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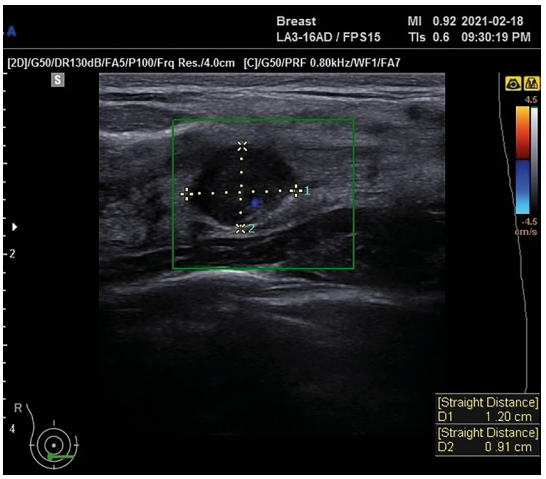

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Cervical cancer — a preventable (?) disease in Poland

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Dear Editors,

a great majority of cervical cancers (CCs) may potentially be prevented by 1) primary prevention through vaccination against the aetiological factor of this disease — the Human Papillomavirus (HPV), and 2) secondary prevention — identification of precancerous lesions through screening and effective treatment to avoid development of invasive CC. In 2020 World Health Organization (WHO) issued a "Global strategy to accelerate the elimination of cervical cancer as a public health problem" (the threshold of 4 cases/100 000 women-years) [1]. It assumes achieving: 1) 90% of girls fully vaccinated with HPV vaccine by age 15 years; 2) 70% of women screened with a high-performance test by 35 years of age and again by 45 years of age and 3) 90% of women identified with cervical disease receiving treatment (90% of women with precancer treated, and 90% of women with invasive cancer managed). Some countries [2, 3] including Poland [4] elaborated consecutive plans or roadmaps to tackle the burden of CC. However, implementation of required solutions to achieve WHO goals might be a challenge not only for developing but also for some of the more developed countries.

Currently CC ranks as the fourth most common cancer and cancer related cause of death in the world [5]. Both CC incidence and mortality have been gradually decreasing for more than thirty years in Poland [6] but age-standardized incidence and mortality rates are still considerably higher than in European countries with most effective CC prevention programmes. In 2006/2007 an organized population-based cervical cancer screening was implemented in Poland offering free-of-charge Pap test for women aged 25–59 (extended to age of 64 in year 2023) at 3-year intervals and colposcopy with/without biopsy for women when clinically indicated. The programme has never obtained coverage of more than 30% of the target population but between 2004–2019 the declared participation in CC screening rose markedly [7]. A 20%-point jump in participation was noted between years 2004 and 2009 in age groups 30–69 most evidently in opportunistic screening. This was the result of popularisation of CC prevention through cytology, rise in awareness among women and a wider access to screening, most likely because of the introduction of the programme. In 2016 regional coordination of the programme was stopped as well as postage of the invitations by the decision of the Ministry of Health. The Ministry took over the funds and the responsibility from the Central Coordination Centre for reaching and maintaining of the high level of the programme coverage. Fail-safe-system was however introduced (tracking women with positive results and no consecutive triage/diagnostic procedures) and quality assurance measures including audit of false-negative Pap smears and interval cancers were implemented [8]. Audits of quality assurance have been undertaken and published only for single centres operating in opportunistic screening [9]. Central Coordination Centre has no legal bases to audit performance of opportunistic screening. The quality of opportunistic screening is largely unknown and most likely unsatisfactory since population coverage is considerable, but CC burden is higher than in some countries with similar or worse structure of the self-reported participation in screening [10]. Only screening procedures in the programme are registered and audited since there is no central registry of opportunistic screening. More sensitive than exfoliative cytology, HPV molecular testing is available within both reimbursed and private-based gynaecological services. Advanced works are under way to introduce HPV-based screening into the screening programme [11, 12]. HPV-based screening with the use of self-sampling has been proposed to facilitate access to screening [13] as well as guidance on triage/further diagnostics during COVID pandemic [14]. Measures have been undertaken to standardise colposcopy procedures [15]. Efforts are made to measure

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Table 1. Current availability and reimbursement of HPV prophylactic vaccines in Poland

Vaccine	Gardasil-9	Cervarix
HPV vaccination programme for 12–13-year-old teenagers (both sexes–gender neutral)	Yes	Yes
100% reimbursement (free-of-charge) in prescription for individuals aged 9–18 years	No	Yes
50% reimbursement for individuals aged 18 and above	No	Yes

Table 2. Current status of HPV-vaccination programme for 12–13-year-olds in Poland [21]

12–13-year-old teenagers — target cohort		e-Vaccination Cards — n (%)
Girls	418 233	85 193 (20.37%)
Boys	440 602	49 300 (11.19%)
Total — both sexes	858 835	134 493 (15.66%)

Data on target cohort for 31st of December 2022. Data for vaccination for 15th of November 2023

Table 3. Use of products in the HPV-vaccination programme in Poland — data for November 2023 [21]

Vaccine type	Gardasil-9	Cervarix
Number of doses provided (%)	121 870 (89.85%)	13 761 (10.15%)

the quality of healthcare services [16] in Poland however the data on the quality of management of invasive and preinvasive cervical neoplasia are scarce. Considerable regional differences are however noted for CC incidence and mortality in the country [17] which may result from inequalities in access to healthcare services and their differing performance.

No effective treatment of HPV infection is available yet worldwide. Despite very common use of intravaginal gels and other products and their promotion even with active engagement of respectable experts in Poland, current scientific evidence-based data are insufficient to support any idea of "accelerating spontaneous regression" or treatment of HPV [18]. Therefore, prophylactic immunisation remains the only registered and evidence-based method on pharmaceutical market to impact HPV infection burden.

Table 4. Proposed key steps to increase effectiveness of CC prevention in Poland

Primary prevention — HPV vaccination	Secondary prevention — screening	Tertiary prevention — treatment of invasive CC
• Multidimensional education of the parents of the teenage target cohort • Education of HCP including family nurses, midwives and doctors • Analysis of the logistics of the programme and implementation of solutions to decrease administrative work burden and facilitate execution of the programme • Inclusion of other than family medicine centres as vaccination providers in the programme • Reimbursement of Gardasil-9 for catch-up vaccination in older cohorts and active promotion of catch-up vaccination • Analysis of feasible solutions from successful local HPV vaccination programmes and implementation into the national programme [22]	• Integration of screening data — implementation of central screening registry of opportunistic screening tests and merging with the programme registry • Identification of non-attenders and irregular attenders in the integrated registry • Targeted interventions to reach non-attenders e.g., invitation letters, direct contacts by family medicine centres, direct contact by occupational medicine personnel during mandatory health check-ups • Provision of widest possible access to screening tests through contracts with existing gynaecological clinics operating within National Health Insurance, private gynaecological offices and clinics, family medicine centres and midwife centres • Implementation of molecular HPV-based technologies into the screening programme • Implementation of cervico-vaginal self-sampling or sampling by midwives without the use of vaginal speculum in family medicine centres without gynaecological chairs • Quality audits and quality assurance at all steps of screening • Introduction of fail-safe system for women in opportunistic screening • Certification of colposcopy and cytology personnel • Further standardisation of screening procedures and evaluation	• Coordination of care through National Oncological Network • Further training of personnel of gynaecological oncology units • Implementation of national guidelines for CC treatment • Implementation and reporting of performance indicators of CC treatment by centres • Audits of centres providing care of CC

After many years of efforts from medical societies, experts, patient organisations and other stakeholders, population-based, free-of-charge HPV vaccination programme for 12–13-year-old teenagers was implemented in Poland on the 1st of June 2023 because of execution of National Strategy for Oncology [11]. Current availability and reimbursement of HPV vaccines in Poland is presented in Table 1. Despite media campaigns run by the Ministry of Health and various educational activities for Healthcare Professionals (HCP) after almost six months of programme the coverage is insufficient (Tab. 2) and will probably not exceed 35–40% after the first year and Gardasil-9 is most commonly provided (Tab. 3).

Therefore, multilevel and multidirectional actions are required both in primary and secondary prevention for Poland to approach the WHO goals of CC elimination. Proposed key steps and activities are presented in Table 4. Progress in achieving WHO goals for CC elimination should be regularly monitored and reported. On these bases conclusions for future solutions should be formulated. Cervical cancer elimination goals and centres were established in several countries [19, 20] and creation of such a centre should be considered also in Poland. In close collaboration with the Ministry of Health it could take on responsibilities to advance WHO CC elimination goals, coordinate and monitor comprehensive CC prevention in Poland. Reorganisation of CC prevention in Poland will require proper decisions by the ministry decision-makers, consensus and collaboration of stakeholders including professional societies, experts and dedicated organisations. However, the crucial factor will be the education of the society to increase uptake of CC screening and HPV vaccination as an important part of health literacy.

Article information and declarations

Conflict of interest

MSD, GSK — lectures, educational and scientific projects.

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Expression profiles of human somatic mesenchymal stem cells derived from fresh endometrium, ectopic-endometrium and umbilical cord

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ABSTRACT

Objectives: The study investigated the stem cell expression profiles and differentiation capacities of mesenchymal stem cells (MSCs) from different tissues, specifically human eutopic endometrium MSCs (eut-MSCs), ectopic endometrium MSCs (ect-MSCs), and umbilical cord MSCs (UC-MSCs). Our aim was to identify any similarities in subpopulations among these MSCs and lay a foundation for MSCs repair.

Material and methods: MSCs were isolated from endometrial tissue (n = 5), endometriosis tissue (n = 6), and umbilical cords (n = 7). Flow cytometry was used to examine cell phenotype, and three lineage tests were conducted to evaluate the differentiation capacity of the MSCs.

Results: Eut-MSCs expressed CD44 (98.00 ± 0.96%), CD73 (99.54 ± 0.02%), CD140b (99.16 ± 0.50%), CD146 (93.87 ± 2.27%), SUSD2 (50.76 ± 8.15%), and CD271 (2.1 ± 1.22%). Ect-MSCs expressed CD44 (98.23 ± 1.60%), CD73 (99.63 ± 0.04%), CD140b (98.13 ± 0.53%), CD146 (93.88 ± 3.19%), SUSD2 (49.33 ± 6.36%), and CD271 (2.85 ± 1.17%). UC-MSCs expressed CD44 (99.11 ± ± 0.42%), CD73 (99.65 ± 0.12%), CD140b (99.84 ± 0.42%), CD146 (88.09 ± 4.20%), SUSD2 (72.87 ± 7.13%), and CD271 (6.19 ± ± 2.08%). The expression of SUSD2 and CD271 in UC-MSCs was slightly but not significantly higher than that in ect-MSCs and eut-MSCs. However, CD44, CD73, CD140b, and CD146 showed similar expression levels in UC-MSCs, ect-MSCs, and eut-MSCs. All three types of MSCs demonstrated the capacity to differentiate into osteoblasts, adipocytes, and chondrocytes.

Conclusions: Our findings indicate that ect-MSCs, eut-MSCs, and UC-MSCs have similar stem cell phenotypes and the ability to differentiate into three lineages.

Keywords: endometrium; umbilical cord; mesenchymal stem cells; phenotypic expression; differentiation potential

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INTRODUCTION

Mesenchymal stem cells (MSCs) are primitive cells that possess the ability to self-renew and differentiate in multiple directions. They can be found in various tissues and organs, including bone marrow [1, 2], human adipose tissue, endometrium, umbilical cord (UC), amniotic fluid, deciduous pulp, and skeletal muscle [3–5]. Due to their capacity for self-renewal and multi-lineage differentiation, MSCs are highly regarded as attractive candidates for regenerative medicine and tissue engineering [6, 7].

In recent years, bone marrow-derived MSCs (BM-MSCs) in disease treatment has declined due to potential complications and limited availability of bone tissue [8]. As a result, researchers have focused on other somatic materials for tissue repair considering their easier accessibility. One such material is the endometrium of the uterus, known for its regenerative capacity. Studies have demonstrated the presence of a small group of highly proliferative MSCs with multi-directional differentiation potential in the human endometrium. These endometrial MSCs (eMSCs) are considered promising for endometrial repair since they may contribute to the partial repair of the functional layer during shedding cycles. Additionally, Sampson's hypothesis suggests that eMSCs may aberrantly migrate to the peritoneal or pelvic cavity, leading to the formation of endometriosis [9]. Gargett et al. [10] have identified the existence of stem cells in ectopic endometrial lesions. Similar to eutopic endometrial stem cell colony-forming units (CFUs), endometriotic stromal cell CFUs have displayed multipotency and undergone over 25 passages before reaching senescence.

Furthermore, UC-derived MSCs (UC-MSCs) have emerged as therapeutically efficient alternatives for several diseases. They are isolated from Wharton's jelly, which not only provides access to raw materials from medical waste tissue but also exhibits stable biological properties, rapid proliferation, and low immunogenicity [11]. *In vitro* experiments have demonstrated the ability of UC-MSCs to differentiate into fat, bone, cartilage, heart, and neuronal cells [12]. Based on these advantages, UC-MSCs may serve as another potential material for repairing endometrial lesions. However, it remains unclear whether UC-MSCs share similar phenotypic characteristics with MSCs derived from the endometrium.

This study hypothesized that eMSCs located in the basal layer lose their regenerative potential when the endometrium is severely damaged. Consequently, our objective was to explore the possibility of increasing the number of eMSCs for endometrial repair. For this purpose, UC-MSCs and ect-MSCs were considered as suitable options due to their easy accessibility and fewer associated ethical concerns. As a first step towards mimicking eMSCs for the repair of severely damaged endometrium, we sought to determine if UC-MSCs and ect-MSCs exhibit similar phenotype and characteristics.

MATERIAL AND METHODS

Collection tissues

Following the guidelines outlined in the declaration of Helsinki and adhering to ethical standards, approval was obtained from the ethical committee at Henan Province People's Hospital. Prior to enrollment in the study, patients provided informed consent and approved the use of their tissue samples. Five healthy women with no prior medical interventions (mean age: 30.05 ± 5.67 years, during the follicular phase), six patients diagnosed with endometriosis (mean age: 29.15 ± 6.55 years), and seven healthy pregnant women (mean age: 28.85 ± 6.55 years) were recruited. Normal endometrial tissues were collected through uterine curettage. Ectopic ovarian cyst tissues were obtained from patients diagnosed with endometriosis during surgery. Confirmation of the endometrial and endometriosis tissues was conducted by at least two pathologists. Umbilical cord samples were collected from healthy women undergoing cesarean section. Within 30 minutes of surgery, all samples were transferred from the hospital to the laboratory on ice, using a sterilized container containing Dulbecco's Modified Eagle Media supplemented with Nutrient Mixture F-12 (DMEM/F-12, Hyclone, USA). The tissues were immediately washed multiple times with phosphate buffer saline (PBS, Hyclone, USA). The UC was stripped of blood vessels, and the remaining UC tissues, endometrial tissues, and endometriosis tissues were retained in a sterile culture dish containing DMEM/F12.

Hematoxylin-eosin (HE) staining & Immunohistochemical (IHC) analysis

Eutopic/ectopic endometrial, and UC tissues were fixed in 4% formalin for paraffin section preparation. Each segment was sliced to a thickness of 3 microns. Hematoxylin-eosin staining was performed to identify the morphological structure of the segments. Additionally, these slides were stained with vimentin or cytokeratin7 (CK7) antibodies using immunohistochemistry to determine the cell types. The rabbit SP detection kit (ZSGB, Beijing, China) was utilized for IHC analysis following the manufacturer's instructions. Antigen retrieval was conducted using sodium citrate buffer (pH 6.0) in a pressure cooker. The slides were incubated overnight at 4°C with primary antibodies against vimentin (1:100 dilution; BS1491; Bio-world Technology) or CK7 (1:100 dilution; 22208-1-AP; Protein tech). PBS was used as a negative control. Chromogenic reaction was achieved using the DAB kit (ZSGB, Beijing, China).

Mesenchymal stem cell isolation and primary culture

Fresh tissues were subjected to enzymatic digestion to isolate stromal cells. After washing the samples three

times with sterile PBS, they were cut into 1 mm^3 fragments. Fragments from each sample were placed in a 15 mL tube containing 400 U/mL collagenase II (Sigma) and digested in a YKW-303 shaker incubator (Yong le kang, Hunan, China) at 37°C for approximately 45 minutes with a speed of 120 rpm. The cell suspension was filtered through a 100 μm cell strainer (Corning, New York, USA), followed by a 40 μm cell strainer (Corning, New York, USA) to remove excess tissue debris. The final filtered liquid was centrifuged at 1500 rpm for 8 minutes. The supernatant was discarded, and the cell pellets were resuspended in 2 mL complete culture medium DMEM/F-12 supplemented with 10% fetal bovine serum (FBS) and 1% penicillin-streptomycin mixture (Gibco, Grand Island, NY). The cells were seeded in a flask (25 cm^2) in the complete culture medium and cultured at 37°C in a humidified incubator with 5% CO_2. A similar isolation and culture protocol was employed for stromal cells from UC as for endometriosis samples. The culture medium was refreshed every 3 days. When reaching 90% confluence, the cells were passaged using 0.25% Trypsin-Ethylene Diamine Tetraacetic Acid (Trypsin-EDTA, Gibco, Grand Island, USA) at a ratio of 1:2. At each passage, a small portion of cells were frozen in FBS supplemented with 20% dimethyl sulfoxide (DMSO, Solarbio, Beijing, China) for future evaluation. Differentiation studies were conducted on cells from passages 3 and 4.

Flow cytometry analysis

For flow cytometry analysis, cells from passages 3 and 4 were harvested using 0.25% Trypsin-EDTA into flow tubes, then centrifuged at 1000 rpm for 5 minutes. The cells were washed with PBS, diluted to a density of 1×10^6/mL, and incubated in the dark at 4°C for 30 minutes with 5μL of antibodies (CD31-PE cy7, CD45-PerCP, SUSD2-PE, CD73-APC/cy7, CD140b-APC, CD146-FITC, CD271-FITC, CD146-Alexa647, and CD44-Alexa488) (Table S1). Afterward, the cells were washed with 1 mL of PBS and centrifuged at 1000 rpm for 4 minutes. The supernatant was discarded, and the cells were resuspended in PBS. One tube without antibody served as a blank control. The antibody-labeled cells were analyzed using FACS Calibur flow cytometry (BD Canto, San Jose, USA), and the resulting data were analyzed using Flowjo 10 software (Leonard Herzenberg, USA).

Three lineages differentiation

In this study, three lineages of differentiation were investigated. MSCs were seeded in a 24 well plate (Corning, New York, USA) at a density of 5×10^4 cells/well using 500 μL of complete culture medium.

For adipogenic differentiation, cells were cultured until they reached 80% to 90% confluence. The culture medium was then replaced with an adipocyte-genic medium containing Human MSC Adipocyte-genic Basal Medium A and B, FBS, Penicillin-Streptomycin, Rosiglitazone, Glutamine, Insulin, Dexamethasone, and IBMX (Cyagen, California, USA), according to the manufacturer's instructions. The medium was changed every 3 days for 21 days. The adipocyte capacity of MSCs was evaluated using oil red staining. Cells were fixed with 4% paraformaldehyde for 35 minutes, washed thrice with PBS, and then stained with 60% Oil Red solution for 25 minutes (Cyagen, California, USA). After gently washing the plates twice with PBS, adipocyte-like cells were observed under a microscope (Olympus, Japan).

For osteogenic differentiation, to prevent MSCs from floating during induction, gelatin coating (Cyagen, California, USA) was applied to the surface of osteoblast-induced culture plates for 30 minutes. Afterwards, cells were seeded and cultured until they reached 60–70% confluence. The medium was replaced with an osteoblast-genic medium consisting of Human MSC Osteoblasts-genic Basal Medium, FBS, Glutamine, Penicillin-Streptomycin, Ascorbate, β-Glycerophosphate, and Dexamethasone (Cyagen, California, USA), as per the manufacturer's instructions. Cells were then cultured in this medium for 2 weeks. The osteoblast-genic capacity was assessed using Alizarin red dye solution (Cyagen, California, USA). Cells were fixed with 4% paraformaldehyde for 30 minutes, washed twice with PBS, and stained with Alizarin red dye solution for 3–5 minutes. Following three washes with PBS, the cells were imaged using a microscope (Olympus, Japan).

For chondrogenic differentiation, once cells adhered to the surface of the well, the medium was replaced with a chondrocyte-genic medium containing Human Stem Cell Chondrocyte-genic Basal Medium, Ascorbate, Dexamethasone, ITS + Supplement, Proline, Sodium Pyruvate, and TGF-β3 (Cyagen, California, USA), following the manufacturer's instructions. Cells were cultured for 21 days, with the medium changed every 2–3 days. To evaluate chondrogenic capacity, cells were stained with Alcian Blue. After fixing the cells with 4% paraformaldehyde for 30 minutes, they were washed twice with PBS and then stained with Alcian Blue (Cyagen, California, USA) for 30 minutes. Following three washes with PBS, images were captured using a microscope (Olympus, Japan). Positive staining with Alcian Blue indicated the presence of acid mucopolysaccharides in the chondrocytes.

Statistical analysis

Statistical analysis was performed using GraphPad Prism software (GraphPad Software Inc, version 5.00). Data were presented as mean ± standard error of the mean (SEM). Statistical comparisons between groups were conducted using the t-test or non-parametric Mann-Whitney test. A p-value of less than 0.05 was considered to indicate a statistically significant difference.

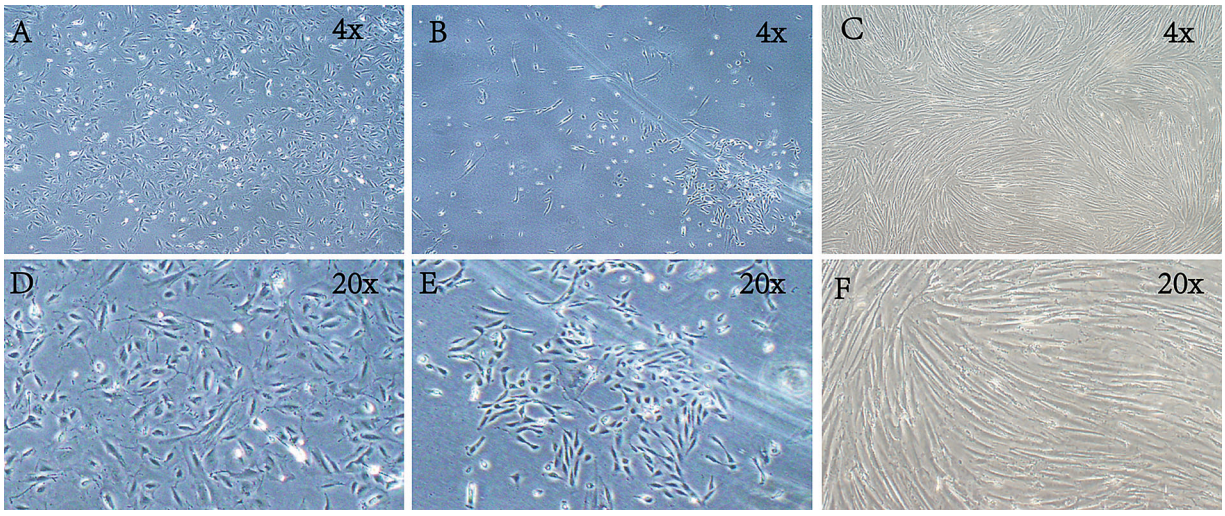

Figure 1. Morphology of primary eut-stromal cells, ect-stromal cells and umbilical cord-stromal cells — eut-stromal cells (**A, D**), ect-stromal cells (**B, E**), umbilical cord-stromal cells (**C** and **F**)

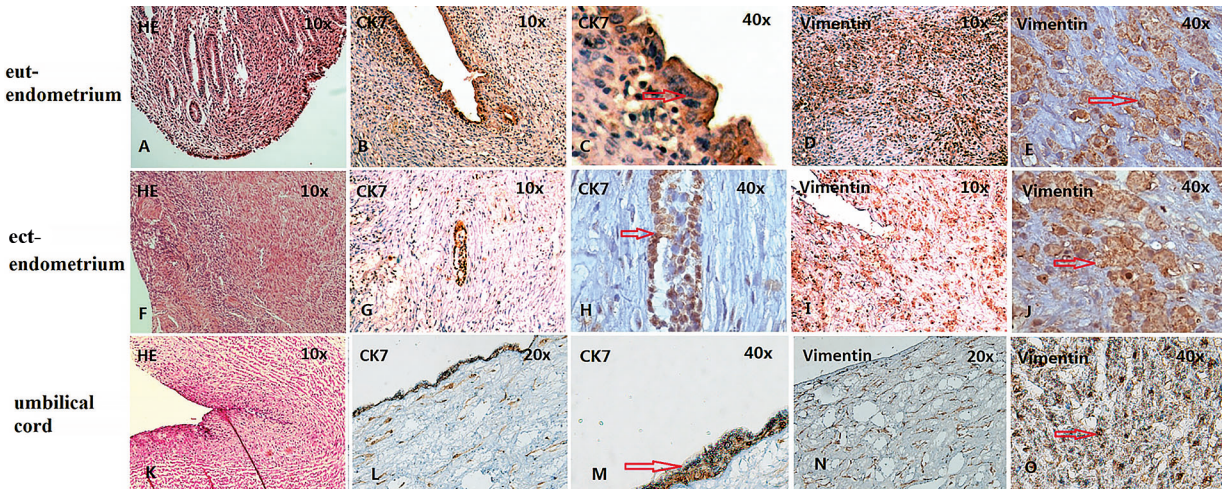

Figure 2. Identification of eut-endometrial and ect-endometrial tissues and umbilical cord; Hematoxylin-eosin (HE) staining identified the types of tissues (**A, F and K**); Expression of vimentin and CK7 in eut-endometrial (**B–E**), ect-endometrial (**G–J**), and umbilical cord **(L–O**) tissues were confirmed. Positive cells were presented with brown-yellow staining (red arrow); Eut-endometrial tissues (n = 5), ect-endometrial tissues (n = 6), and umbilical cord (n = 7)

RESULTS

Isolation and culture of eut-stromal cells, ect-stromal cells and UC-stromal cells

Figure 1 (A–F) presents the morphological characteristics of freshly isolated primary stromal cells from eutopic, ectopic endometrium, and UC, respectively. In Figure 1A and D, primary stromal cells from the healthy endometrium were cultured for five days, showing a predominantly triangular morphology. Figure 1B and E display the cell morphology after changing the culture medium on the third day, where small clusters of cells are visible. In Figure 1C and F, the morphology of primary stromal cells from the UC is shown on the fifth day after isolation, with approximately 90% of the cells exhibiting a long spindle-shaped appearance.

Identification of UC, ectopic–endometrium and eutopic-endometrium

Through HE staining, the cellular cytoplasm was stained pink, while the nuclei appeared blue. IHC results demonstrated that vimentin was primarily expressed in stromal cells of all three tissues, whereas CK7 was mainly expressed in the glandular epithelial cells (Fig. 2).

Cell surface antigen expression

Phenotypic analysis (Fig. 3) using flow cytometry with CD45- and CD31-gating (to exclude peripheral blood mononuclear cells and endothelial cells) revealed that primary stromal cells from UC expressed CD44 (99.11 ± 0.42%), CD73 (99.65 ± 0.12%), CD140b (99.84 ± 0.42%), CD146 (88.09 ± 4.20%),

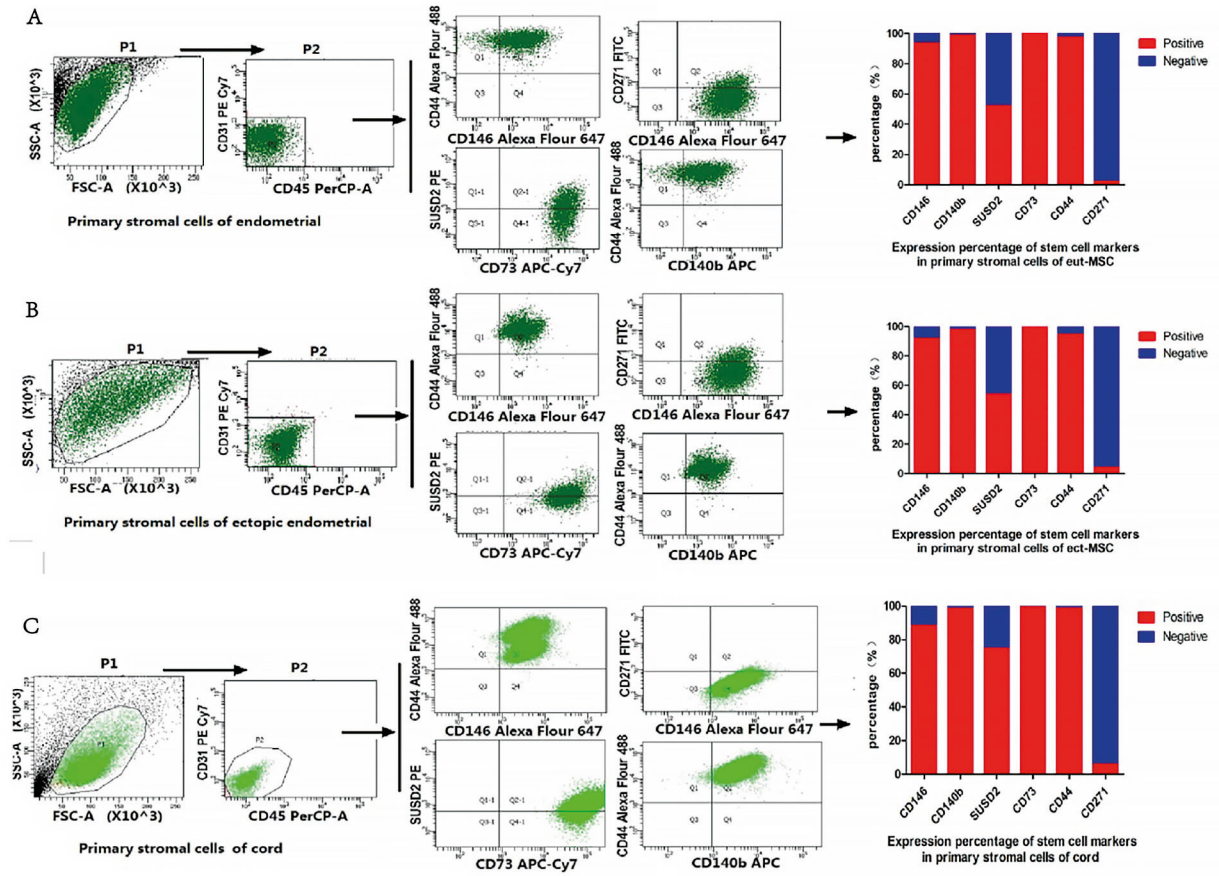

Figure 3. Expression profiles of primary mesenchymal stem cells (MSCs) derived from eut-,ect-endometrium and umbilical cord. Flow cytometry of MSC markers. Cells were gated by CD31-&CD45-. Data were presented with mean expression percentage of stem cell markers; **A.** Eut-endometrial tissues (n = 5); **B.** Ect-endometrial tissues (n = 6); **C.** Umbilical cord (n = 7)

Sushi-domain-containing-2 (SUSD2) (72.87 ± 7.13%), and CD271 (6.19 ± 2.08%). Similarly, primary stromal cells from the eutopic endometrium expressed CD44 (98.00 ± 0.96%), CD73 (99.54 ± 0.02%), CD140b (99.16 ± 0.50%), CD146 (93.87 ± 2.27%), SUSD2 (50.76 ± 8.15%), and CD271 (2.1 ± ± 1.22%). Additionally, primary stromal cells from the ectopic endometrium expressed CD44 (98.23 ± 1.60%), CD73 (99.63 ± 0.04%), CD140b (98.13 ± 0.53%), CD146 (93.88 ± ± 3.19%), SUSD2 (49.33 ± 6.36%), and CD271 (2.85 ± 1.17%). Notably, UC-MSCs, eutopic endometrial MSCs (eut-MSCs), and ectopic endometrial MSCs (ect-MSCs) strongly expressed CD44, with a percentage exceeding 98% (Fig. 4A). The expression percentages of CD73 and CD140b were over 95% in all three types (Fig. 4B–C). Furthermore, the average expression of SUSD2 in primary MSCs from the UC slightly exceeded that in eut-MSCs and ect-MSCs, with an expression level above 75% in 5 out of 7 cases of primary MSCs from the UC. The percentage spread was more uniform among the five samples (Fig. 4F). There was no significant difference in the expression of CD146 and SUSD2 between eut-MSCs and ect-MSCs, as indicated by similar p-values (1.000 and 0.931, respectively) (Fig. 4D and F). While the expression ratio of CD271 cells was less than 10% in all three MSC types, the percentage of CD271-positive eut-MSCs and ect-MSCs was similar but lower than that in UC-MSCs (Fig. 4E).

Multi-lineage differentiation

Eutopic endometrium MSCs, ect-MSCs, and UC-MSCs differentiated into adipocytes, osteoblasts, and chondrocytes when cultured with the corresponding differentiation medium. Oil drop-like fat particles indicative of adipocyte differentiation was visible on day 10 for eut-MSCs and ect-MSCs, while UC-MSCs displayed these particles on day 12. Formalin terminated the differentiation process once the fat particles reached 80% growth under the microscope (Fig. 5). During osteoblast differentiation, formalin termination occurred when osteocytes fused to 80% on day 18. As a result, the red staining of eut-MSCs and ect-MSCs appeared brighter compared to UC-MSCs (Fig. 5). Similarly, after 21 days of stimulation, chondrocyte differentiation was halted using formalin. The blue stain of UC-MSCs appeared lighter than that of eut-MSCs and ect-MSCs (Fig. 5). However,

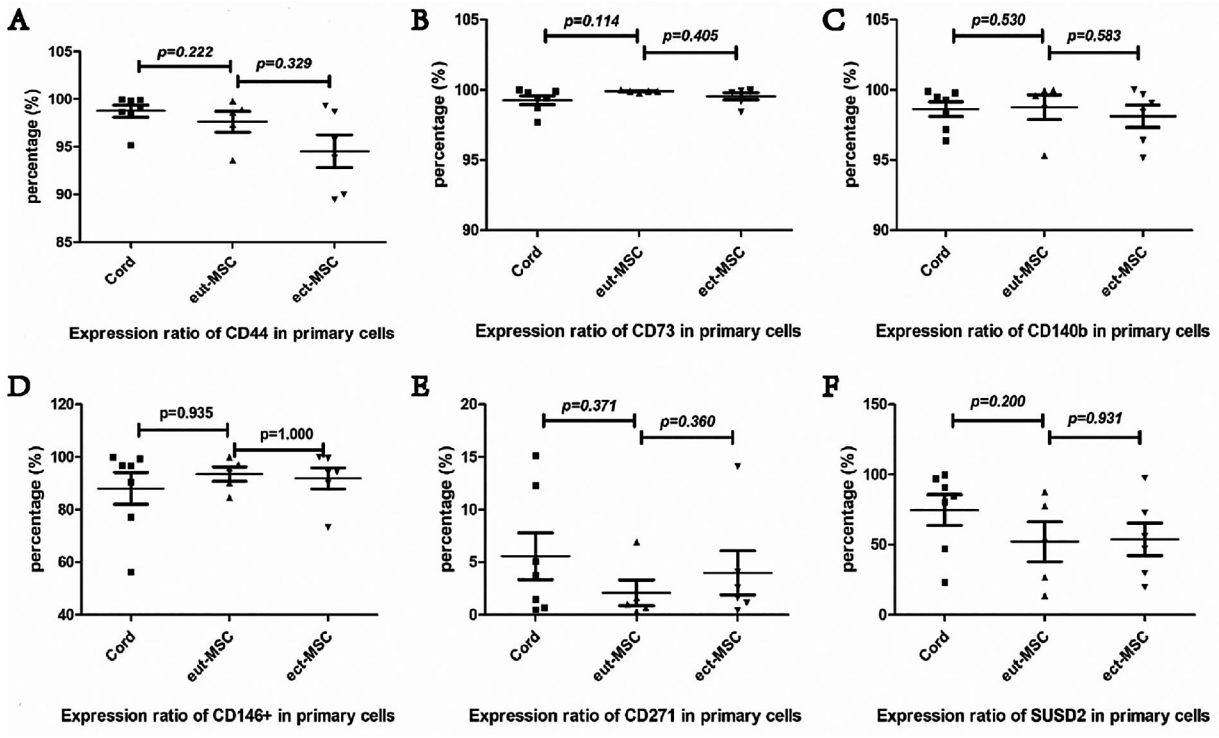

Figure 4. Percentage of the mesenchymal stem cells (MSCs) markers. The expression percentage of MSC markers: CD44 (**A**), CD73 (**B**), CD140b (**C**), CD146 (**D**), CD271 (**E**) and Sushi-domain-containing-2 (SUSD2) (**F**), respectively. Umbical cord (n = 7); Eutopic endometrial MSC (eut-MSC) (n = 5); Ectopic endometrial MSC (ect-MSC) (n = 6)

no changes were observed in eut-MSCs, ect-MSCs, and UC-MSCs cultured with complete medium as negative control.

DISCUSSION

Eutopic endometrium MSCs and ect-MSCs share similar surface marker expression. This study was aimed to compare and evaluate the potential enrichment of different components in MSCs derived from the eutopic endometrium, ectopic endometrium, and UC. This is a crucial step in identifying a reliable source of MSCs for endometrial repair.

Single endometrial CFUs have the ability to differentiate into classical mesodermal lineages and express typical MSC surface markers, namely CD44, CD73, CD90, and CD29 [13]. However, they lack the surface markers on hematopoietic stem cells and epithelial cells, such as CD45, CD34, and CD31. The expression profiles of MSCs differ significantly among different tissues [1]. The colocalization of eMSCs with CD140b, CD146, and SUSD2, which are derived from human endometrium, indicates a high enrichment of these markers in eMSCs [3, 5, 14]. These findings suggest the existence of multiple subpopulations of eMSCs with different phenotypes.

Our data demonstrated that the expressions of CD44 and CD73 in UC-MSCs, eut-MSCs and ect-MSCs were all over 98%. Previous studies have consistently shown that CD73+ UC-MSCs comprise more than 98% of the isolated cells [15]. Consistent with our results, Kang et al. found that the expression of CD44 and CD73 in human UC blood was 99.12% and 98.69%, respectively [16]; while Kao et al. demonstrated that the expressions of CD44 in eut-MSCs and ect-MSCs using flow cytometry were 98.6% and 97.6%, respectively [17]. Therefore, we speculated that UC-MSCs, eut-MSCs and ect-MSCs express CD44 and CD73 in significant quantities.

Sushi-domain-containing-2 was positive in approximately 4.2% endometrial stromal cells [18]. Our study observed SUSD2 expression in 49.33% of ect-MSCs and 50.76% of eut-MSCs, respectively. However, UC-MSCs showed higher enrichment at 72.87% compared to eut-MSCs and ect-MSCs. The percentage of SUSD2 expression varied greatly among individual endometrial samples, ranging from 13.73% to 99.85%, which may be attributed to differences in age and menstrual phase, requiring further confirmation with a larger sample size. Previous reports suggested SUSD2 as a stem cell marker mainly detected in eut-MSCs. However, we found a similar expression percentage of SUSD2 in ect-MSCs and eut-MSCs, suggesting a comparable MSC subpopulation. CD271 expression percentages in our results were 6.19% in UC-MSCs, 2.1% in eut-MSCs, and 2.85% in ect-MSCs. CD271 is known for enriching BM-MSCs [19] but had a low occurrence rate of only 0.71% [20]. Our results indicated that UC-MSCs

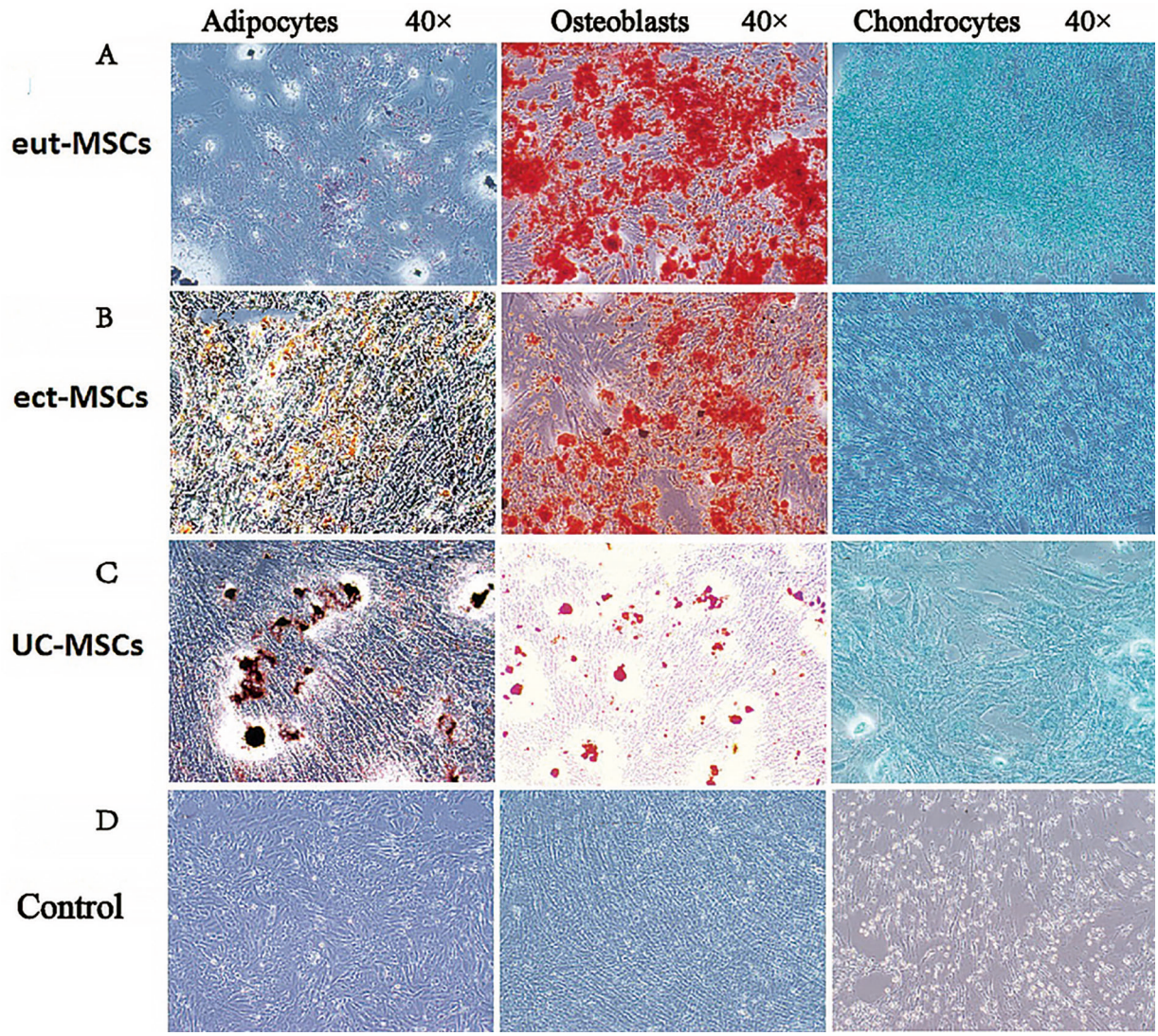

Figure 5. Multi-lineages differentiation of mesenchymal stem cells (MSCs). Adipose differentiation: the red lipid vacuoles stained by oil red; Osteoblastic differentiation: red phosphatases stained by Alizarin red dye solution; Chondrocytic differentiation: blue acid mucopolysaccharide stained by alcian blue. The differentiation assays for adipocytes, osteoblasts and chondrocytes were terminated at day 22, day18 and day21; **A–C.** Showed that eutopic endometrial MSCs (eut-MSCs) (passage 4), ectopic endometrial MSCs (ect-MSCs) (passage 4) and umbilical cord MSCs (UC-MSCs) (passage 4) began to differentiate into adipocytes, osteoblasts and chondrocytes, respectively; **D.** Representatively showed MSCs which were cultured with complete medium as negative control

rarely expressed CD271, and the expression of CD271 in human eut-MSCs and ect-MSCs was lower than that in UC-MSCs. Several studies have demonstrated that MSCs can be isolated from the endometrium using CD140b+CD146+ phenotypes, exhibiting similar differentiation abilities to other MSCs. In our study, CD146+ stromal cells accounted for approximately 90% of UC-MSCs, eut-MSCs, and ect-MSCs, with the average percentage of CD140b+ cells exceeding 98%. Rajaraman et al. [21] reported that eMSCs expressed 69% CD140b and 37% CD146. Masuda et al. [22] showed that freshly isolated human endometrial SUSD2+ cells expressed MSC markers, including CD146 (28.3 ± 4.3%) and CD140b (73.1 ± 11.5%) [13]. To our knowledge, this was the first study to demonstrate CD140b expression in UC-MSCs [23, 24].

Undoubtedly, the use of eut-MSCs for repairing thin endometrium represents an ideal therapeutic strategy for endometrial lesion-associated infertility. However, several obstacles hinder the clinical application of eMSCs, such as their rarity in normal endometrium, donor age [1], and the invasive acquisition method. Therefore, finding a substitute for eMSCs would be advantageous. Since primary eut-MSCs and ect-MSCs express similar percentages of stem cell phenotypes, we speculate that ect-MSCs might serve as an ideal alternative for lesion endometrial therapy.

Moreover, studies have shown that UC-MSCs possess high proliferation ability, multifunctional differentiation capacity, and low immunogenicity, making UC-MSCs efficient alternatives for the treatment of various diseases [25–27], including improving damaged human endometrium. Recently, multiple studies have reported on the potential of UC-MSCs to enhance endometrial repair [28–30]. These results provided a promising source of MSCs for repairing damaged or thin endometrium in women.

CONCLUSIONS

In summary, based on our data, it could be inferred that that: (1) eut-MSCs and ect-MSCs had similar phenotypes, with a high expression percentage for CD44, CD73, CD140b, CD146, and SUSD2; (2) SUSD2-positive expression was slightly higher in UC-MSCs compared to eut-MSCs and ect-MSCs without statistical significance; and (3) MSCs derived from these three tissues had the potential to differentiate into adipogenic, osteogenic, and chondrogenic cells. This study laid the foundation for further research on the application of UC-MSCs and ect-MSCs in repairing damaged endometrium. However, this study had several limitations, including a small sample size and variations in menstrual phase among patients with endometriosis. These limitations should be addressed through future studies with larger sample sizes.

Article information and declarations

Data availability statement

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Ethics statement

Following the guidelines outlined in the declaration of Helsinki and adhering to ethical standards, approval was obtained from the ethical committee at Henan Province People's Hospital.

Author contributions

Chunmei Li — perform experiments, article writing; Tong Wang — article writing, article revision; Suiyu Luo — study design; You Wu — flow cytometry analysis; Yan Song — collect samples; Ying Su — IHC analysis; Yuhui Zhang — statistical analysis; Yuanyuan Zhang — correspondence, study design, article revision; Guangzhi Liu — article revision, supervision; Lu Wang — collection tissues, concept.

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Conflict of interest

The authors declare no conflict of interest.

Supplementary material

Supplementary Table S1. Antibodies used to phenotype human endometrial cells and umbilical cord cells by flow cytometry.

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SUPPLEMENTARY MATERIAL

Table S1. Antibodies for cell phenotypes of human endometrial cells and umbilical cord cells using flow cytometry

Primary antibodies	Isotype	Clone	Concentration	From
CD31	Mouse IgG1	WM59	100 μg/mL/10^6cells	Biolegend, San Diego, USA
CD44	Rat IgG2b	IM7	500 μg/mL/10^6cells	Biolegend, San Diego, USA
CD45	Mouse IgG1	2D1	100 μg/mL/10^6cells	Biolegend, San Diego, USA
CD73	Mouse IgG1	AD2	200 μg/mL/10^6cells	Biolegend, San Diego, USA
CD140b	Mouse IgG1	18A2	300 μg/mL/10^6cells	Biolegend, San Diego, USA
CD146	Mouse IgG1	SHM-57	200 μg/mL/10^6cells	Biolegend, San Diego, USA
CD146	Mouse IgG1κ	541-10B2	100 μg/mL/10^6cells	Miltenyi Biotec, USA
CD271	Mouse IgG1	ME20.4	300 μg/mL/10^6cells	Biolegend, San Diego, USA
SUSD2	Mouse IgG1	W5C5	200 μg/mL/10^6cells	Biolegend, San Diego, USA

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The impact of limited access of photodynamic therapy during COVID-19 pandemic on patients with vulvar lichen sclerosus

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ABSTRACT

Objectives: Stressful situations have an impact on progression of lichen sclerosus. The aim of the study was to investigate fears and complaints of patients with vulvar lichen sclerosus and progression of disease at the beginning of the COVID-19 pandemic.

Material and methods: The analysis was based on 103 women with mean age was 64.81 ± 11.36 years divided into two groups. The first one comprised of patients with stabilization of disease during the pandemic with mean age 66.02 ± 10.01 (32–87), while the second one with progression of vulvar symptoms with mean age 63.49 ± 12.66 (25–87).

Results: Delay of diagnosis was reported to be a problem for respectively 25.93% of women from both groups. Fear about COVID-19 was described respectively by 57.4% and 55.1%. Stabilization of disease was more frequent in patients after photodynamic therapy before pandemic. Progression of vulvar symptoms and features were observed more in patients who did not conduct PDT previously. All patients from the second group who underwent photodynamic therapy reported disappointment because of no access for continuation of treatment. On the other hand, 81.4% (43 women) regret that have no chance for trying photodynamic therapy.

Conclusions: Photodynamic therapy seems to be a method of treatment with longer survival without progression of lichen sclerosus in times of pandemics. There has been no investigation until now about concerns of patients with vulvar lichen sclerosus. Better understanding of problems connected with the pandemic can help medical personnel in taking care of patients with vulvar lichen sclerosus.

Keywords: COVID-19; vulvar lichen sclerosus; fear; pandemics; photodynamic therapy

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INTRODUCTION

Lichen sclerosus (LS) is one of the most frequent chronic inflammatory vulvar dermatoses with morbidity estimated as from 1:300 to as high as 1:9000. It is relatively high in women in postmenopausal age [1].

The anogenital region is affected in 85 to 98% of cases of lichen sclerosus [2, 3]. Lichen sclerosus can also affect extragenital regions, such as the chest, axillae or buttocks [4].

The most frequent symptoms are burning and itching, which cause continuous discomfort and psychological distress in many women [4–6].

The precise pathogenesis of lichen sclerosus is not known, but in 12% of patients a familial background is described [3]. The presence of autoimmune disorders often correlates with LS [7, 8]. It is believed that the development and progression of LS are closely associated with oxidative stress [9]. Excessive amounts of reactive oxygen species cause deoxyribonucleic acid (DNA) damage and peroxidation of lipids and accelerate malignant transformation. In this mechanism, smoking cigarettes induces the progression of LS. Moreover, stressful situations have an impact on

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progression of lichen sclerosus or promote development of new lesions of this dermatosis [9].

The most distressing aspect of this disease is the symptoms, mainly itching and burning, disturbing everyday life and significantly reducing quality of life. Everyday usage of ointments can delay the onset of symptoms. The first line of treatment in the case of progression of this disease is glucocorticosteroid therapy [10, 11]. Lack of results after conservative treatment is an indication for induction of alternative method of treatment — photodynamic therapy with 5-aminolevulinic acid. Photosensitizer applicated on the skin before the procedure is cumulated in the tissues and induce cytooxygen reactions causing death of cells. This kind of therapy causes decreasing vulvar changes [12]. Photodynamic therapy has proven to be an effective treatment in vulvar lichen sclerosus [13].

Patients with vulvar lichen sclerosus used to come to follow-up visits and routine vulvoscopy to prevent recurrence of symptoms. Vieira-Baptiste et al. [14] reported a higher risk of progression of vulvar lichen sclerosus to vulvar cancer in the first three years after the diagnostic biopsy. However, use of ultrapotent topical steroids can reduce the risk of malignancy. Systematic gynecological visits are necessary to properly apply methods of treatment and prevent progression to vulvar cancer [14].

Halonen et al. conducted research in Finland based on 7616 women with diagnosis of vulvar lichen sclerosus in follow-up from 1970 to 2012 and confirmed that the risk of vulvar cancer was the highest in the first year of observation [15]. Extragenital lichen sclerosus does not progress to vulvar intraepithelial neoplasia (VIN) or malignant changes [16].

The coronavirus disease 2019 (COVID-19) pandemic began in December of 2019 in Wuhan. Isolation and social distancing dominated interpersonal relations and led to psychological disorders for many people. Sars-CoV-2 infection induced anxiety, stress, sadness, distress, sleep disturbances and depression [17, 18]. Psychiatric disorders were more frequently diagnosed in men, while acute mental disorders were present more often in women [19]. After COVID-19 infection, more posttraumatic stress disorder (PTSD) and fear of death were observed [18, 20].

Public health organizations decided to reduce access to outpatient clinics. Also, the number of surgical procedures was limited because of the pandemic and the need for places in intensive care and anesthesiologists. Most patients with chronic diseases have no chance for follow-up. Some of the patients refused to attend follow-up visits because of fear of the pandemic. There was a group of patients who decided to apply to an outpatient clinic in the event of progression of chronic disease.

The aim of the study was to investigate fears and complaints of patients with vulvar lichen sclerosus and progression of disease at the beginning of the COVID-19 pandemic from 20th November 2020 to 28th April 2021.

MATERIAL AND METHODS

The analysis was based on 103 women with vulvar lichen sclerosus diagnosed and treated in the Outpatient Clinic of Vulvar Diseases. Every patient was treated with potent and very potent topical corticosteroids (clobetasol propionate, clobetasol dipropionate, mometasoni furoas, betametason dipropionate, hydrocortisone) in the past. About 54.4% of analyzed group (56 patients) underwent minimum one line of photodynamic therapy consists of ten courses ended minimum three months before onset the pandemic. While COVID-19 pandemic was announced possibility of follow-up visits in Outpatient Clinic were reduced.

A cross-sectional study consisted of 20 questions was performed (Appendix 1). The first part of study concern general information of patients regarding everyday usage of emollients and rules of hygiene before pandemic. The second part gathered information about protection used by patients during the pandemic. In the third part data about the status of vulvar lichen sclerosus were collected including intensity of vulvar symptoms and new changes.

Inclusion criteria: pathological result of vulvar lichen sclerosus, visit to Outpatient Clinic of Vulvar Diseases during pandemic from 20th November 2020 to 28th April 2021, age over 18 years, no previous history of neoplasms or cancer, agreement to participate in the study. Exclusion criteria: chemotherapy and/or radiotherapy in the past, active COVID-19 infection.

Results of the questionnaires were therefore compared with clinical examination during appointment in Outpatient Clinic. The assessment was based on objective method of visualization — vulvoscopy.

According to cross-sectional study and objective assessment during visit in Outpatient Clinic, all analyzed population was divided into two groups.

The first one comprised 49 patients with stabilization of disease during the pandemic with mean age 66.02 ± 10.01 (range 32–87) years, while the second one consisted of 54 women with progression of vulvar symptoms with mean age 63.49 ± 12.66 (range 25–87) years.

Progression of vulvar lichen sclerosus was defined as increasing intensity of vulvar symptoms and new features and progression of presented changes. Patients who had stabilization of vulvar lichen sclerosus reported no symptoms and only made routine visits to the outpatient clinic.

What is more, in the first group 91.8% of patients (45 women) were treated by photodynamic therapy. In the second group, photodynamic therapy was introduced in 20.4% (11 women). The rest of the second group did not begin photodynamic therapy because of the onset of pandemic.

Table 1. Characteristics of analyzed population

Chronic diseases	Group 1	Group 2
Hypertension	21.36%	28.57%
Heart arythmia	4.85%	2.04%
Osteoporosis	0.97%	8.16%
Irritable bowel syndrome	3.88%	0%
Rheumatoid arthritis	1.94%	4.08%
Unstable angina	0.97%	4.08%
Depression	1.94%	2.04%
Glaucoma	2.91%	0%
Hypercholesterolaemia	1.94%	2.04%
Smoking	9.71%	*17.48%*
Neoplastic diseases	**Group 1**	**Group 2**
Breast cancer	1.94%	2.04%
Endometrial cancer	0%	2.04%
Thyroid cancer	0%	2.04%
Myeloma multiplex	0%	2.04%
Lung cancer	0%	4.08%

At the beginning of pandemic situation there was no possibility to continue photodynamic therapy because of the risk of COVID-19 infection.

Characteristics of the whole analyzed population are presented in Table 1.

Statistical methods

Means and standard deviations were used for characterization of patients. Calculation was done using Microsoft Excel (version 16.60). Statistical analysis was performed using RStudio (version 2021.09.1). Shapiro-Wilk's test was used for normality of continuous variables. To compare continuous variables the U-Mann Whitney test was performed, to evaluate categorical variables, the chi-square test was used. A p value of < 0.05 was considered significant.

RESULTS

The analysis was based on 103 women with vulvar lichen sclerosus with mean age 64.81 ± 11.36 (range 25–87) years treated in the Outpatient Clinic of Vulvar Diseases from 20th November 2020 to 28th April 2021. Results are divided according to the main points of analysis.

Fears related to visits to the outpatient clinic

Around 44.44% of the first group and 53.06% of the second group were afraid of visiting the outpatient clinic during the pandemic. Contact with medical personnel was a fear in 5.55% and 10.2% of cases. Other patients in the outpatient clinic waiting for an appointment were a reason for fear in 24.07% of the first group and 30.61% of the second group. The risk of being in quarantine was 18.52% and 12.24%.

Protective products during the pandemic

Special rules due to the pandemic situation were provided in all countries all over the world. However, all analyzed populations used different forms of protection. Percentages are presented in Figure 1.

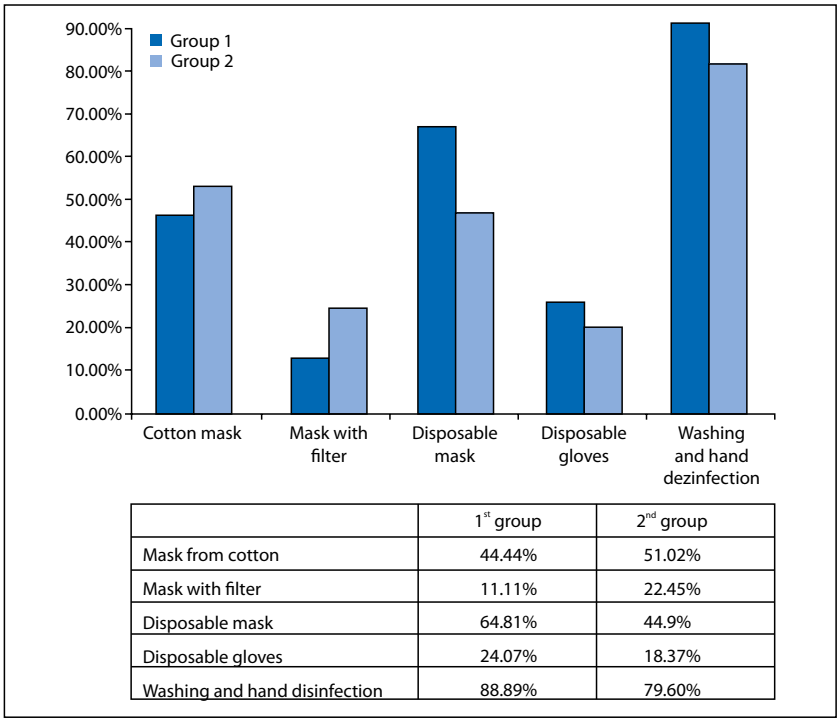
On the other hand, 5.56% and 2.04% from both groups decided not to go outside because of the pandemic. Most patients limited their visits to town, respectively 75.93% and 67.35%. Contact only with inmates was reported by 42.6% and 30.61%, respectively. No difference between the pandemic situation and normal life was reported by 14.81% from the first group and 6.12% from the second.

Vulvar clinical symptoms during the pandemic

The first group of analyzed patients do not complain of vulvar symptoms. They use everyday ointments with no progression and observe no worsening of status, but they decided to come for a follow-up appointment.

In the second group of the analyzed population were women with progression of vulvar lichen sclerosus beginning from the onset of the pandemic. The most frequent locations of symptoms were the ostium of the vagina (18.36%), the clitoris (12.24%), the inguinal area (6.12%), the anus (4.08%), the urethra (2.04%) and the whole vulva (2.04%).

Burning of the vulva and itching were present in most cases, respectively 28.57% and 22.45%. Reddening of the



	1st group	2nd group
Mask from cotton	44.44%	51.02%
Mask with filter	11.11%	22.45%
Disposable mask	64.81%	44.9%
Disposable gloves	24.07%	18.37%
Washing and hand disinfection	88.89%	79.60%

Figure 1. Usage of protective Staff by patients

Table 2. Characteristic of clinical symptoms of patients from group 2

Syndrome	Median value	±	Minimum value	Maximum value
Itching	5.16	3.39	6	10
Burning	4.63	3.27	5	10
Stinging	1.08	2.27	0	9
Pain	2.12	3.03	0	10
Bleeding	0.16	0.65	0	3

vulva was observed in 16.32% of women, while leukoplakia occurred in 6.12% and pain in 6.12%. In subgroups collected patients after photodynamic therapy in the past intensity of clinical symptoms were observed less than others.

For better assessment of intensity of syndromes, a 10-degree scale was used. All patients from the second group evaluated the intensity of every syndrome. All results are presented in Table 2.

Fears related to COVID-19 infection

Patients were asked about their fears of gynecological visits in the future. The pandemic is a situation with no end, and probably it will last for a long time. Around 29.63% of patients with no symptoms yet are afraid of progression of lichen sclerosus in the future, compared to 36.73% of the second group. Every second women from the first group are afraid of visit postponement, and 40.82% in the second group. More patients (27.78% vs 10.2%) without progression of disease were worried about transformation of the outpatient clinic to a pandemic clinic. Delay of diagnosis was reported to be a problem for 25.93% of women from the first group and 30.61% from the second one. Fears of limited access of photodynamic therapy was reported by 71.4% patients (35/49 patients), where 94.3% (33/35 patients) underwent photodynamic therapy in the past. Patients from the second group were afraid of limited access of photodynamic therapy in 83.3% (45/54 patients) including all 11 patients after photodynamic therapy in the past.

COVID-19 is a disease with various courses. This fear was described by 57.4% of women with no symptoms of lichen sclerosus and 55.1% of the group with progression of this disease. Other reported problems were lack of specialists (42.6%, 34.7%), lack of medicaments (24.07%, 16.33%), and lack of contact with family because of isolation (33.33%,

Table 3. Correlations of patient's fear

Correlations		p value	OR	CI_{min}	CI_{high}
Group 1 with no symptoms					
COVID-19 infection	Contact with other patients in outpatient clinic	0.00007546	27.17	3.37	1271
	Contact with medical personnel	0.0816	Inf	0.5335	Inf
	Contact only with inmates	0.0533	3.191	0.9263	11.73
	Obligatory quarantaine/isolation	0.002977	16.54	1.98	784.7
	Avoiding shopping	1	0.8212	0.06334	7.846
	Limited leaving the house	0.111	3.423	0.7357	22.17
Group 2 with intense vulvar symptoms					
COVID-19 infection	Contact with other patients in outpatient clinic	0.002066	9.996	1.823	105.4
	Contact with medical personnel	0.3532	3.9	0.3489	205.5
	Contact only with inmates	0.01515	5.51	1.186	36.07
	Obligatory quarantaine/isolation	0.6707	1.885	0.2404	22.91
	Avoiding shopping	0.2372	Inf	0.3731	Inf
	Limited leaving the house	1	1.196	0.3067	Inf

OR — odds ratio; CI — confidence interval; Inf — infinity

28.57%). The influence of COVID-19 on lichen sclerosus was found to be a problem for 22.22% of the first group and 16.33% of the second. All patients from the second group who underwent photodynamic therapy reported disappointment because of no access for continuation of treatment. On the other hand, 81.4% (43 women) regret that have no chance for trying photodynamic therapy.

Contact with other patients in the outpatient clinic and with inmates in correlation with fears of Sars-CoV-2 infection was statistically significant in both groups in our study ($p < 0.05$). Higher risk of fear of COVID-19 infection was dependent on contact with medical personnel and other patients ($p < 0.05$). Patients are afraid of diseases and consequences of the pandemic such as quarantine or isolation. The statistical significance of correlations above are presented in Table 3.

DISCUSSION

The Sars-CoV-2 pandemic causes fears and concerns of everyone all over the world. At the onset of the pandemic there were no medicaments and no possibility of vaccination, which created increasing fear, especially among patients which chronic diseases. Vulvar lichen sclerosus is a noninflammatory chronic disease, whose etiology relates to dysregulation of the immunological system. Hence, it is possible that the permanently stressful situation during the pandemic raises the risk of progression of this disease.

The pandemic situation and disturbances in taking part in routine visits cause have led to new recommendations being developed by experts [21]. During the COVID-19 pandemic vulvar cancer treatment algorithms have been modified. VIN 2 and 3 qualified for resection can be operated on with a delay of 10–12 weeks [22].

Most of the previous research estimated the risk of progression of vulvar lichen sclerosus to vulvar squamous cell carcinoma at up to 5% [23, 24].

Van de Nieuwenhof [25] analyzed 60 biopsies of vulvar lichen sclerosus and reported progression of 42% of cases to differentiated VIN and 30% with no change. Nevertheless, follow-up visits are important for monitoring progression of vulvar lichen sclerosus.

Some patients during the pandemic did not decide to attend routine visits because of fear of COVID-19 infection. Delay of these visits may be a problem in the future due to the advanced stage of cancers or intensity of symptoms with no treatment. Our study revealed the fears and concerns of patients with diagnosis of vulvar lichen sclerosus, a topic not previously reported. This group of women due to the irritating symptoms and immunological etiology of diseases is more often predisposed to exacerbating symptoms in response to a stressful situation.

The pandemic is an unexpected situation, triggering high levels of anxiety and vigilance. It is very important to study human behavior and concerns to prevent infection and prepare for everyday life [26]. Patients with lichen sclerosus suffer from various psychiatric disorders, most often anxiety (58%), depression (27%) and insomnia (19%) [9]. Moreover, due to cosmetic changes in the vulvar area, lichen sclerosus leads to a decrease in libido [27]. In China populations of adolescents during the pandemic self-reported depression and anxiety at respectively 43.7% and 37.4% [28]. Akbarpour et al. [29] confirmed that fears of COVID-19 are

associated with depression, anxiety and insomnia. In our study, there was no problem of insomnia, however, anxiety and fears concerning pandemic was observed.

Due to the COVID-19 crisis the Portuguese population had the possibility to ask the government about problems connected with the pandemic. Questions from Portuguese people were sent online, by radio or newspaper. The most frequent doubts concerned how to proceed with symptoms, how long the disease takes to develop and what treatment is available. The use of masks and gloves was often asked about. People were interested in isolation requirements and preventive behaviors. The frequency of questions was higher at the start of the study. After three weeks, the number of unknown areas gradually decreased. However, there was observed an increasing number of concerns about fake news and contradictory information regarding the pandemic [30]. In our study, patients with lichen sclerosus are afraid of contact with medical personnel and other patients. However, some of them did not use any kind of protection. On the other hand, there are also patients who do not go outside because of the pandemic.

A correlation of the COVID-19 pandemic with intensity of symptoms of vulvar lichen sclerosus has not been previously described. However, there were some cases of complications after Sars-CoV-2 vaccination.

A few cases of post-vaccination vulvar ulcers have been reported. Drucker et al. observed vulvar aphthous ulcer two days after Pfizer vaccination in a 14-year-old with no previous sexual relations and no medical history [30, 31]. Asymmetric labia, fatigue, fever and pain were also detected in a 16-year-old girl vaccinated a day before [32].

Another type of lichen striatus was reported after COVID-19 vaccination in a 42-year-old woman with no history of dermatological disorders. This kind of self-limited inflammatory dermatosis was present on the right wrist, right shoulder and chest [33]. In our study, there were no vulvar features which can be associate with COVID-19 infection.

Dermatosis after COVID-19 vaccination which appeared in a 56-year-old woman was lichen planus. She complained of lesions located on the ankles, wrist and forearms, periumbilical area, and breast with axillary folds [34]. In our study we did not observe any new atypical changes of vulvar disorders, which can develop after COVID-19 infection. The analyzed population was not affected by Sars-CoV-2.

No research has presented information about the intensity of symptoms in vulvar lichen sclerosus. Nevertheless, Souaid et al. reported that 10.3% of a group treated with topical steroids and topical tacrolimus because of psoriasis and atopic dermatitis infected by Sars-CoV-2 did not present severe symptoms. Neither hospitalization nor oxygen therapy was needed. No complications in these patients were observed [35].

Patients with dermatological disorders treated with methotrexate were most hospitalized due to COVID-19 infection; however, no complications were registered [36]. Interestingly, in our analyzed population steroid therapy was introduced when clinical symptoms appeared. No one was infected by COVID-19, so we have no data about interaction between glucocorticosteroid therapy and treatment of Sars-CoV2 infection. On the other hand, there was no publication about the influence of photodynamic therapy using during COVID-19 pandemic. We only observed higher risk of progression of vulvar lichen sclerosus in case of not using photodynamic therapy before. There was no possibility of this kind of treatment at the beginning of COVID-19 pandemic what influence on disappointment of patients.

All over the world during the pandemic many rules relating to hygiene were introduced. Daily facemasks use increased. It was observed that in urban populations the percentage of people using a protective facemask was higher in Europe, North America, South America and Oceania (respectively 74.5%; 82.6%; 85.5% and 67.8%) than in Asia and Africa (50.9%; 43.8%) [37]. According to our investigation, patients prefer to use disposable and cotton facemasks. There was observed definitively lower usage of facemasks with a filter and disposable gloves. According to WHO recommendations during the pandemic, hands should be washed with 3 mL of antiseptic fluid applied for 30 seconds [38]. Interestingly, in our research, 88.89% of patients with no vulvar symptoms and 79.6% from the second groups reported performing hand disinfection during the pandemic.

Martinelli et al. [39] developed a social survey about modification of practice in gynecologic oncology during the pandemic from 49 countries all over the world. There were no modifications for treatment if the patients were COVID-19 negative in the opinion of 59% of respondents. In our study, access to an ambulatory outpatient clinic was available, but some of the patients were afraid to come. Every second patient describes fears for her life connected with the consequences of COVID-19.

CONCLUSIONS

COVID-19 is a new disease with no knowledge at the onset of the pandemic. Fears, anxiety and concerns have affected everyone everyday. Lichen sclerosus is a dermatosis with progression occurring during stressful situations, such as happened during the pandemic. Previous photodynamic therapy reduces the risk of progression of vulvar lichen sclerosus in case of stressful situation like pandemic. There has been no investigation until now about concerns of patients with vulvar lichen sclerosus. Better understanding of problems connected with the pandemic can help medical personnel in taking care of patients with vulvar lichen sclerosus.

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Conflict of interest

All authors declare no conflict of interest.

Supplementary material

Supplementary material 1.

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SUPPLEMENTARY MAERIAL 1.

Part 1. General information about patient

1. Did you attend for a gynecological visit regularly before the pandemic?
2. Are you being treated for any chronic diseases?
3. Do you smoke?
4. Which ointments do you use every day?
5. How many times a day do you use ointments?
6. Do you feel relief after daily use of ointments?
7. Do you use hygiene protective products?

Part 2. Information about symptoms

8. Have you seen new changes since the beginning of the pandemic?
9. Which location of new changes has been the most frequent since the pandemic started?
10. What was the feature of new changes on the vulva?
11. Which symptoms were the most common during the pandemic (scale 0–10)?
    A. Itching
    B. Burning
    C. Stinging
    D. Pain
    E. Bleeding
12. Which part of the day was the most often associated with clinical symptoms?
13. Did itching cause scratching?
14. Do you often have vaginal discharge?
15. What were you afraid of during a visit to the Outpatient Clinic at the beginning of the pandemic?
16. Which protective items do you use during a visit to the Outpatient Clinic?
17. What were you afraid of during a visit to the Outpatient Clinic at the beginning of the pandemic?
18. What would you be afraid of if you were COVID-19 infected?
19. What problems did you have before a routine visit to the Outpatient Clinic at the beginning of the pandemic?
20. Which protective products do you use every day?

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Retained products of conception — a retrospective analysis of 200 cases of surgical procedures for the diagnosis of residua postpartum

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ABSTRACT

Objectives: Postpartum retained products of conception are a relatively rare diagnosis occurring in approximately 1% of cases after spontaneous deliveries and abortions. The most common clinical signs are bleeding and abdominal pain. The diagnosis is based on clinical signs and ultrasound examination.

Material and methods: Retrospective analysis of 200 surgical procedures for the diagnosis of residua postpartum obtained in 64 months. We correlated the method and accuracy of diagnosis with definitive histological findings.

Results: During 64 months, we performed 23 412 deliveries. The frequency of procedures for diagnosis of retained products of conception (RPOC) was 0.85%. Most (73.5%) of the D&C were performed within six weeks of delivery. Histologically, the correct diagnosis was confirmed in 62% (chorion + amniotic envelope). There was interestingly lower concordance of histologically confirmed RPOC in post-CS patients (only 42%). In women after spontaneous delivery of the placenta, the diagnosis of RPOC was confirmed by histological correlate in 63%, and the highest concordance occurred in women after manual removal of the placenta in 75%.

Conclusions: Concordance with histological findings of chorion or amnion was seen in 62% of cases; this means that the incidence rate in our study was around 0.53%. The lowest concordance is after CS deliveries, 42%. D&C for RPOC should be performed after adequate clinical evaluation and in the knowledge of 38% false positivity. There is certainly more space for a conservative approach under appropriate clinical conditions, especially in patients after CS.

Keywords: retained products of conception; D&C; hysteroscopic resection; manually removed placenta

Ginekologia Polska 2023; 94, 12: 967–971

INTRODUCTION

Post-partum retained products of conception are a relatively rare diagnosis occurring in approximately 1% of cases after spontaneous deliveries and abortions. [1, 2] The most common clinical signs are bleeding, abdominal pain, fever and uterine subinvolution. These symptoms commonly appear during the six weeks of labour but may also occur several months after delivery. The diagnosis is based on clinical signs and ultrasound examination (echogenic focus and distension of the uterine cavity, flow parameters). The definitive diagnosis is confirmed by histological examination. The sensitivity and specificity of the ultrasound examination range from 44–85% and 88–92%, respectively [3–6]. Postpartum residues with minimal clinical manifestations can be managed by conservative management with the administration of uterotonics and monitoring their effect by follow-up ultrasound. The published success rate of this procedure has been nearly 50% [6, 7]. The preferred method is the instrumental revision of the uterine cavity with a curette, preferably under ultrasound guidance. Hysteroscopic resection of residual tissue is another option and is recommended to be performed no earlier than six weeks after birth. The most common complications of surgical management are significant blood loss, uterine perforation during surgery, or even the need for a hysterectomy. Late complications include the development of Asherman's syndrome, sterility, and the possible development of arteriovenous malformations.

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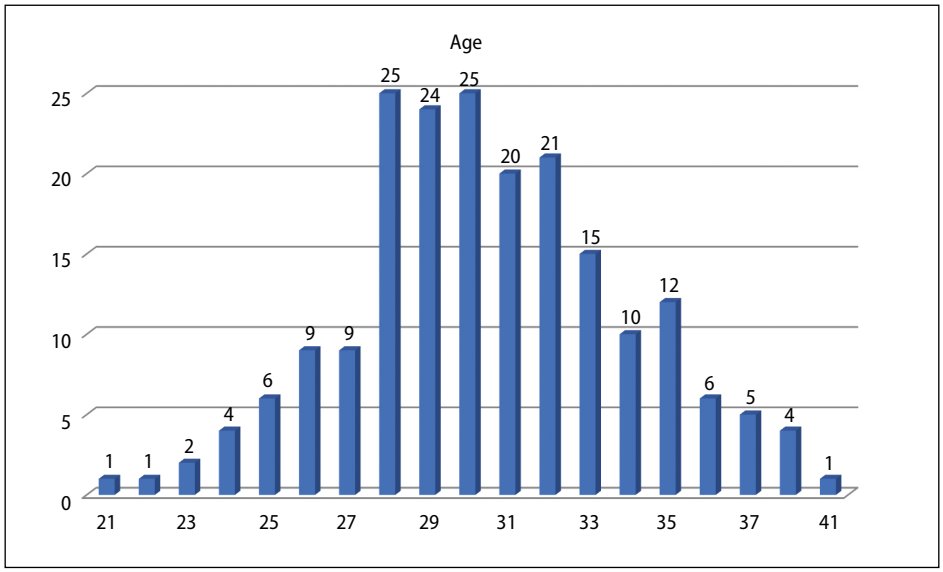

Figure 1. Distribution of age

Aim of the study

To evaluate procedures for postpartum residua and to find possible associations with parity, age, mode of delivery, gestational week, gynaecological and obstetric history, and other variables.

MATERIAL AND METHODS

Retrospective analysis of 200 surgical procedures for the diagnosis of residua postpartum. Data were obtained from our hospital information system for 64 months. We analyzed the relationship of the diagnosis of residuum postpartum with parity, age, mode of delivery, obstetric complications, uterine procedures, manual removal of the placenta and days since delivery. Ultrasonographic diagnosis of retained products of conception was made by assessing the width of the uterine cavity and the presence of hyperechogenic material. We correlated the method and accuracy of diagnosis with definitive histological findings and the possible presence of inflammation. We considered the chorion or amniotic envelope finding from the retrieved material as histologically confirmed residues. Data were processed using SPSS PC statistical software (for Windows).

RESULTS

We performed 200 procedures for diagnosing postpartum retained products of conception (RPOC) in 64 months at our institution. During this period, we performed 23,412 deliveries, and out of these, 5,567 were caesarean sections (28%), 234 were forceps (1%), and 16,539 (71%) were spontaneous deliveries. After vaginal deliveries, we had to manually remove the placenta (MRP) and instrumental revision of the uterine cavity in 677 (4.1%) women. Thus, if we take all

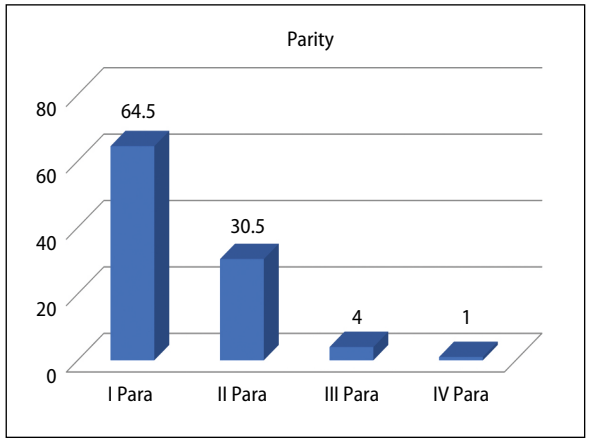

Figure 2. Distribution of parity

the procedures for RPOC during this period in our health facility, their frequency was 0.85% of all deliveries.

Figures 1–5 show the distribution of age, parity, week of gestation, mode of delivery and beginning of the delivery. The composition of parturients in the study population corresponds to the typical design of the population of parturients in our health facility (4). It consisted of 70% of patients after vaginal delivery with spontaneous delivery of the placenta, 14% of women after caesarean section (CS) and a group of 16% of women after vaginal delivery where we had to perform manual removal of placenta and instrumental revision of the uterine cavity (D&C). Hence 4.75% of women after MRP had later D&C performed for suspected RPOC, *i.e.*, one in 21 women. Similarly, it can be inferred that 0.6% of women had a vaginal delivery, and 0.45% of women after CS D&C procedure for RPOC was performed in women after

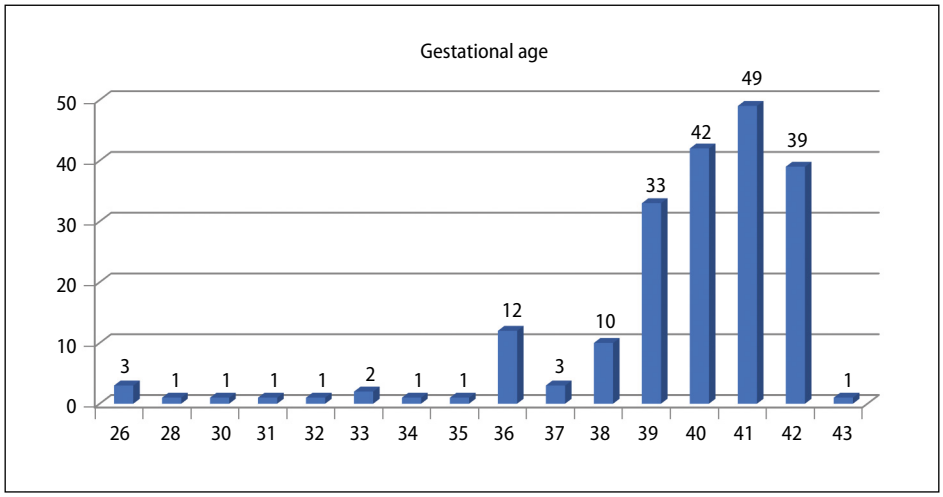

Figure 3. Distribution of gestational age

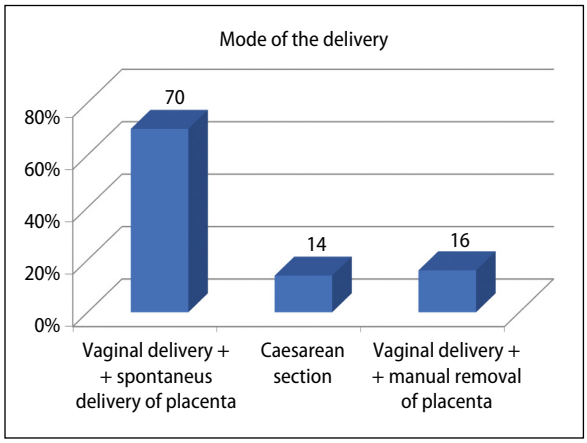

Figure 4. Mode of the delivery

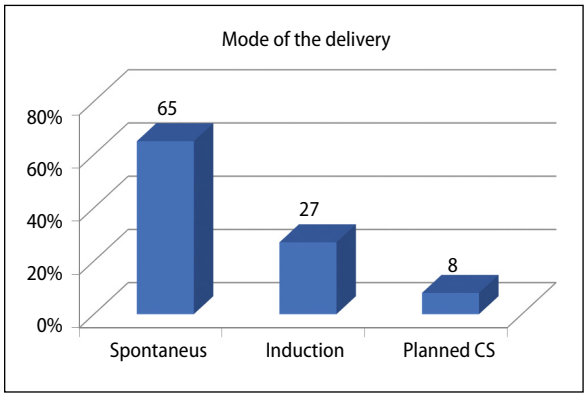

Figure 5. Beginning of the delivery; CS — caesarean section

MRP 7.9 times more often than after spontaneous delivery and 11 times more often than after caesarean section. Labour started spontaneously in 65%, induction was in 27% and planned CS in 8%. Of the total number of caesarean sections, 66% of CS were acute and 34% planned, which is undoubtedly surprising but may be an error of small numbers. Most (73.5%) of the D&C were performed within six weeks of delivery. Of these, 16% of procedures were performed on days 1 to 5. In our health facility, we perform an ultrasound on every woman after MRP and CS on day 3 during hospitalization, and therefore D&C is performed within 5 days after delivery.

Further, we performed 28% of procedures from days 6 to 14 and 29.5% of procedures from days 15 to 42. After day 42, it was 26.5% of operations (Fig. 6). The longest time span from delivery to D&C performance was 198 days. The diagnosis of residua was 59.5% based on clinical signs and ultrasound examination, 17% based on clinical signs only and 23.5% based on ultrasound examination only. The most frequent clinical manifestations were bleeding, abdominal pain elevated temperature. Ultrasound findings suspicious of RPOC were uterine cavity dilatation over 10 mm, hyperechogenic content, and present flow was not a condition. Histologically, the correct diagnosis was confirmed in 62% (chorion + amniotic envelope). In 34% only decidua was described; in 2%, only myometrium and in 2%, only coagula. In the complete histology findings, myometrial fragments were described in 59 patients (29.5%), which could be a risk factor for further pregnancies. Inflammation was described histologically in 46%. There were 47% of women with a history of mild or no complications. Thirty per cent of the women had a history of uterine cavity surgery (abortion, D&C, suction curettage), indicating a significant effect (Chi-square = 80.554, p = 0.0001) of this factor on the subsequent occurrence of RPOC in following pregnancies. A risk factor for RPOC could also be a caesarean section in the previous pregnancy (occurrence in 5.5% of women)

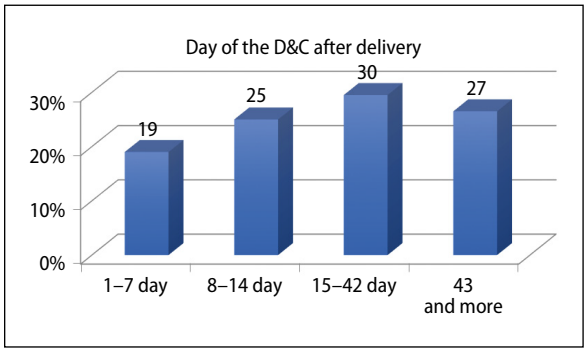

Figure 6. Day of manual removal of placenta and instrumental revision of the uterine cavity (D&C) after delivery

or pre-eclampsia in this pregnancy (7.5% of women). When testing the concordance between mode of delivery and clinical diagnosis of RPOC confirmed by histological correlate, at the significance level (Chi-square = 19.599, p = 0.46), there was interestingly lower concordance of histologically confirmed RPOC in post-CS patients (only 42%). In women after spontaneous delivery of the placenta, the diagnosis of RPOC was confirmed by histological correlate in 63%, and the highest concordance occurred in women after MRP in 75%. Histological concordance with the diagnosis of RPOC was lower in the women after acute CS group than in women after elective caesarean section. No statistical significance (Chi-square = 217.274, p = 0.84) was found between this factor and the mode of delivery of the placenta when the time of the procedure was observed.

Similarly, there was no correlation (Chi-square = 4.966, p = 0.291) between the mode of delivery and the presence of inflammation confirmed by histopathology. When the way of onset of the labour (planned SC, induced labour, spontaneous labour) was correlated with the final histological findings (Chi-square = 27.13, p = 0.028), a false positive diagnosis of RPOC was found to be almost 50% in patients after induced deliveries. Also, inflammation was more frequently described by the histopathologist in patients after induced deliveries, but this factor appeared only at the level of significance (Chi-square = 4.539, p = =0.209). Surprisingly, when testing the concordance between parity and inflammation confirmed by a histopathologist, inflammation was less frequently described in second and multiple births (Chi-square = 6.355, p = 0.096).

In 8.5% (17 women), we were forced to perform a repeated D&C for persistent RPOC. In three cases, the uterus was perforated and uterine perforation was corrected by subsequent laparoscopic suture.

The pathologist described placenta accrete in two cases (1%). We performed a hysterectomy in one patient, and ligation of internal iliac arteries and hysteroscopic resection of the placental remnants was needed in the other patient after six weeks of gestation.

DISCUSSION

In other studies [1, 2], the incidence of RPOC was around 1%, with a higher incidence after preterm termination of pregnancy. This study performed D&C for suspected post-delivery RPOC in 0.854% of women. Histological concordance occurred in 62% of cases, suggesting that only 0.53% of postpartum women had histologically proven RPOC. We are aware of the factors that may reduce the actual number of RPOC in this study, namely incomplete D&C, surgeon bias in the selection of material sent to the Pathologist, the possibility of the Pathologist's error, and the fact that we are a perinatology centre and some women with complications in the sixth-week visit other facilities closer to their homes. All these could lead to a slight underestimation of RPOC in our setting. Striking was the relatively high number of procedures for suspicion of RPOC in women after CS (28%). In fact, in our health facility, we perform D&C or at least digital revision of the uterine cavity in every woman during CS Furthermore, the higher incidence after elective CS is surprising. However, the histological concordance with the diagnosis of RPOC is only 42% after CS compared to the concordance after spontaneous delivery when we get to 62% and 75% after MRP. The greater concern of patients could be an explanation, but also the more significant concern of physicians about possible complications after CS and thus the more frequent decision to perform D&C when clinical signs such as bleeding or febrile.

Furthermore, MRP is one of the most critical risk factors for RPOC. The performance risk for RPOC after MRP is 11 times higher than after CS and 7.9 times higher after spontaneous delivery, and concordance with histology is most common here. This ratio is, of course, due to the condition that led to the need for MRP, which is the placenta accreta spectrum and subsequent D&C on the after-delivery distended uterus. The risk factor is the recurrence of retained placenta in the next pregnancy, reported to be around 13.8%. [8]. Risk factors for placental retention include abnormal placentation (history of uterine surgery, uterine curettage, postpartum endometritis, hysteroscopic surgery and endometrial ablation, in vitro fertilization conception), which is consistent with the anamnestic frequency of intrauterine procedures we have described in our study. Another risk factor related to surgery on the uterus is a previous caesarean section. A large population-based cohort study from Sweden described the risk of retained placenta after a previous caesarean section at 3.4% versus 1.9% after spontaneous delivery p= 0.0001. In this study, there was a higher association with placental failure in older parturients, but

the location of the placenta on the anterior or posterior wall had no effect [9].

The other risk factors are poor uterine contraction (prolonged use of oxytocin and high parity) and other factors, such as preterm delivery, congenital uterine anomalies and prior history of retained placenta. [10, 11] The question of possible complications after D&C where the myometrium has been described in the histological findings seems interesting. In a study by Pather [6], a 39% incidence of myometrium from D&C is described, but only one evidence of Asherman's syndrome (however, the group was not properly followed up long term). The risk factor for developing intrauterine adhesions (IUA) is the caesarean section itself, and the risk further increases with the subsequent need to perform D&C for RPOC. A higher incidence of IUA has also been described in patients after procedures for retained placenta [12].

Our histological results with findings of myometrium and inflammation, especially after induced deliveries, could explain the higher risk of IUA.

We have to consider other possible complications such as foss route during D&C, risk of placenta accreta spectrum in subsequent pregnancies and development of arteriovenous malformation.

CONCLUSIONS

Retained products of conception after delivery is a rare diagnosis with an incidence of about 1%. They occur with greater frequency after MRP and spontaneous deliveries than CS deliveries when we perform perioperative D&C. Concordance with histological findings of chorion or amnion was seen in 62% of cases; this means that the incidence rate in our study was around 0.53%. The lowest concordance is after CS deliveries, 42%. D&C for RPOC should be performed after adequate clinical evaluation and in the knowledge of 38% false positivity. There is certainly more space for a conservative approach under appropriate clinical conditions, especially in patients after CS.

Uterine procedures in personal history are a statistically significant risk factor for the RPOC occurrence in following pregnancies. Thus, there should be more efforts to reduce the number of uterine procedures and conservatively manage complications such as missed abortion or incomplete or complete abortion. The history of the caesarean section could also be a risk factor in the future, especially with its increasing trend.

Article informations and declarations

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Conflict of interest

All authors declare no conflict of interest.

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The amenorrhea as a protective factor for healing of hysterotomy — a retrospective analysis one year postpartum

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ABSTRACT

Objectives: The good healing of the hysterotomy after cesarean section is important for subsequent pregnancies. However, the factors which improve this healing have not been completely described, yet. In this study, we focused on factors which may affect healing of hysterotomy within one year after delivery, such as menstruation, breastfeeding, and the use of the contraception.

Material and methods: Following delivery, total of 540 women were invited for three consecutive visits at six weeks, six months, and 12 months postpartum. The presence of menstruation, frequency of breastfeeding and contraception use were recorded. The scar was evaluated by vaginal ultrasound as already described. The impact of menstruation, breastfeeding, and contraception method on presence of niche was evaluated.

Results: The presence of menstruation increased odds to have niche by 45% (CI 1.046–2.018, p = 0.026). Secondarily, our results demonstrated a statistically significant protective effect of breastfeeding on the incidence of niche with OR 0.703 (CI 0.517–0.955, p = 0.024). Breastfeeding decreases odds to have niche by 30%. Also, the use of gestagen contraception lowered the odds by 40% and intrauterine device (IUD) or combine oral contraceptive (COC) by 46.5%. The other possibly intervening factors were statistically controlled.

Conclusions: Amenorrhea, breast-feeding and progesterone-contraceptive decreases the risk of uterine niche within one year follow up.

Keywords: cesarean section; uterus; contraception; niche; breastfeeding

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INTRODUCTION

Over the last few decades percentage of Caesarean section (CS) deliveries has dramatically increased worldwide [1, 2]. The increasing trend is most probably related to the demographic changes taking place in the society (aging population of pregnant women, declining number of children, legal consequences of delivery complications *etc.*). The increasing CS rate has stimulated an interest in the related short- and long-term morbidity of CS scars and niche. The most common long-term consequence of the CS niche may cause intermenstrual spotting (34–64%), dysmenorrhea (53.1%), chronic pelvic pain (36.9%), dyspareunia (18.3%) and infertility (4–19%) [3–6]. The scar defect may also cause serious complications in the subsequent pregnancy, *i.e.*, uterine dehiscence (0.6–3.8%), uterine rupture (0.2–3.8%), or pregnancy in the scar, and placenta accreta spectrum. Postpartum evaluation of the CS scar is usually performed by a transvaginal ultrasound, or by contrast-enhanced sonohysterography which offers even better visibility of niche. Another option is hysteroscopy or hysterosalpingography. The prevalence of niche is between 24 and 80.9% using the transvaginal sonography [7–11] and 56–84% [4, 8, 12] when using sonohysterography.

Interestingly, not all women have a niche after a caesarean section. Thus, there must be risk and protective factors for niche development. The risk factors can be: 1) obstetrical and partially un-avoidable such as acute caesarean section, vaginal dilatation before CS, duration of labor, oxytocin use,

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preeclampsia; 2) surgical and mostly avoidable, i.e., uterine incision location, one or two layer hysterotomy suture, ex-/ /inclusion of the endometrium in the suture, un-/locked suture, peritoneum closure, formation of adhesions in the hysterotomy area, etc.; 3) lastly, there are patient-related risk factors such as individual pre-disposition to healing process, BMI, smoking [13].

The impacts of amenorrhea, breastfeeding and contraception have not been, to our knowledge, investigated yet. Therefore, hereby, we present retrospective analysis of the available data on impact of amenorrhea (breastfeeding, contraception) on healing of hysterotomy.

MATERIAL AND METHODS

Within this study we retrospectively analysed available secondary data obtained from large prospective study, carried out 2011–2014 in the tertiary perinatological center [7]. The study was approved by the institutional ethics committee (ethics committee number 3/2010).

Included were healthy primiparous women with a singleton pregnancy delivered at or beyond 37 weeks, who underwent CS and signed informed consent. Patient characteristics, which were recorded and have a relation to our study are in Table 1. The follow up was set on 6 weeks, 6 months and one year postpartum.

Table 1. Demographic and other characteristics at 6 weeks postpartum related to A/menstruation B/breastfeeding C/contraception

A/	Menstruation		
Parameter	**Yes (n = 51)**	**No (n = 417)**	**p value**
Age (years)	30 (28–34)	31 (29–34)	0.121[a]
BMI (kg/m^2)	23.4 (21.4–26.8)	22.2 (20.3–24.4)	0.002[a]
Gestational week	40 (39–41)	40 (39–41)	0.906[a]
Type of caesarean section			
Acute by delivery	20 (10.4)	172 (89.6)	0.967[b]
Acute in pregnancy	1 (6.3)	15 (93.8)	
Planned by delivery	24 (11.9)	178 (88.1)	
Planned in pregnancy	6 (10.3)	52 (89.7)	
B/	**Breastfeeding**		
Parameter	**More than 4 in day (n = 404)**	**None or less than 4 in day (n = 69)**	**p value**
Age (years)	31 (29–34)	31 (28–34.5)	0.701[a]
BMI (kg/m^2)	22.3 (20.4–24.7)	22.2 (20.1–25.1)	0.884[a]
Gestational week	40 (39–41)	40 (39.5–41)	0.993[a]
Type of caesarean section			
Acute by delivery	169 (86.2)	27 (13.8)	0.074[b]
Acute in pregnancy	12 (75)	4 (25)	
Planned by delivery	178 (88.1)	24 (11.9)	
Planned in pregnancy	45 (76.3)	14 (23.7)	

C/	Contraception			
Parameter	**Gestagen (n = 69)**	**IUD or COC (n = 21)**	**None (n = 302)**	**p value**
Age (years)	30 (28–32.5)	32 (28.5–35)	32 (30–34)	0.002[a]
BMI (kg/m^2)	22,8 (20.7–24.4)	21.2 (19.7–22.7)	22.3 (20.2– 24.8)	0.143[a]
Gestational week	40 (40–41)	41 (39.5–41)	40 (39–41)	0.775[a]
Type of caesarean section				
Acute by delivery	32 (19.6)	6 (3.7)	125 (76.7)	0.100[b]
Acute in pregnancy	5 (33.3)	0 (0)	10 (66.7)	
Planned by delivery	28 (16.9)	9 (5.4)	129 (77.7)	
Planned in pregnancy	4 (8.3)	6 (12.5)	38 (79.2)	

[a]Wilcoxon-Mann-Whitney test; [b]Fisher's Exact Test; Characteristics are presented as median and interquartile range. Categorical variables are presented as total number (percentage in group); BMI — body mass index

We recorded presence of menstruation or amenorrhea, defined as the absence of menses [14]. Additionally, we noted breastfeeding frequency (> 4 times a day, < 4 times a day, or not breastfeeding) and contraception type (none, combined oral contraceptive (COC), gestagen, or intrauterine device (IUD). The presence of niche was evaluated by transvaginal ultrasound as already described [7, 15]. Within this study niches were categorized as A/niche present or B/ /not present. As niche we recognized any defect (missing part) of the myometrium, including defects without contact with endometrial cavity. The special niche characteristics (*i.e.*, niche length) were not in the scope of this study.

Statistics were carried out in SPSS software version 13.0 (IBM Corp., Armonk, NY, USA). The homogeneity was tested with Fisher's exact test. The p value < 0.05 was considered significant. To test the development of categorized variables (including dichotomous variables) over time and dependence on amenorrhea (breastfeeding, contraception), we used the generalized linear mixed model with logit link function, binomial distribution, and first-order autoregressive covariance structure. The dependent variable was the presence of niche diagnosed at visits. Hence the reference category is absence of the niche the estimated odds ratios are related to presence of the niche.

RESULTS

Population characteristics

A total of 540 women and were included in the study. During the follow up 477 women attended at 6 weeks, 391 women at 6 months and 324 women at one year postpartum. Their demographic and other characteristics are in Table 1. We observed statistically more frequent menstruation in women with higher BMI (p = 0.002). Due to low count of women using COC, IUD those data were pooled to group called other contraception. The group of women using gestagen contraception had lower mean age compared to groups with other or no contraception (30 vs 32 years; p = 0.002). There were no other significant differences in demographic and other characteristics, between groups related to 1) menstruation 2) breastfeeding frequency and 3) type of contraception (Tab. 1).

The breastfeeding as causative factor for amenorrhea

We observed that with the decrease in breastfeeding the presence of menstruation gradually increased from 10.6% at six weeks to 88.7% in one year after the CS (Fig. 1). Frequency of breastfeeding more than 4 times per day decreased from 85.3% at 6 weeks to 59.7% at 6 months and further to 15.3% at 1 year follow up. While only 9.9% of women did not breastfeed at all at 6 weeks, more than half did not breastfeed at 1 year (Tab. 2). The relation of breastfeeding and menstruation is described in Table 3. Breastfeeding and menstruation effect were statistically insignificant in models containing both effects together. This fact is in concordance

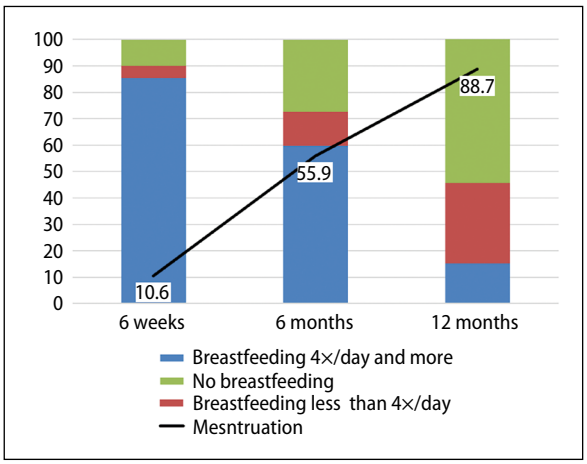

Figure 1. Frequency of breastfeeding and menstruation during follow up

Table 2. Breastfeeding, menstruation and a use of contraception during follow up

	6 weeks, n = 477	6 months, n = 391	1 year, n = 324
Menstruation	51 (10.6%)	221 (55.9%)	287 (88.7%)
Breastfeeding			
> 4 times a day	407 (85.3%)	233 (59.7%)	50 (15.3%)
< 4 times a day	23 (4.7%)	51 (12.9%)	99 (30.5%)
none	47 (9.9%)	107 (27.3%)	175 (54.2%)
Contraception			
Gestagen	44 (9.3%)	71 (18.2%)	44 (13.7%)
IUD	7 (1.5%)	12 (3.0%)	9 (2.7%)
COC	9 (1.9%)	9 (2.3%)	10 (3.3%)
none	417 (87.4%)	299 (76.5%)	261 (80.3%)

COC — combined oral contraceptive; IUD — intrauterine device

Table 3. Relation of menstruation and breastfeeding at 6 weeks. Variables are presented as total number (percentage in group)

	Menstruation		
Parameter	**Yes (n = 52)**	**No (n = 424)**	**p value**
Breastfeeding			
More than 4 in day	28 (6.9)	379 (93.1)	< 0.001[a]
None or Less than 4 in day	24 (34.8)	45 (65.2)	

[a]Fisher's Exact Test

Table 4. Effect of menstruation, contraception and breastfeeding on presence of defect

Estimated Odds Ratios (Subjects = 481)					
Parameter	**Value**	**OR[b]**	**P**	**95% CI for OR**	
				Lower	**Upper**
Menstruation	Yes	1.453	0.026	1.046	2.018
	No[a]	1.000			
Contraception	Gestagen	0.607	0.031	0.386	0.954
	IUD or COC	0.535	0.073	0.270	1.059
	None[a]	1.000			
Breastfeeding	Yes	0.703	0.024	0.517	0.955
	No[a]	1.000			

[a]Reference category; [b]Reference category of dependent variable Scar Defect is No.; Only subjects with non-interrupted sequence of values are included in the model; CI — confidence interval; COC — combined oral contraceptive; IUD — intrauterine device; OR — odd ratio

with the assumption that the direct effect on scar presence has presence of menstruation. The effect of breastfeeding is indirect and is meditated by menstruation.

Contraception use one year postpartum

When evaluating the use of contraception, we have found that the most frequent was gestagen hormonal contraception in all three post-partum periods (9.3 % at 6 weeks, 18.2% at 6 months, and 13.7% at 1 year) (Tab. 2).

Impact of menstruation on presence of cesarean niche

Based on statistical models menstruation increases the risk of cesarean niche by 45% (Tab. 4). Breastfeeding indirectly decreases the risk of niche by 30%. The use of gestagen contraception lowers the risk of niche by 40% and IUD or COC by 46.5%.

DISCUSSION

This study confirmed our hypothesis that amenorrhea might decrease the risk of niche. Breastfeeding and contraception, the most usual causative factors of amenorrhea, also showed an indirect positive impact on CS-scar healing.

Our hypothesis comes out of the general wound healing process. Even though under physiologic conditions, non-injured endometrium completely restores the lost structure each month [16], the situation may change after the external injury [17]. In example, the extensive amount of fluid may impair wound healing [18]. Either blood or exudate can either flow or create a collection, both having a possible impact on healing. The mechanical effect could be pressure or washing out cells or chemokines. The presence or absence of chemokines may impact tissue healing and remodeling. All these factors can change the healing process and lead to prolonged inflammation and weaker scar tissue. The remodeling process is known to take up to one-year post-injury [19]. That is why we think amenorrhea after puerperium still could have an impact. Prolonged or excessive pressure at the wound site may compress the capillary network and disrupt the blood supply resulting in delayed healing. We hypothesize, but we have no data to confirm, that menstruation may increase intrauterine pressure and, therefore, may put pressure on the healing scar. We would like to further investigate this. In the case of a vulnerable wound, these collapses and creates a niche. Also, regular menstruation can be a repetitive trauma and can lengthen the healing process or stop it completely [20]. It has long been recognized that the collection of free blood, liquefied fat, and cellular debris are both physical and chemical deterrents to wound healing.

We acknowledge several limitations of our study. Firstly, we set the study hypothesis after completing the primary

project [7]. Therefore, the available data are limited and obtained retrospectively. However, we think that our finding is clinically very relevant and needs further investigation. For further study, we suggest enrolling more women using different types of contraception. We are aware that healing wildly differs concerning wound location. Therefore, we encourage the investigation of the healing processes of the uterine myometrium and endometrium complex. We are aware that puerperium is a period of lochia discharge; in this period, we can in future investigate if some stage of lochiometra may have impact on the healing process.

This study also has several strengths. By the statistical model, we confirmed that the primary impact is caused by amenorrhea, and breastfeeding and contraception are indirect. Moreover, we statistically controlled for possible confounders (age, BMI, type of CS, and suture type (single, double layer — not reported).

With an increased CS and knowledge of the risk of uterine rupture, we should pay attention to the healing of hysterotomy as any other body wound. We should try to find factors that increase the risk (find correlates with risk factors for general wound healing, *i.e.*, diabetes mellitus or protective factors (*i.e.*, good nutrition and rest). We can postpone menstruation using various methods of contraception or by lactation amenorrhea. Therefore, breastfeeding support among women after CS may positively impact the child's health as well as maternal health. We consider this an essential additional argument for early initiation and duration of breastfeeding after cesarean birth. We can assume that the absence of menstruation, regardless of the cause, provides a better condition for un-disturbed healing. Considering the potential risks and health problems related to improperly healed scars, the finding that delayed menstruation lowers the risk of niches is essential and may have significant public health consequences.

CONCLUSIONS

Our main finding is that women delivered by caesarean section who did not menstruate within the one-year period had lower risk of uterine niches. Breastfeeding had a positive effect mediated by absence of menstruation.

Article information and declarations

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Authorship confirmation/contribution statement

Author 1 (HH): investigation, writing — original draft, formal analysis; Author 2 (PV): conceptualization, review and editing; Author 3 (IU): writing – original draft; formal analysis; Author 4 (PK): conceptualization, review and editing, methodology (lead); Author 5 (ME): conceptualization (supporting), funding acquisition, resources, review and editing; Author 6 (LH): project administration, writing – original draft (supporting); Author 7(LK): supervision; Author 8 (JH): conceptualization, investigation, writing – original draft and editing

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Conflict of interests

None for all authors.

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Application of virtual reality technology combined with moderate perineal protection in natural childbirth

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ABSTRACT

Objectives: To explore the application effect of virtual reality (VR) combined with moderate perineal protection on singleton primipara delivery.

Material and methods: The study utilised a two-group design intervention and a randomised clinical trial. A total of 200 singleton primiparas who had a regular prenatal examination in a third-class hospital (between 1 September 2018 and 30 December 2018) and were willing to give birth naturally were randomly divided into treatment (traditional prenatal health mission combined with desktop VR health education system mode) and control (traditional health education mode) groups. The delivery conditions of the two groups were surveyed, recorded, analysed and compared.

Results: There was no significant difference in the time of the second stage of labour between the treatment and control groups, and the comparison of neonatal Apgar scores and neonatal weight between the two groups showed that the different modes of prenatal education had no effect on newborns ($p > 0.05$). The amount of postpartum haemorrhage in 2 h and the pain score in the treatment group were significantly lower than in the control group, and the degree of perineal injury in the treatment group was not as serious as that in the control group. Meanwhile, there was a statistically significant difference in the anxiety score, self-efficacy score and quality of life satisfaction between the treatment and control groups ($p < 0.05$).

Conclusions: VR technology combined with moderate perineal protection could improve the delivery outcome of a primipara, maternal self-confidence of delivery and the quality of vaginal delivery; effectively alleviate the anxiety of a primipara; have no adverse effects on both mothers and newborns; and be widely used in clinical settings.

Keywords: virtual reality technology; moderate perineal protection; natural labour; self-efficacy

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INTRODUCTION

With the implementation of the two-child policy, the number of births in most cities in China has increased sharply [1]. Since childbirth is a natural event, all deliveries should ideally be spontaneous [2]. Childbirth is a natural physiological process that every parturient has to go through [3]. Although labour is a natural phenomenon, its accompanied pain is severe in more than half of pregnant women [4]. About 5–40% of pregnant women fear childbirth in western countries, and a recent study reported that Chinese pregnant women have moderate levels of childbirth fear and anxiety [5]. It is estimated that out of every five pregnant women, one has a fear of natural childbirth, and, in most women, fear of birth leads to increased anxiety, pain and prolonged labour [6]. Depression and anxiety are common mental disorders during pregnancy and after childbirth worldwide [7]. In addition, during childbirth, perineal trauma may occur, either spontaneously or after episiotomy. Perineal injuries are a common occurrence during childbirth, affecting approximately 90% of women to varying degrees during natural vaginal delivery [8]. In the face of the current grim situation, the goals of midwifery staff are to change traditional concepts, reduce intervention during delivery, create a non-invasive and comfortable delivery process and promote natural delivery. McCandlish [9] proposed the moderate perineal protection technique. In 2010, the China Maternal and Child Health Association also proposed the 'China Action to Promote Natural Childbirth', stating

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that efforts should be made to promote moderate perineal protection delivery technology in China. In February 2016, our hospital began to gradually promote moderate perineal protection.

Virtual reality (VR) is a rapidly improving emerging technology [10]. Virtual reality technology refers to the use of computer technology to form a realistic virtual world. Users can participate in the virtual world and interact through certain input or output devices, and they can control objects in the virtual world with their real-world actions and behaviours [11]. Virtual reality technology has made great advances in recent years, and it is increasingly being used in healthcare settings [12, 13]. Little is known about childbirth fear and childbirth preparation experiences among primigravid women before childbirth in low-resource settings [14]. With the help of VR technology for prenatal health education, pregnant women can be immersed in or participate in the virtual delivery room environment, interact with the VR system and achieve immersive feelings and experiences in mutual response and feedback. In this study, a randomised clinical trial was conducted to explore the effect of VR technology health education combined with appropriate perineal protection on parturients with a natural delivery so as to provide data support to promote the use of VR technology in medicine.

MATERIAL AND METHODS

Research objective

Primigravid women with singleton pregnancies who underwent routine antenatal examination in third-class hospitals between 1 June 2018 and 31 December 2018 were selected as the study group. The inclusion criteria were as follows: parturients with single full-term pregnancies, a normal external pelvic measuremen, no obvious cephalopelvic disproportion, no complications in pregnancy and delivery and aged 20–34 years. The exclusion criteria were as follows: an estimated fetal weight of ≥ 4000 g and fetal biparietal diameter of > 9.7 cm indicated by B-ultrasound, a mental illness or communication disorder and the use of analgesia during labour. The 200 selected subjects were equally divided into the treatment group and the control group by a random number table. All the parturients and their family members had signed informed consent forms, and this study has been approved by the medical ethics committee of our hospital.

Research methods

Both groups of parturients were fully evaluated for fetal size, maternal pelvic conditions and maternal mental state, and fetal heart rate was closely monitored before delivery to ensure a safe and natural delivery. The nurses communicated effectively with the puerpera before surgical hand disinfection to obtain their support and cooperation. Both groups of parturients adopted the moderate perineal protection technique during delivery: when the fetal head is exposed, the midwife places one hand on the head and applies appropriate pressure when the head is delivered so as to prevent the fetal head from being delivered at an excessive speed. In contrast, the conventional supporting and pressing of the perineum intends to let the fetal head fully expand the perineum and comply with the physiological process of fetal delivery, so as to assist fetal delivery. Moderate perineal protection delivery is completed with the cooperation of pregnant women and midwives. Midwives should have good communication skills and rich experience in delivery, be able to accurately identify changes in the childbirth process and help pregnant women deliver the fetus smoothly between contractions.

Treatment group:

Traditional health education is carried out in combination with VR technology. Using the virtual delivery room SpaceMax software, the real scene shooting in the delivery room is added to the system to bring the 3D interactive virtual scene to life, including characters, sites, objects, environments, time and voices. Various scenes in the delivery room and precautions during delivery are preset; pregnant women experience the operation through the computer VR system.

Control group:

Carry out traditional health education, which includes watching videos and looking at pictures in the simulated labour room, experiencing the delivery bed and various auxiliary delivery instruments during labour and listening to the explanation of midwives. Both groups of parturients received routine clinical treatment and nursing after delivery.

Observation indexes

1. The delivery outcome: This includes the time of the second stage of labour, postpartum haemorrhage in 2 h, neonatal Apgar score and neonatal weight.
2. The level of pain: A visual analogue scale (VAS) was used, consisting of a 10 cm horizontal line with pain descriptors indicating 'no pain' on the left and 'the worst pain imaginable' on the right. One centimetre represents one point, and the total score is 0–10 points. The higher the score, the stronger the degree of pain [15].
3. The level of anxiety: A visual analogue anxiety scale (VAS-A) was used to measure the accuracy and sensitivity of anxiety levels during labour [16]. The VAS-A is a 10 cm horizontal line with 0 on the left, representing 'no anxiety', and 10 on the right, representing 'the most severe anxiety'. The pregnant women draw lines representing the intensity of their anxiety, and the total score is 0–10.

Table 1. Comparison of general data of pregnant women between the two groups [$\bar{x} \pm s$, n (%)]

General information		Groups		χ^2/t	P
		Treatment group (100)	Control group (100)		
Average age [year]		30.29 ± 1.14	30.35 ± 1.07	0.275	0.789
Gestational week [week]		38.41 ± 0.96	38.63 ± 1.18	0.809	0.434
Weight index [kg/m^2]		23.39 ± 2.52	22.76 ± 1.97	1.762	0.256
Educational background	High school and below	9 (9%)	10 (10%)	0.992	0.083
	College and Bachelor degree	78 (78%)	75 (75%)		
	Bachelor degree or above	13 (13%)	15 (15%)		
Place of residence	Countryside	17 (17%)	19 (19%)	0.007	0.904
	Town	83 (83%)	81 (81%)		
Medical insurance	Have	90 (90%)	91 (91%)	1.310	0.861
	Don't have	10 (10%)	9 (9%)		

Table 2. Comparison of delivery outcomes between the two groups ($\bar{x} \pm s$)

Group	Cases	The time of the second stage of labor [min]	The amount of postpartum hemorrhage in 2h [mL]	Pain [score]	Neonatal Apgar score [score]	Neonatal weight [g]
Treatment group	100	95.23 ± 10.12	151.28 ± 50.73	3.73 ± 1.87	8.82 ± 0.49	3604.4 ± 321.9
Control group	100	98.58 ± 12.03	248.95 ± 39.67	5.97 ± 2.66	8.78 ± 0.57	3672.6 ± 294.8
t		2.002	0.013	–2.231	1.428	–0.635
P		0.815	0.008	0.00	0.669	0.527

4. General self-efficacy: The general self-efficacy scale is used to measure general self-efficacy and has good reliability and validity [17]. There are 10 items on the scale, with a total score of 10–40. The higher the score, the higher the level of self-efficacy.
5. Ouality of life: The self-made quality of life satisfaction scale is used for evaluation. The scores range from 0 to 100 and include particularly satisfied, relatively satisfied and dissatisfied. If dissatisfied, the score does not exceed 60 points; if relatively satisfied, the score is 60–80 points; if particularly satisfied, the score exceeds 80 points. Total satisfaction rate = special satisfaction rate + comparative satisfaction rate.

Statistical method

The SPSS 19.0 statistical software was used to process and analyse the data. The T-test and the χ^2 test were used for counting data. A value of $p < 0.05$ means that the difference was statistically significant.

RESULTS

Comparison of general data between two groups of parturients

There was no significant difference in average age, gestational age, body mass index, education, place of residence and medical insurance between the two groups ($p > 0.05$) (Tab. 1). This suggests that the data from the two groups were comparable.

Comparison of delivery outcomes between the two groups

The time of the second stage of labour between the treatment group and the control group was not significantly different ($p > 0.05$). The amount of postpartum haemorrhage in 2 h and the pain score in the treatment group were significantly lower than those in the control group ($p < 0.05$). The comparison of neonatal Apgar scores and neonatal weight between the two groups showed that the different modes of prenatal education had no effect on newborns ($p > 0.05$) (Tab. 2).

Comparison of the rate of lateral episiotomy and the degree of perineal laceration between the two groups

The complete rate of lateral episiotomy and the rate of grade I laceration in the treatment group were higher than those in the control group, and the rate of grade II and above laceration was lower than that in the control group. There were two cases of grade III laceration in the control group, and there was no grade IV laceration in both groups. The difference between the two groups was statistically significant ($p < 0.05$) (Tab. 3).

Table 3. Comparison of lateral episiotomy rate and perineal laceration degree between the two groups [n (%)]

Group	Cases	Degree of perineal trauma				
		Integrity	I degree	II degree	III or IV degree	Lateral episiotomy
Treatment group	100	9 (9.00)	80 (17.00)	1 (1.00)	0 (0.00)	11 (11.00)
Control group	100	3 (3.00)	59 (59.00)	5 (5.00)	2 (2.00)	31 (31.00)
χ^2	16.83					
P	< 0.01					

Table 4. Comparison of general self-efficacy and anxiety scores between the two groups ($\bar{x} \pm s$)

Group	Cases	Anxiety level		Self-efficacy		Quality of life satisfaction	
		Before education	During labor	Before education	During labor	Before education	During labor
Treatment group	100	3.53 ± 1.42	3.63 ± 1.42	28.08 ± 2.82	30.27 ± 2.74	65.10 ± 2.76	85.05 ± 4.72
Control group	100	3.18 ± 1.33	6.58 ± 1.33	28.23 ± 2.30	23.52 ± 2.14	63.98 ± 3.38	73.12 ± 3.46
t		0.763	0.175	2.871	3.560	2.213	4.558
P		0.947	< 0.001	0.875	< 0.001	0.798	< 0.001

Comparison of the quality of life satisfaction, scores of general self-efficacy and anxiety between the two groups

There was no significant difference in the quality of life satisfaction and the scores of anxiety and self-efficacy before education between the two groups ($p > 0.05$). The anxiety score of the treatment group was lower than that of the control group, while the quality of life satisfaction and the self-efficacy score of the treatment group were higher than those of the control group ($p < 0.05$) (Tab. 4).

DISCUSSION

Application of VR technology in health education

Not only can the application of VR technology in obstetric health education increase interest in and improve the effectiveness of the education, but it is also more conducive to the collection of users' feedback and further improvements of the education system. Fateme utilised a Solomon four-group design intervention and a randomised clinical trial to prove that medical treatment using VR technology, as well as distraction and drowning in VR, reduced pre-operative anxiety in children [18]. Generally, creators can generate medical and nursing content in the form of 3D modelling and live shooting and create scientific and standardised health education content in combination with technical conditions and medical and nursing theory in order to achieve the expected education objectives. Virtual reality technology can bring abstract knowledge to life by integrating vision, hearing and touch [19]. This study uses novel VR technology to achieve a sense of immersion, human–computer interaction and entertainment. It can help pregnant women understand the delivery environment and experience the delivery process in advance; improve the initiative and effectiveness of pregnant women and their spouses; and promote health education based on information technology. It also shows that pregnant women and their spouses have high acceptance and evaluation of the system. With the deepening of research and the increase of the patient population and demand content, the system should be updated and improved to add more functional modules and enhance interest.

VR technology combined with moderate perineal protection can alleviate pain

Natural delivery is a normal physiological process. Due to the severe pain caused by the regular contraction of the uterus and the long labour process, many pregnant women are afraid of natural delivery. It is reported that labour pain can cause maternal sympathetic excitement and increase the release of catecholamines in the body, which inhibits uterine contraction, prolongs the labour process, causes an acid–base imbalance, decreases uterine blood flow and causes fetal distress [20–22]. For pregnant women, especially primiparas, childbirth pain causes strong psychological and physiological stress responses, resulting in slower expansion of the uterine orifice and a prolonged labour process, which makes it difficult to deliver smoothly [23]. Virtual reality technology can distract patients, reduce pain and relieve discomfort in nursing operations. Virtual reality technology can provide an effective non-pharmacological means for reducing acute and traumatic injury pain [24]. In this study, delivery pain in the treatment group was significantly less than that in the control group ($p < 0.05$); it is suggested that

the use of VR technology combined with moderate perineal protection can reduce pain during parturition.

VR technology combined with moderate perineal protection can improve the outcome of delivery

Clinically, in order to shorten the second stage of labour and avoid severe perineal laceration, lateral episiotomy is one of the most commonly used operations during delivery [25]. However, studies have shown that lateral episiotomy can lead to massive bleeding, intense pain, increased probability of infection, poor scar healing and other consequences, which have a serious impact on the postpartum quality of life of pregnant women, and lateral episiotomy has no significant improvement on the outcome of newborns [26]. Therefore, the rate of lateral episiotomy and perineal laceration should be reduced to the greatest extent. In this study, there was no grade IV perineal laceration in either group, indicating that VR technology combined with moderate perineal protection not only reduces the rate of lateral episiotomy and the degree of perineal injury but also does not increase the risk of severe perineal laceration.

VR technology combined with moderate perineal protection can improve self-efficacy and reduce anxiety

Among the four factors of delivery, maternal psychology is one of the important influencing factors [27]. Self-efficacy has been related to decreased pain perception during labour [28]. In this study, the anxiety score of the treatment group was lower than that of the control group, and the self-efficacy score of the treatment group was higher than that of the control group ($p < 0.05$). During childbirth, pregnant women often have anxiety. In this study, the pain degree of pregnant women in the treatment group was reduced, the anxiety level was reduced and the sense of self-efficacy was enhanced. With the help of VR technology, the treatment group gives play to its sense of immersion, human–computer interaction and entertainment; improves the enthusiasm of pregnant women and the effectiveness of prenatal education; promotes full communication between midwives and pregnant women; increases maternal self-confidence in childbirth; alleviates childbirth pain, anxiety and tension; enhances self-efficacy; and enables pregnant women to have a good childbirth experience in a relatively relaxed environment.

Deficiencies in this study

There were some limitations in this study; a professional psychological scale was not used to objectively evaluate the psychological state of pregnant women. In future research, this should be addressed.

CONCLUSIONS

Based on the moderate perineal protection technique, this study conducted VR technology health education for pregnant women in the treatment group, deepened the understanding of the pregnant women and their families about natural childbirth, recognised the benefits of natural childbirth for mothers and infants, improved and relieved the delivery anxiety to a certain extent, established confidence in natural childbirth and alleviated pain during childbirth. Moderate perineal protection also reduces the rate of perineal lateral resection and the degree of perineal wound laceration and plays a certain role in the prevention of postpartum haemorrhage. It provides a positive childbirth experience for puerpera, making it worthy of clinical application.

Article information and declarations

Data availability statement

All data generated or analyzed during this study are included in this published article.

Ethics

This study was conducted in accordance with the declaration of Helsinki.This study was conducted with approval from the Ethics Committee of Heze Jia Zheng Vocational College. Written informed consent was obtained from all participants.

Author contributions

Xie JQ: conception and design; Zeng QX: administrative support; All authors: provision of study materials or patients, collection and assembly of data, data analysis and interpretation, manuscript writing, final approval of manuscript.

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Conflict of interest

The authors declare that they have no competing interests.

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Comparison of labor duration of induced labor with dinoprostone insert vs spontaneous labor

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ABSTRACT

Objectives: Labor induction is one of the most common procedures in modern obstetrics. One in five pregnant women and 30–40% of women delivering vaginally undergo this procedure. If the cervical status is unfavorable, a ripening process is used prior to induction to shorten the duration of oxytocin administration and maximize the possibility of vaginal birth. The aim of this study was to compare the duration of labor induced with dinoprostone vaginal insert to spontaneous labor.

Material and methods: It was a retrospective study conducted between May 2019 and February 2021 in the tertiary reference center, the Obstetrics and Perinatology Department of the Jagiellonian University Hospital in Krakow. The research group involved 182 patients in singleton pregnancy at term, qualified for cervical ripening procedure. The control group consisted of 178 patients that were delivering spontaneously and admitted to the delivery ward in the first stage of labor. Statistical analysis was performed to compare the duration of labor between groups. To find factors affecting the procedure we compared different models consisting of maternal and fetal characteristics.

Results: Successful vaginal delivery in the dinoprostone group was achieved in the group of 88% of patients. There was no significant difference in labor duration between the groups: 315 minutes in the study group and 300 min in the control group. Only being primipara was a factor related to longer labor in both groups.

Conclusions: Pre-induction with dinoprostone insert and additional foley catheter, if indicated, does not make labor longer in comparison with spontaneous labor.

Keywords: labor; induced; dinoprostone; cervical ripening; pregnancy

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INTRODUCTION

Labor induction is a procedure of artificial stimulation of childbirth before the natural, spontaneous onset of labor. It is one of the most common procedures in modern obstetrics. Currently, one in five pregnant women and 30–40% of women delivering vaginally undergo this procedure [1]. The reasons for the induction include reduction of the perinatal mortality and morbidity of the fetus and newborn as well as the reduction of maternal complications. However, as with every medical intervention, labor induction is associated with a risk of complications. The decision to induce labor should always be justified on medical grounds and preceded by obtaining written informed consent from the pregnant woman [2]. When labor is induced, cervical status has an impact on the duration of induction and the likelihood of vaginal birth. If the cervical status is unfavorable, a ripening process is generally used prior to induction to shorten the duration of oxytocin administration and maximize the possibility of vaginal birth. There are two major modalities for cervical ripening: mechanical interventions, such as insertion of a balloon catheter or hygroscopic cervical dilators, and the application of pharmacologic agents, such as prostaglandins.

Prostaglandins stimulate collagenase activity, synthesis of glycosaminoglycans, elastase and hyaluronic acid in the cervix. They sensitize also the myometrium to the action of oxytocin and directly induce contractions of the uterus [3]. Dinoprostone vaginal insert (Cervidil®; Propess®) is a retrievable vaginal pessary containing 10 mg of dinoprostone [prostaglandin E2 (PGE2)] in

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a controlled-release drug delivery device. The initiation (or continuation) of cervical ripening in patients prior to labor induction is approved in Poland and in many countries worldwide. The effectiveness of dinoprostone vaginal insert has been demonstrated in multiple of randomized clinical trials in women at term. The demonstrated effectiveness and safety of the system, simple application, and efficient dose control, suggest that a dinoprostone vaginal insert is a valuable option for cervical ripening in patients with an unfavorable cervix [3, 4].

Objectives

The aim of this study was to compare the labor duration of induced labor with the use of a dinoprostone vaginal insert to the spontaneous labor.

MATERIAL AND METHODS

Data collection and study sample

It was a retrospective study conducted between May 2019 and February 2021 in the tertiary reference center, the Obstetrics and Perinatology Department of the Jagiellonian University Hospital in Krakow. The research group involved 182 patients in singleton pregnancy at term, qualified for cervical ripening procedure according to Polish Gynecological Society indications with unfavorable cervix. The indications include hypertension, gestational or pregestational diabetes mellitus, cholestasis and fetal growth restriction as well as gestational age of 41 + 0. Although the gestational age for the procedure differs regarding a particular indication, the gestational age was at least 37 + 0 weeks. Our facility uses the following regime for labor induction. For an unprepared cervix (Bishop score < 6 points), a dinoprostone vaginal insert is used (Cervidil®). After 24 hours (when the 1st labor stage does not occur and the cervical dilation is < 3 cm), mechanical methods for labor induction are introduced, namely, Foley catheter, with filling of 60–120 mL for 24 hours. The intravenous oxytocin infusion is initiated when the balloon falls out and there is no contractile function or is removed after 24 hours.

The control group consisted of 178 patients that was delivering spontaneously and admitted to the delivery ward in the first stage of labor. The labor onset was defined as regular uterine contractions, at least one in 10 minutes that cause progressive dilation and effacement of the cervix. Labor duration was counted for successful vaginal delivery patients, that is 120 of the study group and 149 patients in the control group.

The medical data was taken from electronic medical history. The study received consent from the Ethics Committee No. 1072.6120.291.2021.

Statistical analysis

To compare the duration of labor between groups and to find factors affecting it, we compared the models preferring those with lower AICc (the second-order Akaike Information Criterium) as giving greater support for data relative to the others. AICc is analogous of classical AIC and its use is recommended when the sample size n is relatively smaller than the number of estimated parameters K, namely $n/K < 4$ [5]. The dependent variable in all analyses was the duration of the vaginal labor treated as continuous or dichotomized. Four variables: the main explanatory (Cervidil induction) and three others which can potentially influence the duration of labor (woman's age at birth together with being multiparous or primiparous and gestational age) were regarded as 'basic' predictors and were retained in all constructed models. We used an approach focusing on searching the most parsimonious models based on subsets of 'basic' predictors and some other covariates potentially influencing tested association. We considered nine features characterizing both mother and child, namely: parity (multiparous or primiparous), baseline characteristic (woman's age at birth (continuous), body mass index (BMI) before pregnancy (continuous), variables relating to a woman's pregnancy (pregnancy duration, change weight during pregnancy (continuous), child's birth weight (< 2500, 2500–4000, ≥ 4000 g) and interventions (Cervidil preinduction (yes/no), Foley catheter (yes/no). Linear regression was applied to estimate coefficients of change in the duration of labor associated with switching from the reference category to others or per unit increase in a covariate. Analogically, logistic regression was engaged to compare the chances of a longer duration of labor with a cut-off point of 450 minutes used as a threshold. The odds ratios (ORs) with 95% confidence intervals (Cis) were calculated with the classical method of logistic regression or Firth's bias reduction method (in the case of zero cells) by applying the Wald test. The comparison of alternative models with different subsets of predictors was done with the MuMIn package. The difference in AICc (Δ) between the two competing models reflects the extent of their equivalence. The value of $\Delta \leq 4$ indicates that both models are plausible, and when $\Delta \geq 14$ there is little evidence in the data for model with greater AICc [5, 6]. All analyses were conducted in R software version 4.0.4.

RESULTS

A total of 6,300 childbirths took place in 2019–2021 at the Department of Obstetrics and Perinatology, UH, of which 3,400 were by Caesarean section. In the analyzed period, 300 pregnant women were qualified for labor induction, of whom 182 met the inclusion criteria and were included in the analysis. The control group included

Table 1. The comparison of characteristics of patients in the study and the control group (only successful vaginal labors)

Variable	Inducted labor N = 120	Spontaneous labor n = 149	p
Mothers characteristics			
BMI at baseline [kg/m^2], Q2 (Q1; Q3)	23.8 (20.9; 25.7)	21.9 (20.5; 23.9)	0.006$^{\#}$
Age [years], Mean (SD)	30.8 (4.8)	31.4 (4.2)	0.288
Change in body weight [kg], Mean (SD)	14.0 (6.0)	13.2 (4.8)	0.233
Labor characteristics			
Gestational age [days], Q2 (Q1; Q3)	277.0 (273.0; 286.0)	276.0 (270.0; 281.0)	0.047$^{\#}$
Length of vaginal delivery [min], Q2 (Q1; Q3)	315.0 (195.0; 450.0)	300.0 (205.0; 450.0)	0.569
Neonatal characteristic			
Birth weight [g], Mean (SD)	3 421.4 (427.6)	3 441.6 (433.0)	0.702
Apgar < 7, 1 min	3 (2.5)	0 (0.0)	0.175
Apgar < 7, 5 min	1 (0.8)	0 (0.0)	0.913
Apgar < 7, 10 min	1 (0.8)	0 (0.0)	0.910
Apgar < 8, 1 min	3 (2.5)	0 (0.0)	0.175
Apgar < 8, 5 min	1 (0.8)	0 (0.0)	0.913
Apgar < 8, 10 min	1 (0.8)	1 (0.7)	1.000
Apgar < 9, 1 min	5 (4.2)	2 (1.3)	0.289
Apgar < 9, 5 min	4 (3.3)	3 (2.0)	0.771
Apgar < 9, 10 min	3 (2.5)	4 (2.7)	1.000
Apgar < 10, 1 min	6 (5.0)	9 (6.0)	0.918
Apgar < 10, 5 min	5 (4.2)	7 (4.7)	1.000
Apgar < 10, 10 min	4 (3.4)	8 (5.4)	0.622

p value based on Student's t-test except of denoted by $^{\#}$ based on Mann-Whitney U test

178 patients admitted at the first stage of labor. Successful vaginal delivery occurred in 120 patients of the study group and in 149 of the control group on which this study was focused on. The rest of the patients in both groups had a caesarean section.

Among the study group, hypertension was diagnosed in 25% of patients (pregnancy-induced and chronic inclusively), diabetes mellitus in 38% of cases (pregestational and gestational inclusively), cholestasis in 1% and fetal growth restriction in 4% of patients. 13% of patients were qualified for the induction of labor because they achieved 41 weeks of gestational age. Some of the patients suffered from more than one disorder or abnormality related to pregnancy. A Foley catheter was used in 24 patients as an additional method to ripen an unfavorable cervix. 88% of inducted labor women had successful vaginal labor within 24 hours.

The characterization of each of the groups was presented in Table 1. Statistically significant difference regarded two following features — BMI before pregnancy and gestational age. Otherwise, BMI of both groups was defined as normal weight in both groups (Me (Q1–Q3): 23.8 (20.9; 25.7) vs 21.9 (20.5; 23.9), p = 0.006). The median gestational age differed only by one day. These differences, even if statistically significant, were not of clinical importance.

The Chi-square test had been used to check which variables had a significant difference between both groups that could affect the labor duration. Merely, being primigravida made labor duration longer (Tab. 2).

Another different model was compared. The model with the lowest AICc value is the best-supported one among those compared. The difference in AICc values between model i and the best model is Δi, number of estimated parameters is K, w — Akaike weight. The best model was primipara model, then model primipara with preinduction with Cervidil — AICc 3495.55 (Tab. 3).

DISCUSSION

The main goal of this study was to compare the time of induced labor to the spontaneous one. As it was mentioned in the introduction, the procedure of labor induction is nowadays one of the most commonly performed in the obstetrics, thus needed to improve safety for the mother and the child [1, 2]. Many studies compare the efficiency and safety of pharmacological and mechanical methods of labor induction. Patients with unfavorable cervixes are candidates for the procedure of cervical ripening. Compared with the use of oxytocin infusion alone, cervical ripening probably increases the chances of achieving vaginal birth

Table 2. Tested variables

Variable	Categories	Inducted vaginal delivery n = 120	Spontaneous vaginal delivery n = 149	p value
Primigravida	No	58 (48.3)	94 (63.1)	
	Yes	62 (51.7)	55 (36.9)	0.021
BMI	< 18.5	5 (4.2)	5 (3.4)	
	18.5–25	76 (63.3)	124 (83.2)	0.001
	25-30	31 (25.8)	13 (8.7)	
	≥ 30	8 (6.7)	7 (4.7)	
Primipara	No	52 (43.3)	77 (51.7)	
	Yes	68 (56.7)	72 (48.3)	0.215
Birth weight	< 2500	106 (88.3)	133 (89.3)	
	2500–4000	5 (4.2)	1 (0.7)	0.126
	≥ 4000	9 (7.5)	15 (10.1)	

BMI — body mass index; p value based on Chi-square test of independence

Table 3. Model comparison results based on second-order Akaike Information Criterium (AICc) values

Model	AICc	Δ	K	w
Primipara[#]	3494.45	0.00	3	0.32
Primipara + preinduction with Cervidil	3495.55	1.10	4	0.18
Primipara + gestational age	3496.08	1.63	4	0.14
Primipara + mother's age	3496.46	2.01	4	0.12
Primipara + preinduction with Cervidil + gestational age	3497.09	2.64	5	0.09
Primipara + preinduction with Cervidil + mother's age	3497.59	3.13	5	0.07
Primipara + gestational age + mother's age	3498.05	3.60	5	0.05
Basic[##]	3499.1	4.64	6	0.03
Full model	3507.61	13.15	12	0.00
Mother's age	3537.81	43.36	3	0.00
Preinduction with Cervidil + mother's age	3539.61	45.16	4	0.00
Gestational age + mother's age	3539.87	45.42	4	0.00
Preinduction with Cervidil + gestational age + mother's age	3541.68	47.23	5	0.00
Null model	3543.32	48.87	2	0.00
Preinduction with Cervidil	3545.26	50.81	3	0.00
Gestational age	3545.27	50.82	3	0.00
Preinduction with Cervidil + gestational age	3547.21	52.76	4	0.00

[1]Basic = Preinduction in Cervidil (yes/no) + woman's age at birth (continuous) + primipara (yes/no) + gestational age; [#]Best model; [##]Full model with all considered variables

within 24 hours and does not increase, but may decrease, the risk for cesarean section [7, 8]. There is no single, best practice for the choice of agent adopted for cervical ripening: both mechanical and pharmacologic agents are acceptable options unless the patient has a contraindication to the use of a specific procedure. A 2016 Cochrane meta-analysis comparing misoprostol, dinoprostone, and the balloon catheter for cervical ripening concluded that no method was clearly superior in terms of diminishing the over-24-hour vaginal birth or tachysystole with adverse FHR changes along with cesarean birth [9]. Another 2019 meta-analyses showed that choosing mechanical methods of cervical ripening is less satisfactory for women [10]. Many patients feel anxious about labor induction that it may last longer or will be more painful than spontaneous vaginal one [11], but after the delivery, most women report little overall effect on satisfaction with induced labor compared with a spontaneous one but feel an increased sense of control [12]. There are multiple studies and meta-analyses regarding the efficiency of labor induction. Most authors compare the percentage of successful

labor within 24- or 48-hours' time and time intervals of induction to labor activated by different agents [9]. This study aimed to compare the duration time of induced labor with dinoprostone insert with spontaneous labor and to identify factors that influence that time. We found that there is no significant difference in labor duration between the groups in comparison to the active phase of labor (the first and the second stage of labor): 315 minutes in the study group and 300 min in the control group. A similar duration time, 4 hours of the first stage of labor, was observed in Zielinska K. et al. study [13] and in Gornisiewicz T. study [14] (5.4 h of first stage of labor in dinoprostone group). In 2019 Wei Y. study [15] on 1,400 term pregnancies also showed no difference between time intervals of the first and second stage of labor in comparison to the one induced with dinoprostone and oxytocin in late-term pregnancies. (Latent phase: 3.75 h vs 3.68, active phase: 1.71 h vs 1.82 h, second stage: 0.45 h vs 0.53 h). However, for patients with a Bishop's score between 4–6, the duration of the active phase was significantly reduced in the subgroup who were given dinoprostone [15]. Similarly, Poma S. at al. [16] observed shorter time of induced labor compared to spontaneous one. Successful vaginal delivery in the dinoprostone group was achieved in our study in 88% of patients. That is a higher rate than expected according to other studies like in the MVI and EXPEDITE trials comparing dinoprostone and misoprostol vaginal inserts (72,9% and 71,6%) [17, 18]. There was no substantial difference in Apgar score between the analyzed groups. Other studies confirm that there are also no significant concerns regarding the safety of the dinoprostone for neonates [4, 19]. A variety of maternal and fetal factors have been suggested to predict labor induction success. Certain characteristics of the woman like parity, age, weight, height and body mass index, and of the fetus (including birth weight and gestational age) are associated with the duration of stages of labor and success of labor induction; with parous, young women who are taller and of lower weight have a higher rate of induction success. Fetuses with a lower birth weight or increased gestational age are also associated with increased induction success [20, 21]. Our research shows that pre-induction with pharmacological and additionally mechanical method if indicated, does not make labor longer in comparison with spontaneous labor. Only being primipara was a factor related to longer labor in both groups. Our findings are similar to the trends described in Poma et. al study that has proven shorter duration of the first stage of labor among patients qualified to use dinoprostone as a pre-induction method and with effective epidural labor analgesia in comparison to spontaneous labor [16]. Furthermore, the Cochrane systematic review including over 21,000 patients has showed that overall length of labor was shorter for women undergoing induction compared with the expectant management [22]. Pre-pregnancy BMI is important factor that makes an impact on labor duration and must be mentioned. Obesity increases the risk of prolonged spontaneous or induced labor duration and cesarean section rates [23]. Despite of significantly higher BMI of the study group, still both groups are characterized as normal weight. BMI is not a considered feature to have an impact on the labor duration or to disturb the research scores. Higher BMI among patients demanding labor induction is consistent with mentioned systematic review and meta-analysis which has proven that obesity women are less likely to go into labor spontaneously [22].

This study had some limitations as it was retrospective, not controlled and dependent on the quality and availability of data present in the medical records. It also had a small study sample. The strength is a different statistic approach that finds the best model of predicting factors for labor duration.

CONCLUSIONS

The aim of this study was to compare the duration time of induced labor to spontaneous one. Pre-induction with dinoprostone insert and additional foley catheter, if indicated, does not make labor longer in comparison with spontaneous labor. Statistical model showed that only being primipara was a factor related to longer childbirth. There are also no significant concerns regarding the safety of the dinoprostone for neonates based on Apgar score.

Article Information and declarations

Conflict of interest

All authors declare no conflict of interest.

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Investigating the predictive role of uterocervical angle in predicting preterm labor ın singleton pregnancies: a meta-analysis

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ABSTRACT

Objectives: In this meta-analysis, we aimedto demonstrate the relationship between uterocervical angle and preterm labor in singleton pregnancies more clearly and reliablywith this meta-analysis.

Material and metods: In this study, we use keywords such as "uterocervical angle," "cervical angle," "angle," "cervix," "cervical," "preterm," and "preterm labour." We searched various databases, including PubMed, MEDLINE, ClinicalKey, Scopus, ScienceDirect, Web of Science, and Google Scholar. The search encompassed the period from January 1, 2010, to December 27, 2020. As a result of the literature review, a total of 585 articles were identified. After the screening and selection process, six studies met the inclusion criteria and were included in the analysis. These six studies were deemed relevant and provided valuable information on the research topic.

Results: When the Egger test ($p = 0.020$) and Begg test ($p = 0.188$) were performed, no significant publication bias was found in the studies examined. These statistical tests assess publication bias, and the resulting p-values indicate a low probability of bias in the included studies. Cochran's Q test revealed the presence of heterogeneity among the included studies. Heterogeneity indicates variability in the results beyond what would be expected by chance alone. This finding suggests that the studies may differ in methodologies, populations, or other factors, which could impact the overall results and require further investigation. There was a significant difference between the patient and control groups ($p < 0.001$). This result provides strong evidence to support the importance of the difference between the two groups compared.

Conclusions: Based on the findings of this study, a wider uterocervical angle appeared to be significantly associated with an increased risk of preterm delivery in overall effect. It concluded that a wide uterocervical angle may be a potential risk factor for preterm delivery. Moreover, the study revealed a significant association between wider uterocervical angles and an elevated risk of preterm labour in singleton pregnancies. In this study, the definition of preterm birth accepts as birth before 37 weeks of gestation. These results highlight the potential significance of evaluating the uterocervical angle as a meaningful predictor for identifying the propensity of preterm labour in singleton pregnancies.

Keywords: meta-analysis; preterm labor; singleton pregnancy; uterocervical angle

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INTRODUCTION

Preterm birth (PB) is defined as birth between 20 0/7 and 36 6/7 weeks of gestation [1]. Despite advancements in technology and medical care, preterm labour remains a significant cause of neonatal morbidity and mortality. Premature birth is associated with several complications, such as cerebral palsy, bronchopulmonary dysplasia, retinopathy of prematurity, and several other health issues problems common in premature infants. These morbidities highlight the importance of addressing preterm labour and implementing effective interventions to improve the outcomes for preterm infants [1, 2]. This situation, which is seen in 5–18% of pregnancies and is an important reason for hospitalizations, creates a serious charge on the economies of the countries [3]. Less than 10% of patients with preterm labor who are hospitalized give birth within

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7 days. Therefore, it is essential to develop strategies that will prevent unnecessary hospitalizations and identify at-risk pregnant women and thus indirectly improvethe country's economies.

In recent years, different measurements and tests have been developed for the prediction of preterm labor [2]. The leading ones include cervical length measurement, fetal fibronectin testing, and biochemical markers obtained from maternal serum and amnion [4]. Maternal blood and amniotic fluid inflammatory markers may cause anxiety in pregnant women due to the interventional nature of the procedures. The cervical length measured in the second trimester is a more commonly used measurement for preterm labor [5]. According to previous reports, the 10th percentile threshold for cervical length at 24 weeks of gestation was defined as 25 mm, indicating the risk of preterm birth (PB) [6]. Sensitivity at this threshold was reported to be about 37.3%, meaning that 37.3% of pregnancies at risk of preterm labour were correctly identified. The specificity, on the other hand, was reported to be around 92.2%, indicating that 92.2% of pregnancies not at risk for preterm birth were correctly identified as such. The most effective threshold for predicting true preterm labour was found to be a cervical length of 15 mm or less, yielding a specificity of 81% and a positive predictive value of 83% [2].

Newer tools, such as uterocervical angle (UCA),have beendeveloped to predict PB. With the widespread use of UCA in studies in the last decade, UCA has become more prominent. However, most studies have a small sample size. The subject of UCA is relatively new, and there is limited availability of systematic reviews on this topic. These reviews indicate the necessity for more robust scientific evidence to establish the success of UCA in predicting preterm birth (PB). In such cases, conducting a meta-analysis can be an appropriate approach to enhance the sample size and consolidate findings from similar studies. Therefore, our objective is to use this meta-analysis to provide a clearer and more reliable understanding of the relationship between UCA and preterm labour in singleton pregnancies. By synthesizing the available data, we aim to contribute valuable insights and strengthen the existing evidence on this topic.

MATERIAL AND METHODS

Search strategy

For our research, we implemented a systematic electronic search strategy to explore published literature. We conducted searches across multiple databases, namely PubMed Medline, ClinicalKey, ScienceDirect, Web of Science, and Google Scholar. Our search encompassed the period from January 1, 2010, to December 27, 2020. We employed a combination of the following keywords: uterocervical angle, cervical angle, angle, cervix cervical, preterm, and preterm labour. The appropriate database-specific suffixes were employed in the search to optimize results. We focused exclusively on studies conducted on humans and published in the English language. The search process and results are presented in a structured flow diagram, as depicted in Figure 1 of our thesis.

Study selection

All included studies in our meta-analysis were prospective observational studies that examined the relationship between preterm labour and the anterior uterine cervix. While these studies varied in terms of diagnosing preterm labour, parity, gravidity, presence of previous preterm births, and prior cervical or uterine surgeries, they were all considered for inclusion in the meta-analysis. In addition, studies that defined preterm labor as delivery before 37 weeks were subgrouped and evaluatedseparately. However, our study excluded studies that involved patients with preterm premature rupture of membranes, polyhydramnios, multiple gestations, and cerclage. Additionally, conference abstracts were also excluded. Furthermore, trials were excluded if they reported results in a manner that hindered pooling for meta-analysis, such as failure to provide mean and standard deviation values.

All the studies included in our analysis provided a clear definition of the method used for ascertaining the uterine cervical angle. Most of the studies utilized similar measurements, concerning Dziedz et al. [7], to ensure uniformity in the assessment of the uterine cervical angle. The UCA was defined as the value obtained by measuring the triangle formed between the lower uterine segment and the cervical canal using transvaginal ultrasound. During the measurement process, the first line of callipers was placed at the junction where the anterior and posterior walls of the cervix meet, including the internal and external os along the endocervical canal. If the cervix appeared curved, the measurement was taken vertically from the internal os to the external os. The second line was drawn by averaging a 3 cm line from the internal os of the cervix to the upper uterine segment. The angle formed between these two lines was recorded. It is worth noting that all participants in the trials had an empty bladder during the ultrasound scan.

Quality and risk of bias assessment

Before conducting the meta-analysis, the publication bias of the included studies was assessed using Begg's and Egger's tests.

Data extraction

The studies were selected in three consecutive stages. Following deduplication, the titles and abstracts of all electronic articles were screened by N.N.Y. to assess their

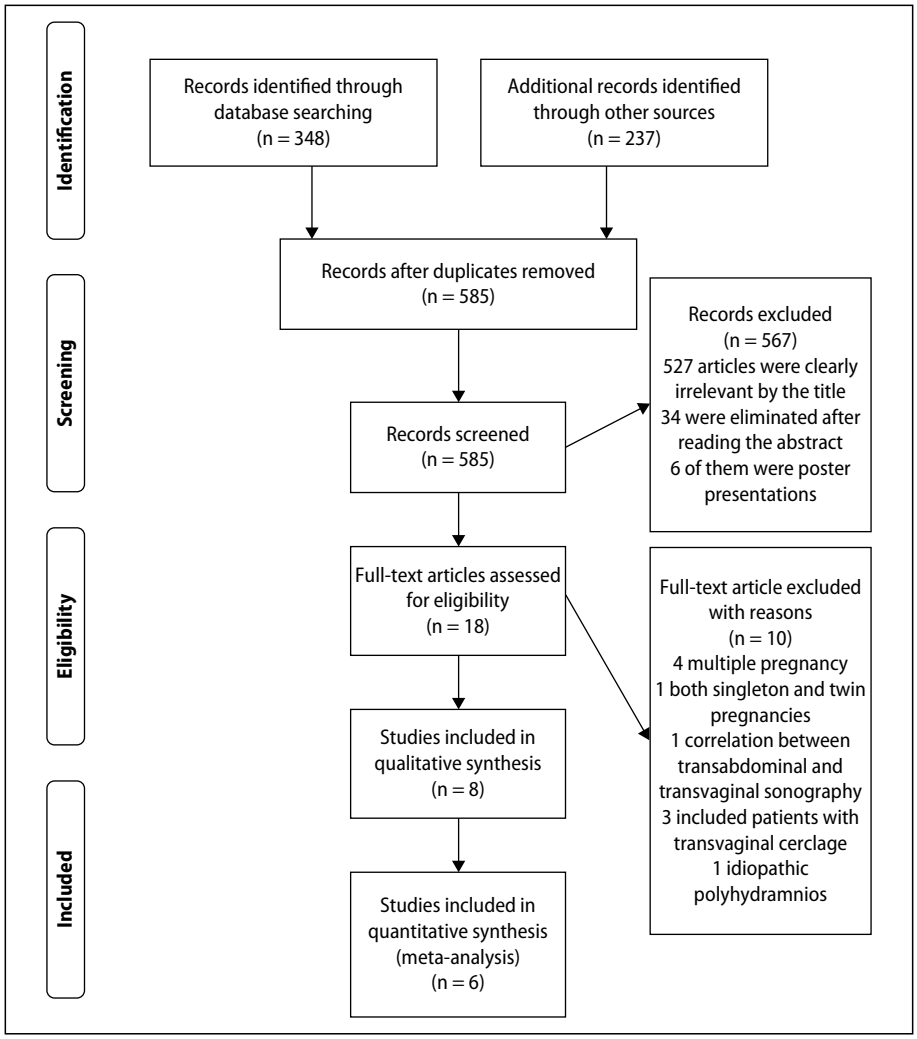

Figure 1. Flow diagram

eligibility. The decision to include studies in the present meta-analysis was made after retrieving and reviewing the full text of articles that were held potentially eligible. Potential discrepancies in this latter stage were resolved by the consensus of all the authors.

Summary measures

The main outcome measure chosen for the present meta-analysis was the success of the UCA in preterm labor prediction. Subgroup analyses were done for studies that described preterm labor as before 37 weeks.

Quantitative data synthesis

The heterogeneity of the studies was evaluated according to Cochran's Q test, while to determine the degree of statistic was employed. In the meta-analyses, the lowest number of studies taken for analysis was three. In the studies, the value of α was taken as 0.10 for the homogeneity and publication bias tests.

In cases where heterogeneity was determined in the publications following Cochran's Q test, the DerSimonian-Laird method was carried out using the random-effects model. In the statistical analyses, MedCalc version 20.009 program was used.

RESULTS

Literature search and study characteristics

The literature search uncovered 585 articles (Fig. 1). Among these, 527 articles were considered unrelated due to their titles, 34 articles were excluded after reviewing the abstracts, six articles were in the format of poster presentations [8–13], and 18 articles were thoroughly examined in their entirety.

Of the 18 full-text articles evaluated, four were excluded because patients with multiple pregnancies were includedin the studies [14–17], 1 because patients with both singleton and twin pregnancies were included [18], and 1 because it was difficult to determine the correlation between transabdominal

Table 1. Study characteristics

Source	Studydesign	No. of patients	Including criterias	Week of UCA measurement	UCA value (mean ± SD)
Martinez et al. [20]	Retrospective	318	Singleton pregnancies with history of preterm labor	20–24 week	106.1 ± 26.4 (preterm) 99.5 ± 26.4 (term)
Dziadosz et al. [1]	Retrospective	972	Singleton pregnancies with history of abnormal smear, cervical surgery and preterm labor	16–24 week	120 ± 27 (preterm) 93 ± 26 (term)
Sur et al. [21]	Prospective	100	Singleton pregnancies with history of preterm labor	Second trimester	127.66 ± 6.61 (preterm) 103.65 ± 14 (term)
Llobet et al. [22]	Prospective	275	Singleton pregnancies with history of preterm labor	18–24 week	105.2 ± 21.6 (preterm) 94.5 ± 22.7 (term)
Sawaddisan et al. [23]	Prospective	356	Singleton pregnancies with a history of cesarean or D/C	16–24 week	111.8 ± 25.4 (preterm) 104.8 ± 26.7 (term)
Borna et al [24]	Prospective	100	Singleton pregnancies that had bleeding during pregnancy	18–24 week	102.12 ± 7.13 (preterm) 86.15 ± 5.78 (term)

UCA — uterocervical angle; SD — standard deviation

and transvaginal sonography UCA measurement [19]. Two additional articles were excluded because they compared the UCA as predictors of preterm delivery in patients with transvaginal cerclage [20, 21], and one other because they included the patients who underwent cerclage in the study groups [22]. One article was excluded because it specifically included pregnant women diagnosed with idiopathic polyhydramnios [23]. Of the eight articles remaining for a more thorough evaluation, one was excluded from the quantitative meta-analysis, as it hadan uninterpretable or incomplete data set [24], andanother one because it presented the data as median, not mean values [25]. Thus, six articles remained to be included in the meta-analysis [7, 26-30]. Relevant characteristics of the trials included in this review are given in Table 1.

This meta-analysis includes 6 articles with a sample size between 100 and 972 published in 2016 and 2020. The studies determined that UCA values were assessed using transvaginal ultrasound during the second trimester. In the articles, alterations were observed in the weeks of the second trimester when the measurements were conducted: four of them were taken between 17/18 weeks and 24 weeks [7, 28–30], one between 20–24 weeks [26], and one during the second trimester [27].

Qualitative analysis

All studies reported that UCA is a good predictive tool for preterm labor that was measured at the begining of the second trimester. Only Borna et al.'s [30] reported that UCA could be a good predictive tool for preterm labor in patients with vaginal bleeding complaints. In all thestudies included, birth weeks were correlated with the UCA measurement performed at different time intervals at the beginning of the second trimester. Only Sawaddisan et al. [24] evaluated the UCA prediction success according to the weeks in which UCA measurement was performed. In this study, while comparing UCA values with term and spontaneous preterm deliveries, the patients were divided into two groups: gestational age $16^{0/7}$-$24^{0/7}$ weeks (n = 356) and gestational age above 19.5 weeks (n = 141). There was a statistically significant difference in value between the groups when the UCA measurement was made only over 19.5 weeks (p = 0.017).

There were some differences in terms of the definition of preterm labor in the studies. Martinez et al. [26] defined preterm labor as less than 34 weeks. On the other hand, Llobet et al. [28] divided the patients into those who gave birth after 37 weeks and those who gave birth after 34 weeks. Dziadosz et al. [7] Llobet et al. [28] and Borna et al. [30] defined preterm labor as births less than 37 weeks. In Sur et al.'s [27] study, we did not find a specific week definitionfor preterm labor. All casesdefined as preterm labor independent of the week were included in this meta-analysis. In addition, subgroup analysis was performed in three studies in which preterm labor was defined as less than 37 weeks [7, 28, 30].

Quantitative analysis

As a result of Egger's test (p = 0.220) and Begg's test (p = 0.188), it was determined that there was no publication bias. Cochran's Q test revealed that there was heterogeneity ($p < 0.001$ = 94.49%). There was a significant difference between the patient and control groups($p < 0.001$) (Tab. 2).

In the subgroup consisting of studies in which preterm labor wasdefined as before 37 weeks, through Egger's test (p = 0.704) and Begg's test (p = 0.601), it was determined that there was no publication bias. Cochran's Q test revealed that there was heterogeneity ($p < 0.001$ = 95.11%). There was a significant difference between the patient and control groups (p = 0.012) (Tab. 3). The results of the meta-analysis were shown in Figures 2 and 3.

Table 2. Meta-analysis of all studies

Study	Preterm (n1)	Term (n2)	Total	SMD	SE	95% CI	t	p	Weight [%]	
									Fixed	Random
Martinez	93	225	318	0.249	0.123	0.006–0.492			29.46	17.54
Dziadosz	84	888	972	1.034	0.116	0.806–1.263			33.08	17.60
Sur	37	63	100	2.013	0.250	1.517–2.509			7.18	16.08
FarrasLlobet	34	241	275	0.473	0.184	0.111–0.835			13.28	16.93
Sawaddisan	31	325	356	0.263	0.188	–0.107 to 0.632			12.71	16.89
Borna	17	83	100	2.632	0.323	1.991–3.273			4.30	14.97
Total (random effects)	296	1825	2121	1.068	0.302	0.476–1.660	3.537	< 0.001	100.00	100.00

SMD — Standart mean difference; SE — standart error; CI — confidence interval

Table 3. Meta-analysis of the subgroup with diagnosis preterm labor before 37 weeks

Study	Preterm (n1)	Term (n2)	Total	SMD	SE	95% CI	t	p	Weight [%]	
									Fixed	Random
Dziadosz	84	888	972	1.034	0.116	0.806–1.263			66.04	34.98
Sawaddisan	31	325	356	0.263	0.188	–0.107 to 0.632			25.38	33.96
Borna	17	83	100	2.632	0.323	1.991–3.273			8.58	31.07
Total (random effects)	132	1296	1428	1.269	0.503	0.283–2.254	2.524	0.012	100.00	100.00

SMD — Standart mean difference; SE — standart error; CI — confidence interval

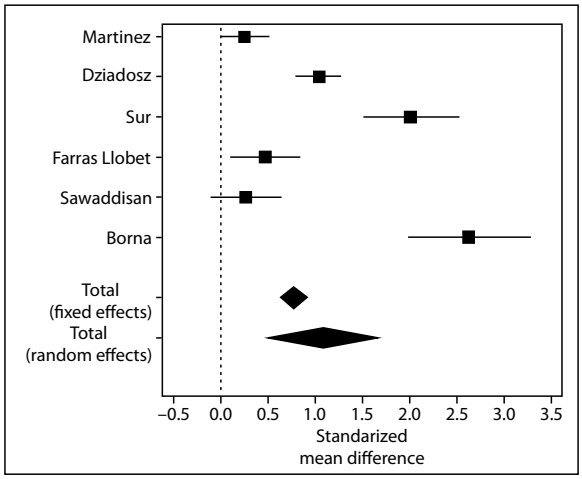

Figure 2. Forest graph in evaluating the success of anterior uterocervical angle in predicting preterm labor

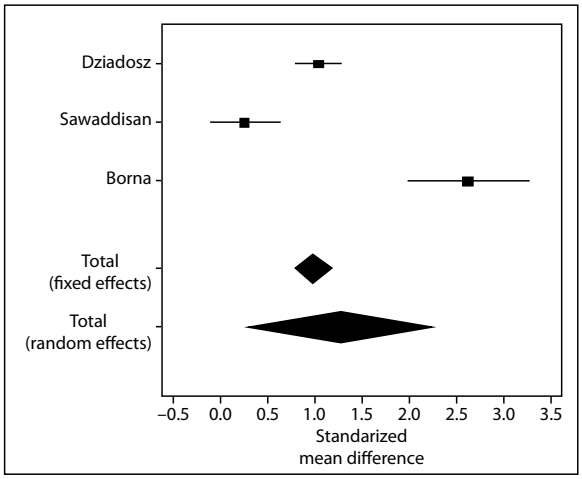

Figure 3. Forest graph in evaluating the success of anterior uterocervical angle in predicting preterm labor before 37 weeks

DISCUSSION

Principal findings

The meta-analysis, results indicated that a wider UCA was associated with a higher risk of preterm labour in the overall effect. A significant correlation was also observed between UCA and preterm labour occurring before 37 weeks.

Results in the context of what is known

Uterocervical angle, in the prediction of preterm labor, is an important tool that has been emphasized in recent years [7]. Studies have continued to assessseveral areas, such as preterm labor, termination time, and latent phase periods of labor. A recent indirect comparison between

collagen fiber orientation and dispersion in the upper cervix of pregnant and nonpregnant women suggested that collagen fiber dispersion and direction may influence cervical remodeling during pregnancy [31]. In this sense, a predictive tool originating from the upper cervix and uterus may be more meaningful than biochemical markers. Since 2016, many studies have been conducted showing the success of UCA in preterm labor prediction. However, there is no meta-analysis to increase the level of evidence, except for the systematic review in 2018 [32]. Outcomes of the present study can provide clinical applicability for UCA.

Two of the studies [7, 26], UCA measured depends on previously measured and archived cervical length images. Hovewer, both studies were written prospectively and the journals in which they were published accepted these publications as prospective. For this reason, we accepted these two articles as prospective in accordance with the literature. Our most important inclusion criteria were singleton pregnancies. However, the preterm labor risk status of the patients included in the analysis was not similar. For example, we could not exclude studies that included patients with a history of preterm labor or previous cervical surgery because we have reached only a few studies in the literature on low-risk pregnant women in terms of singleton and preterm labor.

Clinical implications

The study's analysis was not the standardized diagnosis of preterm labour diagnosis. All patients are defined as preterm regardless of week. Even in this way, we tried to create a more specific and near-standard subgroup to increase the power of our analysis, which turned out to be meaningful. We performed a subgroup analysis of studies defining preterm labor as less than 37 weeksand found a significant difference from the control group [7, 29, 30]. Moreover, UCA measurement weeks were not standard. This prevented us from drawing attention to a cut-off value obtained by measuring in a certain week.

Research implications

Studies show that UCA measurement can be a good tool for predicting preterm labor. But none of these studies were randomized. Ensuring randomization in future studies will also be important for publications to be included in future meta-analyses.

Strengths and limitations

One of the strengths of the present study is thatwe discussed a subject that becamepopular recently, but little is known about it. To the best of our knowledge, this is limited data evaluating the role of UCA in prediction of preterm labor in singleton pregnancies. In addition, we analyzed preterm labor independent of the week and preterm labor defined as before 37 weeks; therefore, rendering our results more reliable.

One of the limitations of this meta-analysis is that we retained broad criteria for the inclusion of studies. For example, patients with a history of preterm labor were not further subgrouped or mechanical reasons that could affect UCA measurements such as conization and previous cesarean history could not be excluded from all the studies included in the meta-analysis. In other words, patients could not be analyzed according to risk groups for preterm labor. The primary factor that limited us is the fact that UCA is a new subject, and there were only a few studies with similar patient groups. Second, the literature search strategy was limited to the published papers that were used, which were in English, whilestudies published in other languageswere excluded.

CONCLUSIONS

This meta-analysis found that preterm births both before 34 weeks and up to 37 weeks could be predicted by UCA measurement in the second trimester. To improve the diagnostic value of the uterine cervical angle in predicting preterm birth, further studies should establish more specific patient groups and standardise the cut-off value. In addition, further larger studies should be performed to confirm these findings.

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The authors reports no conflict of interest.

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MicroRNAs (miRNAs) and long non-coding RNAs (lncRNAs) in endometriosis — review of literature

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ABSTRACT

Endometriosis is a disease of the female genital organs, the causes of which are not fully understood. Recent studies have shown that non-coding RNAs (ncRNAs) like long non-coding RNAs (lncRNAs) and microRNAs (miRNAs) can contribute to the pathogenesis of endometriosis. Profiling of miRNA and lncRNA expression is carried out using state-of-the-art molecular biology techniques (RT-PCR, sequencing, microarray analysis). The use of the latest technologies may make it possible to establish a genetic profile, which is a promising prospect for early diagnosis of endometriosis. In the future, genetic testing may become the gold diagnostic standard and eliminate invasive laparoscopy. In the case of endometriosis, it is important to extend the research to molecular aspects, which may facilitate the diagnosis of the disease or indicate new (based for example ncRNA) treatment methods. The paper presents the latest data on the importance of miRNA/lncRNA in endometriosis.

Keywords: endometriosis; miRNA; lncRNA

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INTRODUCTION

According to the classical definition, endometriosis is the surgical detection of endometrial tissue outside the uterine cavity, however, this narrow anatomical definition turns out to be insufficient to explain the pathogenesis of endometriosis, the molecular substrate, the full spectrum of its clinical manifestations, frequent relapses and reactions to modern methods of treatment [1]. Women wait an average of 8–10 years for a diagnosis. The basic method of recognizing endometriosis is laparoscopy (called the gold standard), which consists in excision of endometrial lesions [2].

The pathogenesis of endometriosis is controversial — immune, hormonal, genetic and environmental factors are involved [3]. There is no single theory that would fully explain the emergence of endometriosis. A very popular theory is the Sampson theory. It seems that the disease may arise as a result of the phenomenon of "retrograde menstruation". During menstruation, part of the menstrual secretion enters the peritoneal cavity through the fallopian tubes. The live endometrial cells delivered in this way can inhabit the peritoneal cavity, creating ectopic lesions. However, it has been shown that 90% of women without endometriosis experience retrograde menstruation. Another theory of the cause of endometriosis is the so-called metaplasia theory, *i.e.*, the transformation of cells lining the peritoneal cavity into endometrial cells outside the uterine cavity. A malfunctioning immune system may be responsible for the causes of the disease. Weakened immunity or autoimmune diseases promote the formation of foci of endometriosis. Another theory about the causes of endometriosis speaks of a genetic predisposition. If your grandmother, mother or sister has endometriosis, you are more likely to suffer from the disease as well. As a result of changes at the level of genes that participate in the differentiation of anatomical structures of the genitourinary system, abnormal location of stem cells may occur. The above phenomenon, together with immunological changes and pro-inflammatory

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environment of the peritoneum, determines the progression of endometriosis.

In the treatment of symptomatic endometriosis, hormone therapy and analgesics are used, however, endometriosis often returns [3]. Therefore, it is important to have a comprehensive and individualized approach to the patient and to find a non-invasive diagnostic marker of the disease. In the research plans of the area associated with endometriosis is the identification of the molecular basis of this disease.

RNAs are divided into two classes: messenger RNA (mRNA), which is involved in protein synthesis, and non-coding RNA (ncRNA). First, the work focuses on the analysis of non-coding RNAs (miRNA/lncRNAs) in patients affected by endometriosis. ncRNAs are candidates for reliable laboratory biomarkers of this disease [4, 5].

RNA molecules can become desirable biomarkers in the non-invasive diagnosis of endometriosis because they are characterized by tissue specificity and high stability in biological fluids [6].

MicroRNA (miRNA)

MicroRNAs circulating in the blood have potential as useful biomarkers of endometriosis [7]. In tissues, miRNAs are stable. They are detected in the serum of patients using quantitative methods (qPCR). Mature miRNAs are single-stranded molecules of non-coding RNA with a length of about 22 nucleotides. They regulate gene expression by influencing the translation process [8]. The greatest prognostic power is given by the determination of several microRNAs, whose change in expression is observed in endometriosis.

Genes for microRNAs can occur between protein-coding sequences and function as stand-alone transcription units, or they can be in coding sequences [9]. Genes for miRNAs are found both in exons, introns, and in untranslated regions [10]. Such a transcription unit arrangement may lead to the simultaneous creation of miRNA and mRNA transcripts [9]. The miRNA genes are organized in a manner characteristic of polymerase II and III, transcribing the genes of small RNAs [9, 10].

In the process of transcription, the primary pri-miRNA transcript is created. Pri-miRNA is then treated with Drosh ribonuclease, which releases pre-miRNAs with a length of about 60–70 base pairs [9]. Exportin-5 transfers pre-miRNAs from the cell nucleus to the cytoplasm, where the resulting molecules undergo further processing by the Dicer enzyme [9–11].

The catalytic reaction results in a double-stranded miRNA-miRNA* duplex consisting of a leading strand and a lagging strand [11]. After duplex breakdown, the passenger thread is usually degraded, sometimes combining with Ago proteins to maintain miRNA functions. The leading strand, on the other hand, binds to a number of proteins, including RNA-binding proteins and the aforementioned catalytic Ago proteins (Argonaute), forming a complex miRNP (microribonuclear protein complex), called RISC (RNA-induced silencing complex) [10, 11]. The resulting complex, mainly due to Ago proteins, performs mRNA degradation or translational reprisals, and therefore negatively regulates gene expression at the post-transcriptional level [10, 11]. This is possible due to the complementarity of miRNA with target mRNA in the 3'UTR region [11]. In the case of full complementarity, mRNA degradation occurs. If complementarity is incomplete, translation is inhibited [10, 11]. It is believed that up to 30% of protein-coding genes can be regulated by the corresponding miRNAs. The microRNAs are "guardians" that take care of the proper course of processes such as cell division, proliferation, differentiation or cell apoptosis, which are of fundamental importance for the proper functioning of the body [12].

MiRNA IN ENDOMETRIOSIS

In endometriosis, there is a pool of genes regulated by miRNAs. The miRNAs dominant in endometrial cells include miRNAs from the let family. It is known that Let-7b with pleiotropic activity regulates the expression of ER α/ß, KRAS 4A/4B, Cyp19 or IL-6 [13] genes, which is important in the pathophysiology of endometriosis. The development of this disease is also influenced by the altered expression of miR449b3p [14]. In ectopic endometrium, altered levels of miR-139-5p and miR-375 expression have been detected that can regulate the expression of transcription factors HOXA9 and HOXA10 and the endothelin 1 gene (EDN1), influencing the development of endometriosis [15].

MicroRNAs in endometriosis regulate the expression of mTOR kinase (the mammalian target of rapamycin) and genes of the VEGF pathway [16].

mTOR kinase affects the regulation of cell growth, proliferation and movement, as well as translation and transcription processes. VEGF enhances the process of angiogenesis in endometriosis.

An analysis of the miRNA profile in the eutopic endometrium of women with endometriosis was performed. A pool of 667 human miRNAs in patients with endometriosis was studied. Two of the miRNA pools studied were shown to be subject to increased expression, while 13 miRNAs were characterized by reduced levels of expression in these patients.

In addition, hsa-miR-483-5p and miR-629 have been shown to have significantly reduced expression in patients with endometriosis [17]. Studies of the pool of various microRNAs in endometriosis have shown that they can have a significant impact on the development of lesions (Tab. 1).

* complementary RNA

Table 1. MicroRNA (miRNA) regulatory functions in endometriosis	
Biological process	miRNA
Hypoxic injury	miR-15b and miR-16
Tissue repair and TGFβ-regulated pathways	miR-1, miR-21, miR-141 and miR-194
Inflammation	miR-199a, miR-16, miR-302a, miR-542-3p
Cell growth, proliferation and apoptosis	miR-15b/16, miR-143, miR-145, miR-20a, miR-221 and miR-222
Extracellular matrix remodelling	miR-29c
Angiogenesis	miR-126

Recent research indicates that plasma miRNAs may be potential diagnostic markers of endometriosis [18]. The search for miRNAs as biomarkers and modeling was conducted on a group of 120 patients (38 people in the control group and 82 people with endometriosis as a study group), which was then validated in an independent group of 90 patients (30 in the control group and 60 in the study group) [19].

The researchers identified a set of 42 miRNAs that can distinguish women with endometriosis from women without endometriosis, based on genome-wide miRNA expression profiling. The method has diagnostic power for mild endometriosis, which confirmed the biological relationship between some miRNAs (such as hsa-miR-125b-5p, hsa-miR-28-5p and hsa-miR-29a-3p) and endometriosis.

A possible biological link between some miRNAs and endometriosis has therefore been confirmed, but their potential as useful biomarkers require well-designed, large cohort studies and detailed analyses.

MicroRNAs are involved in the pathogenesis of endometriosis by alleviating inflammation, proliferation, angiogenesis, and tissue remodeling [20, 21]. It has been shown that potential biomarkers of endometriosis may be miR-21, miR-29c, miR-100 and miR-143 [20, 21]. These miRNAs are regulated upwards in ectopic endometrial tissues. The target for miR-29c during the late secretory phase is c-Jun mRNA, a gene that drives proliferation, apoptosis, and invasion of endometrial cells. Increased expression of miR-100 inhibits cell proliferation, migration, and invasion in the cancer model. Lowering the expression of miR-100 stimulates metastasis. Thus, increasing the expression of miR-100 and miR-143 in endometrial tissues triggers a defense mechanism against the possibility of transformation to malignant changes in the phenotype of benign endometriosis [20, 21].

MOMENDO project (https://cordis.europa.eu/article/id/418294-molecular-cues-into-the-pathogenesis-of-endometriosis/pl) detected that miRNAs are dysregulated in endometriotic tissue, thereby contributing to the invasive development of endometriotic cells. Importantly, the experimental increase in the expression of selected microRNAs inhibited many pathogenic features of patient-taken endometriotic cells in cell culture, including their growth, invasiveness, and stem status. Using transcriptomics, it has been shown that some patients' endometriotic cells are like cancer cells; This new data can be used in personalized therapies. The positive therapeutic effects obtained in experimental preclinical models paved the way for some strategies to emerge therapeutic targets, including gamma-secretase inhibitors, microRNA-based drugs, and anti-inflammatory compounds that will be evaluated in clinical trials of endometriosis.

Abnormal expression of individual miRNAs may result from changes in the genome, abnormalities in their biogenesis, or may be related to epigenetic factors regulating gene expression. Attention is paid not only to the genetic causes of changes in miRNA expression, such as single nucleotide polymorphisms (SNPs) in miRNA genes, affecting the transcription and formation of pri-miRNAs or subsequent interactions between mature microRNAs and mRNAs, but also to the possibility of changes in the level of methylation of these genes. Therefore, not only structurally determined changes in the level of expression of miRNAs are important, but also their epigenetic regulation. Perhaps these mechanisms will become a target in the future for the development of new therapies that modulate the expression of miRNAs through changes in the level of methylation of their genes. However, the use of microRNAs in the diagnosis of endometriosis is only in the initial phase of research.

LncRNA

According to the ENCODE consortium (Encyclopedia of DNA Elements, 2012) human genetic material is transcribed in 93% (of which 39% of tranxrypts correspond to introns and UTR sequences of protein-coding genes, 1% to exons, and 54% to protein-coding genomes) [22, 23]. Before non-coding sequences were studied, they were thought to be nothing more than "junk DNA".

The first long non-coding RNAs, treated as mRNAs at the time of their discovery, were the H19 and Xist genes

(X-Inactive Specific Transcript, a transcript specific for X chromosome inactivation) [24–28].

The H19 gene was identified on chromosome 7 of mice. H19 forms a group together with the insulin-like growth factor Igf2 (Insulin Like Growth Factor 2) gene, but unlike it, it is transcribed but not translated [24].

The Xist gene belongs to a complex of genes in one of the regions of the X chromosome, called XIC (X Inactivation Center, the center of X chromosome inactivation). The Xist gene is crucial for the correct phenomenon of lionization described by geneticist Mary Lyon [28, 29]. It is the process of switching off one of the X chromosomes in women (or other female mammals), thanks to which gene expression is equalized in women and men [30]. The function of shutting down the entire chromosome is unique in the world of lncRNA.

Long non-coding RNAs have a length of more than 200 base pairs [23]. Exon regions are located within the lncRNA genes. Their large amount as a result of splicing allows the formation of diverse forms of this family. lncRNAs perform various functions, including those of clinical relevance [23]. The structure of lncRNAs is similar to protein-coding genes (PCG). However, the level of expression of lncRNA genes is much lower than PCG.

The reduced level of expression is the result of differences in thestructure of lncRNA gene promoters and amplifiers (this applies mainly to epigenetic changes in histones). The change in expression reduces the severity of the transcription process and with less stability of the lncRNA molecule from the mRNA molecule [23].

Depending on the type of lncRNA, their stability varies. Less stable are lncRNAs associated with the intron and promoter. Intergenic lncRNAs, antisense or 3'UTR end are more stable [23]. lncRNAs are specifically expressed in tissues and even cells [31, 32]. LncRNA expression may be associated with single nucleotide polymorphisms located within genes and their promoters. This may affect the pathogenesis of diseases [32]. lncRNAs due to the specificity of expression can play an important role in the regulation of processes in the organisms, as well as participate in the repair of pathological processes.

LncRNAs are common throughout the cell [33] and can therefore perform a variety of functions. lncRNAs localized in the nucleus affect chromatin, transcription, RNA processing. lncRNAs located in the cytoplasm affect mRNA stability, translation, and cellular signaling pathways. As a result of environmental changes or infection, lncRNAs can travel from one cell location to another [33]. Thanks to the flexible and dynamic structure of lncRNA (it can take on a secondary structure), the functions of these molecules are very versatile. They can change locations, especially nuclear ones, and interact with proteins [33]. lncRNAs are characterized by low sequence conservatism, which allows for variability of the structure and subsequent function and regulatory specialization of lncRNAs [34, 35]. lncRNAs can interact in two ways: cis and trans (according to Kopp F. and Mendell J) [35, 36]. The cis method means the effect of lncRNA on the expression of neighboring genes [36–39], *i.e.*, directly affecting the transcription process as an enhancer, "stopping" transcription factors, affecting chromatin looping and gene methylation [39]. The trans method involves controlling the expression of distant genes by influencing their promoters and enhancers. lncRNAs can also affect proteins that bind to these regions and, in complex with them, affect chromatin conformation and polymerase activity [39].

One of the first trans-function lncRNAs discovered were the HOTAIR (Homeobox (Hox) Transcript Antisense Intergenic RNA), intergenic RNAs antisensibly complementary to the Homeobox transcript and MALAT1, which, as it turned out in further studies, play a significant role in the development of endometriosis [40–42].

LncRNA IN ENDOMETRIOSIS

Recently, in endometriosis research, long non-coding RNAs [42] have been of interest, which tend to have a greater sequence matching and thus the specificity of the action on target genes. All stages of the transfer of genetic information from DNA to protein require the participation of non-coding RNA molecules. Their participation is particularly marked in the mechanisms leading to the inclusion or exclusion of the expression of individual genes.

Altered expression of lncRNAs in endometriosis is involved in the regulation of numerous processes include epithelial–mesenchymal transition (EMT), endometriosis cell stemness, angiogenesis, lesion establishment and growth, endometriosis cell survival, proliferation and invasion, oxidative stress, autophagy, and endometrial receptivity (Fig. 1).

In the research of Zhou et al. [43], 388 lncRNA transcripts studied were overexpressive and 188 were overexpressed, and 188 were reduced in ectopic endometrial compared to eutopic endometrial.

It is known that lncRNA expression varies in the serum of women with endometriosis, eutopic endometrial of women with endometriosis compared to healthy women, and in ectopic endometrial ovaries compared to eutopic endometrial in women with endometriosis [43].

The types of lncRNAs and their changes in endometriosis expression are presented in Table 2.

However, the clinical relevance and biological mechanism of lncRNA in the development of endometriosis remain largely unknown.

Important for endometriosis lncRNA is H19. H19 is 2–3 kb lncRNA. It is located on the human chromosome

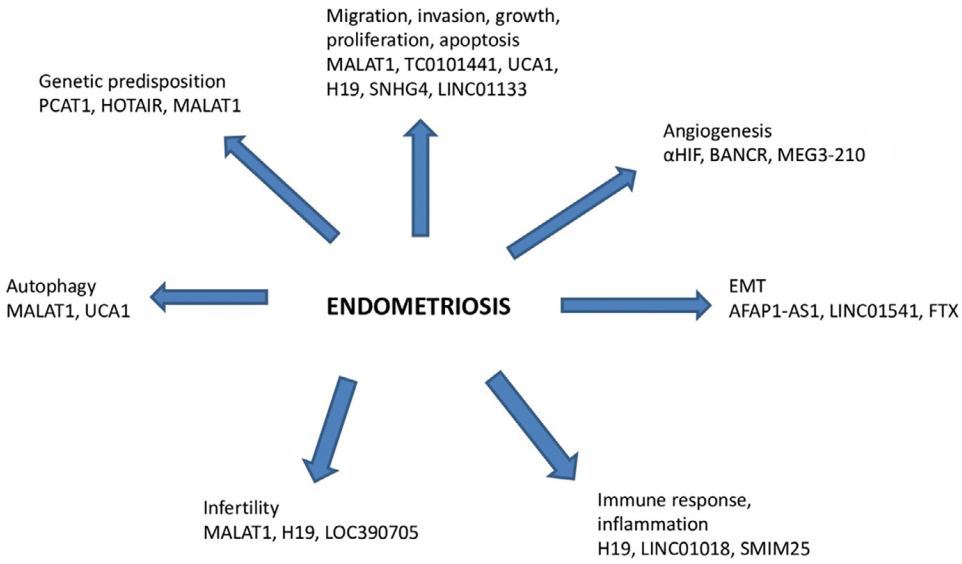

Figure 1. Scheme of phenotypic changes that occur as a result of altered lncRNA expression in endometriosis

Table 2. Differentially expressed lncRNAs in endometriosis

lncRNA			
Upregulated		**Downregulated**	
Endometriosis tissue	**Body fluids**	**Endometriosis tissue**	**Body fluids**
MALAT1 CCDC144NL-AS1 AC002454.1 TC0101441 AFAP1-AS1 H19 UCA1 SNHG4 LINC01133	TC0101441	LINC00261 LINC01541 MEG3-210 FTX UCA1 H19	MALAT1 H19 (T17) UCA1

11p15.5, which can be transcribed but not translated. Together with insulin-like growth factor 2 (IGF2), H19 forms a pair of imprinted genes [44]. A reduction in H19 lncRNA levels has been demonstrated in patients with endometriosis in the eutopic endometrium. Decreased H19 expression leads to increased let-7 activity, which in turn inhibits IGF1R (insulin-like growth factor 1 receptor). This process limits the proliferation of endometrial stroma [45].

MALAT1 is another important lncRNA in endometriosis. It was shown that miR-200c, which is regulated by MALAT1, was down-regulated in endometrial tissue inendometriosis [46]. Many studies have confirmed that the MALAT1 gene is associated with recurrence, metastasis and epithelial-mesenchymal transformation of various tumors [47, 48].

A unique pool of serum lncRNAs was detected, which was associated with the severity and progression of endometriosis. Thanks to the detected lncRNAs, it is possible to distinguish between early and severe stages of endometriosis. lncRNAs can therefore be non-invasive biomarkers for diagnosing endometriosis and act as important regulators of its development [49].

Huang et al. concluded that lowering UCA1 lncRNA levels cannot be a biomarker for the diagnosis of ovarian endometriosis. They pointed out that in most patients with endometriosis, UCA1 expression was increased in ectopic tissue compared to expression in eutopic endometrial tissue. Most importantly, at the time of discharge, serum UCA1 levels were reduced in relapsed patients compared with non-relapsed patients [50].

lncRNA TC0101441 has been identified as a potential extracellular follicular biomarker for endometriosis. Serum extracellular vesicle levels TC0101441 were

significantly higher in patients with stage 3/4 endometriosis compared to patients with stage 1/2 endometriosis and healthy subjects. This indicates the importance of circulating extracellular vesicles TC0101441 as a biomarker of endometriosis [51].

Whole-genome DNA sequencing studies identified genetic variations in lncRNA loci that may affect the pathogenesis of endometriosis. A possible mechanism is disruption of lncRNA function by single nucleotide polymorphisms. A specific variant of polymorphic may predispose patients to endometriosis. Studies of Korean patients showed that SNP rs10965235 in the CDKN2B-AS gene located on chromosome 9p21.3 is associated with severe endometriosis [52].

Another polymorphism SNP rs3820282 located in the WNT4 intron on chromosome 1p36.12 is associated with endometriosis. This polymorphism can affect the amplifier-promoter interaction, resulting in a decrease in the level of LINC00339 and an increase in the level of CDC42 [53].

Genetic changes at SNP sites rs1838169 and rs17720428 on chromosome 12q13.3 in HOTAIR are commonly detected in patientswith endometriosis [54]. These variants appear to increase lncRNA stability, resulting in reduced levels of HOTAIR-regulated HOXD10 and HOXA5 transcripts.

The SNP variant rs591291 located on chromosome 11q13.1 in the MALAT1 promoter region was associated with an increased risk of endometriosis in the Chinese population, indicating that a change in MALAT1 expression level may affect the risk of endometriosis [55]. SNP rs710886 in PCAT1 is known to be associated with an increased risk of developing endometriosis [56]. rs710886 appears to interfere with PCAT1 miR-145 sponging, affecting the expression of FASCIN1, SOX2, MSI2, SERPINE1, and JAM-A and the proliferative and invasive capacity of endometriosis stem cells. In summary, genetic variants associated with endometriosis may predispose patients to disease by disrupting the regulatory function of the lncRNA gene through various mechanisms.

In conclusion, genomic and transcriptomic studies of the whole genome showed correlations of lncRNA with endometriosis.

CONCLUSIONS

The literature data presented in the article indicate that work is still underway to search for markers of endometriosis. These studies may contribute to a better understanding of the mechanisms of this disease and the development of new treatments. Perhaps with appropriate manipulations at the molecular level (including miRNA/lncRNA), in the future some diseases, including endometriosis, can be completely eliminated.

Article information and declarations

Author contributions

TS, BS contributed to the conception of the study. HR and KS contributed significantly to manuscript preparation. TS, BS wrote the manuscript.

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Conflict of interest

The authors declare no conflict of interest.

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Personalized embryo transfer (pET) guided by endometrial receptivity (ER) assessment — a possibility to increase effectiveness of *in vitro* fertilization (IVF) procedures. Review of available methods

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ABSTRACT

The continuous development of assisted reproductive techniques (ART) implies the search for solutions that could increase the effectiveness of available methods. In the context of *in vitro* fertilization (IVF), a significant proportion of failures are due to unsuccessful embryo transfers. At this stage the most important issue is proper dialogue between implanting embryo and the maternal endometrium. Therefore, it seems justified to assess endometrial receptivity (ER), defined as the tissue's ability to accept an embryo to attach and invade into the mucosa. Window of implantation (WOI), is a certain period in which implantation of the properly developed embryo is possible. The cause of endometrial receptivity disorders is believed to be the disturbed expression of cytokines and endometrial surface proteins, the presence of which has been proven in commonly diagnosed diseases such as endometriosis or chronic endometritis. Despite many years of research on endometrial receptivity, the area of diagnostic methods enabling clinical monitoring of ER still remains undeveloped. The aim of this study is to review the utility of selected markers and the available methods of ER assessment, ranging from noninvasive ultrasound, through endometrial fluid analysis, to genomic studies based on endometrial biopsy, in order to increase the effectiveness of IVF. Such an approach could potentially be a significant step towards personalizing medical procedures especially in patients diagnosed with repeated implantation failure (RIF).

Key words: *in vitro* fertilization; embryo transfer; personalized medicine; endometrium; endometrial receptivity

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INTRODUCTION

Reproductive health is undoubtedly one of the factors that constitute human well-being. The problem of infertility affects a significant percentage of the world's population. It significantly reduces the quality of life and deepens the demographic crisis [1]. According to World Health Organization (WHO) data between 48 million couples and 186 million individuals suffer from infertility globally. A properly running implantation process is essential in achieving clinical pregnancy. For many years, conducted research focused on embryonic defects as the main causative factor of implantation failure. The available *in vitro* fertilization (IVF)-related procedures allow the genetic selection of aneuploid embryos, but despite that fact the pregnancy rates remain at constant levels in recent years. It is estimated that the cause of implantation failure may be related to the condition of the endometrium in 2/3 of cases [2]. Endometrial receptivity (ER) is defined as the tissue's

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ability to accept an embryo to attach and invade into the mucosa resulting in establishing an ongoing pregnancy [3]. For fertilization to take place, the embryo at the appropriate stage of development must appear in the uterine cavity at a strictly defined, individually differentiated time called window of implantation (WOI), in which numerous hormonally controlled cellular, molecular and biochemical processes determine the proper development of the endometrium [4, 5]. In natural cycle, this period occurs in mid-secretory phase, between days 6–10 after ovulation and is limited to approximately 48 hours [6]. The cause of endometrial receptivity disorders is believed to be disturbed expression of cytokines and endometrial surface proteins. Such alternations were also observed in several conditions such as endometriosis or chronic endometritis (CE). Moreover, both aforementioned diseases are associated with higher prevalence of infertility resulting in necessity of ART implementation compared with the general population. The establishment of ER assessment schemes and their implementation as a constant element in IVF protocols poses an opportunity to synchronize the transfer with the individual moment of maximal endometrial receptivity of a given patient. Such personalized embryo transfer (pET) is likely to increase the effectiveness of the procedure. The potential clinical benefits of endometrial assessment are numerous. It is believed that decreased or altered ER may be the cause of defective implantation, resulting in early pregnancy loss or further complications of the gestation as gestational hypertension or pre-eclampsia [7].

DESCRIPTION OF THE CURRENT STATE OF KNOWLEDGE

During the physiological menstrual cycle, the female endometrium cyclically proliferates, transformates and secrets under the influence of ovarian hormones. Biochemical and morphological changes, resulting in its thickening and a change in the pattern, lead to the normal receptivity [8]. The first attempts to assess the histological maturity of the endometrium and its correlation with the day of the onset of menstruation were made by Rock and Bartlett [9]. Their study showed 16% agreement of biopsy estimates with the actual occurrence of menstruation, 17% of patients had their periods later and 68% earlier than expected [9]. Based on these results, Noyes et al. [10] developed histological criteria on the ground of own studies, that have been the standard assessment of endometrial maturity for many years. With the introduction of new examination techniques and the emergence of requirements for an individual assessment of patients' endometrium in IVF procedures, the universal criteria for histological evaluation have become outdated and insufficient. Among others Murray et al. [11] showed that the histological dating of the endometrium is not sufficiently accurate and reliable to allow its clinical use in the management of patients with reproductive failure, as the variable duration of endometrial maturation applies to fertile women as well as to those with fertility disorders. Attention was paid to the individual variability and some systemic conditions that may reduce the credibility of obtained results.

Certain conditions may reduce ER and impair female fertility by shifting or narrowing the WOI. According to Zhao et al. [12] lower expression of Hypoxiainducible factor1α (HIF1α) in patients with polycystic ovary syndrome (PCOS) might be the cause of endometrial disfunction, due to proven in previous studies crucial role of this protein in establishment of proper ER during WOI. Endometriosis, as a chronic inflammatory disease is proved to be associated with an overexpression of endometrial B-cell lymphoma 6 (BCL6) [13] as well as Sirtuin 1 (SIRT1) [14]. Both appear to be biomarkers of this disease and are key factors involved in the pathogenesis of progesterone resistance. Furthermore, according to Almquist et al. [15] overexpression of BCL6 is associated with poor pregnancy rates in IVF cycles. Histone deacetylase 3 (HDAC3) is shown in the study of Jae-Wook Jeong and his team [16] to be downregulated in endometrium of women with endometriosis. It is a causative factor for increased fibrosis and disturbed hormonal impact on endometrium, that impairs its receptivity. This study also emphasizes the possibility that excessive fibrosis of various pathogenesis within the endometrium may translate into a decrease in ER and constitute one of the so far unexplored causes of infertility. Based on this discovery, a discussion about other potential causes of increased endometrial fibrosis has opened and sets trends in new research [17]. Described by Osiński et al. [18] significant increase in 3β-hydroxysteroid dehydrogenase type II (HSD3B2) and estrogen receptor 1 (ESR1) transcripts in follicular eutopic endometrium from infertile women with endometriosis might also have a negative impact on biological effect of E2 in endometrium, further impairing implantation mechanisms and the development of possible pregnancy. The inclusion of the indicated molecules in future tests may increase the prognostic value of ER assays. Also, chronic endometritis (CE), is characterised by an abnormal expression of cytokines and other molecules that regulate receptivity of the endometrium. The most sensitive way of diagnosing this pathology seems to be immunohistochemistry (IHC) for Syndecan-1 (CD138), a marker for plasmatic differentiation [19]. By examining seventy-five patients with CE and RIF Wang et al. [20] showed, that they have decreased endometrial TGF-β and IL-10 expression and increased IL-17 expression compared to patients with male factor infertility. The consequence is promotion of proinflammatory phenomena resulting in a defective ER.

Currently, wide range of methods to assess ER are available. From noninvasive ultrasound, through endometrial fluid analysis, search for biochemical markers or study of molecular markers in endometrial samples, to genomic studies based on endometrial biopsy. Ultrasonography is an easily accessible and universal tool enabling the assessment of the endometrium in the peri-implantation period. Evaluation of certain parameters in 3D power Doppler scans may add further benefits. In the study of Mercé et. al. [21] 80 infertile patients underwent their first IVF cycle. On the day of human chorionic gonadotropin (hCG) administration endometrial pattern, endometrial thickness, endometrial volume (EV), and PDA vascularization index (VI), flow index (FI), and vascularization flow index (VFI) were measured. Results showed that EV and 3D power Doppler indexes such as VI, FI and VFI are useful in assessing ER in IVF/ICSI and embryo cycles, as they were statistically significantly higher in the group of patients who became pregnant. However according to mentioned study there was no statistically significant difference in endometrial thickness and endometrial pattern between pregnant and nonpregnant groups. Similar data is provided by Rashidi et al. [22] in prospective study of 150 infertile patients undergoing IVF/ICSI. It concludes that the ultrasonographic characteristics of the endometrium, such as thickness and pattern on the day of hCG administration, were of no prognostic value in terms of the occurrence of pregnancy. A potentially reliable source of information on the status of the endometrium is endometrial fluid, the relatively non-invasive collection of which, with proven pregnancy safety in this cycle [23], is a chance to assess the ER. A comprehensive proteomic analysis of human endometrial fluid aspirate led to the successful identification of 803 different proteins in the International Protein Index (IPI) human database [24]. It may constitute the basis for further research to detect reliable ER markers, but nowadays no grounds for introducing any specific marker into clinical diagnostics are available [25]. As a summary of described methods serves a study of Li Wang and colleagues [26], conducted on 396 women, half of whom were diagnosed with unexplained infertility, and the rest were fertile controls. The blood flow, endometrial thickness and EV did not differentiate patients from both groups, unlike VI, FI and VFI which were much higher in fertile patients. Also, the levels of markers obtained from the uterine fluid of the patients, including integrin avb3, VEGF, TNF-a, and LIF levels were significantly higher in the control group. The best parameters for predicting ER in WOI was FI (AUC = 0.894, sensitivity 93.8%, and specificity 83.1%) and among biomarkers integrin avb3 had the best predictive value, (AUC = 0.921, sensitivity 96.7%, and specificity 89.5%) [26].

The previous researches proved the purposefulness of endometrial biopsy analyzes in terms of the presence of molecular biomarkers and their possible correlation with the histological picture. Prospective case control study carried out by Franasiak et al. [27] proved that the usage of leukemia inhibitor factor (LIF) combined with αvβ3 integrin as biomarkers of ER can be useful in predicting poor reproductive outcomes in both monitored natural and stimulated cycles. Decreased concentration of both molecules was observed in women with unexplained infertility. Despite this, insufficient convincing evidence from the studies on larger sample size implicates the lack of clinical tests based on molecular markers.

A breakthrough in the approach to ER assessment and personalization of IVF procedures by determining patient's individual WOI, was the presentation by Diaz-Gimeno et al. [28] of a brand-new diagnostic test — endometrial receptivity array (ERA). It is based on the evaluation of 238 selected genes expression in endometrial sample and can determine endometrial status of the patient by comparing obtained results with control samples. Using this method, it becomes possible to detect WOI shifts in a patient and to synchronize the embryo transfer (ET) with the presence of endometrium at the time of its maximal receptivity. This enhances the probability of proper implantation and is a step towards personalizing medical procedures in order to increase the effectiveness of embryo transfer. Another advantage of the ERA is the reproducibility of the results in the middle secretory phase in successive cycles or over long periods [29]. In randomized controlled trial conducted on 458 infertile patients undergoing IVF procedures, cumulative pregnancy rate was significantly higher in the pET guided by ERA testing (93.6%) compared with frozen ET (79.7%) and fresh embryo transfer groups (80.7%) [30]. Such results indicate the potential utility of pRT guided by ERA test at the first appointment.

A beREADY test based on the highly sensitive Targeted Allele Counting by sequencing (TACseq) methodology facilitates the ability to analyze the expression of 57 genes related to ER in endometrial sample [31]. All the genes are involved in endometrial growth, maturation and receptivity. Using robust rank aggregation analysis, a statistically significant meta-signature of 52 up-regulated and five down-regulated genes in mid-secretory vs 'pre-receptive' endometrium was identified [32]. The expression of among others membrane associated proteins, secreted enzymes, binding proteins, secreted immune response proteins, different enzymes, transcription factors is tested. A beREADY test provides 93% to 96% compliance with the ERA results and enables the classification of the patient's endometrium as pre-receptive, early-receptive, receptive, late-receptive or post-receptive [33]. As part of the result, the receptivity score, the

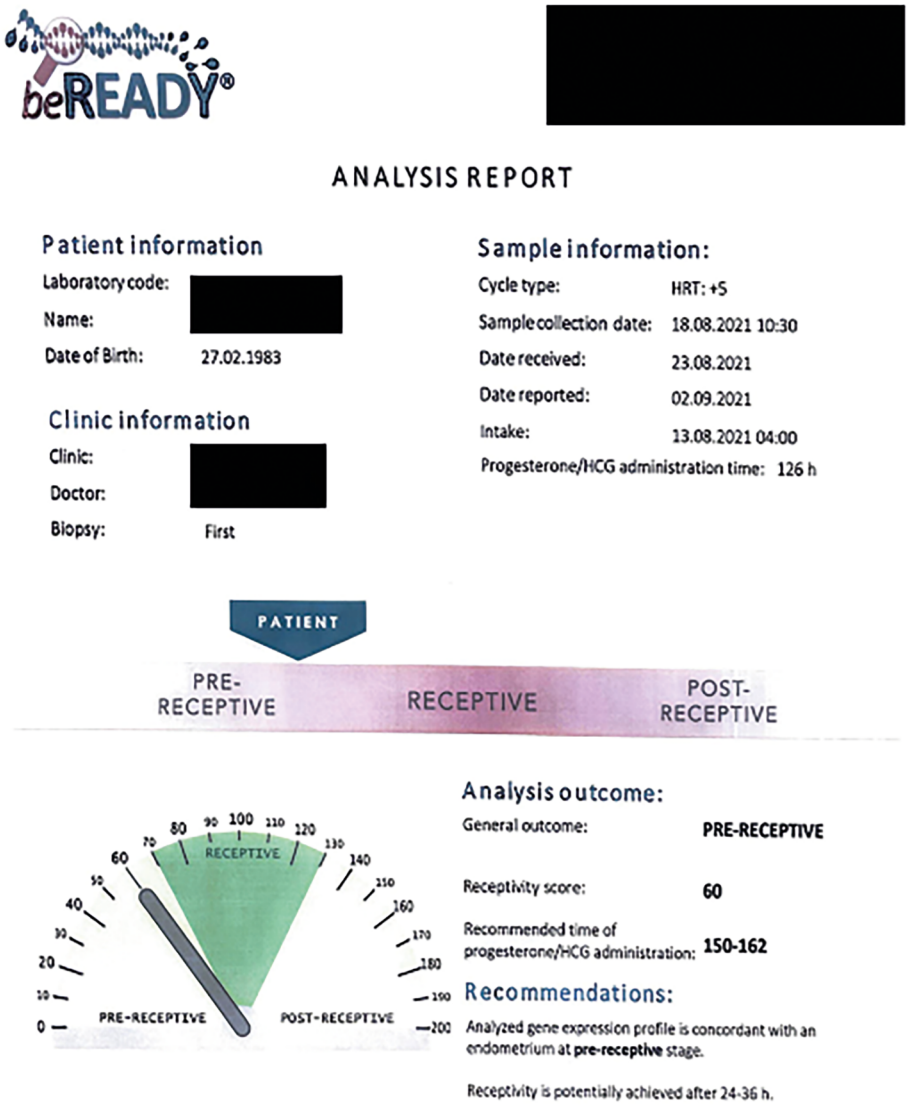

Figure 1. Exemplary Be-ready test result. Endometrium in a pre-receptive state; HCG — human chorionic gonadotropin

recommended time of progesterone administration and the estimated time of obtaining receptivity in the case of pre-receptive results are determined. Therefore, it is possible to adjust the transfer day to the receptive period (WOI) and maximize the chances of successful implantation just as in case of exemplary Be-ready test result presented at Figure 1.

Testing for BCL6 overexpression in endometrial samples has high positive value for diagnosing endometriosis and associated progesterone resistance [34]. Both of them may lead to decreased ER. Moreover, according to Likes et al. [35] patients with detected BCL6 overexpression might benefit from medical or surgical treatment before undergoing IVF procedure by achieving higher live birth rates. The study proves that women with higher level of BCL6 in endometrial sample treated by medical suppression and those undergoing laparoscopy for endometriosis had a significantly higher LBR, (5/10; 50%; 95% CI 23.7 to 76.3%) and (11/21; 52.4%; 95% CI 32.4 to 71.7), respectively, compared to controls (4/54; 7.4%; 95% CI 2.9 to 17.6).

CONCLUSIONS

A significant proportion of unsuccessful IVF procedures are due to missed embryo transfers. Implantation failure may be related to the condition of the endometrium in 2/3 of cases, what makes the assessment of ER potentially crucial in increasing the effectiveness of IVF. Reliable assessment of the endometrium could enable the embryo transfer personalization, contributing to the increase in the effectiveness

Table 1. Characteristics of papers included in the study

Author	Analysed ER assessment method	Nationality	Sample size	Exclusion criteria	Calculation	Results
Mercé et al.	Three dimensional ultrasonography and power Doppler angiography (3D US-PDA) Parameters: endometrialpattern, ET, EV, PDAVI, FI, VFI	Spain	80 infertile women, mean (± SD) age (34.5 ± 3.5) (range: 27 to 41 years)	Endometrialormiometral anomalies Congenitaluterine abnormalities	Chi-squaretest, Fisher's exact test Receiver operaing characteristic (ROC) curve	EV and theendometrial VI, FI, VFI — statistically significantly increased in the group of patients who became pregnant
Rashidi et al.	Ultrasonography: Endometrial pattern, ET	Iran	150 infertile patients The mean ± SD) age was 30.8 ± 5 years	History of uterine surgery, uterineanomalies, endometrial pathologies, hydrosalpinges, tubal factor in infertility, abnormal laparoscopicfindings	Chi-squaretest, Fisher's exact test Receiver operaing characteristic (ROC) curve	ET and endometrial pattern — no prognostic value intermsof the occurrence of pregnancy
Li Wang et al.	Detection of uterine fluid biomarkers [integrin avb3, vascular endothelialgrowthfactor (VEGF), tumor necrosis factor alpha (TNF-a), andleukemiainhibitory factor (LIF)] by enzyme-linked immunosorbent assay (ELISA) Three dimensional ultrasonography and power Doppler angiography (3D US-PDA)	China	392 women (196 infertile, 196 fertile)	Gynecological surgery, thyroid disease, pelvic inflammatory diseases,endometriosis	Chi-squaretest, Fisher's exact test Receiver operaing characteristic (ROC) curve	Blood flow of uterine artery and subendometrial region, ET, and EV did not differ between the two groups. The endometrial VI, FI, and VFI and the integ-rinavb3, VEGF, TNF-a, and LIF levels in uterine fluid were significantly higher in fertile women compared with unexplained infertile women ($p < 0.05$)
Franasiak et al.	Endometrial biopsy — immunohistochemistry(IHC) and messenger RNA by real time reverse transcriptase — polymerasechainreaction (PCR) (quantitative real-time reverse transcriptase — PCR)	USA	55 infertile women (1 year of unexplained infertility) 20 paid controls	PCOS, uterine fibroids Irregular menses Abnormal sperm parameters	Student's t-test using 95% confidence ($p < 0.05$) for significance, Fisher's exact test — comparisons of categorical data	Leukemia inhibitor factor (LIF) combined with αvβ3 integrin — biomarkers of ER, useful in predicting poor reproductive outcomes
Simón et al.	Endometrialbiopsy ERA test	Spain, Bulgaria, Turkey, Japan,Brasil, Belgium, Panama, Australia	458 infertile patients [pET guided by the ERA n = 148, frozen embryo transfer (FET) n = 154, fresh embryo transfer ET(n = 156]	Recurrent miscarriage, > 3 failed IVF cycles with good-quality embryos Transferred, severe male factor infertility	Chi-squared test, two-sided Fisher's exact test to compare the study groups Differences were estimated as relative risks with 95% CI	Statistically significant improvement in pregnancy, implantation and cumulative LB rates in pET compared to FET and ET

ET — embryo transfer; EV — endometrial volume; PDA — power doppler angiography; VI — PDA vascularization index; FI — flow index; VFI — vascularization flow index; SD — standard deviation; PCOS — polycystic ovary syndrome; pET — personalized embryo transfer; IVF — in vitro fertilization; LB — live births

of implantation and would lead to growth of pregnancy rates. Regarding to the cited research results presenting and evaluating the numerous available methods, it seems justified to propose a comprehensive assessment of the endometrium in order to guarantee patients the highest possible effectiveness of the IVF procedure (Tab. 1). Methods based on the analysis of the genes expression related to endometrial receptivity seem to be the most objective and clinically useful. There are many studies on the effectiveness of ERA test, however, there still remain a need to evaluate the beREADY test clinical utility in randomized controlled trials.

Patients with a history of RIF in IVF procedures, as well as patients with endometriosis, in whom the exact mechanism of infertility is presumably multifactorial and has not been concretely defined, seem to be a particularly interesting target groups for further research. The potential clinical benefits of endometrial assessment are numerous, as it is believed that decreased endometrial receptivity may also be the cause of defective implantation, resulting in early pregnancy loss, or incompletely correct implantation leading to the development of pre-eclampsia.

Article information and declarations

Conflict of interest

All authors declare no conflict of interest.

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VIA MEDICA

RECCOMENDATIONS

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Guidelines of the Polish Society of Gynecologists and Obstetricians on the obstetric care of women with obesity

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Guidelines of the Polish Society of Gynecologists and Obstetricians present the most up-to-date treatment and management recommendations, which may be modified and altered after detailed analysis of a specific clinical situation, which in turn might lead to future modifications and updates.

INTRODUCTION

Recent decades have witnessed an epidemic of obesity, which has become a global health concern. According to the World Health Organization (WHO), overweight or obese adults outnumber the population of underweight individuals. In 2016, almost 2 billion people over the age of 18 were overweight (40% — women and 39% — men), and over half a billion were obese (15% — women and 11% — men) [1]. Excess body mass indices increased dramatically over the last four decades, predominantly in the developed and developing countries. If the current trends persist, an estimated 2.7 billion people will have been overweight and 117 million will have been diagnosed with Class III obesity (formerly known as morbid obesity) by 2025 [2]. With the increasing prevalence of obesity among the general population, the number of reproductive-age (15–44 years) women with obesity reached 100 million [1]. According to the epidemiological data from Poland, in 2019 obese individuals comprised 23% of the population, and the number of obese reproductive-age women increased significantly between 2009 and 2019 — by 53% and 42% among 15–19 and 20–29-year-olds, respectively and by 27% among people in their forties [3].

Obesity in pregnancy is defined as a maternal body mass index (BMI) of ≥ 30 kg/m^2 in the first weeks of gestation. Based on the BMI values, three classes of obesity have been distinguished (Tab. 1). The main causes of excess body weight include poor eating habits, low physical activity, and some endocrine syndromes [polycystic ovary syndrome (PCOS), Cushing's syndrome, hypothyroidism].

Due to its high prevalence and harmful effects on the mother and the child, obesity in pregnancy has become one of the greatest challenges of obstetric care. Obese women face more difficulty conceiving and more often experience complications in pregnancy (Fig. 1). They are at a particularly high risk for developing hyperglycemia, gestational hypertension, preeclampsia, and venous thromboembolism. Also, the literature demonstrated increased risk for obstetric interventions, genital tract trauma, perinatal hemorrhage, and mortality [4–6]. Maternal obesity affects fetal health and is associated with higher incidence of fetal abnormalities, congenital malformations, and abnormal fetal growth, including hypotrophy and macrosomia. That, in turn, increases the risk for intrauterine fetal demise or neonatal complications [7, 8]. Sleep apnea in pregnant women with obesity constitutes

Table 1. Classes of obesity

Class I Obesity	Class II Obesity	Class IIII Obesity (morbid obesity)
BMI 30.0–34.9 kg/m^2	BMI 35.0–39.9 kg/m^2	BMI ≥ 40 kg/m^2

BMI — body mass index = weight [kg]/height^2 [m]

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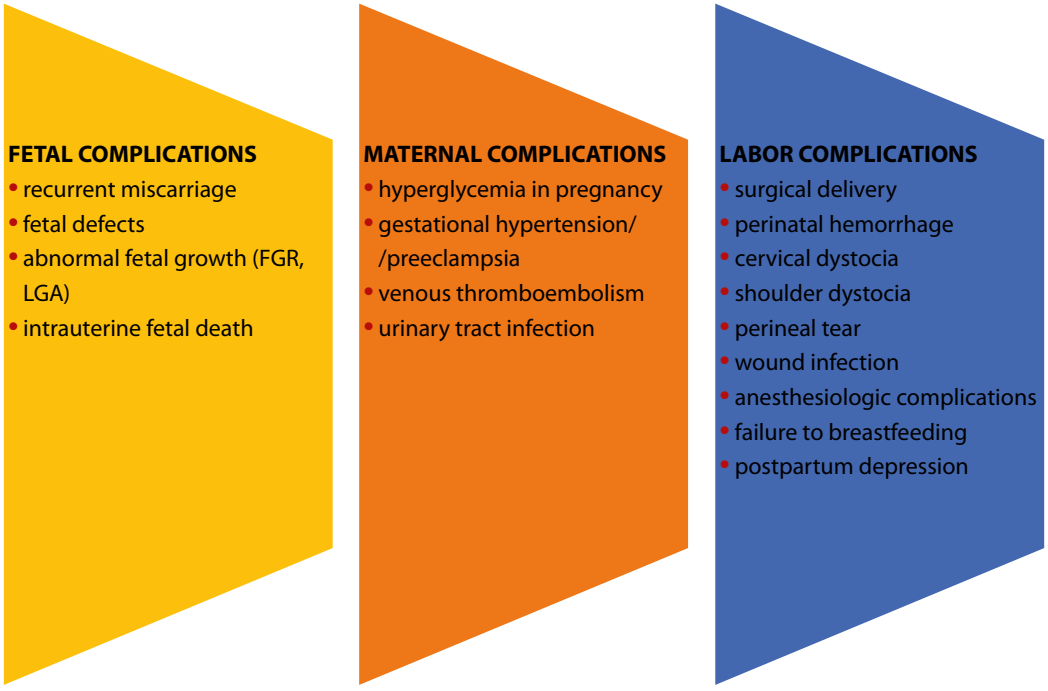

Figure 1. Complications in pregnancy among obese women; FGR —fetal growth restriction; LGA — large for gestational age

yet another negative prognostic factor for the obstetric outcome [9]. During the puerperium, obese women more often present with depression and problems with wound healing and/or breastfeeding [10, 11]. Moreover, excess body weight during pregnancy in the mother increases the risk for later obesity in the offspring [12].

The present guideline aimed to acquaint gynecologists and obstetricians with the most common problems as well as diagnostic-therapeutic management of pre- and post-conception care of women with obesity.

Recommendation

In light of a steadily growing number of reproductive-age women with obesity, all healthcare centers should be prepared, both in terms of knowledge and equipment, for providing care to obese mothers during pregnancy and labor. Only obese mothers with comorbidities and/or Class III — morbid obesity (BMI ≥ 40 kg/m^2) should be referred to a high level of care center (category D).

PRE-CONCEPTION CARE

Weight reduction is the primary therapeutic goal of pre-conception care of obese women. According to the literature, negative effects of excess weight on fertility and the incidence of complications in pregnancy are rarely addressed by physicians during the pre-conception period and infertility treatment [13, 14], **whereas decreased BMI, even by only one unit or a 10% body mass loss, may significantly increase the chances of conception and lower the risk for maternal and fetal complications [13, 14].** Therefore, it is vital to launch initiatives which will lead to lifestyle modifications, in particular those associated with eating habits and physical activity, among women with obesity. Alas, reviews of randomized trials found little, if any, evidence for successful non-pharmacological interventions in obese women [15, 16], probably due to the complexity of the etiopathogenesis of obesity, including the disturbed mechanism of central regulation of food intake. Also, the recommended low-caloric diets are associated with decelerated metabolic rate and increased the appetite, which contributes to ineffective weight reduction in the long run. Therefore, much attention has been paid to the importance of metabolism boosters and appetite suppressors in recent years. Also, normal intestinal flora, whose content depends on the diet, plays an essential role. Gut microbiota and physical activity affect the neuro-hormonal reward system, which is responsible for eating behaviors [17]. Women with obesity are more prone to food cravings for sweets, bread, fast-foods, and fatty foods [18]. Patients find it challenging to differentiate between the actual and the emotional hunger, and to stop eating once the hunger has been satiated. Hunger and satiety are regulated by a number of hormones excreted by the gastrointestinal system, *i.e.* ghrelin, glucagon-like peptide 1 (GLP-1), pancreatic peptide YY (PYY), cholecystokinin, insulin, and leptin, which is released by fat cells in the adipose tissue [17]. Obese individuals were found to present with higher fasting concentrations and impaired postprandial inhibition of ghrelin — an appetite-stimulating

hormone, as well as abnormal release of anorexigenic gastrointestinal peptides [17].

In light of the above, the role of methods which affect the activity of the gastrointestinal peptides has significantly increased as far as management of obesity is concerned. **Recent studies have demonstrated high effectiveness of incretins, drugs used to treat type 2 diabetes, in weight reduction** [19, 20]. Obese patients who received analogues of glucagon-like peptide 1 receptor agonists (GLP-1 RA) achieved a 6–8% body mass reduction in the course of one year [19]. Chronic medication is necessary to maintain this effect. So far, there have been no data on the safety of using GLP-1 RA drugs in pregnancy. Discontinuation of GLP-1 RA treatment is recommended if the patient attempts to conceive.

Bariatric surgeries have been used to treat Class II and III obesity for years. Typically, they help to achieve a long-term effect of up to even 20% reduction of the body mass. Apart from reducing stomach volume and ghrelin-releasing cells, these surgeries also stimulate the GLP-1 and PYY secretion. Women after bariatric surgeries are recommended to **postpone pregnancy for 12–24 months postoperatively, until the desired weight loss and stabilization are achieved,** and in order to lower the risk for macro- and microelement deficiency resulting from malabsorption. **Iron, folic acid, vitamin B and calcium** need to be supplemented in those women, if deficient. Shorter time interval between the surgery and conception increases the risk for prematurity, fetal hypotrophy, anemia, excess weight gain in pregnancy, and cesarean section [21].

The dumping syndrome, which usually occurs an hour after the consumption of simple carbohydrates, may be the consequence of decreased stomach volume in bariatric patients. Typical manifestations include lightheadedness, hot flashes, and tachycardia [21]. Therefore, it is recommended to avoid simple carbohydrate consumption and replace the oral glucose tolerance test (OGTT) with continuous glucose monitoring when diagnosing impaired carbohydrate tolerance.

Fertility disorders in women with obesity

Obese women are more likely to experience problems with conception, including the use of assisted reproductive techniques (ARTs), as compared to their non-obese peers [22]. Impaired function of the hypothalamus-pituitary-gonadal axis, low-quality oocytes, and decreased endometrial receptivity are the main causes of failure to achieve a pregnancy [22]. Higher concentrations of circulating insulin and ovarian overproduction of androgens are more often found in individuals with obesity. Enzymatic activity of excess adipose tissue contributes to aromatization of the androgens to the estrogens, which in turn, by reversible inhibition of the hypothalamus-pituitary axis, affect gonadotropin production and menstrual cycle disorders [22].

Hyperinsulinemia and insulin resistance play important roles in the pathogenesis of the polycystic ovary syndrome (PCOS). Management which aims at improving sensitivity to insulin increases the chances of spontaneous conception, also in ARTs, among obese women with PCOS. Inositol, which is insulin second messenger, and metformin are the first-line therapy [23, 24]. Also, recent years have brought attempts to use GLP-1 analogs in these patients [8]. **Metformin therapy in women with obesity lowers the risk for miscarriage during the periconception period, but it does not prevent other pregnancy-related complications and should not be continued after 12 weeks of gestation [25]**.

The effectiveness of ARTs decreases with increasing BMI values. Apart from the abovementioned mechanisms, it is also associated with poor quality embryos. In light of the above, and taking into consideration the high risk for complications, **women with Class II and III obesity should not be deemed eligible for *in vitro* fertilization procedures** [22].

Prevention of neural tube defects in the fetus

Numerous cohort studies demonstrated a positive correlation between class of obesity and the prevalence of neural tube defects (NTD) in the fetus [26, 27]. Insufficient maternal concentration of folic acid during fetal organogenesis in individuals with obesity is believed to be one of the main causes of NTD. Obese women are less likely to use supplements or consume foods with high folic content [26]. Metabolic disorders associated with obesity, including release of proinflammatory cytokines by adipose tissue, hyperinsulinemia, and hyperglycemia, are responsible for higher folic demand in the body. An imbalance in the normal gut microbiota in obese individuals also results in deficient levels of vitamin B12, a cofactor for the conversion of folates.

Folate and vitamin B12 supplementation seem to play a crucial role in preventing NTD in children born to obese mothers. Alas, the literature lacks reliable data about the effective dose of the folic acid. Various academic societies and associations recommend high daily doses (4–5 mg) of folic acid, which may cause a potentially neurotoxic accumulation in individuals with defective folate metabolism [26–28].

According to the Polish Society of Gynecologists and Obstetricians (PTGiP) guidelines, a **daily dose of 800 ug of folic acid, containing 400 ug of active folates,** is recommended in obese women who attempt to conceive, which is 2-fold higher as compared to the general population [29]. The experts emphasize that the dose needs to be tailored to the individual needs of women with BMI > 30 kg/m^2 by **measuring serum folic acid concentration after 4-6 weeks of**

supplementation [30]. If the concentration is < 28 nmol/L, an increased dose (max. 5 mg/day) is recommended until week 12 of gestation.

As far as NTD prophylaxis in children born to obese mothers is concerned, the role of myo-inositol should not be ignored. Folic acid supplementation does not prevent NTD in approximately 30% of the cases in the high-risk group [26]. Studies on small populations of women with history of infants born with spina bifida demonstrated the effectiveness of additional supplementation with **myo--inositol at a daily dose of 1000 mg** [31]. Lower concentrations of inositol were found in women who gave birth to spina bifida children. Supplementation with inositol preparations in pregnant women with obesity was also found to decrease the risk for gestational carbohydrate intolerance [31].

Recommended pre-conception diagnostics in women with obesity

Obesity, which is currently perceived as a chronic disease, affects the functioning of numerous systems and organs. During the pre-conception period, it is recommended to determine the efficiency of the cardiovascular system, and check for metabolic and endocrine disorders, which might increase the risk for maternal and neonatal complications. It is also necessary to take patient medication history to screen for possible teratogenic effects. The recommended diagnostic tests are presented in Table 2.

Pre-conception recommendations

1. Management of obese women with reproductive plans should include body mass reduction to improve fertility and lower the risk for pregnancy-related complications in the mother and the child (category B).
2. Pharmacotherapy for management of obesity should be discontinued during pregnancy (category D).
3. Pregnancy in women after bariatric surgeries should be delayed for 12–24 months after the optimal weight was achieved and stabilized (category B).
4. Folic acid supplementation at a daily dose of 800 ug, including 400 ug of active folates, is advised in obese women with reproductive plans. It is recommended to measure serum folic acid concentration after 4–6 weeks of supplementation and, if the level is < 28 nmol/L, to increase the dose to 5 mg/day, max. up to 12 weeks of gestation (category B).
5. Myo-inositol preparations should also be considered for pre-conception supplementation in women with obesity to lower insulin resistance and to prevent neural tube defects (category C).

Table 2. Recommended pre-conception diagnostic management in obese women

Condition	Test	Management
Gestational carbohydrate intolerance	OGTT (glycemic profile in patients after bariatric surgery) Fasting glycemia 100–126 mg/dL repeated (several times) HOMA fasting insulinemia (mU/L) × fasting glycemia (mmol/L)/22.5	Intensive treatment for carbohydrate intolerance HOMA > 2.5 — therapy implementation Diet, physical activity, myo-inositol supplementation, metformin, GLP-1 RA
Thyroid disorders	TSH in case of TSH > 2.5 mIU/mL Additional tests to measure FT4, FT3, aTPO, aTG	Depending on the test results, hormone replacement therapy is recommended, after a consultation with an endocrine specialist
Lipid disorders	Triglycerides Cholesterol fractions	Dietary modifications and physical activity are recommended if the levels are elevated; statin therapy needs to be stopped during the peri-conception period
Circulatory system disorders	Self-monitoring of the blood pressure and heart rate ECG Echocardiography	Cardiology consultation, if required; modification of hypotensive treatment with discontinuation of convertase inhibitors and angiotensin receptor inhibitors
Disorders of other systems	Transaminase Creatinine GFR general urine test	Specialist consultations, if required
Vitamin, macro- and micro-nutrient deficiency	CBC, ferritin, Folic acid Vitamin B12 Vitamin D	Supplementation for any deficiency Fetal NTD prophylaxis with folate supplementation (800 ug/day)

OGTT — oral glucose tolerance test; TSH — thyroid stimulating hormone; ECG — electrocardiogram; GFR —glomerular filtration rate, CBC —Complete Blood Count, NTD — neural tube defects

CARE DURING PREGNANCY

Pregnant women with obesity need to receive thorough and comprehensible information about the risk for complications and how to minimize it. Apart from the standard information given to all pregnant women, additional tips about nutrition and physical activity during pregnancy should be offered. In ambulatory and hospital care, special attention needs to be given to adequate training of the physicians and midwives. Also, healthcare centers need to be adequately equipped: blood pressure monitors with extra large cuffs, bariatric/obesity scales, extra large couches, wheelchairs, therapy (examination and treatment) chairs and operating tables, which are suitable for higher load capacity.

Monitoring of maternal weight gain

During the last months of pregnancy, maternal energy demand is only slightly (by 10%) elevated as compared to the pre-gestational values. Low weight gain in obese mothers decreases the risk for gestational diabetes, preeclampsia, cesarean delivery, and fetal macrosomia. **Maternal weight gain in women with obesity should not exceed 7 kg during the entire course of pregnancy [32].** A retrospective observational study demonstrated a lower risk for complications in mothers with Class III obesity (BMI > 40 kg/m^2), who lost weight during pregnancy, which is why weight reduction is recommended in that group of women [33]. However, the literature offers solid evidence that insufficient weight gain in pregnancy is often associated with fetal hypotrophy and preterm labor. In morbidly obese women, obstetric outcomes improved if the weight loss was 0.19 kg/day or 7.6 kg throughout the entire pregnancy [34]. A combination of diet and even moderate, but regular, physical activity is particularly effective in preventing excessive weight gain in pregnancy. Unlike in case of energy, maternal demand for vitamins and minerals/trace elements is significantly higher, so pregnant women should pay special attention to the quality of their food [35].

Dietary recommendations

A well-balanced and diversified diet is essential for maternal and fetal health, although it is important to bear in mind that the caloric demand in pregnancy increases by 250–300 calories/day as compared to the pre-pregnancy values. Regular meals not only contribute to maternal well-being, but also to optimal weight gain and fetal development. Recommendations for the quality and quantity of various nutrients in maternal diet are presented in Table 3.

Overweight and obese pregnant women should take special care to include vegetables, fruit, whole-grain products, low-fat milk as well as low-fat meat and fish products into their diet. Animal products should be consumed in moderation. Products with high content of saturated fats, sweets, and snacks which have high-energy but low-nutrient content should be consumed with caution or completely eliminated.

Table 3. Dietary recommendations for pregnant women

Fruit and vegatables	Cereal products	Proteins	Fats
Fruit and vegetables should be the base of all meals — source of vitamins, minerals, carbohydrates, and fiber **Daily recommended amount: 4–5* servings of vegetables** **Choose green vegetables, rich in folates and polyphenols, which stimulate the metabolic processes: kale, arugula, celery, parsley, lovage** **1–2* servings of fruit** **Choose fruits with lower content of sugar, preferably partially ripe. Fruits should be avoided in the evening due to high monosaccharide content and the possibility of fermentation, which leads to flatulence**	**Fiber** content is vital. It is necessary to choose whole-grain pastas, groats, bread, or brown rice It is advised to use earlier cooked and cooled rice, pasta, or groats in the salad for supper instead of bread. These products contain **resistant starch**, which slows down glucose absorption	It is advised to consume nutritious, easily digestible protein found in milk and fermented milk products, eggs, lean meat ,and fish **40% of the protein should be plant-based:** lentil, chickpeas, beans, peas, fava beans, soy	High-quality fats, with the best Omega-3:Omega-6 ratio, should be chosen: extra virgin olive oil, canola oil Other sources of good fats include avocados, seeds, and nuts **Consumption of saturated fats should be limited (< 10%) and trans isomers should be avoided.** Consumption of butter should be limited. Avocado or leguminous plant pastes may be used as bread spreads instead. **Omega 3 fatty acids, including DHA and EPA,** which are found in fatty fish, play an important role. Due to the risk for heavy metal contamination, it is advised to choose smaller fish: herrings, sardines, and mackerels
BEVERAGES: water 2–2.5 L/day, additionally: tea, coffee — weak infusions (up to 200 mg caffeine/day)			

*1 serving = 100 g; EPA — (omega 3-fatty acids (Eicosapentaeiconic acid)

Physical activity in pregnancy

Regular physical activity during pregnancy and after delivery is recommended to all pregnant women and parturients, unless contraindicated [36]. **At least 150 minutes of moderate-intensity aerobic physical activity per week as well as aerobic and muscle-strengthening exercises are advised**. Stretching exercises might also be beneficial. During pregnancy and postpartum, the patients should engage in physical activity, starting with light training and gradually increasing its intensity, and should also include pelvic floor exercises. Additionally, women who before pregnancy engaged in high-aerobic intensity physical activity on daily basis, or who were physically active, may continue to do so during pregnancy and puerperium, unless medically contraindicated [37].

The most recommended types of aerobic activity include walking, running, cycling (ideally on a stationary bike), and swimming. According to WHO, any kind of physical activity is better than no activity at all, and that engaging in physical activity is necessary to achieve optimal health results [36].

Tests recommended during pregnancy

Biochemical diagnostics in pregnant women with obesity should be carried out in accordance with the standards of care for pregnant women. The scope of testing should be extended (see: Tab. 2, with the exception of insulin resistance) if the diagnostic assessment of the systems in question had not been performed, or if the pregnancy was unintentional. Due to the high risk for carbohydrate intolerance, adequate diagnostic process and management are vital.

Diagnostics and management of gestational hyperglycemia

Pregnant women with obesity are at a higher risk for developing gestational hyperglycemia. Several-fold higher risk for that complication has been demonstrated in pregnant women with obesity as compared to their normal weight pregnant peers [38]. Timely diagnosis of hyperglycemia in obese pregnant patients and treatment (dietary recommendations, glycemia control, and insulin therapy, if necessary) significantly lower the risk for developing complications such as fetal macrosomia and shoulder dystocia [39].

The 75 g OGTT after earlier fasting glycemia test should be performed at the first antenatal visit in all pregnant women with obesity. If no glycemic abnormalities are found, the diagnostic test needs to be repeated between 24–28 weeks of gestation, or if the first symptoms indicative of diabetes have been observed. Hyperglycemia diagnosed first-time during pregnancy should be classified in accordance with the 2013 WHO recommendations:

Diabetes in pregnancy — if the general criteria for diagnosing diabetes are met, *i.e.*, fasting glycemia ≥ 7.0 mmol/L (126 mg/dL) or glycemia at 2 hours of the 75 g OGTT ≥ 11.1 mmol/L (200 mg/dL) or random glycemia ≥ 11.1 mmol/L (200 mg/dL) with accompanying clinical symptoms of glycemia. Gestational diabetes mellitus (GDM) — if at least one criterion from Table 4 is met.

Table 4. Diagnostic criteria for gestational diabetes based on the 75 g oral glucose tolerance test (OGTT) results according to 2010 International Association of Diabetes and Pregnancy Study Groups (IADPSG) and 2013 World Health Organization (WHO) reports

	Plasma glycemia	
	Mg/dL	Mmol/L
Fasting	**92–125**	**5.1–6.9**
After 1 hour	**≥ 180**	**≥ 10**
After 2 hours	**153–199**	**8.5–11.0**

If fasting glycemia of 126 mg/dL is observed twice, it is recommended to forgo the test and diagnose diabetes in pregnancy. If the OGTT result is normal, the test should be repeated between 24 and 28 weeks of gestation. In light of the fact that pregnant women with obesity are at a particularly high risk for hyperglycemia in pregnancy, even if the glucose test is negative, it is still advised to repeat it at 32 weeks of gestation in women with BMI of ≥ 35 kg/m^2. Regardless of gestational age, women with abnormal fasting or OGTT glycemia require specialist care. Routine management consists in self-monitoring of glycemic levels and low simple carbohydrate diet; if that fails it is necessary to implement insulin therapy.

Insulin is the only hypoglycemic drug recommended in pregnancy. According to the current state of knowledge, other medicines which decrease glycemia, oral or GLP-1 agonists and SGLT-2 inhibitors, are not recommended. **Metformin used in women with PCOS to treat insulin resistance or to induce ovulation should be stopped until the end of the first trimester** [40]. RCT (Randomized Clinical Trial) meta-analysis demonstrated that metformin treatment during pregnancy does not lower the risk for developing GDM in high-risk women with obesity, PCOS, or earlier diagnosis of insulin resistance [41]. If metformin is used in the first trimester, glycemia should be monitored by the patient, and the diagnostics for hyperglycemia needs to be performed at least one week after metformin was stopped. If self-monitoring reveals glycemic levels above the norm for pregnant patients during metformin therapy, further diagnostics is not necessary and hyperglycemia in pregnancy should be declared, and appropriate recommendations should be followed.

Hyperglycemia in pregnancy increases the risk for complications in the mother and the fetus, as well as further development of the child. Therefore, regardless of the type of

carbohydrate metabolism disorder, the goal of the therapy is to achieve glycemic levels which are normal for pregnant women.

According to the current state of knowledge, the target self-monitored glycemic values are as follows:

- fasting and before meals: 70–90 mg/dL (3.9–5.0 mmol/L);
- max. glycemia in the 1st hour since the meal has been started: < 140 mg/dL (< 7.8 mmol/L) or after 2 hours < 120 mg/dL (6.7 mmol/L);
- between 2.00 and 4.00 a.m.: 70–90 mg/dL (3.9––5.0 mmol/L).

Pregnant women should self-monitor their glycemia, after being instructed by a physician or a nurse with experience in caring for diabetic patients. The number of glucose concentration measurements and their timing should depend on the seriousness of the carbohydrate metabolism disorder and the treatment.

Continuous glucose monitoring (CGM) in pregnant women is also possible, in which case the patients should achieve > 90% of the target glycemic values, *i.e.*, 63–140 mg/dL (3.5–7.8 mmol/L). The management in case of diabetes or hyperglycemia should follow the PTGiP and PTD guidelines [42, 43].

Prenatal diagnostics

The recommended path for prenatal diagnostics in pregnant women with concomitant obesity does not differ much from a physiological pregnancy [44–46]. At least four ultrasound tests, at 11^{+0}–$13^{+6/7}$, 18–22, 28–32, and due date, are recommended.

As far as the technical aspects of ultrasound testing are concerned, it is advised to use lower-frequency ultrasounds as well as harmonic imaging, compound imaging and speckle reduction filters to improve visualization in obese patients [47]. A full bladder and the use of the so-called tissue windows, *i.e.* areas of lower cumulation of adipose tissue such as the umbilical region, the area above mons pubis, or the iliac fossa, offer another possibility to improve the quality of imaging in pregnant women with obesity [47].

First trimester ultrasound

The aim of the first screening test is to determine the gestational age, evaluate fetal anatomy, and assess the risk for the most common chromosomal aberrations and preeclampsia. So far, no relationship between maternal obesity and increased risk for fetal aneuploidy has been found. However, it has been confirmed that obesity significantly increases the rate of failed attempts to assess nuchal translucency and of inadequate imaging of the nasal bone in the first trimester. Also, maternal obesity significantly prolongs the duration of the test [48–50]. The recommended path for the prenatal diagnostics in the first trimester of pregnancy in obese women is presented in Figure 2 [51–55].

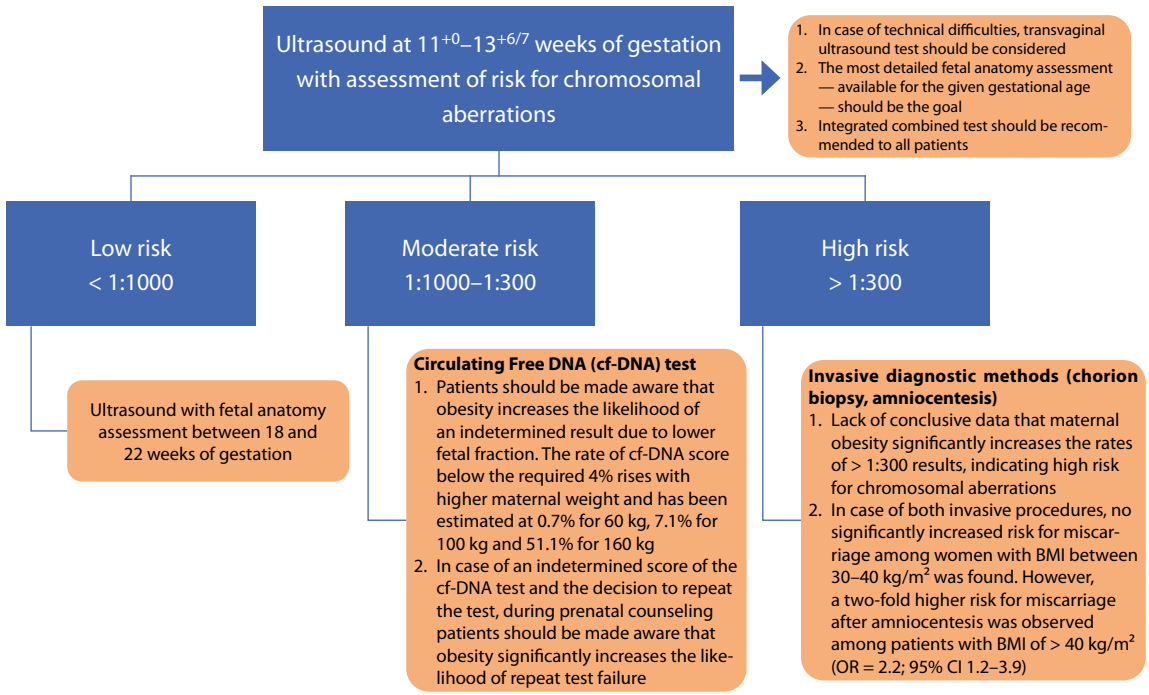

Figure 2. The recommended path for prenatal diagnostics in the first trimester of pregnancy in women with obesity [51–55]; BMI — body mass index; OR — odds ratio; CI — confidence interval

Table 5. The risk for structural defects in the fetuses born to mothers with obesity [56, 57]

Structural defect in the fetus	Odds ratio (OR) and confidence interval (CI)
Neural tube defects	OR = 1.87; 95% CI 1.62–2.15
Spina bifida	OR = 2.24; 95% CI 1.86–2.69
Cardiovascular defects	OR = 1.30; 95% CI 1.12–1.51
Split palate	OR = 1.23; 95% CI 1.03–1.47
Split lip and palate	OR = 1.20; 95% CI 1.03–1.40
Anorectal atresia	OR = 1.48; 95% CI 1.12–1.97
Hydrocephalus	OR = 1.68; 95% CI 1.19–2.36
Hemimelia	OR = 1.34; 95% CI 1.03–1.73
Umbilical hernia	OR = 1.63; 95% CI 1.07–2.47

Second trimester ultrasound

The aim of the ultrasound test performed between 18 and 22 weeks of gestation is a detailed evaluation of fetal anatomy. A link has been found between maternal obesity and an elevated risk for NTD, including spina bifida, cardiovascular defects, split palate, split lip and palate, anorectal atresia, hydrocephalus, hemimelia, and fetal hernia (Tab. 5). In contrast, pregnancy in obese women is significantly less often associated with gastroschisis [odds ratio (OR) = 0.17; 95% confidence interval (CI) 0.10–0.30] [56, 57].

According to the literature, maternal obesity significantly lowers the detection rate for fetal structural defects on second trimester ultrasound [50, 58]. In a retrospective cohort study, conducted among 11,135 singleton pregnancies, the detection rate for fetal malformations was 66% among patients with BMI of < 25 kg/m^2, but only 48% and 25%, respectively in women with Class I (BMI 30–34.9 kg/m^2) and Class III (BMI > 40 kg/m^2) obesity [58]. Another study found that complete evaluation of fetal anatomy in the second trimester of pregnancy was successfully performed in only 30% of patients with BMI of > 40 kg/m^2 [59].

Third trimester ultrasound

The main goal of fetal ultrasound at 28–32 weeks of gestation is reevaluation of fetal anatomy, combined with fetal growth assessment. **It is especially important in mothers with obesity due to a correlation between maternal excess weight and fetal macrosomia, as well as higher incidence of small for gestational age (SAGA) neonates (< 10 percentile) born to mothers after bariatric surgery [60, 61]**. As far as the additional late-third trimester ultrasound test (*i.e.*, between 34^{+0} and 36$^{+6/7}$weeks of gestation) is concerned, the findings of studies published so far have not validated the need for such a test [62–64]. When it comes to low birthweight fetuses, the sensitivity and the positive predictive values of ultrasound evaluation of the fetal weight at that stage of pregnancy are 8.1–32% and 58.5–100%, respectively, while for fetuses with birthweight of > 90 percentile the values are 38.6–87.1% and 30.2–77.1%, respectively [62–64]. The abovementioned percentile values are the reason why, in a group of mothers with obesity, a significant number of fetuses with birthweight of <10 percentile remain undiagnosed, whereas in case of excess fetal growth, approximately half of the readings are false positive. In light of the above, it is not recommended to perform an additional ultrasound test, with the evaluation of fetal weight, between 34^{+0} and 36$^{+6/7}$weeks of gestation, in women with isolated obesity. However, such a test should be considered in obese women with concomitant diabetes or hypertension, after bariatric surgery, and in cases when the 28–32 weeks ultrasound revealed fetal growth abnormality. **A relationship between maternal obesity and fetal growth abnormalities as well as shoulder dystocia is the reason why an ultrasound should be performed before elective labor induction and at term.**

HYPERTENSION IN PREGNANT WOMEN WITH OBESITY

Cardiovascular changes during pregnancy include, among others, volume overload. Also, obesity is additionally associated with increased circulating blood volume, stroke volume, systemic and pulmonary blood pressure, which may predispose the affected individual to hypertrophic cardiomyopathy and left ventricular hypertrophy. As far as function is concerned, left ventricular systolic as well as diastolic functions may be impaired, and in severe cases obesity may even lead to right ventricular heart failure [65].

Left ventricular hypertrophy, with signs of diastolic dysfunction and abnormal deformation indices, was observed in women with class II and III obesity as compared to normal weight pregnant women [66]. These changes constitute a cardiac response to excessive strain and may explain higher incidence of unfavorable pregnancy results associated with dysfunctions of the uteroplacental circulation, which is observed among pregnant women with obesity.

Abnormal maternal BMI constitutes an independent risk factor both, for preeclampsia and pregnancy-induced hypertension [5–7, 67]. In a review of 13 cohort studies, including almost 1.4 million pregnant women, the risk for preeclampsia doubled each time BMI increased by 5–7 kg/m^2, and that correlation persisted after individuals with chronic hypertension, diabetes or multiple pregnancy had been excluded [68]. Studies of patients after bariatric surgery indicate that loss of weight significantly lowers the risk for preeclampsia [69].

Obesity-related pathophysiological changes such as insulin resistance, hyperlipidemia, or elevated concentrations of pro-inflammatory and oxidative stress factors may

be responsible for higher incidence of preeclampsia, as these factors affect placental development and function. Adipose tissue is an important source of proinflammatory cytokines, which may promote the expansion of maternal anti-angiogenic factors engaged in the pathogenesis of preeclampsia [70, 71]. In patients with obesity, the course and the progression of hypertension and preeclampsia may be more dynamic and more severe. Therefore, the number and frequency of follow-up visits as well as laboratory tests should be adjusted accordingly. Regular blood pressure measurement, Blood Pressure Diary, and monitoring for symptoms of preeclampsia are essential. The rules for proper blood pressure measurement need to be followed. **In obese women, it is necessary to select adequate size of the cuff to fit the patient arm (the bladder length inside the cuff should be 80% and the width 40% of the patient's arm circumference) [72]**.

Obesity is a known risk factor for preeclampsia and prophylaxis is vital in case of such patients. Meta-analyses of numerous randomized studies demonstrated that administration of acetylsalicylic acid (ASA), initiated late in the first trimester, significantly lowers the risk for preeclampsia [73, 74]. The use of aspirin was associated with an 80% decrease in preeclampsia rates at < 34 weeks and a 63% reduction at < 37 weeks of gestation [75]. Due to a high number (even up to 30%) of pregnant women who are resistant to acetylsalicylic acid at a dose of < 100 mg, **ASA at the dose of 150 mg is advised in the evening** [72]. Preventive measures should be implemented in patients with at least one high-risk factor or two moderate-risk factors (Tab. 6). The use of the Fetal Medicine Foundation (FMF) algorithm, used to calculate individual risk for developing preeclampsia, might be considered, especially in patients with obesity. The screening tests combine medical history, biophysical methods, and maternal serum markers. In case of high risk for PE (preeclampsia), (cut-off > 1:150), prophylaxis using acetylsalicylic acid is recommended.

As the rates of unintended pregnancies remain high, every menstruating woman needs to be treated as potentially pregnant. It is advised to select adequate pharmacotherapy and **avoid using angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and mineralocorticoid receptor antagonists in reproductive-age women.** Due to limited availability of labetalol and nifedipine (special-request import), methyldopa remains the main medication for hypertensive pregnant women in Poland. It needs to be mentioned that a multi-drug combination therapy is often used to achieve satisfactory control of patient blood pressure (calcium channel blockers, alpha- and beta-blockers). The criteria for pharmacotherapy and target blood pressure values should be tailored to individual patients.

Table 6. Risk factors for preeclampsia

Risk factors for preeclampsia	
Moderate risk	**High risk**
Primipara	HT in previous pregnancy
Age > 40 years	Chronic renal diseases
Interpregnancy interval > 10 years	Systemic lupus erythematosus
Pre-pregnancy BMI > 35 kg/m^2	Antiphospholipid syndrome
History of PE in patient's mother	Type 1 or 2 diabetes
Multiple pregnancy	Chronic HT

HT —Hypertension, BMI — body mass index; PE — Preeclampsia

Thromboprophylaxis

Due to elevated risk for thrombotic complications, **pregnant women with Class III or lower obesity with concomitant risk factors (one high- or two low-risk), should receive thromboprophylaxis with the use of low-molecular-weight heparins, since the beginning of pregnancy and throughout the entire puerperium period, at a pre-pregnancy weight-dependent dose.** The risk should be individually assessed, documented, and discussed during the first antenatal visit, and also during the perinatal period. The risk factors for venous thromboembolism (VTE) in pregnancy are presented in Table 7.

Patients who present with more than two additional risk factors are advised to wear compression stockings. Also, the beneficial role of physical activity should not be overlooked. Early postpartum mobility is recommended in patients with obesity [76, 77].

Recommendations: care during pregnancy

1. Low gestational weight gain is advised in pregnant women with obesity in order to lower the risk for complications during pregnancy and delivery (category B).
2. Obese women should receive reliable information about balanced and diversified diet and the benefits of engaging in moderate-intensity physical activity during pregnancy (category B).
3. Pharmacotherapy with metformin for insulin resistance should not be continued beyond the first trimester of pregnancy (category A).
4. Women with more than one moderate risk factor (BMI ≥ 35 kg/m^2, primipara, maternal age > 40 years, family history of preeclampsia, multiple pregnancy) might benefit from receiving 150 mg/day of aspirin from week 12 to week 36 of gestation (category B).
5. Pregnant women with at least Class II or Class I obesity and additional risk factors should receive thromboprophylaxis since the very beginning of pregnancy, up until day 7 postpartum, with small-molecular-weight heparins, using pre-pregnancy weight-based dosing (category B).

Table 7. Risk factors for venous thromboembolism in pregnancy

High risk factors
Personal history of VTE
Concomitant diseases: malignancy in pregnancy, circulatory failure (NYHA III/IV), active SLE, exacerbation of inflammatory bowel diseases, active inflammatory polyarthritis (*e.g.*, rheumatoid arthritis), nephrotic syndrome > 3.5 g/day, type 1 diabetes with nephropathy, sickle cell anemia, intravenous drug use
High-risk thrombophilia: AT III deficiency, double heterozygous prothrombin gene mutation and factor V Leiden, homozygous factor V Leiden and prothrombin gene mutation, antiphospholipid syndrome
Surgical intervention during pregnancy
Hyperemesis gravidarum with the need of hospitalization
Ovarian hyperstimulation syndrome (only in the 1st trimester)
Morbid obesity
Low risk factors
Low-risk thrombophilia without personal history of VTE: heterozygous factor V Leiden, heterozygous prothrombin gene mutation, protein C deficiency, protein S deficiency.
First-line family history of VTE
Obesity
Large varicose veins (lower extremities, vagina, vulva)
Parity ≥ 3
Smoking
Age > 35 years
Preeclampsia in current pregnancy
Multiple pregnancy
Surgical delivery (cesarean section, VE, forceps, manual extraction of the placenta)
Postpartum hemorrhage (> 1000 mL), or blood transfusion, or Hb drop to 4 g/dL
Graviditas obsoleta in current pregnancy
In vitro fertilization (peri-conception)
Systemic infection with clinical symptoms and elevated inflammatory indices
Immobilization, dehydration
Postpartum proteinuria > 1.0 g/24 h

VTE — venous thromboembolism; NYHA —New York Heart Association, SLE —Systemic Lupus Erythromatosus; AT —Antithrombin, VE — Vacuum extractor

6. Obese women should be tested for carbohydrate intolerance as early as the first antenatal visit (category B).
7. At least four ultrasound tests at 11^{+0}–$13^{+6/7}$, 18–22, 28–3 weeks of gestation and at term are recommended in women with obesity (category A).
8. During each of the above-recommended ultrasound tests, obese pregnant women should be informed about the technical limitations associated with maternal excess weight and the resulting lower effectiveness of detecting fetal structural defects on ultrasound. An annotation about informing the patient, together with pre-pregnancy BMI values, should be included in the test report. A record of all elements whose imaging was either incomplete or impossible, together with recommendations for further management, should be included in the patient ultrasound report. In such cases, and if fetal structural defect is suspected, it is prudent to consider referring the patient to higher-level of care center (category C).

CARE DURING DELIVERY

The center which provides care to pregnant women with obesity should be equipped with proper size and load capacity transport chairs and trolleys, as well as operating tables. Pregnant women with BMI of ≥ 30 kg/m^2 should be informed about elevated risk for perinatal and postpartum complications, including perinatal injury, shoulder dystocia, perinatal hemorrhage, venous thromboembolism, problems with wound healing, and postoperative wound infection. Active management of the third stage of labor is advised in obese women due to higher risk for postpartum hemorrhage [78]. The mode of delivery should be selected to meet the individual needs of the woman, after consulting with the patient and presenting the benefits and risks associated with every mode of delivery.

Labor induction

Recent years have witnessed a notably higher rates of pregnant patients with obesity. Obesity has been demonstrated to be correlated with higher odds for post-term pregnancy [79]. Moreover, it also increases the duration of labor, especially in primiparas [80, 81]. It is believed that myometrial dysfunction might be the cause of higher risk for post-term pregnancy and prolonged labor in that population of patients [82]. As a result, weaker uterine reaction to oxytocin is found in obese women as compared to patients with normal BMI.

As far as induction of labor is concerned, there is no consensus which method — the Foley catheter vs vaginal administration of prostaglandins E2 (PGE2) — is more effective in patients with obesity. In one of the randomized studies, the Foley catheter was found to significantly shorten the duration of labor, but it did not lower the risk for cesarean section delivery [83]. However, Beckwith et al. [84], compared obese women with their normal weight peers and found that the effectiveness of labor induction using the Foley catheter was not significantly different between the groups, whereas prostaglandins were statistically significantly less effective in patients with obesity. However, the amount of data is insufficient to determine which method of labor induction might be more beneficial for women with obesity [85].

In a retrospective cohort study among patients from California (n = 74 725), labor induction in obese women at

term significantly decreased the risk for cesarean section delivery, without increasing the risk for perinatal complications as compared to conservative management [86]. In 2021, the results of the largest retrospective cohort study, which investigated whether labor induction in patients with isolated obesity at 39 weeks of gestation increased the risk for a cesarean section, were published [87]. A total of 1 184 058 pregnant patients with BMI ≥ 30 kg/m^2 were included in that study, which demonstrated that labor induction at 39 weeks of gestation in those patients significantly lowered the risk for cesarean section delivery, without increasing the risk for perinatal complications (OR: 95% CI 0.58–0.60), especially among multiparous women. In light of the abovementioned findings, labor induction at 39 weeks of gestation may be recommended to pregnant women with obesity.

Additionally, it needs to be emphasized that in cases with suspected fetal macrosomia, labor induction does not decrease the risk for a cesarean section, as was demonstrated in the 2016 systematic review of the Cochrane database. In such case, the patient should be informed about the risk associated with fetal macrosomia [88].

Anesthesia during delivery

The patients should receive information about the possibility of technical difficulties with regional anesthesia, and a higher risk for general anesthesia for cesarean delivery if regional anesthesia proves unsuccessful. The anesthesia care team should be informed in advance about hospitalization of obese pregnant patients.

Fetal monitoring during labor

Fetal monitoring during labor may present a challenge in obese patients due to excess adipose tissue within the abdominal cavity. The patients should be informed about potential difficulties with fetal monitoring using CTG. If external cardiotocography proves ineffective, internal CTG (if available) needs to be considered. It is also possible to use ultrasound imaging directly in the delivery room in order to monitor fetal well-being.

Cesarean section

Obesity is not an indication for cesarean section delivery. Subramaniam et al. [89], demonstrated that elective cesarean section in women with Class III obesity does not lower the risk for perinatal complications as compared to women with induced labor. The literature offers no consensus about the preferred technique for cesarean section incision (midline vs. transverse); the technique should be individually adjusted to the patient. However, some authors emphasize the advantage of a longitudinal midline incision, below the umbilicus, over the Pfannenstiel incision, claiming better visualization of the operative field and, in consequence, decreased operative time and blood loss [90]. Obesity constitutes a risk factor for poor postoperative wound healing. The available sources unequivocally recommend suture closure of the subcutaneous tissue if the thickness is > 2 cm to significantly lower the risk for impaired wound healing [91]. **Higher dose antibiotic prophylaxis should be considered in obese patients with BMI of ≥ 30 kg/m^2 and weight of ≥ 120 kg [92]**. Data on the effectiveness of using wound retractor or negative pressure wound therapy in obese patients remain limited [93, 94].

Vaginal birth after previous cesarean section (VBAC)

Pregnant women with obesity are at an elevated risk for failed vaginal birth after earlier cesarean delivery. In a retrospective cohort study, Durnwald et al., demonstrated that only 54.6% of obese women with history of cesarean section managed to deliver vaginally, as compared to 70.5% of women with normal BMI (p = 0.003) [95]. **Class III obesity is associated with higher risk for inter-delivery uterine rupture.** Additionally, emergency cesarean section in obese women is associated with higher risk for perioperative complications as compared to women with normal BMI. Therefore, obese patients with history of caesarean delivery should be informed about all benefits and complications before making the decision to deliver vaginally.

Recommendations: care during delivery

1. Active management of the third stage of labor is advised in obese women due to higher risk for postpartum hemorrhage (category A).
2. Pregnant women with obesity should receive antibiotic prophylaxis during the cesarean section due to higher risk for wound infection (category A).
3. In obese women, subcutaneous tissue layer should be sutured in order to lower the risk for wound infection and dehiscence (category A).

CARE DURING PUERPERIUM

During the puerperium, the risk for complications in obese women increases with BMI values. Obesity-related health problems may require careful patient monitoring during the short postnatal period, as well as support from the medical personnel throughout the entire puerperium. The most common complications result from patient immobility, poor wound healing after cesarean section incision and episiotomy, venous thromboembolism, and problems with breastfeeding. Higher-quality postnatal care may result in improved health outcomes in that group of patients.

Postnatal clinical surveillance

Morbid obesity is a well-known risk factor for respiratory failure [96]. Obesity constitutes a risk factor for hypoventilation and respiratory tract blockage while the patient emerges from anesthesia and during the postoperative time [97]. Due to elevated risk for obstructive sleep apnea and aspiration syndrome, based on patient health, it is prudent to monitor oxygen saturation and breath frequency, especially when narcotic medicines or tranquilizers have been administered [98]. Positioning the headrest at a 45-degree angle may also be beneficial. Temperature monitoring, to detect early signs of infection, and estimation of blood loss volume, to prevent postpartum hemorrhage, constitute essential elements of clinical surveillance.

Early mobility

Early mobility is vital to lower the risk for deep vein thrombosis, pulmonary embolism, respiratory complications, or bed sores, and adequate and effective postnatal analgesia may help to achieve that. Women after cesarean section should be mobilized early and encouraged to use physiotherapy. In that group of patients, it is important to monitor areas of the body where bed sores might develop and, if possible, encourage the woman to change position frequently [76].

Wound care

Regardless of the delivery mode and antibiotic prophylaxis, obese mothers are at a higher risk for infection and wound dehiscence. Infection may affect the following areas: vagina, endometrium, episiotomy, and the cesarean section wound [99, 100]. One in ten obese women present with poor wound healing after a cesarean section. The risk for that complication is approximately 1.5 higher as compared to normal weight women, and increases with BMI values [101, 102]. Extra caution is advised during the interval between day 6 and 12 after a cesarean section in women with BMI of ≥ 50 kg/m^2 [9, 103]. Episiotomy and the abdominal wound should be carefully monitored for signs of infection, hematomas, and wound dehiscence during hospitalization and after the patient is discharged.

Anti-Rh(D) prophylaxis

A few reports have suggested that intramuscular administration of the anti-D immunoglobulin at a standard dose may not be optimal and effective in Rh-D-negative mothers with BMI over 30 kg/m^2. At present, the available data are not sufficient to change immunoglobulin dosing. Immunoglobulin is administered by deep intramuscular injection, so appropriate injection site and length of the needle need to be selected for women with obesity [104].

Thromboprophylaxis

Obesity, pregnancy, puerperium, and cesarean section constitute independent risk factors for developing venous thromboembolism, especially in women with obesity. The risk for VTE increases 5-fold during pregnancy and 60-fold during the puerperium, especially during the first six weeks postpartum [105]. Other factors which increase the risk for VTE include surgical delivery (especially emergency delivery), and other demographic and medical factors (maternal age, smoking, infections, varicose veins, thrombophilia, and postpartum hemorrhage) [106].

Venous thromboembolism is one of the leading causes of maternal morbidity and mortality, especially during the postpartum period [107]. The risk for venous thromboembolism increases with BMI values [108]. Compression stockings and antithrombotic prophylaxis should be considered for all obese women with risk factors for VTE. Pharmacological thromboprophylaxis, dosing and duration of therapy should be individually adjusted.

Antithrombotic prophylaxis should be implemented in all women with Class III obesity (BMI > 40 kg/m^2), regardless of the mode of delivery [109]. Routine antithrombotic prophylaxis is not indicated in patients with Class I and II obesity after vaginal delivery [110]. Proper hydration is necessary and early mobility should be encouraged. While making the decision to start antithrombotic prophylaxis, it is necessary to take into account individual risk factors other than BMI. Low-molecular-weight or unfractionated heparins should be used and the dose should be adjusted to patient weight, not BMI [111]. Early mobility is advised in patients after cesarean section delivery. Patients who experience problems with mobility should be offered a chance to work with a physiotherapist.

Antithrombotic prophylaxis should be considered in all patients with Class I and II obesity after a cesarean section delivery, especially those with additional (one high or two low) risk factors (Tab. 7) [102]. The literature offers no conclusive evidence to support routine dosing and duration of antithrombotic prophylaxis in that population of women. Dosing and duration of the treatment should be individually adjusted, based on the calculated risk. It is advised to continue the antithrombotic prophylaxis at least until the patient has regained full mobility [110].

In patients with BMI of ≥ 30 kg/m^2 and at least two other risk factors, compression stockings for 7 days are advised, apart from low-molecular-weight heparins. Heparin therapy needs to be continued throughout the entire duration of the puerperium, *i.e.* 6 weeks, in women who received antithrombotic prophylaxis during pregnancy [109].

Lactation and breastfeeding

Problems with breastfeeding, delayed and shortened breastfeeding are observed among women with

obesity [112–114]. A Danish cohort study found a link between a BMI index and early cessation of breastfeeding - higher BMI correlated with higher incidence of breastfeeding cessation [115]. Patient constitution may affect breastfeeding in case of obese women. Larger breasts may make it challenging to position the infant comfortably for breastfeeding. Postpartum shifts of fluids may cause breast edema, flat nipples, and difficulty latching [116, 117]. Delayed lactogenesis may be responsible for failure to attempt breastfeeding [118].

Complications during pregnancy and delivery are more often reported among pregnant women with high BMI as compared to normal weight women. Diabetes and caesarean sections are statistically significantly more often observed in that group of women, while their neonates are more often hospitalized at an intensive care unit. In such circumstances, the child is separated from the mother, which is yet another reason why breastfeeding is delayed and stopped [7, 119–121].

Other puerperium-related complications

Women with BMI of > 30 kg/m^2 are more likely to experience postpartum depression, which may also result in maternal unwillingness to breastfeed the child [122]. In accordance with the Ministry of Health directive of 16 August, 2018, about the standards of perinatal care, postnatal assessment of maternal emotional condition, including the risk for postpartum depression, should be performed up to 8 weeks after delivery [123]. The assessment should be performed by a Primary Health Care midwife during the postnatal home visits.

Higher risk for postpartum anemia may also affect the care of a newborn and breastfeeding [124]. Therefore, routine screening for postpartum anemia seems justified in that group of patients.

Lactation support during hospitalization and after the patient is discharged should be considered in order for the obese mothers to start and continue breastfeeding. Women with obesity should be encouraged to breastfeed. It is necessary to emphasize the benefits of breastfeeding both, for the mother and the child, especially since lack of neonatal breastfeeding is yet another, apart from maternal obesity, risk factor for obesity in the offspring.

Recommendations: care during puerperium

1. Early postpartum mobility should be encouraged among obese women to lower the risk for venous thromboembolism (category B).
2. Thromboprophylaxis needs to be implemented in all women with BMI of ≥ 40 kg/m^2 postpartum, regardless of the delivery mode (category D).
3. Preoperative thromboprophylaxis (the dose needs to be adjusted to patient BMI) is advised in all obese women after cesarean section delivery due to higher risk for venous thromboembolism (category C).
4. Screening for postpartum depression and anxiety is recommended as obesity constitutes a risk factor for both these conditions (category B).
5. Women with obesity should have access to a lactation consultant and receive lactation support after delivery (category D).

LONG-TERM RECOMMENDATIONS

Excess weight gain in pregnancy constitutes a significant risk factor for maintaining excessive weight after delivery, which elevates the risk for metabolic disorders and overweight or obesity in the subsequent pregnancies. All women should be made aware that weight reduction between pregnancies is associated with significantly lowered risk for intrauterine fetal demise, hypertension-related complications, and fetal macrosomia. Weight reduction increases the chances for a successful vaginal delivery after cesarean section (VBAC) [125–127]. It has been demonstrated that interpregnancy weight loss in obese women lowers the risk for LGA infant. The literature presents no evidence for elevated risk of SGA infant as long as maternal weight loss did not exceed 8 BMI units [128]. **All obese women should receive advice about dietary approaches to weight management and be encouraged to engage in regular physical activity in order to decrease their weight, and as prophylaxis for diseases associated with the metabolic syndrome [129].** Women who were diagnosed with gestational diabetes should undergo OGTT testing at 6–12 weeks postpartum [130].

Children born to obese mothers present with more fatty tissue as compared to infants born to normal weight mothers. Also, the metabolic syndrome [131] and childhood obesity [132, 133] are more often observed in children born to obese mothers. In a study from Scandinavia, a relationship between higher maternal BMI and elevated risk for asthma in the children was demonstrated [134]. Maternal obesity in pregnancy may be associated with behavioral disorders, attention deficits, hyperactivity, and symptoms related to autism in the offspring [8].

Birth control

Contraceptive counselling is especially important among women with obesity. Safe and effective contraception is vital, as it prevents unintended pregnancy and the risk for pregnancy-related complications is significantly elevated in that group of women, especially in patients with concomitant diseases [135–137].

Obstetric care of obese women — summary
Guidelines of the Polish Society of Gynecologists and Obstetricians on the obstetric care of women with obesity
In light of a steadily growing number of reproductive-age women with obesity, all healthcare centers should be prepared, both in terms of knowledge and equipment, for providing care to obese mothers during pregnancy and labor. Only obese mothers with comorbidities and/or Class III — morbid obesity (BMI ≥ 40 kg/m^2) should be referred to a high level of care center (category D)
Recommendations — pre-conception care
1. Management of obese women with reproductive plans should include body mass reduction to improve fertility and lower the risk for pregnancy-related complications in the mother and the child (category B)
2. Pharmacotherapy for management of obesity should be discontinued during pregnancy (category D)
3. Pregnancy in women after bariatric surgeries should be delayed for 12–24 months after the optimal weight was achieved and stabilized (category B)
4. Folic acid supplementation at a daily dose of 800 ug, including 400 ug of active folates, is advised in obese women with reproductive plans. It is recommended to measure serum folic acid concentration after 4–6 weeks of supplementation and, if the level is < 28 nmol/L, to increase the dose to 5 mg/day, max. up to 12 weeks of gestation (category B)
5. Myo-inositol preparations should also be considered for pre-conception supplementation in women with obesity to lower insulin resistance and to prevent neural tube defects (category C)
Recommendations — care during pregnancy
1. Low gestational weight gain is advised in pregnant women with obesity in order to lower the risk for complications during pregnancy and delivery (category B)
2. Obese women should receive reliable information about balanced and diversified diet and the benefits of engaging in moderate-intensity physical activity during pregnancy (category B)
3. Pharmacotherapy with metformin for insulin resistance should not be continued beyond the first trimester of pregnancy (category A)
4. Women with more than one moderate risk factor (BMI ≥ 35 kg/m^2, primipara, maternal age > 40 years, family history of preeclampsia, multiple pregnancy) might benefit from receiving 150 mg/day of aspirin from week 12 to week 36 of gestation (category B)
5. Pregnant women with at least Class II or Class I obesity and additional risk factors should receive thromboprophylaxis since the very beginning of pregnancy, up until day 7 postpartum, with small-molecular-weight heparins, using pre-pregnancy weight-based dosing (category B)
6. Obese women should be tested for carbohydrate intolerance as early as the first antenatal visit (category B)
7. At least four ultrasound tests at 11^{+0}–$13^{+6/7}$, 18–22, 28–3 weeks of gestation and at term are recommended in women with obesity (category A)
8. During each of the recommended ultrasound tests, obese pregnant women should be informed about the technical limitations associated with maternal excess weight and the resulting lower effectiveness of detecting fetal structural defects on ultrasound. An annotation about informing the patient, together with pre-pregnancy BMI values, should be included in the test report. A record of all elements whose imaging was either incomplete or impossible, together with recommendations for further management, should be included in the patient ultrasound report. In such cases, and if fetal structural defect is suspected, it is prudent to consider referring the patient to higher-level of care center (category C)
Recommendations — care during delivery
1. Active management of the third stage of labor is advised in obese women due to higher risk for postpartum hemorrhage (category A)
2. Pregnant women with obesity should receive antibiotic prophylaxis during cesarean section due to higher risk for wound infection (category A)
3. In obese women, subcutaneous tissue layer should be sutured in order to lower the risk for wound infection and dehiscence (category A)
Recommendations — care during puerperium
1. Early postpartum mobility should be encouraged among obese women to lower the risk for venous thromboembolism (category B)
2. Thromboprophylaxis needs to be implemented in all women with BMI of ≥ 40 kg/m^2 postpartum, regardless of the delivery mode (category D)
3. Preoperative thromboprophylaxis, at a dose adjusted to patient BMI, is advised in all obese women after cesarean section delivery due to higher risk for venous thromboembolism (category C)
4. Screening for postpartum depression and anxiety is recommended as obesity constitutes a risk factor for both these conditions (category B)
5. Women with obesity should have access to a lactation consultant and receive lactation support after delivery (category D)
Long-term recommendations
1. After the delivery, women with obesity should receive nutrition advice and be encouraged to engage in regular physical activity; they should also consider pharmacotherapy or surgical therapy, to reduce their weight and lower the number of complications in the subsequent pregnancy, and prophylaxis for metabolic syndrome-related diseases (category B)
2. Women with obesity should be informed about potentially lower effectiveness of contraceptives in their weight group (category D)

BMI — body mass index

Obesity may alter both, the pharmacokinetics and the pharmacodynamics of oral contraceptives. Peak levels of the contraceptive hormones are lower in women with obesity as compared to their normal weight peers. The effectiveness of oral contraceptives and transdermal patches may be limited due to lower serum concentrations of a given preparation, which results in insufficient levels of hormones to maintain the contraceptive effect. These women should be informed about potentially lower effectiveness of the abovementioned methods [138–140].

Intrauterine devices (IUDS), which contain copper and levonorgestrel (LNG), proved to be highly effective in obese women, and are the method of choice for those patients as far as hormonal contraception is concerned. The half-life of levonorgestrel is prolonged in obese women, and levonorgestrel levels plateau later in normal weight women. Contraceptives have been demonstrated to inhibit ovulation and to effectively prevent pregnancy in most women with obesity. However, they may be associated with a higher failure rate as obesity significantly affects pharmacokinetics [140]. Due to a 2- or 3-fold higher risk for venous thromboembolism, it is always advised to choose a preparation with the lowest available ethinylestradiol content (20–30 µg of ethinylestradiol) when considering hormonal contraceptives for women with obesity [136, 137].

A limited number of reports have indicated that the use of combined contraceptives in women with obesity is not associated with an elevated risk for acute myocardial infarction or stroke, as compared to obese women who do not use such preparations.

Contraceptives containing estrogens should be considered after a thorough analysis of the additional risk factors for VTE, and should not be administered earlier than 4–6 weeks postpartum [141–143]. An etonogestrel implant seems to be effective, irrespective of body weight, although some sources suggest that its pharmacokinetics may be altered in obese individuals.

The use of oral contraceptives, progestogen implants, and intrauterine devices is not correlated with weight gain. Medroxyprogesterone acetate (MPA) is believed to be safe for women with obesity, but caution is advised since MPA has the highest pro-thrombotic activity among the available progestogens [138, 139, 144]. Nevertheless, a link between weight gain and the possibility of menstruation disorders has been reported.

Long-term recommendations

1. After delivery, women with obesity should receive nutrition advice and be encouraged to engage in regular physical activity. Also, they should consider pharmacotherapy or surgical therapy, to reduce their weight and lower the number of complications in the subsequent pregnancy, and prophylaxis for metabolic syndrome-related diseases (category B).
2. Women with obesity should be informed about potentially lower effectiveness of contraceptives in their weight group (category D).

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Data availability statement

All data are available in supplemented literature.

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Conflict of interest

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Supplementary material

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CLINICAL VIGNETTE

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Large left heart ventricle — difficulties in recognizing the Aorto-left ventricular tunnel (ALVT)

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INTRODUCTION

Aorto-left ventricular tunnel (ALVT) is an extremely rare congenital cardiac malformation, accounting for 0.03% to 0.46% of all congenital heart diseases. Since its first description as a congenital lesion in 1963, fewer than 300 cases of this heart defect have been reported in the English literature. Aorto-left ventricular tunnel creates an abnormal connection between the lumen of the left ventricle and the aorta, although less frequently, it may involve the aorta and the right ventricle. The incidence of ALVT is twice as high in boys compared to girls. Despite ongoing research, the embryological pathomechanism underlying ALVT remains elusive. However, it appears to be associated with abnormal development of the endocardial processes responsible for dividing the common trunk into the aorta and pulmonary trunk [1, 2].

CLINICAL CASE

A 26-year-old primigravida woman with no comorbidities was referred for fetal echocardiography due to suspected ventricular septal defect and tricuspid valve regurgitation detected during a second-trimester prenatal examination. At the 30th week of gestation, fetal echocardiography at a reference center revealed a disproportion between the heart chambers and a slightly enlarged heart size (heart area to chest area (HA/CA) ratio of 0.36). The left ventricle was hypertrophic and enlarged, with hypokinesis (fractional shortening of the left ventricle — 23%) and a hyperechoic endocardium. The Aortic Valve (AoV) had a Z-Score of 1.2, with normal valve leaflets and flow. The 3-vessel view (3VV) showed an enlarged main pulmonary artery and transverse aortic arch, with Z-Scores of 3.2 and 3.1, respectively. An abnormal connection between the Aorta and the Left Ventricle, characteristic of an Aorto-left ventricular tunnel (ALVT) with retrograde flow approximating 2 m/s, was also identified. The fetal middle cerebral arterial (MCA) peak systolic velocity (PSV) was 75 cm/s, likely secondary to the heart defect. Ultrasound findings are presented in Figures 1A through 1E.

The fetus exhibited supraventricular extrasystoles that did not necessitate pharmacological intervention. Despite the cardiac abnormalities, the fetus maintained efficient circulation, scoring 7 points on the cardiovascular score, with deductions for heart size and function. Standard ultrasound care was provided. At the 39th week of gestation, the patient underwent a caesarean section for obstetric reasons and delivered a son, who received an Apgar score of 8/8. On the first day of life, the newborn was transferred to the Department of Cardiac Surgery, Heart Transplantation, and Mechanical Circulation Support in Children in Zabrze, Poland. The defect was confirmed postnatally, and cardiac surgery was performed on the second day of life (Fig. 1F). The tunnel was closed in two layers, and the fistula's wall was secured with a pull-on suture and a continuous suture, preserving a connection between the aorta and the right coronary artery. The tunnel wall and aortotomy were sutured. Postoperative ultrasound confirmed complete closure of the tunnel. Echocardiography revealed slight regurgitation through the aortic valve after the procedure. The patient was started on standard treatment to improve left ventricular function, including captopril, carvedilol, and spironolactone. Currently, the boy is under outpatient follow-up, demonstrating normal development and no cardiovascular symptoms.

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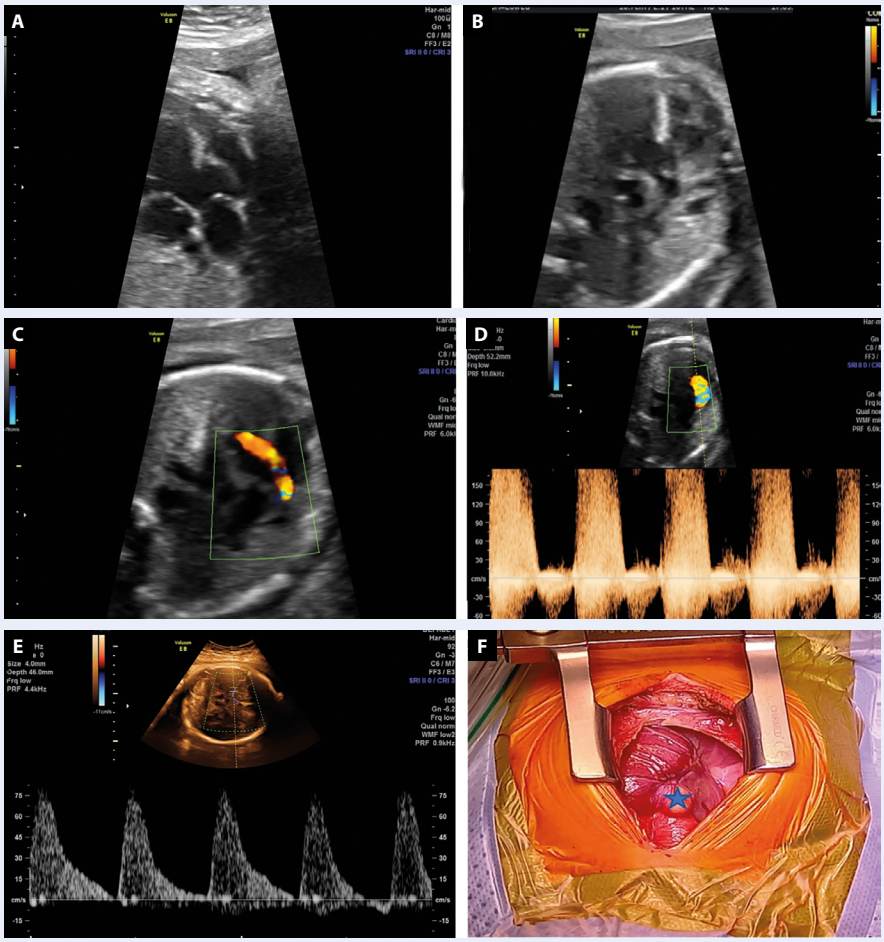

Figure 1. A. Aorto-left ventricular tunnel (ALVT) in gray scale; **B.** AVLT in gray scale; **C.** AVLT in color doppler; **D.** Retrograde flow in AVLT; **E.** Middle cerebral arterial (MCA) peak systolic velocity (PSV); **F.** Visualization AVLT during operation

DISCUSSION

The embryological pathomechanism underlying ALVT remains elusive, but it is thought to be associated with abnormal development of the endocardial processes involved in the division of the common trunk into the aorta and pulmonary trunk. According to the literature, ALVT can be diagnosed after the 18th week of gestation. A dilated left ventricle with increased wall thickness may raise suspicion of ALVT. Approximately 45% of ALVT cases are associated with other heart defects, often coexisting with aortic valve abnormalities [1, 3, 4]. The 'cockade sign', indicative of a tunnel adjacent to the aortic annulus, can aid in making a correct diagnosis [5]. An elevated peak systolic velocity in the fetal middle cerebral artery may also assist in diagnosis. Differential diagnoses include aortic regurgitation, Valsalva fistula, common arterial trunk (CAT), aortopulmonary window, and coronary ventricular fistula. The standard cardiac repair procedure involves closing the tunnel with a patch inserted through an aortotomy [6]. Perioperative mortality is low, and prompt intervention is recommended. Surgical correction is indicated not only to prevent heart failure but also to halt the progression of aortic valve damage. Patients who undergo surgery within the first six months of life have the best-documented normalization of left ventricular size and function [2, 7–9].

Article information and declarations

Ethics statement

None.

Conflict of interest

The authors declare no conflict of interest.

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A biologically "old" breast cancer subtype in a very young woman: a plea of ignorance

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CASE REPORT

A 27-year-old patient, a physician by profession, attended a gynecologist for a first ultrasound (US) breast examination. Until then, she had no oncological burdens or chronic diseases, had been using hormonal contraception (HC) for 11 years, and had not performed breast self-examination. On US examination, an oval lesion in the right breast (6:30), assessed according to the Breast Imaging Reporting and Data System (BIRADS) score 3, was detected and a follow-up examination was recommended for 6 months' time. At the follow-up examination after 7 months, the lesion was classified as BIRADS-US-4b (Fig. 1). The patient was referred for a core-needle biopsy. Histopathological examination of a specimen revealed invasive breast carcinoma of no special type G-1 [World Health Organization (WHO): invasive breast carcinoma of no special type (NST)] luminal A phenotype (cT1c, cN0, cMx). Then an magnetic resonance imaging was performed which confirmed the presence of a 16 mm lesion suspected for malignancy. At the patient's request, breast-conserving surgery with adjuvant radiotherapy was rejected, and instead, the surgical treatment was subcutaneous mastectomy with reconstruction (Fig. 2). Hormone therapy with tamoxifen and goserelin was then commenced.

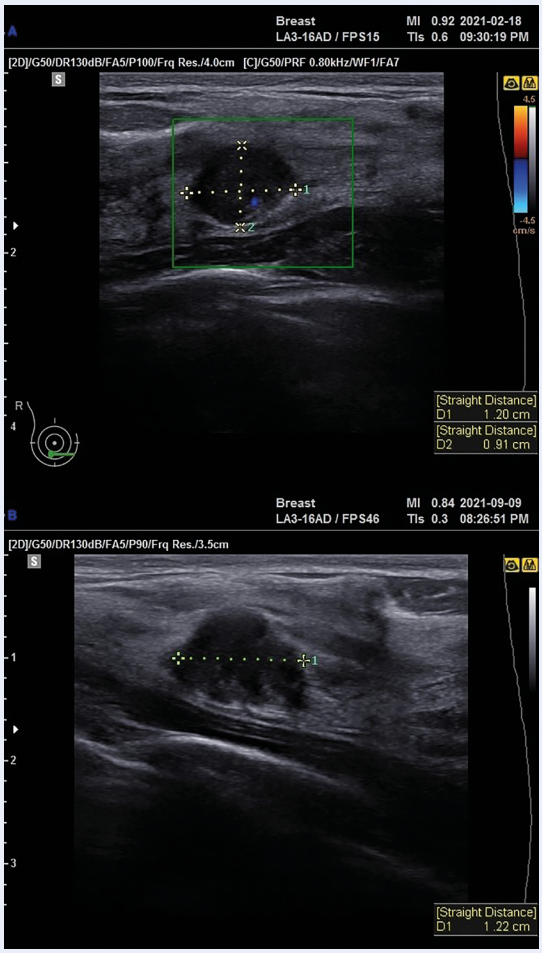

Figure 1. Ultrasound images (B-mode presentation) of the same lesion; **A.** Relatively well delineated lesion, BI-RADS 3; **B.** Slightly ill-defined margins, BI-RADS-4b

DISCUSSION

It is significant that in women < 35 years of age with breast cancer (BC), we observe a higher frequency of BC with triple negative subtypes and significantly fewer luminal A subtypes compared to older premenopausal and postmenopausal women [1]. After sequencing 70 genes, including *BRCA 1/2*, we found no mutations that could predispose our patient to BC at a young

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age. Analysis of additional, known risk factors for BC, *i.e.*, age, family history, body mass index, physical activity, smoking, pregnancy, and breastfeeding, revealed no significantly increased risk of BC. The protective effects on the occurrence of luminal BC of a woman's number of births and a young age at first birth do not include HER2-negative subtypes, which suggests that this risk may be mainly influenced by hormonal mechanisms related to sex hormones [2]. Considering that the patient in our study is nulliparous, the potential influence of taking HC must be discussed. Currently, there is no unequivocal correlation between the use of HC and an increased risk of BC. In some population studies, a slight increase in risk was observed, mainly during the first 5 years of contraceptive use [3]. For the first year, the patient took a combined oral pill, and for the remainder, a intrauterine device containing 19.5 mg of levonorgestrel. According to the Polish Society of Gynecologists and Obstetricians guidelines, an OB&GYN specialist should perform a breast examination before starting HC, and then repeat the examination annually. It is worth noting that these recommendations do not specify the breast examination type that should be undertaken (by default, this is clinical breast examination). The low sensitivity of breast palpation is widely known, so that cannot be recommended as a screening test. Our patient may have been more willing to keep the breast if the lesion had been detected several years earlier and had been a few millimeters in size, preserving, among other things, the possibility of breastfeeding and further prevention of BC [4]. However, in cases of young women, early detection is more likely to be diagnosed with US than mammography. In addition, it should be noted that the BC may not have been luminal A and may have been more aggressive in behavior. Indeed, the patient also decided to remove and reconstruct the other breast. US examination at the age of 16 and further regular examinations could protect the patient from this "favorable" course of BC in our patient.

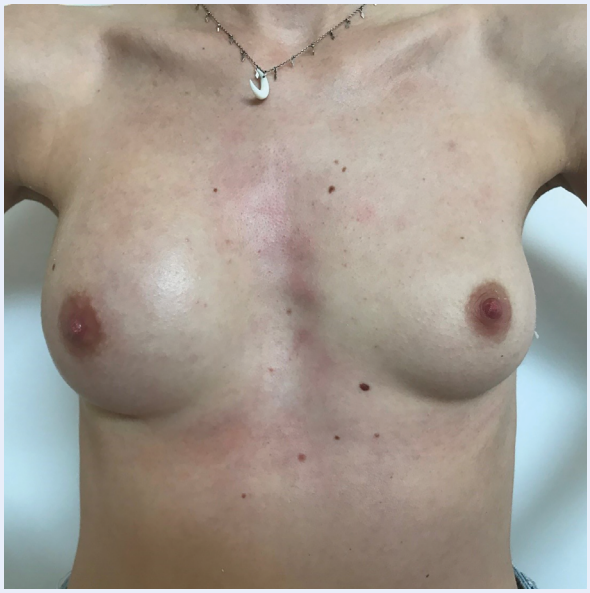

Figure 2. 27-year-old patient after subcutaneous mastectomy with reconstruction of the right breast due to breast cancer

CONCLUSIONS

The development of optimal strategies for the prevention of breast diseases in young and very young women is important, because these women are currently excluded from secondary prevention through screening tests [5]. The age at which breast US should be examined either non-systemically (*i.e.*, by gynecologists during routine visits) or systemically requires further analysis. In the light of the noticeably worsening statistics of BC incidence among young women, it seems reasonable for gynecologists to eliminate the practice of excluding these group of patients from BC screenings as though they are not at risk of developing BC. This is especially so, given that gynecological US check-ups are performed much more regularly, and yet the risk of gynecological cancers is significantly lower than that of BC.

Article information and declarations

Conflict of interest

All authors declare no conflict of interest.

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Postpartum hemorrhage as a result of acquired uterine arteriovenous fistula post-vaginal delivery

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Uterine arteriovenous fistulas (UAVF) occur more frequently and generally result from trauma, such as curettage or pelvic surgery. UAVF is life-threatening, as patients can suffer from profuse bleeding. Most reported cases are acquired as a secondary outcome to cesarean delivery but rarely as a result of vaginal delivery.

A 24-year-old woman gave birth to a healthy 3.11 kg full-term baby via spontaneous vaginal delivery at our obstetrics inpatient department. Her prenatal course had been uneventful, without underlying coagulation defects, medical diseases, or drug exposures. She only had a previous history of spontaneous abortion treated with dilation and evacuation. The ultrasonography revealed that the placenta was lodged in the anterior wall of the uterus, about 31 mm thick, grade III maturity (Fig. 1A). Eventually, the entire placenta ejected itself nine minutes after the baby was delivered without complications and manual exploration. Through visual estimation, she lost about 400 mL of blood during delivery and the post-delivery procedure. However, the patient returned on postpartum day 12 and complained of a hemorrhage gushing rapidly from the uterus. Two massive vaginal bleedings had occurred three days before her admission and resulted in a total blood loss of about 500 mL. Hemorrhaging aside, the patient reported no abdominal pain or anything else. She was hemodynamically stable when she arrived and denied experiencing abdominal pain and dizziness. We noted disseminated intravenous coagulopathy, as laboratory data showed severe anaemia (hemoglobin: 6.5 g/dL). As a result, the patient was supplemented aggressively with intravenous fluids and massive blood components.

Subsequently, she underwent conventional ultrasonography, which revealed that the non-echo structure of the uterus' anterior wall close to the endometrium was 2.99 × 1.67 cm and had ill-defined edges (Fig. 1B). Color Doppler flow imaging exposed a distorted and expanded blood flow signal: dilated, tortuous vessels were visible on the anterior and left sides of the uterus. Pulsed wave ultrasound showed a turbulent spectrum and venous blood flow at the peak of the systole. Uterine and pelvic blood flow exhibited high velocity (78.5 cm/s) and low resistance (0.29) (Fig. 1C). Our patient, who was hemodynamically stable during the first week in the hospital, was administered oral ferrous sulfate. Her platelet count and coagulation profile were normal. Yet the patient reported sudden "gushes" of bright red blood in her vagina on postpartum day 22. The visual estimated

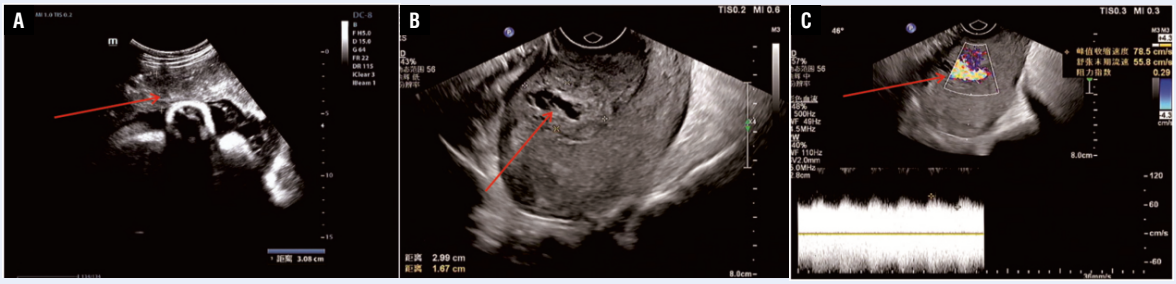

Figure 1A. B-ultrasonography revealed the placenta lodged of the uterus (red arrow); **B.** Transvaginal sonography image of the uterus a low-echoic cystic lesions (red arrow); **C.** Color-flow Doppler revealed a mosaic pattern of blood flow (red arrow)

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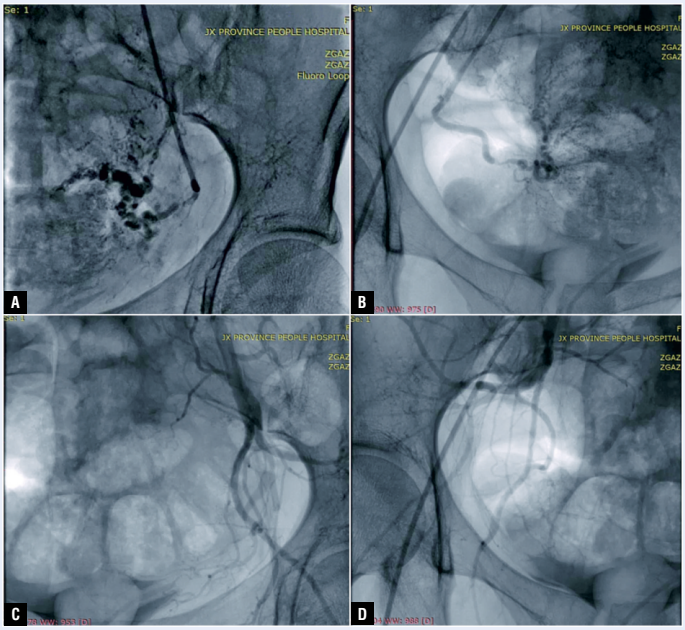

Figure 2. The dilated uterine artery and tortuous arteriovenous net seen during the UAE (uterine artery embolization). Angiography before embolization of the left **(A)** and right **(B)** uterine arteries. Angiography after embolization of the left **(C)** and right **(D)** uterine arteries

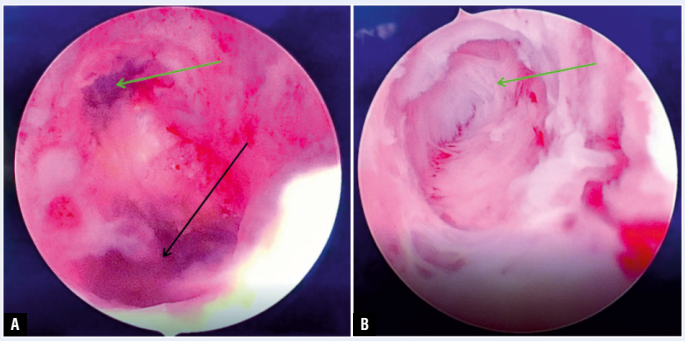

Figure 3. Hysteroscopic image of a false cavity in the uterus. The green arrows point prominent a false cavity in the uterus

blood loss was 400 mL. The vaginal bleeding gradually ceased eventually. However, she suffered from an abrupt and profuse vaginal hemorrhage in the uterine cavity again two days later. Her estimated blood loss this time was 800 mL, and her hemoglobin levels dropped from 10.9 to 6.0 g/dl. She was hemodynamically unstable, and a physical examination showed she was drowsy and hypotensive (88/56 mmHg), with signs of cyanosis in her extremities. She denied abdominal pain but reported dizziness. Laboratory data revealed severe anemia (hemoglobin: 6.5 g/dL) and abnormal coagulation tests. The patient continued to be given oxytocin and prostaglandin to control hemorrhage in postpartum uterine atony, but she failed to respond to treatment.

Her family requested that a uterine-preserving procedure be conducted if possible. Hence, Pelvic Digital subtraction arteriography was promptly performed, disproving the earlier suspicion of a typical UAVF lesion over the left uterine artery. The arterial phase during arteriography showed dilatation of uterine arteries to accommodate high-volume shunting through the uterus. Uterine artery embolization of the bilateral uterine arteries was immediately carried out with microspheres for embolization (Fig. 2).

The woman's follow-up ultrasound images were reviewed and displayed intrauterine residue. However, on hysteroscopic inspection of the uterine cavity, a false cavity in the uterus was discovered in the anterior wall of the uterus (Fig. 3). The anterior wall of the false cavity was situated above the normal intrauterine entrance (Fig. 3A). Observed was a long and narrow lacuna, surrounded by musculo-fibrous tissues, no intimal tissue covering the walls, and no fallopian tube opening (Fig. 3B).

The importance of combinedly reviewing blood loss estimate and laboratory data post birth requires more attention. Timely spectral ultrasonography of the uterus should be considered necessary post-delivery.

Article information and declarations

Conflict of interest

All authors declare no conflict of interest.

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