Some studies also indicate an increased risk of congenital defects in children of mothers treated with SSRI in the first three months of pregnancy, *i.e.*: congenital heart defects, persistent pulmonary hypertension, premature overgrowth of cranial sutures and fibrous skull bone joints and a hernia of the navel ring [59, 60].

Other treatments, including neurostimulation and complementary and alternative psychological strategies, such as: CBT-based therapy deliver by the Internet, CBT-based attention training, pair therapy, supportive psychotherapy and psychodynamic psychotherapy can be considered as third-line interventions.

In severe depression during pregnancy, drugs are used as the primary treatment - alone or in combination with CBT or IPT, as well as the electroconvulsive therapy (ECT). However, many clinicians consider ECT to be the first-choice treatment in severe depression in pregnancy since it is safer and more effective method of treatment than antidepressants [61].

Mild and moderate postpartum depression can be effectively screened and recognized in primary care settings (family doctor, pediatrician, gynecologist). Referral to a psychiatrist is advisable in the case of suicidal thoughts, thoughts of harming the child, when a severe episode of depression, bipolar affective disorder or psychosis is suspected [1, 15, 48].

For women with mild to moderate postpartum depression who are breastfeeding, treatment recommendations include IPT and CBT as a fist-line treatment. Second-line recommendations include pharmacological treatment.

SIGN, NICE, American Psychiatric Association (APA) [10, 15, 48], and Beyond Blue [49] recommend the following methods for mild to moderate postpartum depression:

- computer programs based on behavioral and cognitive therapy (CBT),
- physical exercise,
- psychosocial interventions,
- non-directive counseling (active listening),
- CBT therapy,
- interpersonal therapy,
- antidepressants when the patient does not opt for psychotherapy, when psychotherapy is not available or has not worked, or when there have been episodes of severe depression in the past (NICE, APA).

In the case of severe postpartum depression and moderate depression in women with a history of severe depression, it is recommended to consider the following treatment options [10, 15, 48, 49]:

- CBT therapy or interpersonal therapy,
- antidepressants when the patient does not opt for psychotherapy, or when psychotherapy has not worked (NICE),
- antidepressants combined with psychotherapy if the response to pharmacological or psychotherapeutic treatment is insufficient.

Pharmacological treatment of postpartum depression in a woman who is not breastfeeding does not differ from the guidelines for the treatment of depression not related to pregnancy and postpartum period. Studies on different aspects of pharmacological treatment of postnatal depression in breastfeeding women are insufficient to draw firm recommendations [62].

Beyond Blue, NICE, SIGN and APA recommend that the risks of potential exposure of the child to the drug should be taken into account when starting pharmacological treatment during breastfeeding. It is also important to consider the previous response to the drug and the possible worsening resulting from the switch from current treatment to treatment considered safer for breastfeeding. Some antidepressants are recognized safer than others for breastfeeding, however, there is a limited amount of scientific evidence, especially concerning the potential long-term effects in a child [10]. Weissman et al. [63] demonstrated that serum

concentrations in the child were highest for fluoxetine and citalopram, while nortryptiline, sertraline and paroxetine were undetected. Sertraline and paroxetine can be used during breastfeeding and fluoxetine should be avoided because of its long half-life and cumulative risk [64].

According to SIGN, both SSRI and tricyclic antidepressants (TLPDs) may be recommended for the treatment of moderate and severe postnatal depression (subject to a thorough prior risk assessment for the breastfed child). It should also be stressed that a child breastfed by a mother treated with antidepressants should be regularly monitored for psychomotor development [1].

Guidelines for the management with woman with suicidal thoughts or thoughts of harming the baby

Most available recommendations refer to the possibly most critical situation related to postpartum depression — to assessing the risk of maternal suicide or assessing the risk to the child.

Beyond Blue recommends asking the two simple questions to woman with postpartum depression:

- Do you think it is not worth living?
- Do you have thoughts of hurting your child?

If the answer is positive to at least one of the above question it is advisable to ask the woman about the frequency of such thoughts, possible suicide plans, and to assess the risks of implementing this plan.

If a woman reports thoughts of suicide or harming her child [15, 48] or has scored more than 0 at point 10 on the EPDS scale (relating to thoughts of self-harm), she should undergo further thorough assessment of the mental state and be referred for psychiatric treatment [49].

Postpartum psychosis is also associated with a particular risk of suicide or risk to the child. If this disorder is suspected, all relevant guidelines recommend an urgent referral to psychiatric care.

DIAGNOSIS OF THE SITUATION IN POLAND — BARRIERS AND POSSIBLE SOLUTIONS

Many studies emphasize the need for developing guidelines in individual countries, considering various cultural and demographic factors, as well as the specificity of the healthcare systems [65]. In Poland, no one has so far dealt with the mental health of women after childbirth in a systemic manner. The social awareness in this area also seems to be low and the problem is often underestimated. Women are afraid of the stigma of being a bad mother and social exclusion. Doctors, nurses and midwives usually focus their attention on somatic complications in a woman after childbirth and on the health of the newborn, leaving the issue of a woman's mental condition to psychologists and psychiatrists. The problem is that a woman with PPD may never get into specialist psychiatric care at all. This is partly due to women often not realising that their condition exceeds the physiological norm during this period. Indeed, it is the woman's immediate medical surroundings — the pediatrician (to whom the woman will report with the baby), the gynecologist (who take care during pregnancy and the postpartum period), the midwife and community midwife (having contact with woman in perinatal period, including the patronage visit after childbirth) and the family doctor (who usually knows the patient for a long time and has the best opportunity to apply screening for depression. They all are in frequent contact with the woman and are able to catch the worsening in the patient's behavior and mental health.

An important role in the health care of a pregnant woman and after the childbirth is attributed in Poland to gynecologist. Taking care of a woman during perinatal period creates many opportunities towards paying a closer attention to possible occurrence of depressive symptoms. However, the patient's stay in the maternity ward is currently getting shorter and shorter (average stay after the childbirth in hospital is 3 days). Thus, it is essential to take advantage of that short period to observe her condition not only physically but also in terms of well-being. Researchers recommend performing the screening tests in the early puerperium (during the hospital stay after delivery) to indicate the groups at risk of postpartum depression that should be provided with further care in the following weeks after delivery [66–68]. The problem in Poland concerns the lack of uniform guidelines on how to screen for antenatal and postnatal depression and how to further manage with depressed patients.

The role of the midwife is also particularly important. To a large extent, from her skills and knowledge depends a woman's emotional state in the perinatal period. The tasks of a midwife in the postpartum period include close observation of her general and obstetric condition, but also her mental state. During the patronage visits after childbirth the midwife could, in a safe for woman conditions, assess her mental state more closely. It is also important to build a social support system, which may include contacts with the community midwife and various support groups for women after childbirth. Often intervention is required by the whole family, as it affects all family members. Therefore, the involvement of the whole family system significantly increases the effectiveness of any action taken. Although the recent standards of perinatal care in Poland imposed on midwives involving the obligation to monitor the mental state of women in the perinatal period (including a screening diagnosis for PPD), no strict recommendations about the screening tools were given. Recent Polish studies have also shown that midwives do not have sufficient or reasonable knowledge of perinatal

depression, uncertain how to effectively manage women with PPD, and less likely to suggest appropriate treatment strategies [69]. Thus, it is necessary to educate medical staff in Poland, especially midwives in recognizing the early symptoms of PPD, identification risk groups, and in the effective use of screening tools for this purpose [69].

In the Polish health care system, family doctors and pediatricians do not have as extensive skills and knowledge about mental illnesses as in other countries. In clinical practice, it is rare to treat common mental disorders by non-psychiatrists, usually the patient remains under the care of a specialist. Other professionals , however, can successfully support psychiatrists in screening and recognizing postnatal depression. Especially since, as mentioned earlier, the main problem is not the issue of treatment, but the low level of recognition of postpartum depression. Therefore, recommendations in this area should be mainly focused on the use of screening methods for the detection of PPD by all medical professionals having contact with woman in the perinatal period, and on educational activities aimed at pregnant women, their families and the general public. Close cooperation of these specialists with psychiatrists and psychologists would also be highly recommended. Such teams could provide more coordinated and effective care.

Other barriers, briefly mentioned in previous chapter, are a lack of dedicated perinatal mental health services in Poland and a lack of guidelines concerning referral. The statistics from the Polish National Health Fund (2016) on the treatment of perinatal depression, in comparison with prevalence of this disorder, indicate that only a small percentage of depressed women in the perinatal period receive help. For many Polish women it is still impossible to receive professional and prompt treatment. A waiting period for a refunded psychiatrist consultation after referral by a GP or other specialist takes up to several months depending on the region. There is no special formal prompt track for psychiatrist consultation in case of suspected perinatal depression. Consequently, depressed woman in perinatal period wait as long as others, unless they are fortunate enough to recieve human kindness from a mental health service staff, or when they are able to pay for a private visit. It should be stressed that in this particular case, it would be highly needed as it concerns not only the suffering of one person but is also directly related to the development and well-being of the child, the functioning of the entire family system and decisions on future procreation.

SUMMARY AND CONCLUSIONS

The following summarizes the most important, key issues in the prevention, screening and treatment of PPD resulting from worldwide recommendations in this area:

1. The presence of depressive symptoms should be routinely assessed in every woman in perinatal period with the use of screening tools by medical professionals who are in contact with the pregnant woman (gynecologists, midwives, pediatricians, family doctors).
2. For screening, it is usually recommended to use the EPDS questionnaire or a set of two questions (Whooley questions) combined with EPDS, as part of a comprehensive examination for postpartum depression; additionally, a clinical interview is recommended.
3. First-line treatment for women with mild to moderate postpartum depression who are breastfeeding is psychotherapy (especially cognitive-behavioral therapy and interpersonal therapy); second-line recommendations include pharmacological treatment.
4. The benefits of treatment for the mother should be considered when deciding to start pharmacological treatment during breastfeeding, as well as the risks arising from the child's potential exposure to the drug.
5. The specificity of depression treatment during pregnancy and after childbirth in most cases requires treatment by a specialist psychiatrist. Doctors of other specialties and medical staff in contact with the woman during the perinatal period can support psychiatrists in early diagnosis and monitoring of the patient.
6. Urgent referral to a specialist psychiatrist is advisable in the case of suicidal thoughts, thoughts of harming the child, in the case of severe episode of depression, psychosis or suspicion of bipolar affective disorder.
7. Early recognition and treatment improves the prognosis for the health of women, children and the whole family.

RECOMMENDATIONS FOR THE PREVENTION, SCREENING AND FURTHER MANAGEMENT OF A PATIENT WITH POSTPARTUM DEPRESSION FOR GYNECOLOGISTS, COMMUNITY MIDWIVES, MIDWIVES AND STAFF OF GYNECOLOGICAL AND OBSTETRIC WARDS, NURSES, PEDIATRICIANS AND FAMILY DOCTORS

It is recommended that screening for depressive disorders should be a permanent part of medical and nursing practice performed in every woman in perinatal period.

1. It is recommended to educate pregnant woman about perinatal mental health problems, including the risk and symptoms of postpartum depression.
2. The presence of depressive symptoms should be routinely assessed in every woman in perinatal period using the **Edinburgh Postnatal Depression Scale (EPDS) questionnaire.**

3. The purpose of the examination should be explained to the woman and informed consent should be obtained to complete the EPDS questionnaire.
4. It is recommended that gynecologists and / or midwives routinely carry out screening for depression **at least twice** in all women in perinatal period: **during pregnancy and 6–8 weeks after delivery** (during check-up visit). In addition, it is also recommended to perform a screening during the patient's hospitalization (on the 3rd day after delivery).
5. It is recommended that pediatricians routinely screen all women after the childbirth for depression during their first visit with the child.
6. It is recommended that family doctors and community midwives routinely screen for depression all women during the first visit after the childbirth.
7. If a woman does not agree to complete the EPDS questionnaire, it is recommended to offered it again at the next visit.
8. It is advisable to have an interview about the risk factors for postnatal depression, in specifically ask about:

- postpartum depression in the past,
- postpartum psychosis,
- depression in pregnancy,
- depression independent of the perinatal period,
- bipolar affective disorder,
- mental illness in the family,
- difficult financial and living situation, lack of support in the immediate vicinity,
- stressful life events during pregnancy and after birth.

9. In women with increased risk of postnatal depression, it is advisable to carry out a screening during each visit in pregnancy and in the postpartum period.
10. It is also advisable to collect an interview for alcohol and drug addiction. In case of a positive history, it is recommended to monitor the patient closely and consider referral to psychiatric care.
11. In case of 10, 11 and 12 points on the EPDS scale it is advisable to re-examine in 2–4 weeks.
12. In the case of a score of 13 points or more on the EPDS scale, it is necessary to supplement the examination with an interview for depressive symptoms.

The following questions about the patient's well-being during the last seven days may be helpful:

- feeling tired, exhausted,
- lack of energy and motivation for daily activities,
- sadness, low mood, hopelessness,
- attention deficit and memory problems,
- excessive fear of child health,
- guilt, low self-esteem, failure to cope with the duties of a mother,
- fear of losing control and "crazy",
- no interest in the child,
- fear/thought about hurting a child,
- tearfulness, irritability,
- thoughts of self-harm, suicidal thoughts.

13. A positive screening outcome (13 points and more) should be noted in the medical records. The following actions are then recommended:

- discuss the outcome of the screening with the patient,
- if the patient agrees, inform her relatives about the diagnosis and treatment plan,
- assess the level of support in immediate vicinity,
- inform about possible treatment options (psychotherapy, pharmacotherapy),
- consider recommending psychological support, community visits, referral to support groups, suggest a follow-up plan — referral to a psychiatrist or psychologist.

14. Coordinated care of a patient with a diagnosis of postpartum depression is recommended in cooperation with psychiatrists and psychologists, to jointly establish a visit and treatment plan.
15. In the following cases, the patient should be referred urgently to a psychiatric consultation:

- declaring suicidal thoughts or about self-harm (or a score > 0 in point 10 on the EPDS scale),
- declaring thoughts of hurting a child,
- severe depressive symptoms, clearly impairing the patient's daily functioning,
- suspicion of postpartum psychosis,
- suspicion of bipolar disorder.

The key points of recommendations are presented in Figure 1.

Situations requiring urgent psychiatric consultation are depicted in Figure 2.

Conflict of interest

The development of this recommendation was financed from the funds at the disposal of the Polish Ministry of Health as part of the health policy program entitled "Depression Prevention Program in Poland for 2016–2020".

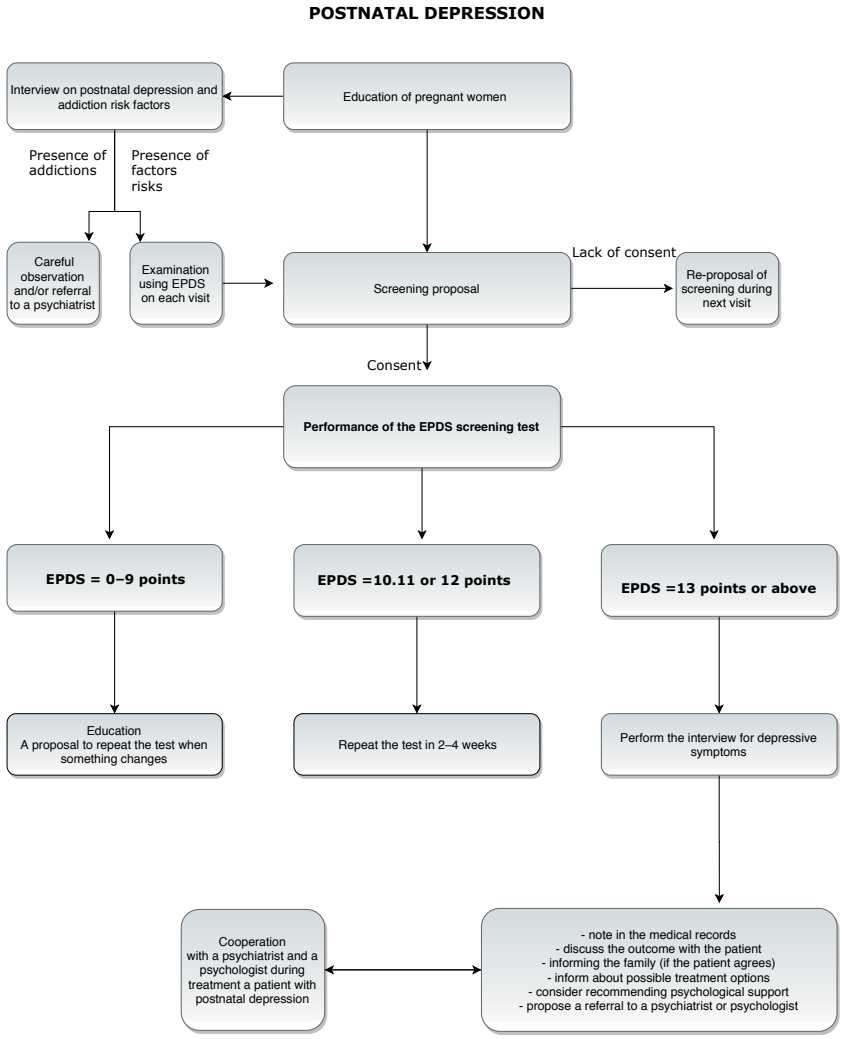

Figure 1. Recommendations for the screening and further management of a patient with postpartum depression

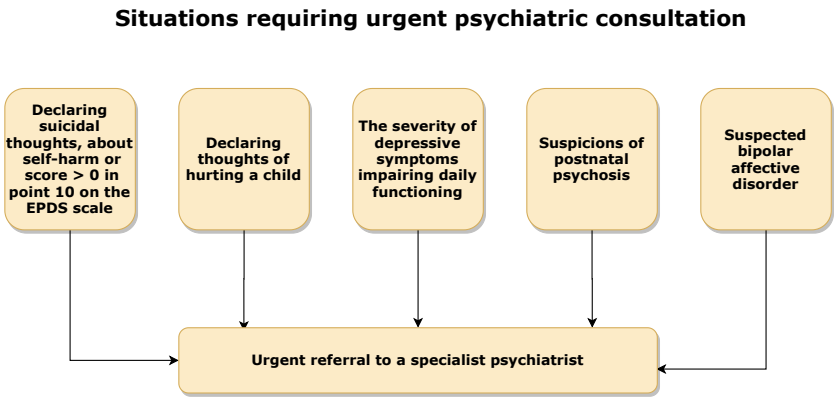

Figure 2. Situations requiring urgent psychiatric consultation

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VIA MEDICA

RECOMMENDATIONS

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Cervical cancer screening in Poland in current SARS-CoV-2 pandemic: Interim guidelines of the Polish Society of Gynecologists and Obstetricians and the Polish Society of Colposcopy and Cervical Pathophysiology — a summary January 2021

Robert Jach*[1], Maciej Mazurec*[2], Martyna Trzeszcz*[3], Mariusz Zimmer[4], Witold Kedzia[5], Hubert Wolski[6]

[1]Division of Gynecologic Endocrinology, Jagiellonian University Medical College, Cracow, Poland
[2]Corfamed Women's Health Center, Wroclaw, Poland
[3]Division of Pathology and Clinical Cytology, University Hospital in Wroclaw, Poland
[4]Second Department of Gynecology and Obstetrics, Wroclaw Medical University, Poland
[5]Division of Developmental Gynecology and Sexuology, Department of Perinatology and Gynecology, Poznan University of Medical Sciences, Poland
[6]Division of Obstetrics and Gynecology, Poviat Hospital in Zakopane, Poland
**Authors should be regarded as the first authors due to the equal contribution to the article*

ABSTRACT

The Polish Society of Colposcopy and Cervical Pathophysiology (PTKiPSM) together with the Polish Society of Gynecologists and Obstetricians (PTGiP) issued a final summary of interim guidelines for secondary cervical cancer prevention during the SARS-CoV-2 pandemic based on the analysis of the latest directional publications and the authors' own experiences. The aim of the summary is to facilitate the implementation of the most effective possible screening of cervical precancerous lesions and cervical cancer due to temporary significant limitation of screening as a consequence of the ongoing epidemiological threat. These final guidelines are taking into account the 2020 call of the World Health Organization (WHO) for global epidemiological elimination of cervical cancer. The guidelines supplement the interim guidelines of PTKiPSM and PTGiP announced in March 2020 on the possible deferral of diagnostic and therapeutic procedures in patients with abnormal screening tests results in secondary prevention of cervical cancer in current pandemic.

Key words: cervical cancer prevention; abnormal screening results; HPV testing; cervical cytology; selfsampling; SARS-CoV-2 pandemic; guidelines

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The recommendations present the current management which may be modified and changed in justified cases, after a thorough analysis of a given clinical situation, which in the future may constitute the basis for their modification and update.

Interim guidelines apply to the period indicated only.

INTRODUCTION

In May 2020, the World Health Organization (WHO) called on all institutions in the world involved in the cervical cancer prevention to take action to eliminate cervical cancer as a population problem by the end of the century, which is to reduce the number of cases to

Corresponding author:
Robert Jach
Division of Gynecologic Endocrinology Jagiellonian University Medical College, Cracow, Poland
phone: +48/ 512 484 102, e-mail: robert.jach@uj.edu.pl

a level of a very rare disease (≤ 4 cases/100,000/year). According to WHO, European countries should achieve this goal earlier, *i.e.* between 2055 and 2059. WHO has also defined goals to be reached in the short term, which will allow the achievement of the indicated main goal. The year 2030 is the time limit for all countries to meet the minimum targets defined by the abbreviation "90–70–90" which includes:

- covering 90% of girls by the age of 15 with the full vaccination against human papillomavirus (HPV),
- covering 70% of women with a highly effective screening test at least twice during their lifetime, in 35 and again in 45 years of age,
- covering 90% of women with diagnosis of precancerous lesions or cervical cancer with appropriate treatment and care [1–3].

The European response to WHO's call is a joint initiative of the European CanCer Organization (ECCO), the European Society of Gynecological Oncology (ESGO) and the European Federation for Colposcopy (E.F.C.). The European proposals for goals that should be achieved by 2030 have a wider scope and have been specified in relation to the WHO base document and include, among others:

- covering 90% of girls and boys with the full vaccination against HPV by the age of 15,
- covering 70% of women in Europe at the indicated age by cervical cancer screening using a clinically validated test for high-risk human papillomavirus types (HRHPV) over the last five years,
- providing 90% of women with diagnosis of histologic histological high-grade squamous intraepithelial lesions (HSIL) with subcategorization to CIN 3 and higher (CIN 3+) with treatment within 3 months from diagnosis, and all women diagnosed with cervical cancer ensure access to appropriate oncological care, including palliative care.

The document also points to the uniqueness of the challenges related to the SARS-CoV-2 pandemic, including the need for European women to access, especially during the pandemic, HRHPV self-sampling kits [4].

The Polish response to the WHO's call is the COLPOSCOPY 2020 Project with already published [5, 6] and planned for publication guidelines for secondary cervical cancer prevention in Poland.

The achievement of the goals set by WHO is obviously hindered by the SARS-CoV-2 pandemic that has significantly inhibited or limited secondary cancer prevention, including cervical cancer. American data indicate a reduction of up to 94% in the number of cervical cancer screening tests performed between week 10 and week 20 of this year compared to previous years. In June, the situation improved slightly, setting the screening tests deficit at 67%, which is still a very high-level [7]. Polish data for 2020 in the secondary cervical cancer prevention financed from public funds are highly worrying — 13.84% of the planned female population was screened [8]. Data for cervical cancer screening in the opportunistic model, apart from public funding, are not known.

Interim guidelines related to the pandemic are the reaction of scientific societies to the rapidly changing screening reality in this period, which could not be foreseen in the planned model of secondary cervical cancer prevention in Poland. That consequently means the need to implement modifications and updates depending on the changing external epidemiological situation [9].

RECOMMENDED CERVICAL CANCER SCREENING APPROACH DURING THE SARS-COV-2 PANDEMIC

The long-term consequences of limiting or discontinuing the population-based cervical cancer secondary prevention tools can be difficult to predict and control. In the persistent SARS-CoV-2 pandemic and its unforeseeable course and completion date, taking into account the WHO's May 2020 call for action on cervical cancer prevention and its goals, the following screening approach is temporarily recommended in Polish conditions during the epidemiological threat associated with the SARS-CoV-2 pandemic. The overriding immediate goal of these guidelines is to achieve in Poland in the time of a pandemic the highest possible share of the population covered by screening, optimally according to the recommended interim screening models, with the most effective diagnostic possible triage of patients requiring referral to colposcopy.

The recommended cervical cancer screening in Poland during the SARS-CoV-2 pandemic includes the following strategies:

1. In the case of an epidemiological situation that allows the collection of material from the cervix by a gynecologist or midwife and the availability of dedicated diagnostic-laboratory facilities, liquid-based screening (LBS), i.e., the use of a liquid preparation as a carrier of the collected cell material, is recommended. LBS is a method that enables the performance of several diagnostic tests from one collection, reduces the number of necessary visits to one in precolposcopy stage and eliminates the use of aerosol fixer.

Liquid-based screening should only use clinically validated tools: liquid media, molecular tests for 14 high-risk human papillomavirus types (HRHPV14), separately for the primary HRHPV14 test and for the cotesting [10], and for the immunocytochemical test p16/Ki67 as well [11]. Until validated diagnostic tools are approved for Polish population, it has been temporarily accepted to rely on the appropriate registrations of the American Food and Drug Administration (FDA), and additionally on the VALGENT (Validation of HPV

Genotyping Tests) and Meijer's protocols for HRHPV14 tests [12, 13, 14].

For liquid-based screening, an implementation of the HPV-based model is recommended, *i.e.*:

- primary test for HRHPV14
- or cotesting which includes HRHPV14 testing and liquid-based cytology (LBC), with further diagnostic-therapeutic management depending on tests results and, in indicated cases, including a past history.

Clinical management based on the HSIL (CIN 3+) risk assessment calculated using the current tests results and screening history, presented in the ASCCP 2019 (American Society for Colposcopy and Cervical Pathology) recommendations, is temporarily acceptable approach in the diagnostic-therapeutic management in Poland. The screening history was defined as recent past tests (in the last 5 years) and/or treatment for histological HSIL with sub-categorization to CIN 2 and higher (CIN 2+) in the previous 25 years [10, 15, 16]. Presented management is applicable only when screening tests approved by the FDA are used.

All HRHPV14 positive cases require further diagnostic procedures using the histologic HSIL-risk triage test (CIN 2+), *i.e.*, cytology or p16/Ki67 test. For HPV positive women, ICC p16/Ki67 testing should be regarded as an alternative reflex test to cytology and as a triage test for abnormal cytology result. A laboratory preparation of p16/Ki67 test should be carried out using fully automated system only and a morphologic evaluation should be performed by trained cytopathologist – both are obligatory FDA conditions for p16/Ki67 testing [11].

An optional management in the time of a pandemic is referring to immediate colposcopy all patients with detected HRHPV types 16 and/or 18, and in the cases of using the molecular testing with extended genotyping beyond types 16 and 18 [HPV extended genotyping (HPV-xGT)], referring to immediate colposcopy patients with detected HPV type 31 it is optionally also recommended [17, 18].

Currently, the use of methylation-based methods does not have sufficient clinical validation in cervical cancer screening [19].

Four basic interim HPV-based screening models are recommended for Polish conditions:

- screening model 1 — primary HRHPV14 testing
  — 1A — with reflex cytology
  — 1B — with reflex p16/Ki67 test
- screening model 2 — primary cotesting (HRHPV14 + LBC)
  — 2A — without reflex testing
  — 2B — with reflex p16/Ki67 test
- screening model 3 — primary HRHPV14 extended genotyping (in patients with previously unknown HRHPV14 status) with reflex cytology
- screening model 4 — primary HRHPV14 testing based on the ASCCP 2019 recommendations [10, 15, 16]; (ASCCP 2019 Recommendations in Polish: Medycyna Praktyczna Ginekologia i Położnictwo No. 05 and No. 06/2020)

The detailed recommended management strategies for screening models 1–3 are shown in Figures 1–7 (see page 169–172).

Due to the lack of obligatory reporting for the required assessment and quality control parameters for liquid-based cytology in Poland, including in particular, the percentage of individual cytological diagnoses compared to the values reported by the College of American Pathologists (CAP), cyto-virological correlations (CVC) and cyto-histological correlations (CHC), it is recommended to report minimally the parameters indicated in the relevant recommendations of the COLPOSCOPY 2020 Project (paper in progress).

2. Self-sampling, defined as a self-collection of vaginal material by the patient with the use of a dedicated brush, is recommended in the primary HPV-based screening as the basic tool for cervical cancer screening for cases when a social distance is necessary and/or concerns of secondary cervical cancer prevention recipients related to risk of infection with SARS-CoV-2 virus occur, which in its extreme form leads to leave of screening [20–22].

Due to the lack of sufficiently validated HRHPV14 tests in Poland for the self-sampling method, in the cases of positive HPV result obtained with this method, a routine material sampling from the cervix is necessary (an appointment and a contact with medical personnel is needed) to confirm the positive result on the validated molecular HRHPV testing. In the cases of a confirmed positive HRHPV result by validated HPV testing, further management is described in point No. 1.

All HRHPV14 negative tests results should be confirmed with the currently recommended HRHPV14 tests collected by qualified medical personnel or with the use of a self-sampling testing approved for Polish population.

3. The self-sampling method is also recommended as a triage tool enabling the reduction of social contacts for the continuation of secondary cervical cancer screening for minor cytological abnormalities [atypical squamous cells of undetermined significance (ASC-US) or low-grade squamous intraepithelial lesions (LSIL)], according to Polish recommendations 2016 [23]. It is applicable, when the original liquid-based cervical material obtained during a routine cervical screening is not available in the laboratory.
4. In the case of an epidemiological situation allowing the cervical sampling by a doctor or midwife, and when

a performing liquid-based preparation in not possible, a conventional cytology is acceptable screening strategy in opportunistic models from public and private funds, with further management depending on cytology results and the availability of diagnostic tests, based on the current recommendations [23–25].

It is emphasized that this screening strategy requires the patient's next appointment, especially in the cases of minor cytological abnormalities (ASC-US or LSIL) or in the cases of unsatisfactory cytology results, which should be considered as suboptimal during a pandemic.

5. Expanding a participation of non-gynecologists (general practitioners, midwifes and community nurses) in secondary cervical cancer prevention, particularly in a promoting and education in self-sampling method is recommended, as an effective screening alternative tool to sampling performed by medical personnel, when patient is unable to participate in a routine cervical cancer screening, and/or the strict national or regional epidemiological cautions are introduced.

INTERIM INDICATIONS FOR COLPOSCOPY

The following results are recommended as decision parameters in the referral of the patient to colposcopy with biopsy within 3 months, regardless of the other tests results:

- positive HRHPV 16 and/or 18 and/or 31 type (HPV type 31 when using the HPV-xGT testing) in the cases of unknown patient's HRHPV status within the last 3 years,
- positive HRHPV 16 and/or 18 and/or 31 type (HPV type 31 when using the HPV-xGT test) detected again after 12 months in the cases of a patient previously monitored,
- positive HRHPV N16/N18 (one or more) or HRHPV N16/N18/N31 (one or more) (N16/N18/N31 type in cases of using the HPV-xGT testing) detected again after 12 months in the cases of a patient previously monitored,
- positive p16/Ki67 test result,
- atypical squamous cells, cannot exclude high-grade squamous intraepithelial lesion (ASC-H), HSIL or atypical glandular cells (AGC) cytology results.

If an invasive process is suspected, further diagnostic-therapeutic management must be undertaken immediately.

The possibility of deferral the diagnostic-therapeutic management is maintained as allowed, based on the PTGiP and PTKiPSM Interim Guidelines of March 22, 2020, with the update of May 2, 2020 [7].

SUPPORTING ACTIONS

An effective and quick education of medical doctors (gynecologists, general practitioners, pathologists), laboratory diagnosticians, community midwives, community nurses and other medical workers is recommended as necessary for the effective implementation of these interim guidelines for secondary cervical cancer prevention in Poland in the SARS-CoV-2 pandemic, with a key role of PTKiPSM and support of the Cervical Pathology, Colposcopy and Cytology Subdivision of PTGiP.

Scientific societies (PTGiP and PTKiPSM) call for an adequate response to the pandemic all of institutions responsible for secondary cervical cancer prevention financed from public funds in Poland, taking into account the presented guidelines and the actual epidemiological situation.

The authors of these guidelines emphasize — in line with the position of opinion-forming European and American directional authorities [4, 10], the need to use only clinically validated liquid-based media in cervical cancer screening and HRHPV14 molecular tests, with a dedicated specific liquid-based laboratory preparation, independently for LBS and self-sampling [10, 21]. This also applies to all recent past screening tests, if included in a risk stratification.

The tests registered by the FDA for cervical cancer screening using the primary HRHPV14 testing or cotesting and screening tests validated with VALGENT or Meijer's protocols are tests of temporary choice for use in Poland due to the lack of Polish clinical validation for any of these screening tests (an organization of tests' validation in the progress). Similarly, when the p16/Ki67 immunocytochemical test is used, only automated preparation is recommended with evaluation by directionally trained cytopathologist to employ the FDA registration [11].

Regarding the selfsampling method, until the tests are validated for Polish conditions, it is temporarily recommended to take advantage of Australia and Netherlands expertise in support cervical cancer screening by this method. The authors of the guidelines also highlight the need to use validated tools to collect material from the cervix and/or vagina, also in the cases of the self-sampling method [21].

For the colposcopy, the need of its standardization and algorithmization according to the colposcopic protocols guidelines and the use of Polish colposcopic nomenclature in accordance with the COLPOSCOPY 2020 Project is pointed [5, 6].

Figures 1–7 describing recommended HPV-based screening models depending on the primary screening tests results are presented below.

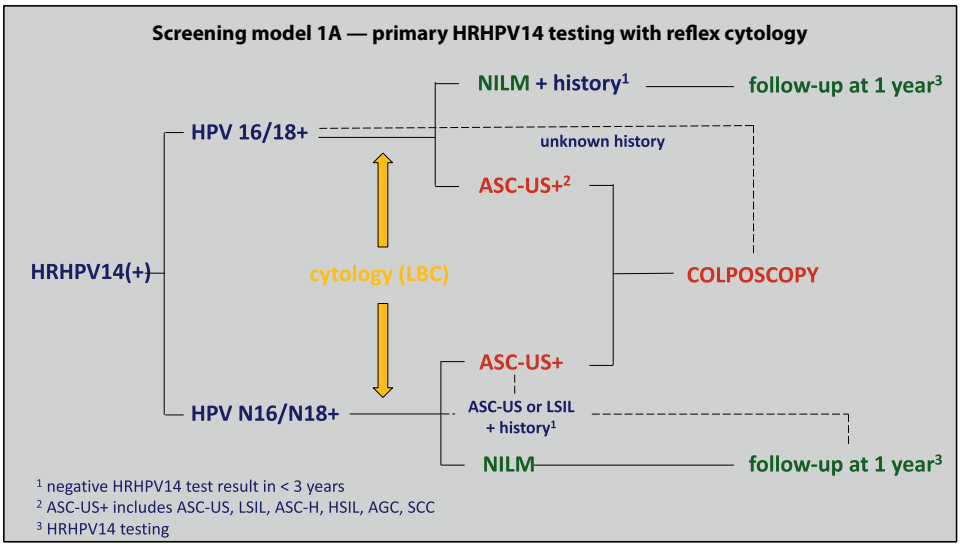

Figure 1. Management algorithm for positive primary 14 types of high-risk human papillomavirus test results with reflex cytology; HRHPV14 — 14 types of high-risk human papillomavirus; NILM — negative for intraepithelial lesion or malignancy; ASC-US+ — atypical squamous cells of undetermined significance and higher cytological abnormalities; HPV — human papillomavirus; LBC — liquid-based cytology; ASC-US — atypical squamous cells of undetermined significance; LSIL — low-grade squamous intraepithelial lesions; ASC-H — atypical squamous cells, cannot exclude high-grade squamous intraepithelial lesion; HSIL — high-grade squamous intraepithelial lesions; AGC — atypical glandular cells; SCC — squamous cell carcinoma

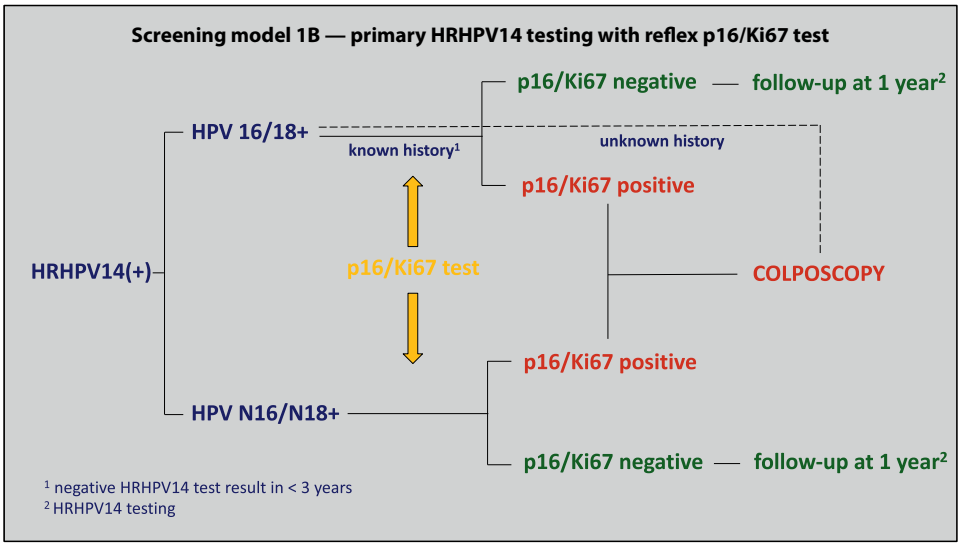

Figure 2. Management algorithm for the positive primary 14 types of high-risk human papillomavirus test results with reflex p16/Ki67 double immunocytochemical test; HRHPV14 — 14 types of high-risk human papillomavirus; HPV — human papillomavirus;

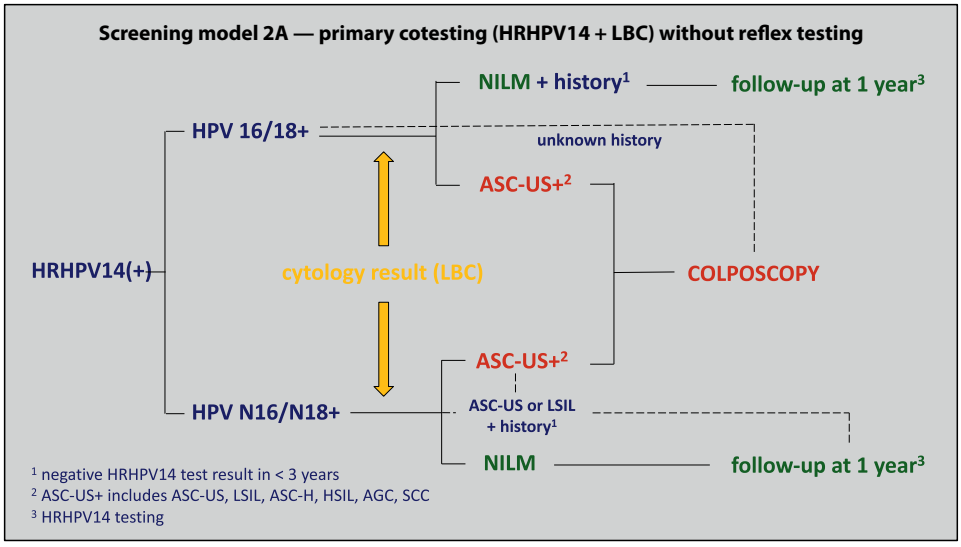

Figure 3. Management algorithm for the cotesting in cases of a positive 14 types of high-risk human papillomavirus test result; HRHPV14 — 14 types of high-risk human papillomavirus; LBC — liquid-based cytology; NILM — negative for intraepithelial lesion or malignancy; ASC-US+ — atypical squamous cells of undetermined significance and higher cytological abnormalities; HPV — human papillomavirus; ASC-US — atypical squamous cells of undetermined significance; LSIL — low-grade squamous intraepithelial lesions; ASC-H — atypical squamous cells, cannot exclude high-grade squamous intraepithelial lesion; HSIL — high-grade squamous intraepithelial lesions; AGC — atypical glandular cells; SCC — squamous cell carcinoma

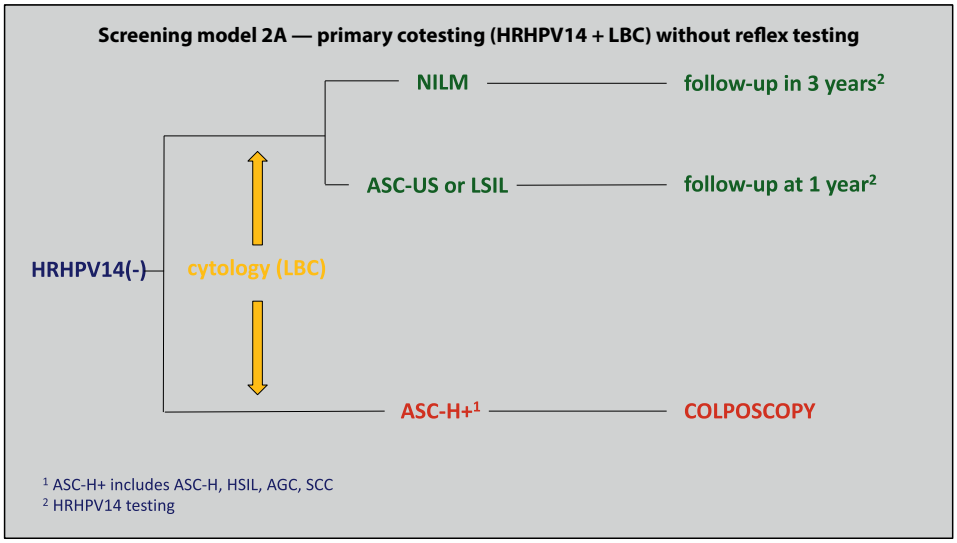

Figure 4. Management algorithm for the cotesting in cases of negative 14 types of high-risk human papillomavirus test result; HRHPV14 — 14 types of high-risk human papillomavirus; LBC — liquid-based cytology; NILM — negative for intraepithelial lesion or malignancy; ASC-US — atypical squamous cells of undetermined significance; LSIL — low-grade squamous intraepithelial lesions; ASC-H — atypical squamous cells, cannot exclude high-grade squamous intraepithelial lesion; HSIL — high-grade squamous intraepithelial lesions; AGC — atypical glandular cells; SCC — squamous cell carcinoma

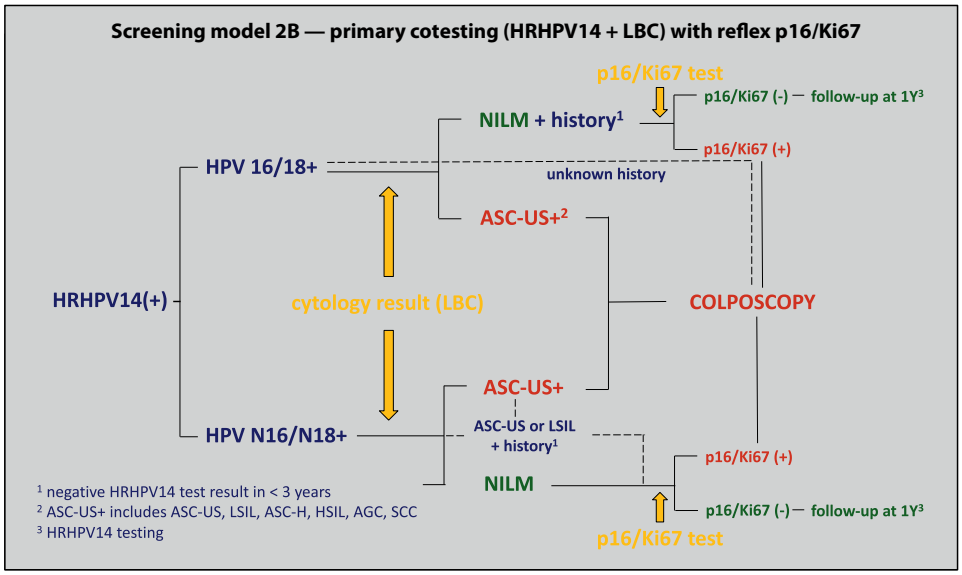

Figure 5. Management algorithm for the positive 14 types of high-risk human papillomavirus test results obtained in cotesting with reflex p16/Ki67 double immunocytochemical test; HRHPV14 — 14 types of high-risk human papillomavirus; HPV — human papillomavirus; LBC — liquid-based cytology; NILM — negative for intraepithelial lesion or malignancy; ASC-US+ — atypical squamous cells of undetermined significance and higher cytological abnormalities; ASC-US — atypical squamous cells of undetermined significance; LSIL — low-grade squamous intraepithelial lesions; ASC-H — atypical squamous cells, cannot exclude high-grade squamous intraepithelial lesion; HSIL — high-grade squamous intraepithelial lesions; AGC — atypical glandular cells; SCC — squamous cell carcinoma

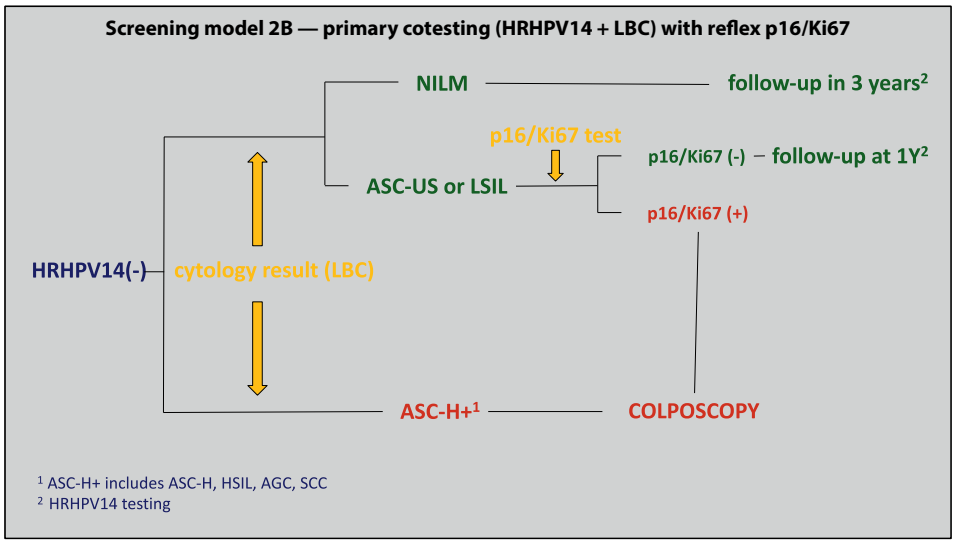

Figure 6. Management algorithm for the negative 14 types of high-risk human papillomavirus test results obtained in cotesting with reflex p16/Ki67 double immunocytochemical test; HRHPV14 — 14 types of high-risk human papillomavirus; LBC — liquid-based cytology; NILM — negative for intraepithelial lesion or malignancy; ASC-US — atypical squamous cells of undetermined significance; LSIL — low-grade squamous intraepithelial lesions; ASC-H — atypical squamous cells, cannot exclude high-grade squamous intraepithelial lesion; HSIL — high-grade squamous intraepithelial lesions; AGC — atypical glandular cells; SCC — squamous cell carcinoma

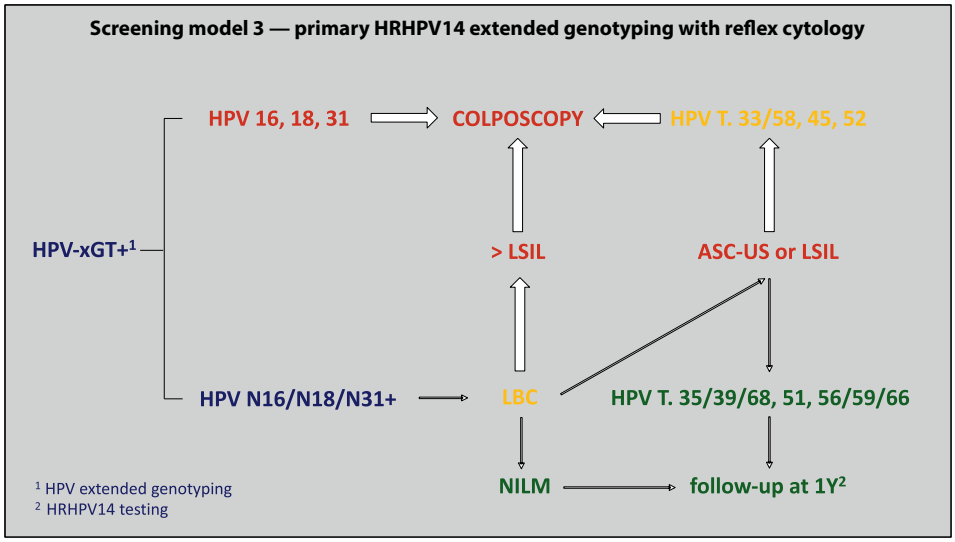

Figure 7. Management algorithm for the primary 14 types of high-risk human papillomavirus extended genotyping results with reflex cytology; HPV-xGT — human papillomavirus extended genotyping; HPV — human papillomavirus; LSIL — low-grade squamous intraepithelial lesions; LBC — liquid-based cytology; NILM — negative for intraepithelial lesion or malignancy; ASC-US — atypical squamous cells of undetermined significance

The above guidelines are not the final diagnostic management approach for abnormal screening tests results in secondary cervical cancer prevention.

They are not a substitute for a complete clinical evaluation of an individual case.

They should always be analyzed in the context of optimizing the diagnostic management in the patient's health interest.

They may be modified depending on changing conditions.

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