Edited since 1922

POLISH GYNECOLOGY

GINEKOLOGIA POLSKA

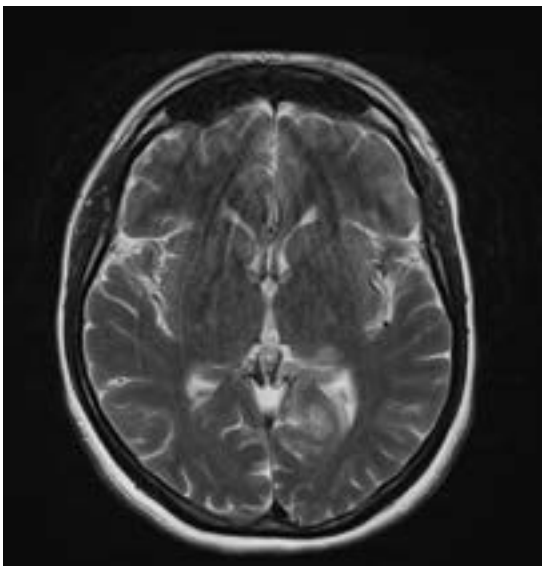
no **2**/vol **96**/**2025**

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

IF: **1.2**, MNiSW: **40**

GINEKOLOGIA POLSKA 2025, VOL 96, NO 2, PAGES 81–160

ORIGINAL PAPERS



ISSN 0017–0011
e-ISSN 2543–6767

VIA MEDICA

THE KOSCIUSZKO FOUNDATION

The 2025 Janczewski Award

For over two decades, the Kościuszko Foundation has been awarding the Bohdan and Zygmunt Janczewski Prize to Polish authors of the most outstanding scientific articles in the field of clinical medicine.

In this edition, the prize amounts to **$15,000**.

The award was established in 2004 by the renowned andrologist Zygmunt Janczewski, a professor at the former Medical Academy in Warsaw. It is granted every two years to a Polish physician permanently residing in Poland.

The competition will consider articles published in international medical journals in English within the last two years (2023–2024) preceding the award year. Applications will be accepted until May 15, 2025.

The award regulations and application form are available at: https://kfpoland.org

Apply today!

warsaw@thekf.org

https://kfpoland.org

POLISH GYNECOLOGY

GINEKOLOGIA POLSKA

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

ISSN 0017–0011
e-ISSN 2543–6767

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

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

Indexed in: Arianta, CrossRef, CNKI (China National Knowledge Index), DOAJ, EBSCO, Google Scholar, Index Copernicus, MEDLINE, Polish Minsitry of Science and Higher Education, Polish Medical Library (GBL), Polish Scientific Bibliography (PBN), Polindex, Proquest, ROAD, Science Citation Index Expanded, Scopus, Ulrich's Periodicals Directory.

Advertising. For details on media opportunities within this journal please contact the advertising sales department,
73 Świętokrzyska St., 80–180 Gdańsk, Poland, phone: (+48 58) 320 94 94, e-mail: dsk@viamedica.pl

Subscription for 2025. Printed institutional subscription — 12 issues for 2138.00 PLN. Printed individual subscription — 12 issues for 1069.00 PLN. More details at: https://journals.viamedica.pl/ginekologia_polska/user/subscriptions

Manuscripts should be submitted using online submission system only.

Editorial policies and author guidelines are published on journal website: www.journals.viamedica.pl/ginekologia_polska

Legal note: www.journals.viamedica.pl/ginekologia_polska/about/legalNote

24-1959.002.001

POLISH GYNECOLOGY

GINEKOLOGIA POLSKA

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

CONTENTS

VIA MEDICA

CLINICAL VIGNETTES

VIA MEDICA

ORIGINAL PAPER / GYNECOLOGY

Ginekologia Polska
2025, vol. 96, no. 2, 81–86

ISSN 0017–0011, e-ISSN 2543–6767

DOI: 10.5603/gpl.100294

Traditional vs novel out-of-office method for collecting cytology and HPV DNA — a comparative study

Marcin Januszewski[1], Laura M. Ziuzia-Januszewska[2], Andrzej Durczynski[1], Jacek Holubka[1], Bogdan Siwek[3], Zofia Siwek[3], Zbigniew Derdziuk[3], Waldemar Wierzba[1], Artur J. Jakimiuk[1]

[1]Department of Gynecology, Oncological Gynecology and Reproduction, National Medical Institute of the Ministry of Interior and Administration, Warsaw, Poland

[2]Department of Otolaryngology, National Medical Institute of the Ministry of Interior and Administration, Warsaw, Poland

[3]Ambulatorium Sp. z o.o., Bialogard, Poland

ABSTRACT

Objectives: The integration of high-risk human papillomavirus (HPV) detection into cervical cancer screening in Poland aims to improve early detection, yet challenges in coverage and adherence persist. Innovative approaches, like sampling for HPV testing and cytology outside medical settings, have been proposed. This study assesses the feasibility and agreement of results between traditional and novel sampling methods.

Material and methods: A cohort of 50 women aged 25–74 underwent HPV DNA and liquid-based cytology sampling both in-office using standard method and outside the medical setting by trained personnel. Samples were analyzed for HPV DNA using real-time PCR and cytology according to the Bethesda system.

Results: Cytology and HPV DNA positivity rates showed substantial agreement between methods, with almost perfect agreement for high-risk HPV types. Visual assessment of the cervix was successfully conducted in all cases. Preliminary results suggest remote sampling for HPV DNA and cytology is a viable alternative to traditional methods, with the effectiveness in detecting HPV and cytological abnormalities comparable to this reported in literature, offering potential benefits for individuals with mobility limitations or logistical barriers to attending medical appointments.

Conclusions: The study highlights the potential role of remote sampling for HPV DNA and cytology in enhancing cervical cancer screening accessibility and adherence. Implementation of such methods could improve coverage, particularly among underserved populations. Further research is needed to validate and optimize these approaches for broader clinical use.

Keywords: HPV testing; cervical cancer; immobilized patients; screening test

Ginekologia Polska 2025; 96, 2: 81–86

INTRODUCTION

The latest techniques for detecting high-risk human papillomavirus (HPV) have been incorporated into primary cervical cancer screening under the Polish National Health Fund in 2022 [1] and are the preferred regimen for primary screening for high-risk types of HPV (HR-HPV) infection among women aged 25 to 74, with testing recommended every five years. If the HPV test is positive, it is recommended to perform a Pap smear, which should be performed on the same sample if possible, or reflex cytology to avoid recitations and encourage adherence to screening [1]. This is in line with the European response to WHO call for cervical cancer elimination and includes cervical cancer screening coverage of 70% of women within the specified age range, using a clinically validated test for HR-HPV in the last five years [2]. The WHO call also pointed out the uniqueness of the challenges related to the SARS-CoV2 pandemic, including the necessity for European women to have access to self-sampling kits for HR-HPV, especially during the pandemic [2].

Corresponding author:
Artur J. Jakimiuk
Department of Gynecology, Oncological Gynecology and Reproduction, National Medical Institute of the Ministry of Interior and Administration, 137 Wołoska St., 02–507 Warsaw, Poland
e-mail: jakimiuk@yahoo.com

Reccieved: 22.04.2024 Accepted: 1.05.2024 Early publication date: 26.08.2024

Polish data for 2020 on publicly funded secondary prevention is highly alarming – only 11.31% of the planned female population was covered by screening [3]. Data on cervical cancer screening outside of public funding are unknown.

In nations with structured screening initiatives, most new cases of cervical cancer are detected in women who have either never been screened or have a limited screening history [4, 5].

A way to ensure both clinical credibility and acceptance among women who have not yet undergone sufficient screening may be to obtain specimens for HPV analysis and cytology testing through patient self-sampling or sampling by medical personnel outside the office [6]

Self-sampling, *i.e.*, the independent collection of vaginal material by the patient using a dedicated brush, has been recommended as a tool in the screening of HPV-dependent cervical cancer. This recommendation applies to cases in which it is necessary to maintain social distance associated with the risk of SARS-CoV-2 infection, which in extreme cases may lead to the abandonment of screening [7–9]. Due to the lack of sufficiently validated HR-HPV14 tests for the self-sampling on the Polish market, in the case of any positive HPV result obtained by this method, it is necessary to confirm it using validated HR-HPV molecular test of the material collected from the patient's cervix onto a liquid medium, which requires contact with medical personnel [10]. In this case, a targeted cervical smear should be taken, which should be combined with a visual assessment of the cervix, vagina and vulva to detect gross abnormalities on their surface. Indeed, combining HPV-DNA testing with cytology and visual examination can significantly speed up the diagnostic and treatment process in some patients excluded from basic screening. The above one-step screening algorithm may be used in high-risk patients with disabilities, including those having difficulty with an examination on a gynecological chair or in nursing homes or retirement homes, often deprived of routine screening.

MATERIAL AND METHODS

Methods

Aim of the study

The aim of the study was to assess the implementation of a new method of collecting cytology and HPV DNA outside the medical office by medical personnel and to evaluate the degree of agreement between the results of cytological and HPV DNA testing obtained by medical personnel with the new method outside the medical office compared to the traditional sampling.

Study group

The research was conducted at the Outpatient Clinic of Gynecology, Oncological Gynecology and Reproduction Department, at the National Medical Institute in Warsaw, Poland, between October 9, 2023 and November 15, 2023. The study cohort comprises 50 patients. The research was approved by the Bioethics Committee by the Regional Chamber of Physicians in Koszalin (decision number 2/2023) and is consistent with the provisions of the Declaration of Helsinki. All the patients signed informed written consent prior to the participation.

Inclusion and exclusion criteria

Inclusion criteria were women aged 25 to 74 years who signed informed consent. Exclusion criteria were pregnancy and the first six weeks of the postpartum period, absence of a cervix (previous hysterectomy or trachelectomy), vaginal bleeding, and use of medications including creams or vaginal douches in the last 48 hours before sample collection.

Study design

From each patient, samples for HR HPV DNA analysis and liquid-alkaline cytology were collected on the same day on the bed using a vaginal swab collection kit outside the medical office by medical personnel and on the gynecological examination chair using the standard Cusco speculum.

Set and laboratory assays

The set includes (Fig. 1):

- camera,
- anoscope,
- cytological brush,
- liquid medium for virological and cytological examinations,
- sterile gloves,
- sterile swab,
- sterile gauze, and
- ampoule with physiological saline.

Technique of collecting samples on a patient's bed using a vaginal swab kit by medical personnel outside the medical office

- First step: insertion of the speculum with the obturator into the vagina, resting the collar of the speculum on the labia without using force (Fig. 2).
- Second step: removal of the obturator and insertion of a brush into the speculum (Fig. 3).
- Third step: inserting the camera above the brush into the speculum (Fig. 4).
- Fourth step: performing four rotations of the brush under visual control, collecting the smear from the external opening of the cervical canal and the surface of the vaginal part of the cervix, and then taking a photograph of the visible area (Fig. 5).

Figure 1. Set for novel sampling method

Figure 2. First step of ovel sampling method

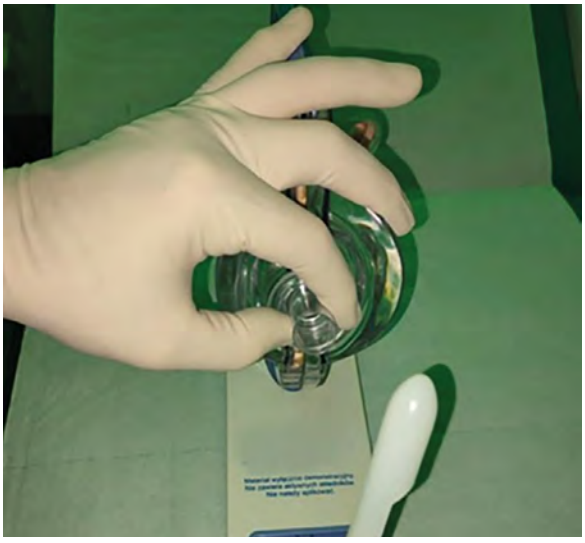


Figure 3. Second step of novel sampling method

Standard sampling technique performed on a gynecological chair using a Cusco speculum

Conventional specimen collection was carried out by gently inserting a disposable Cusco's bivalved speculum oriented at a 45° angle into the introitus. Once inside, it was horizontalized and the cervix was searched, trying not to collide with it.

All samples were collected using BD SurePath Collection Vial, Becton, Dickenson and Company, Sparks, USA and the examination for HPV DNA 14 was performed using the Real-Time PCR method on the Alinity M device from ABBOTT, which holds the CE-IVD certification.

Cytological findings were assessed according to the 2001 Bethesda System and classified as follows: high-grade squamous intraepithelial lesion (HSIL); atypical squamous cells, cannot exclude HSIL (ASC-H); low-grade squamous intraepithelial lesion (LSIL); atypical squamous cells of undetermined significance (ASC-US); atypical glandular cells (AGC); and negative for intraepithelia l lesion or malignancy (NILM).

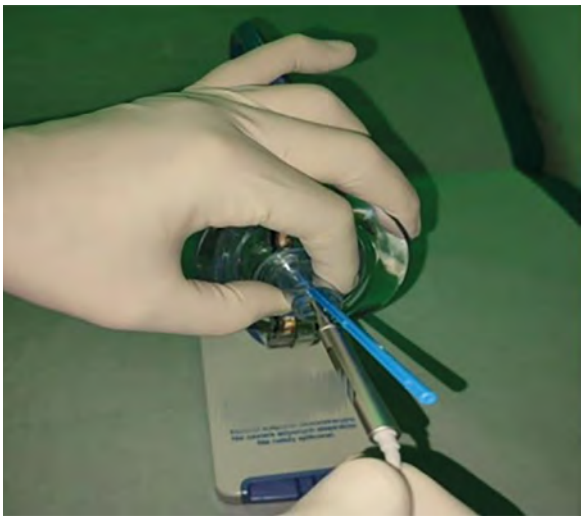


Figure 4. Third step of novel sampling method

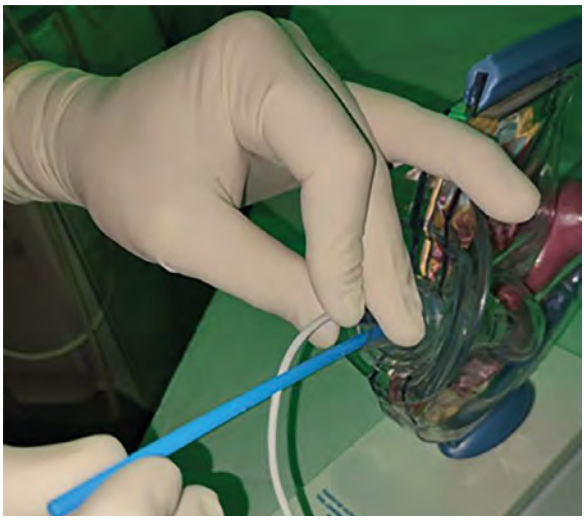


Figure 5. Fourth step of novel sampling method

All samples were collected by two experienced clinicians and evaluated by the same pathologist.

In order to anonymize the samples for the laboratory staff, each of them was labeled with a number from 1 to 50 and the letter A or B. This series of numbers was the result of a simple random sampling conducted at the beginning of the study, with each number assigned to participant according to the order of recruitment and the letter according to the sampling method.

Statistical analysis

Statistical analysis was performed using Statistica software (version 13.3; StatSoft, Poland). Continuous variables were summarized and reported as mean and standard deviation (mean ± SD). Categorical variables were presented as the number of patients and percentages. The agreement of measurement methods between paired cases was reported as percentages and assessed using Cohen's kappa (κ) statistics, with agreement interpreted as poor ($\kappa \leq 0$), slight ($\kappa < 0 \leq 0.2$), fair ($0.2 < \kappa \leq 0.4$), moderate ($0.4 < \kappa \leq 0.6$), substantial ($0.6 < \kappa \leq 0.8$), and almost perfect ($0.8 < \kappa \leq 1$) [11].

RESULTS

In the study group all women (50/50) accepted new method. Cervix was visualized and photographed in all cases. Collected material was send to laboratory to perform liquid based cytology (LBC) and high-risk HPV analysis.

Mean age in the study group was 43 years (± 11). Positivity rate in endocervical cells occurrence in pap smear result was 20% (10/50) in the new method and 78% (39/50) in the conventional sampling.

Cytology positivity rate (*i.e.* a percentage of the cytology results other than NILM) was 6% (3/50) in both the new and the old method groups with substantial agreement rate between the groups of 96% ($\kappa = 0.65$).

Considering the detection for at least one of HR-HPV, positivity rate was 12% (6/50) in the new method and 10% (5/50) in the classic sampling, with almost perfect agreement of 98% ($\kappa = 0.9$). HPV16 and HPV18, the main types responsible for cervical cancer, showed an almost perfect agreement rate of 98%, with $\kappa = 1$. These results are presented in Table 1.

DISCUSSION

Preliminary results indicate that the new sampling technique is a feasible and attractive alternative to standard cytology and HPV DNA sampling. As it can be performed outside the medical office, on the patient's bed, it may be an alternative for immobilized patients burdened by chronic diseases and therefore omitting participation in screening.

Research delving into reasons for not attending screening reveals a diverse array of obstacles, such as fear of pain, embarrassment, limited access to physician care, or inconvenient working hours in outpatient clinics [4, 5]. We believe that the proposed new sampling technique may also address some of those concerns.

Cytology positivity rate (*i.e.* a percentage of the cytology results other than NILM) was 6% (3/50) in both the new and the old method groups, with agreement rate between groups of 96% (with $\kappa = 0.65$). Considering detection for at least one of HR-HPV, positivity rate was 12% (6/50) in the new method and 10% (5/50) in the classic sampling, with agreement of 98% ($\kappa = 0.9$). Detection of HR-HPV using a new method, performed on a patient's bed simultaneously with cervical examination, has been demonstrated to be a good alternative in screening, and the results are

Table 1. Cytological and HPV DNA results

	New method	Conventional sampling
Positivity rate in endometrial cells, n [%]	10 (20)	39 (78)
Cytology NILM, n [%]	47 (94)	47 (94)
Cytology ASCUS	1 (2)	2 (4)
Cytology LSIL, n [%]	2 (4)	1 (2)
Cytology ASC-H, n [%]	0 (0)	0 (0)
Cytology HSIL, n [%]	0 (0)	0 (0)
Cytology AGC, n [%]	0 (0)	0 (0)
HPV DNA (–), n [%]	44 (88)	45 (90)
HPV DNA 16, 18 (+), n [%]	0 (0)	0 (0)
HPV DNA group A (+), n [%] *	3 (6)	2 (4)
HPV DNA group B (+), n [%]**	1 (2)	1 (2)
HPV DNA 16/18(+) and group A (+), n [%]	1 (2)	1 (2)
HPV DNA 16/18 (+) and group B (+), n [%]	1 (2)	1 (2)

*Group A — 31, 33, 52, 58; **group B — 35, 39, 51, 56, 59, 66, 68; AGC — atypical glandular cells; ASC-H — atypical squamous cells, cannot exclude HSIL; ASCUS — atypical squamous cells of undetermined significance; HPV — human papillomavirus; HSIL — high-grade squamous intraepithelial lesion; LSIL — low-grade squamous intraepithelial lesion; NILM — negative for intraepithelial lesion or malignancy

comparable to those obtained from standard sampling using a Cusco speculum and performed on a gynecological examination chair.

This method is a comparable alternative to HR-HPV detection in vagina auto-sampling. In a study by Gibert et al. [12] in 120 patients, the authors assessed agreement between self- and conventional samples concerning HPV-positivity as very good (κ 0.86, κ 0.83) or reasonable (κ 0.73 κ 0.68) depending on test used. Pap smears from self-samples exhibited moderate agreement (κ 0.41 and 0.51) for negative versus ASC-US and worse results [12].

The results of our study are also comparable to the those of an Italian study conducted by Martinelli et al. [13], in a cohort of 245 women with abnormal cytology, from whom self-sampled vaginal, urine, and clinician-administered cervical specimens were collected and HPV28 assays were performed. The results showed HPV positivity rates of 75.1% (cervical), 78.4% (vaginal), and 77.1% (urine). Notably, there was substantial concordance in the detection of HR-HPV between self-collected cervical samples and those collected clinically (κ = 0.898 for vaginal; κ = 0.715 for urine) [13].

Moreover, in our research the detection of HPV16/HPV18, which are responsible for over 70% of cervical cancer cases, showed an almost perfect agreement of 98%, with κ = 1 between new and classic method.

Likewise, in the aforementioned study, the detection of HPV16 and HPV18 between cervical samples and vaginal self-samples showed a very good agreement rate with κ = 0.945 and κ = 0.940, respectively, and a very good concordance rate in HPV16 (κ = 0.874) and HPV18 (κ = 0.866) between cervical and urine samples [13].

In our study, the cervix was visualized and photographed in all cases. In the literature, the reemergence of visual inspection of the cervix with the naked eye using acetic acid (VIA) as a screening tool in resource-limited settings is noted. Despite its modest specificity and a low positive predictive value (of approximately 10%), VIA is considered cost-effective, demands minimal equipment, and yields immediate results [14]. Additionally, the method presented in our study opens the possibility of using modern technologies in such as smartphones to store and consult data, or artificial intelligence to assess the image of the cervix [15, 16].

Finally, current triage guidelines for HR-HPV-positive women require cervical cytology result and cannot be performed on self-collected samples. Hence, in a self-sampling screening initiative, it is crucial for women testing positive for HR-HPV to be recalled for a follow-up visit to obtain a cervical sample for cytology triage. This poses an inherent risk of potential loss during the monitoring of HPV-positive individuals, and this risk could be increased among those who are non-attendant, a demographic already prone to difficulties in maintaining adherence. In fact, combining two screening tests (*e.g.* HPV followed by VIA or cytology) has also been described as the preferred screening test for HIV-infected patients in resource-limited settings [17].

Furthermore, in the study by Denny et al. [18], employing a two-test strategy that begins with direct visual inspection, followed by cytologic testing, HPV DNA testing, or VIA, reduced the number of patients subjected to unnecessary treatment (22 to 41 patients without disease/1000 patients screened) compared with either VIA (182/1000) or HPV alone (137/1000). We believe in the future it would be important

to extend the study to the target group of patients who either lack access to a speculum examination or are reluctant to undergo a pelvic examination in a gynecological chair. A larger sample would also enable us to calculate sensitivity rates for the detection of CIN2+. An alternative avenue to improve our method could involve incorporating the VIA test and performing biopsies in high-risk patients.

CONCLUSIONS

The study highlights the promise of remote sampling for HPV DNA and cytology in enhancing cervical cancer screening accessibility and adherence. Implementation of such methods could significantly improve screening coverage, especially among underserved populations. Further investigations are warranted to validate and optimize these approaches for broader clinical application.

Article information and declarations

Data availability statement

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

Ethics statement

The research was approved by the Bioethics Committee by the Regional Chamber of Physicians in Koszalin (decision number 2/2023) and is consistent with the provisions of the Declaration of Helsinki.

Author contributions

All authors meets the authorship criteria are in agreement with the content of the manuscript.

Acknowledgments

None.

Funding

This research received no external funding.

Conflict of interest

The authors declare that they have no conflicts of interest.

Supplementary material

None.

REFERENCES

1. Polish Gynecology Society recommendations on cervical cancer screening scheme. https://kolposkopia.info/rekomendajce/stanowisko-dotyczace-schematu-postepowania-w-skriningu-podstawowym-raka-szyjki-macicy-polskiego-towarzystwa-ginekologow-i-poloznikow-ptgip-czerwiec-2022-roku/ (4.02.2024).
2. Arbyn M, Gultekin M, Morice P, et al. The European response to the WHO call to eliminate cervical cancer as a public health problem. Int J Cancer. 2021; 148(2): 277–284, doi: 10.1002/ijc.33189, indexed in Pubmed: 32638362.
3. Data on the implementation of National Polish Health Care System screening programs: http://www.nfz.gov. https://www.nfz.gov.pl/dla-pacjenta/programy-profilaktyczne/dane-orealizacji-programow/ (4.02.2024).
4. Bennett KF, Waller Jo, Chorley AJ, et al. Barriers to cervical screening and interest in self-sampling among women who actively decline screening. J Med Screen. 2018; 25(4): 211–217, doi: 10.1177/0969141318767471, indexed in Pubmed: 29649936.
5. Logan L, McIlfatrick S. Exploring women's knowledge, experiences and perceptions of cervical cancer screening in an area of social deprivation. Eur J Cancer Care (Engl). 2011; 20(6): 720–727, doi: 10.1111/j.1365-2354.2011.01254.x, indexed in Pubmed: 21521388.
6. Gibert MJ, Sánchez-Contador C, Artigues G. Validity and acceptance of self vs conventional sampling for the analysis of human papillomavirus and Pap smear. Sci Rep. 2023; 13(1): 2809, doi: 10.1038/s41598-023-29255-y, indexed in Pubmed: 36797261.
7. Ajenifuja KO, Belinson J, Goldstein A, et al. Designing low-cost, accurate cervical screening strategies that take into account COVID-19: a role for self-sampled HPV typing2. Infect Agent Cancer. 2020; 15: 61, doi: 10.1186/s13027-020-00325-4, indexed in Pubmed: 33072179.
8. Hawkes D, Keung MHT, Huang Y, et al. Self-collection for cervical screening programs: from research to reality. Cancers (Basel). 2020; 12(4), doi: 10.3390/cancers12041053, indexed in Pubmed: 32344565.
9. Arbyn M, Smith SB, Temin S, et al. Collaboration on self-sampling and HPV testing. Detecting cervical precancer and reaching underscreened women by using HPV testing on self samples: updated meta-analyses. BMJ. 2018; 363: k4823, doi: 10.1136/bmj.k4823, indexed in Pubmed: 30518635.
10. Polish recommendation on cervical cancer screening during SARS-CoV-2 pandemic https://kolposkopia.info/wp-content/uploads/2023/06/SkriningRakaSzyjkiMacicyWPolsceWOkresiePandemiiSARS-CoV-2_TymczasoweRekomendacje-. https://kolposkopia.info/wp-content/uploads/2023/06/SkriningRakaSzyjkiMacicyWPolsceWOkresiePandemiiSARS-CoV-2_TymczasoweRekomendacje-.pdf%20accessed%20on%2004.02.2024 (4.02.2024).
11. Landis J, Koch G. The measurement of observer agreement for categorical data. Biometrics. 1977; 33(1): 159, doi: 10.2307/2529310.
12. Gibert MJ, Sánchez-Contador C, Artigues G. Validity and acceptance of self vs conventional sampling for the analysis of human papillomavirus and Pap smear. Sci Rep. 2023; 13(1): 2809, doi: 10.1038/s41598-023-29255-y, indexed in Pubmed: 36797261.
13. Martinelli M, Giubbi C, Di Meo ML, et al. Accuracy of human papillomavirus (HPV) testing on urine and vaginal self-samples compared to clinician-collected cervical sample in women referred to colposcopy. Viruses. 2023; 15(9), doi: 10.3390/v15091889, indexed in Pubmed: 37766295.
14. Sankaranarayanan R, Shyamalakumary B, Wesley R, et al. Visual inspection with acetic acid in the early detection of cervical cancer and precursors. Intern J Cancer. 1999; 80(1): 161–163, doi: 10.1002/(sici)1097-0215(19990105)80:1<161::aid-ijc28>3.0.co;2-8.
15. Hu L, Bell D, Antani S, et al. An observational study of deep learning and automated evaluation of cervical images for cancer screening. J Natl Cancer Inst. 2019; 111(9): 923–932, doi: 10.1093/jnci/djy225, indexed in Pubmed: 30629194.
16. Perkins R, Jeronimo J, Hammer A, et al. Comparison of accuracy and reproducibility of colposcopic impression based on a single image versus a two-minute time series of colposcopic images. Gynecol Oncol. 2022; 167(1): 89–95, doi: 10.1016/j.ygyno.2022.08.001, indexed in Pubmed: 36008184.
17. Goldie SJ, Kuhn L, Denny L, et al. Policy analysis of cervical cancer screening strategies in low-resource settings: clinical benefits and cost-effectiveness. JAMA. 2001; 285(24): 3107–3115, doi: 10.1001/jama.285.24.3107, indexed in Pubmed: 11427139.
18. Denny L, Kuhn L, Risi L, et al. Two-stage cervical cancer screening: an alternative for resource-poor settings. Am J Obstet Gynecol. 2000; 183(2): 383–388, doi: 10.1067/mob.2000.105871, indexed in Pubmed: 10942474.

VIA MEDICA

ORIGINAL PAPER / GYNECOLOGY

Ginekologia Polska
2025, vol. 96, no. 2, 87–95

ISSN 0017–0011, e-ISSN 2543–6767

DOI: 10.5603/gpl.100017

Modified laparoscopic sacrocolpopexy for advanced posterior vaginal wall prolapse: a 3-year prospective study

Yifan Yin, Yufang Xia, Shujun Ji, Enhui Guo, Chen Chen, Yanhui Lou

Affiliated Hospital of Qingdao University, Qingdao, Shandong Province, China

ABSTRACT

Objectives: To evaluate and validate the safety and efficacy of modified laparoscopic sacrocolpopexy for advanced posterior vaginal wall prolapse at up to 3 years of follow-up.

Material and methods: As a prospective observational study, we collected 56 cases with advanced posterior vaginal wall prolapse and performed modified laparoscopic sacrocolpopexy (MLSC) with self-cut mesh. The main improvement is the cutting and fixing of the mesh. Patients were followed up at 6, 12, 24 and 36 months. The main indicators of follow-up were postoperative anatomic success rate and Pelvic organ prolapse quantitation (POP-Q) score, and secondary indicators were related to quality-of-life scales and postoperative complication rates.

Results: All patients completed the operation through minimally invasive surgery, and there were no vital organs and blood vessel damage during the operation. The mean age was (58.32 ± 7.63) years. There was no recurrence of stage I or lower during the follow-up maximum of 36 months (median 24 months), and the anatomic success rate was 100%. The quality-of-life scores improved significantly ($p < 0.001$) and the quality of sexual life was not affected ($p = 0.5$). There was 1 case of continuous vaginal mesh exposure at 12 months (2.86%) and 1 case of severe infection with poor healing of vaginal stump within 6 months (1.79%). No one had urinary incontinence (UI) requiring reoperation.

Conclusions: In patients with advanced posterior vaginal wall prolapse, MLSC can provide good and durable pelvic floor anatomical recovery and functional outcomes with no specific complications.

Keywords: laparoscopic sacrocolpopexy; levator ani; mesh; pelvic organ prolapse; quality of life

Ginekologia Polska 2025; 96, 2: 87–95

INTRODUCTION

Pelvic organ prolapse (POP) is a type of dysfunctional disease in today's aging society that seriously affects the quality of life of older women. Anterior vaginal wall prolapse is the most common form of POP, while posterior vaginal wall prolapse is relatively uncommon with a prevalence of 12.9–18.6% [1], accounting for about 1/2 of anterior vaginal wall prolapse [2]. However, the treatment of posterior vaginal wall prolapses, especially of the distal and middle portions of the vagina wall, is relatively challenging. Despite the availability of various surgical approaches, there is currently a lack of high-level evidence to support the preferred surgical approach [3]. The traditional approach is transvaginal repair, with an average success rate of 83%, and complications such as sexual intercourse disorder (with an incidence of about 18%) and defecation disorder (with an incidence of about 26%) have not been effectively resolved [1]. In recent years, a growing number of clinical studies have demonstrated the integrity of pelvic support structures. Magnetic resonance imaging (MRI) evidence supports the overall weakening and general deformation of pelvic floor tissue in patients with POP, rather than specific fascia or site defects [4]. Malik RD. et al. [5] found that 16% of women who underwent anterior vaginal wall suspension also required posterior prolapse repair during long-term follow-up. At the same time, there are more than 20 years of research data demonstrating the critical role of defects in vaginal apical support structures in prolapse of the anterior and posterior vaginal walls [6]. Only transvaginal repair of the posterior wall cannot improve the overall defect of the

Corresponding author:
Yanhui Lou
Affiliated Hospital of Qingdao University, Shinan District, 266071 Qingdao, Shandong Province, China
e-mail: louyh@qdu.edu.cn

Received: 28.03.2024 Accepted: 10.07.2024 Early publication date: 21.10.2024

pelvic supporting structure, which may explain why simple transvaginal surgery cannot achieve the ideal surgical effect.

With the advancement and update of minimally invasive techniques, laparoscopic sacrocolpopexy (LSC) has become the "gold standard" for the treatment of POP caused by mid-pelvic defects in recent years [7–9]. It achieves the overall repair of the pelvic floor support structure by strengthening the uterosacral ligament complex. The surgical effect of LSC is superior to various transvaginal procedures [2]. Although there is currently no strong evidence to prove its superiority in treating posterior vaginal wall prolapse, some studies have shown that apical support plays an important role in posterior wall prolapse, and LSC can also restore the anatomy of the posterior vaginal wall [10, 11].

Many scholars have conducted follow-up studies on SC in patients with posterior vaginal wall prolapse. They found that the recurrence rate of vaginal apex after surgery was 1.47% to 6.1%, while the recurrence rate of posterior wall prolapse was as high as 5.88% to 31.82% [12, 13]. That suggests that SC is effective in supporting the apical vagina but cannot achieve the same ideal effect on the posterior vaginal wall. This is closely related to the complex anatomical structure of the posterior vaginal wall. DeLancey et al. [14] described the vaginal support in three different anatomical levels. In addition to the dominant role of the cardinal–uterosacral ligament complex, the levator ani muscle also plays an important role in support of the posterior vaginal wall and the entire pelvic floor. This provides a theoretical basis for us to treat posterior vaginal wall prolapse by MLSC. It enhances the overall structural support of the pelvic floor by addressing the vaginal apex defect and reinforcing the level II support. This is achieved by securing the two wings of the posterior mesh with the levator fascia on both sides. In this study, we enrolled patients with advanced posterior vaginal wall prolapse, performed the MLSC with self-cut mesh, and evaluated the safety and efficacy of this procedure during up to 3 years of follow-up.

MATERIAL AND METHODS

Baseline characteristics

As a prospective observational study, we identified a total of 56 patients with symptomatic, advanced POP who underwent MLSC with self-cut mesh between January 2019 and December 2021 at the Affiliated Hospital of Qingdao University. All women participated after informed written consent was obtained, and ethics approval was obtained from the Affiliated Hospital of Qingdao University prior to performing the surgical procedure (QYFY WZLL 27716). The following inclusion criteria were applied: (1) presenting with at least stage 3 prolapse of the posterior vaginal wall, with or without other chamber prolapses (anterior vaginal wall, cervical prolapse, or vaginal vault prolapse); (2) age younger than 70 years. The exclusion criteria included: (1) could not tolerate surgery because of serious systemic diseases; (2) a history of pelvic cancer or pelvic radiation therapy. All included patients were graded by the POP-Q score developed by The International Continence Society (ICS). The study flowchart is depicted in Figure 1.

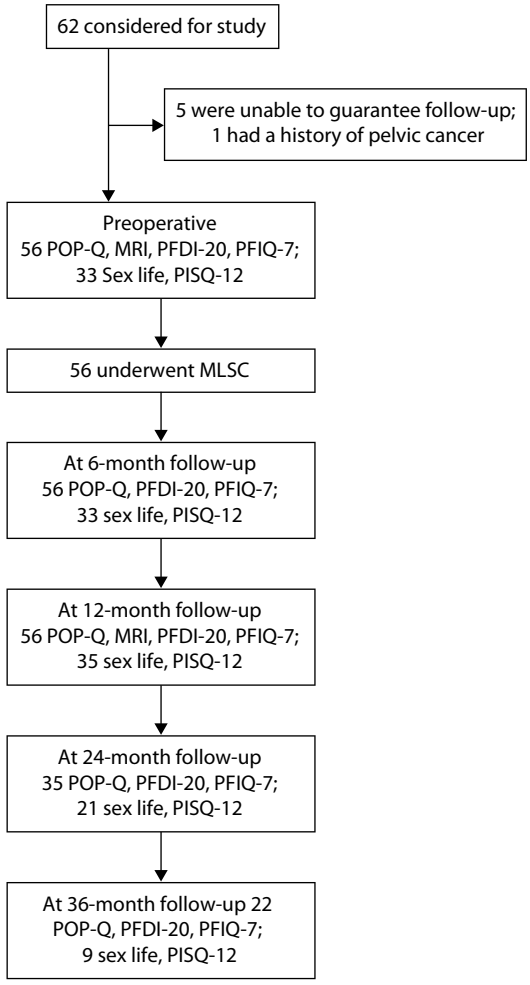


Figure 1. The study flowchart. POP-Q — Pelvic Organ Prolapse Quantitation; PFDI-20 — Pelvic Floor Distress Inventory — Short Form 20; PISQ-12 — The Pelvic Organ Prolapse/Urinary Incontinence Sexual Questionnaire 12; PFIQ-7 — The Pelvic Floor Impact Questionnaire 7; MLSC — Modified Laparoscopic Sacrocolpopexy

Surgical techniques

All operations were performed by the same experienced team via robotic or laparoscopic-assisted surgery. A total hysterectomy was performed following routine steps in cases of uterine prolapse. A 0 absorbable suture was used to continuously suture the vaginal stump. Separated the vaginal rectal space down to the lower third of the posterior vaginal wall and then extended it laterally to visualize the levator ani muscle fascia on both sides (Fig. 2). Opened the peritoneum to reach the presacral space to expose the middle sacral vasculature

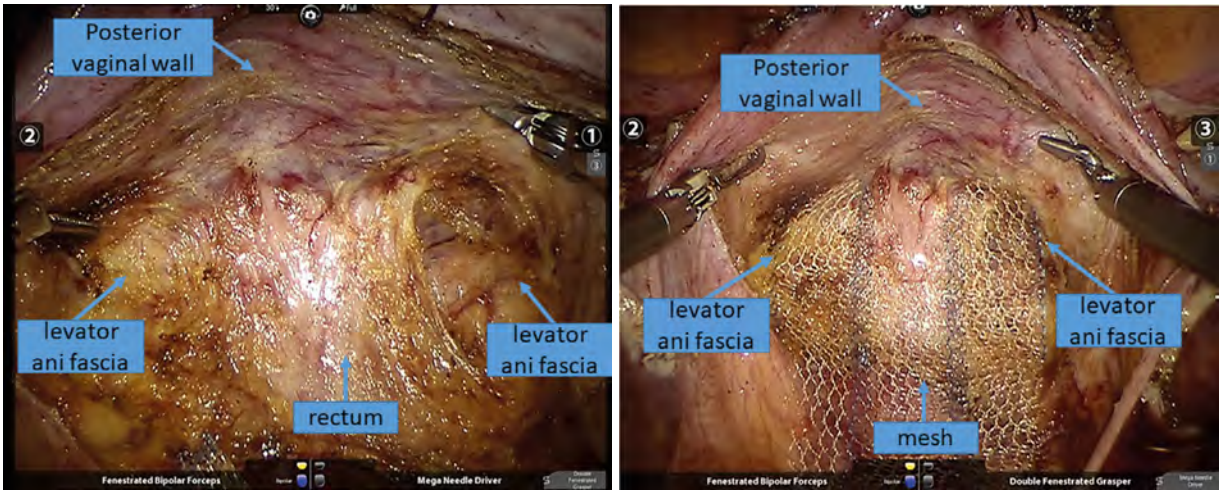


Figure 2. The vaginal rectal spaces were dissected down to the levator ani fascia on both sides, and the posterior mesh was placed over and sutured to this fascia

and the anterior longitudinal ligament of the first sacral vertebra below the promontory and communicated with the opened rectovaginal space below. A polypropylene mesh, Gynemesh PS (Ethicon, 10 cm × 15 cm, Somerville, NJ, USA), was cut into 2 specific shape strips (Fig. 3). The anterior mesh was fixed using conventional sutures, while the posterior mesh was positioned over and sutured to the levator fascia on both sides, and to the uterosacral ligament complex (Fig. 2). The anterior and posterior arms of the meshes were then combined over the vaginal stump and drawn through the peritoneal tunnel. The distal end of the mesh is finally fixed without tension to the anterior longitudinal ligament of the sacrum (Fig. 4). All meshes were sutured with 2-0 nylon sutures (non-absorbable sutures). The peritoneum was sutured continuously with an absorbable suture, and the mesh was completely placed within the peritoneum to ensure complete peritonealization.

Objectives

The objective of this study was to evaluate the safety and efficacy of MLSC for advanced posterior vaginal wall prolapse. Patients were primarily followed up through telephone consultations and outpatient clinic visits, starting 6 months after surgery. The main indicators of follow-up were the postoperative anatomical success rate and POP-Q score, while secondary indicators comprised quality of life scales and postoperative complication rates. Anatomical success was defined as stage I or lower based on the POP-Q. The quality of life of patients was assessed using questionnaires, including Pelvic Floor Distress Inventory — Short Form 20 (PFDI-20), the Pelvic Organ Prolapse/Urinary Incontinence Sexual Questionnaire 12 (PISQ-12), and The Pelvic Floor Impact Questionnaire 7 (PFIQ-7). The PFDI-20 investigates the range of POP symptoms experienced by the patient

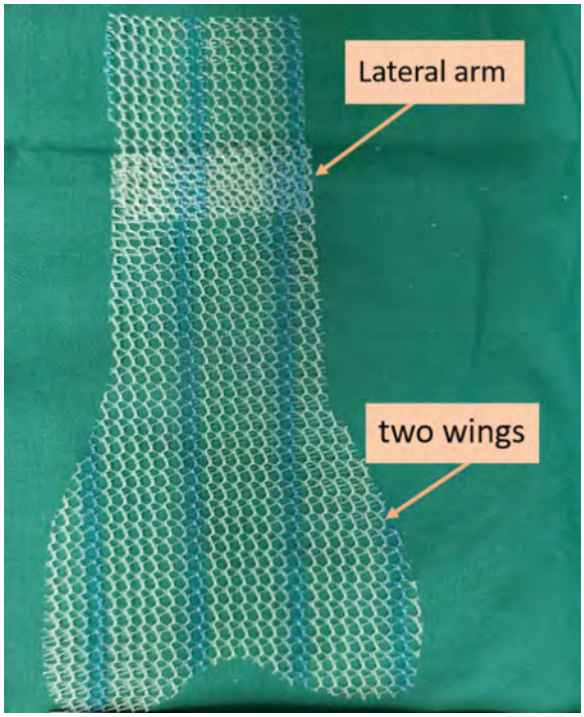


Figure 3. The posterior wall mesh was cut into the shape of the two wings and a lateral arm

and the grade of inconvenience they cause. The PFIQ-7 covers the impact of POP on daily life. The PISQ-12 covers sexual function in sexually active women with POP. These three questionnaires have been used in numerous studies and have also been validated in their Chinese versions [15–17].

Statistical analysis

Data analysis was managed using SPSS 25 statistical software and R version 4.1.0. Data were reported as mean

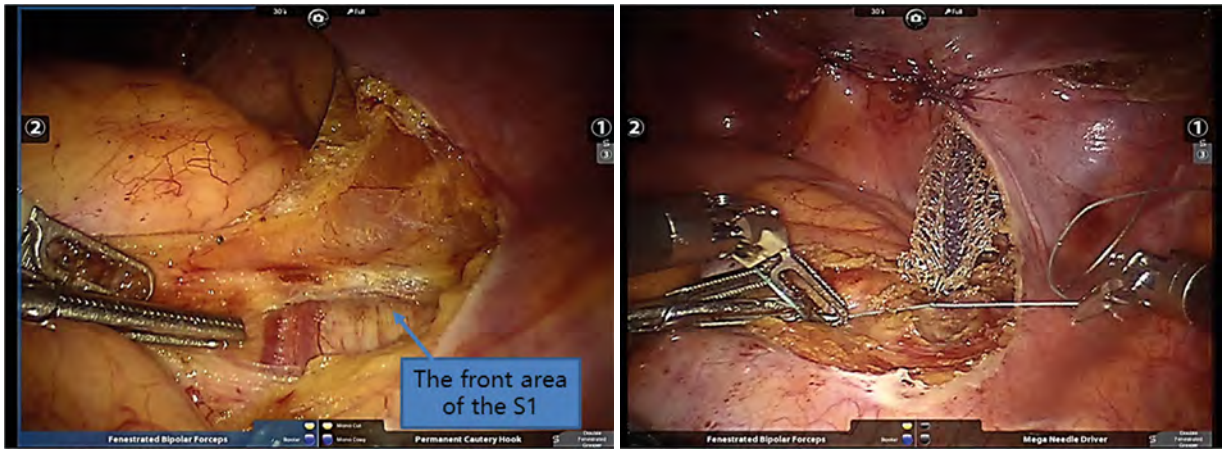


Figure 4. Exposed the front area of the first sacrum and fixed the long arm of the mesh to the anterior longitudinal ligament

± standard deviation for continuous quantitative variables and as number and percentage for qualitative variables. Preoperative and follow-up values were compared on McNemar test and Student's t-test for matched variables. A p value < 0.05 was considered as statistically significant.

RESULTS

A total of 56 patients were included in this study. The demographic information is shown in Table 1. According to MRI assessment, fifteen of these patients combined with intestinal hernia. There were 6 cases had a history of POP surgery, which included 3 cases of simple anterior and posterior vaginal wall repair, 2 cases of sacrospinous ligament fixation, and 1 case of uterine-rectus abdominis suspension. Additionally, 8 patients were complicated with UI, including 3 patients with stress UI (SUI), 2 with urge UI (UUI), and 3 with mixed UI (MUI). None of the patients had previously undergone incontinence surgery; 42 patients (75%) underwent concurrent hysterectomy during the surgery. Among the other patients, six (10.71%) had vaginal vault prolapse, and 8 (14.29%) chose to preserve the uterus. Six cases (10.71%) underwent tension-free vaginal tape-obturator (TVT-O) surgery due to SUI or MUI. In all patients, the surgery was performed using minimally invasive techniques without conversion to laparotomy, and there were no injuries to the gastrointestinal tract, urinary system, or major blood vessels. The urinary catheter was removed within 24 hours after the operation, and none of the patients experienced discomforts such as dysuria, urgency, or dysuria. The perioperative data are presented in Table 2.

All patients underwent gynecological examinations, MRI imaging, and laboratory tests during outpatient follow-up visits. The vaginal capacity of all patients could accommodate 2–3 fingers, and the POP-Q values returned to the normal anatomical range after the operation. The difference was statistically significant compared with the preoperative value ($p < 0.001$). The anatomic success rate was 100% during the maximum 36-month follow-up period (Tab. 3).

Functional pelvic problems (PFDI-20 scores) and their impact on patients' quality of life (PFIQ-7 scores) significantly improved postoperatively ($p < 0.001$). We did not collect information on patients' sexual activity for 6 months after surgery as it was necessary to avoid sexual intercourse in immediate post-surgery period. 33 patients who had a sexual life before the operation recovered and resumed normal sexual activity after the operation, as confirmed during the 12-month follow-up evaluation. In addition, two patients who had no sex activity 6 months before the operation also resumed sexual activity after the procedure. There was no statistically significant difference from the preoperative score ($p = 0.5$). Patients experienced improved urinary system-related symptoms and sensory disturbances after the operation ($p < 0.05$). 19 out of the 25 patients who had constipation before the operation returned to normal 1 month after the procedure, with significant improvement in their anorectal symptoms. 12 cases experienced new-onset constipation, and their symptoms improved or resolved within 6 months after the operation through changes in dietary habits and the use of laxative drugs. Additionally, the 6 patients with UI underwent TVT-O surgery simultaneously, resulting in significant symptom improvement post-surgery without dysuria or urinary retention. There were 5 patients with new-onset UI, two of whom had UUI and were cured with cholinergic receptor blockers and other medications, while three had SUI with mild symptoms, and none required further surgery (Tab. 4).

1 patient with persistent mesh exposure recovered after debridement and suturing of the stump 12 months after the operation. Infection-related complications mainly include vaginal stump inflammation and pelvic infection. 3 vaginal stump infections were observed during an outpatient

Table 1. Baseline characteristics (n = 56)

Characteristics	Value
Type of POP	
Simple posterior wall prolapses	18 (32.14)
Combined with other chamber prolapses	38 (67.8)
Age [years]	58.32 ± 7.63
BMI [kg/m^2]	24.96 ± 3.45
Number of deliveries	1.55 ± 0.63
Menopause	37 (66.07)
Chronic constipation	25 (44.64)
Urinary incontinence	8 (14.29)
Uterine fibroids or adenomyoma	20 (35.71)
Intestinal hernia	15 (26.79)
Previous pelvic surgery	18 (32.14)
Previous POP surgery	6 (10.71)
Comorbidities	
Hypertension	9 (16.07)
Diabetes mellitus	11 (19.64)
Heart disease (arrhythmia, myocardial infarction, *etc.*)	2 (3.57)
Respiratory diseases (emphysema, bronchiectasis, *etc.*)	5 (8.93)
Cerebral infarction	2 (3.57)

Data are mean ± standard deviation or n (%); POP — pelvic organ prolapse; BMI — body mass index

Table 2. Perioperative characteristics

Characteristic	Value
Surgical approach	
Laparoscopic	38 (67.86)
Robot-assisted	18 (32.14)
Concomitant procedures	
Total hysterectomy	42 (75)
TVT surgery	6 (10.71)
Adhesiolysis	7 (12.5)
Duration of surgery [min]	197.39 ± 55.91
Estimated blood loss [mL]	44.19 ± 26.33
Length of postoperative hospital stay [day]	3.45 ± 1.04

Data are mean ± standard deviationor n (%); TVT — tension-free vaginal tape

follow-up visit 1 month after the surgery. During the gynecological examination, none of the patients presented obvious symptoms such as vaginal stump congestion, loose sutures, or poor healing. All patients recovered after treatment with estrogen-containing vaginal suppositories and estrogen cream. There were no serious mesh-related complications such as adhesive bowel obstruction or mesh erosion during the follow-up period (Tab. 4).

DISCUSSION

Traditional LSC is applicable to uterine prolapse with mid-pelvic defects. The mesh is mainly sutured to the upper third of the posterior vaginal wall and the uterosacral ligament. However, it provides less support for the lower part of the anterior and posterior vaginal walls and cannot achieve the same ideal effect [18]. In an analysis by Sullivan et al. [19], in which mesh was fixed to the sacrum to treat multicompartmental POP, 28% of their patients (n = = 236, follow-up 5 years or 3 years) required reoperation for recurrent low posterior vaginal wall prolapse. Moreover, rectocele resulting from uncorrected central or distal defects may create a downward traction force on the apical suspension recurrence sites, which can contribute to the apical plateau recurrence [20]. Wong et al. [21] utilized ultrasound to evaluate the location of the anterior mesh in LSC patients' post-surgery and discovered that the lower the mesh position, the lower likelihood of recurrence rate. Therefore, there is a view that the posterior wall mesh can be fixed to the perineal body in LSC, but excessive dissection of the posterior vaginal wall may increase bowel complications [22].

In this study, we performed MLSC in 56 patients with advanced posterior vaginal wall prolapse. The procedure involved dissecting the rectum from the posterior vaginal wall down to the levator ani fascia on both sides of the rectum. It not only fixes Level I support (vagina apical) but also has major influences on Level II (midvaginal) and Level III (introital) support. In our follow-up, we observed a significant improvement in POP-Q score among all patients, resulting in an overall objective cure rate of 100%. It shows that the MLSC is not only suitable for apex prolapse but also for patients with simple posterior wall prolapse, especially for those experiencing POP recurrence or had a combined intestinal hernia. Carter-Brooks et al. [11] conducted a follow-up study and found that compared to patients who did not undergo Level III support procedures (such as posterior repair and/or perineorrhaphy), those who underwent LSC alone showed similar genital hiatus (GH) 1-year post-surgery, with no difference in recurrence rate. In this study, the 56 included patients did not undergo Level III support procedures, regardless of the presence of anatomical defects in the perineal body. All patients achieved satisfactory anatomical reduction after surgery. Our initial experience showed that MLSC seemed to safely cure advanced posterior vaginal wall prolapse, suggesting that the indications of the MLSC could potentially be expanded. For patients with total pelvic floor deficiencies, this procedure can be used to achieve satisfactory results and maintain long-term outcomes.

Gluck et al. [22] confirmed that numerous technical variants for LSC exist and that there is still little consensus on various issues regarding the technique. Many scholars have improved the LSC procedure in the past. Gadonneix

Table 3. Anatomical results according to POP-Q classification and stage at 6, 12, 24 and 36 months follow-up

	Preoperative n = 56	6 months n = 56	p value	12 months n = 56	p value	24 months n = 35	p value	36 months n = 22	p value
POP-Q point									
Aa [cm]	0.95 ± 1.33	–2.8 ± 0.4	< 0.001	–2.8 ± 0.5	< 0.001	–2.7 ± 0.5	< 0.001	–2.7 ± 0.5	< 0.001
Ba [cm]	2.36 ± 2.13	–2.9 ± 0.3	< 0.001	–2.8 ± 0.2	< 0.001	–2.7 ± 0.4	< 0.001	–2.7 ± 0.5	< 0.001
Ap [cm]	1.25 ± 1.08	–2.9 ± 0.5	< 0.001	–2.6 ± 0.5	< 0.001	–2.5 ± 0.6	< 0.001	–2.3 ± 0.7	< 0.001
Bp [cm]	3.6 ± 1.0	–2.9 ± 0.2	< 0.001	–2.9 ± 0.2	< 0.001	–2.8 ± 0.3	< 0.001	–2.6 ± 0.3	< 0.001
C [cm]	1.9 ± 2.8	–6.4 ± 1.3	< 0.001	–6.6 ± 1.2	< 0.001	–6.5 ± 1.4	< 0.001	–5.5 ± 0.6	< 0.001
Anatomical success rate, n %		56 (100)		56 (100)		35 (100)		22 (100)	

Data are mean ± standard deviation or n (%); p value — compared to preoperative data. Aa, Ba, C, Ap and Bp were the measured parameters, as defined by the ICS POP-Q; C, those with a uterus represent the cervix, and those without a uterus represent the top of the fornix

Table 4. Quality of life scores and complications at 6, 12, 24 and 36 months follow-up

	Preoperative n = 56	6 months n = 56	p value	12 months n = 56	p value	24 months n = 35	p value	36 months n = 22	p value
Quality of life score sheet									
PFIQ-7	159.3 ± 15.7	145.7 ± 15.7	< 0.001	51.2 ± 12.9	< 0.001	46.3 ± 13.8	< 0.001	49.2 ± 11.9	< 0.001
PFDI-20	143.6 ± 31.7	33.5 ± 14.7	< 0.001	33.0 ± 9.4	< 0.001	29.1 ± 9.0	< 0.001	29.5 ± 9.2	< 0.001
Sexual relations	33 (58.9)	–	–	35 (62.5)	0.990	21 (60)	0.500	9 (40.91)	0.990
PISQ-12	26.5 ± 5.5	–	–	27.6 ± 5.0	0.034	29.0 ± 4.7	0.286	28.3 ± 5.9	0.187
Symptoms									
Bowel dysfunction	26 (46.43)	2 (3.57)		1 (1.79)		0 (0)		0 (0)	< 0.001
Urination dysfunction	12 (21.43)	5 (8.93)		4 (7.14)		1 (2.86)		1 (4.55)	0.031
Sensory dysfunction	25 (44.64)	3 (5.36)		2 (3.57)		0 (0)		0 (0)	< 0.001
Complications									
Mesh-related complications		1 (1.79)		1 (1.79)		0 (0)		0 (0)	
Infection		8 (14.29)		3 (5.36)		0 (0)		0 (0)	
Urinary incontinence		5 (8.93)		4 (7.14)		1 (2.86)		1 (5.44)	

Data are mean ± standard deviation or n (%); p value — compared to preoperative data; bowel dysfunction, constipation, digital assistance, fecal incontinence, *etc.* Urination dysfunction, urine leakage, difficulty urinating, *etc.;* sensory dysfunction, dyspareunia, abdominal and lumbosacral discomfort, *etc.;* mesh-related complications, mesh shrinkage, vaginal mesh exposure, *etc.;* infection, vaginal infection, pelvic infection, osteomyelitis, pondyloperiostitis, *etc.*

et al. [23] used two separate meshes along the anterior and posterior vaginal walls to correct multicompartment pelvic organ prolapse, and the recurrence rate was 12% with a median follow-up of 24 months for posterior vaginal wall prolapse. Liang S. [24] performed LSC in 30 patients with the attachment of mesh straps transvaginally, and only 1 patient had a recurrence of the posterior vaginal wall two years after surgery. The patients enrolled in our study were followed up for a maximum of 3 years, and currently, no patient has a recurrence of the posterior vaginal wall. The results herein presented demonstrate the effectiveness of this procedure in reducing the recurrence of posterior vaginal wall prolapse.

In terms of quality of life, it was found that prolapse-related symptoms significantly improved ($p < 0.001$), as did patients' overall quality of life. However, the quality of sexual life was not affected ($p = 0.5$). In our data, 25 patients (44.64%) had chronic constipation before surgery. Among them, 19 patients regained normal defecation function within 1 month after surgery, suggesting that the restoration of the anatomical structure of the posterior vaginal wall

contributes to the improvement of defecation function. Although there were 12 patients with new-onset constipation after surgery, most cases occurred within the first month post-surgery. Anorectal symptoms improved within 6 months after surgery, likely due to the use of medications to facilitate bowel movements and improvements in dietary habits. It was previously believed that deep dissection of the posterior vaginal wall during the operation could alter rectal compliance and anorectal angulation, resulting in obstructed defecation. In addition, pararectal dissection could cause autonomic nerve injury contributing to a reduction in rectal mobility [25]. Fox and Stanton [26] separated the rectum from the posterior vaginal wall down to the perineal body during surgery. With a median follow-up of 14 months, postoperative bowel-related complications increased from 41% to 50%. However, our data suggest that the MLSC may temporarily affect the patient's bowel dysfunction, but the repair of the postoperative anatomical structure is ultimately beneficial to the recovery of the patient's defecation function. This finding is consistent with the conclusions of Grimes et al. [27] and Ramanah et al. [25]. Overall, this procedure can significantly improve prolapse-related symptoms and quality of life of patients for an extended period. And it did not have a negative impact on the sexual life of patients, some patients even experienced improvements. This fully demonstrates the superiority of this procedure compared to transvaginal and transanal routes. Its potential benefits to sexual function (preserving vaginal length and axial direction, thereby reducing the incidence of dyspareunia) makes this procedure the first choice for relatively young, sexually active women. Similar conclusions were drawn in a 1-year follow-up study by Thibault et al. [28] using the same questionnaire.

Intraoperative complications mainly include bladder, ureter, intestinal injury, excessive bleeding, and hematoma formation. Simultaneously, placing the mesh lower requires more dissection of the posterior vaginal wall, which can result in increased intraoperative blood loss, longer operative time, and a heightened risk of intestinal injury. All surgical procedures in this study were performed by a professional physician with nearly ten years of experience in pelvic floor surgery. The data confirms the safety of this operation. However, the LSC is associated with technical challenges and a steep learning. The security of the operation also depends on the surgeon's technical expertise and surgical experience.

In previous reports, mesh-related complications are one of the most common and intractable complications of SC, with a risk as high as 10.5% at 7 years following the procedure [29]. Infections, failure of prolapse repair, and mesh erosions may require mesh removal and, if applicable, repeat LSC [9]. Although the mechanism of mesh exposure is unclear, factors such as infection, hematoma, concomitant uterine resection, history of POP surgery, different types of mesh or suture, vaginal mesh tension, mesh peritoneal coverage, and vaginal use of estrogen may contribute to the pathogenesis of mesh exposure [30–32]. To prevent mesh-related complications, we placed the mesh without tension, strictly carried out the peritonealization of the mesh, and implemented additional measures during the operation. The follow-up data of this study suggested that only 1 patient (1.8%) who had persistent mesh exposure was treated with secondary surgery, which is lower than the 3% reoperation rate for mesh-related complications reported in the recent literature [33].

In recent years, the concept of prophylactic anti-incontinence surgery for women has sparked a popular and controversial debate. It has been reported in the literature that about 5.3% of patients developed SUI requiring surgical treatment after LSC [34]. A high-quality meta-study in 2014 showed that combined surgery reduced the risk of postoperative SUI, but there was also a risk of complications such as overactive bladder symptoms and obstructive urination [35]. We performed TVT-O surgery on patients with preoperative SUI and MUI. In our study, we effectively alleviated post-surgery urinary leakage symptoms without increasing surgery-related complications. None of the patients required anti-incontinence surgery again.

The main advantages of this study include its prospective design and the systematic preoperative and postoperative assessment using the POP-Q system, standardized surgical techniques, standardized scoring scales, *etc*. Dynamic collection and comparison of the result data can clearly and directly reflect the changes in the relevant indicators of the patients after surgery. However, due to the limited number of cases and short observation period in this study, further investigation involving more cases treated with this procedure is needed. In addition, factors such as the depth of rectal dissection and the level of levator ani muscle fascia fixation may also affect the study results. Therefore, we look forward to further research using large sample size, long-term follow-up, and standardized randomized controlled trials to validate the superiority of MLSC in advanced posterior vaginal wall prolapse in the future. This operation is expected to evolve into a first-line surgical approach for treating advanced pelvic defects after adequate evaluation.

Article information and declarations

Data availability statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to the inclusion of information that compromise the privacy of research participants.

Ethics statement

All subjects gave their informed consent for inclusion before they participated in the study. The Ethics Committee of the Affiliated Hospital of Qingdao University approved this study, ethics NO. QYFYWZLL27716.

Author contributions

Yifan Yin — conceptualization, methodology, investigation, formal analysis, writing — original draft; Yufang Xia — data curation, writing, original draft; Shujun Ji — investigation; Enhui Guo — resources, supervision; Chen Chen — writing, original draft; Yanhui Lou — conceptualization, resources, writing, editing.

Funding

The work was supported by the Beijing science and technology innovation medical development foundation (No. KC2023-JX-0288-RZ82).

Acknowledgments

We thank all patients for providing signed permission to publish this article.

Conflict of interest

The authors declare no conflict of interest.

REFERENCES

1. Karram M, Maher C. Surgery for posterior vaginal wall prolapse. Int Urogynecol J. 2013; 24(11): 1835–1841, doi: 10.1007/s00192-013-2174-z, indexed in Pubmed: 24142058.
2. Barber MD. Pelvic organ prolapse. BMJ. 2016; 354(i3853), doi: 10.1136/bmj.i3853.
3. Mowat A, Maher D, Baessler K, et al. Surgery for women with posterior compartment prolapse. Cochrane Database Syst Rev. 2018; 3(3): CD012975, doi: 10.1002/14651858.CD012975, indexed in Pubmed: 29502352.
4. Lewicky-Gaupp C, Yousuf A, Larson KA, et al. Structural position of the posterior vagina and pelvic floor in women with and without posterior vaginal prolapse. Am J Obstet Gynecol. 2010; 202(5): 497.e1–497.e6, doi: 10.1016/j.ajog.2010.01.001, indexed in Pubmed: 20452497.
5. Malik RD, Christie AL, Zimmern PE. Posterior compartment prolapse occurrence after anterior vaginal wall suspension. Urology. 2019; 133: 84–90, doi: 10.1016/j.urology.2019.08.010, indexed in Pubmed: 31425682.
6. Lowder JL, Park AJ, Ellison R, et al. The role of apical vaginal support in the appearance of anterior and posterior vaginal prolapse. Obstet Gynecol. 2008; 111(1): 152–157, doi: 10.1097/01.AOG.0000297309.25091.a0, indexed in Pubmed: 18165404.
7. Maher C, Feiner B, Baessler K, et al. Surgery for women with anterior compartment prolapse. Cochrane Database Syst Rev. 2016; 11(11): CD004014, doi: 10.1002/14651858.CD004014.pub6, indexed in Pubmed: 27901278.
8. Maher C, Feiner B, Baessler K, et al. Surgery for women with apical vaginal prolapse. Cochrane Database Syst Rev. 2016; 10(10): CD012376, doi: 10.1002/14651858.CD012376, indexed in Pubmed: 27696355.
9. Mohr S, Imboden S, Mueller MD, et al. Laparoscopic sacrocolpopexy mesh excision step-by-step. Int Urogynecol J. 2023; 34(8): 1987–1989, doi: 10.1007/s00192-023-05494-5, indexed in Pubmed: 36897370.
10. Haylen B, Wong A, Kerr S. Posterior vaginal compartment repairs: Does vaginal vault (level I) fixation significantly improve the vaginal introital (level III) repair? Neurourol Urodyn. 2018; 37(8): 2740–2744, doi: 10.1002/nau.23737.
11. Carter-Brooks CM, Lowder JL, Du AL, et al. Restoring genital hiatus to normative values after apical suspension alone versus with level 3 support procedures. Female Pelvic Med Reconstr Surg. 2019; 25(3): 226–230, doi: 10.1097/SPV.0000000000000528, indexed in Pubmed: 29210807.
12. Sarlos D, Kots L, Ryu G, et al. Long-term follow-up of laparoscopic sacrocolpopexy. Int Urogynecol J. 2014; 25(9): 1207–1212, doi: 10.1007/s00192-014-2369-y, indexed in Pubmed: 24700356.
13. Higgs PJ, Chua HL, Smith ARB. Long term review of laparoscopic sacrocolpopexy. BJOG. 2005; 112(8): 1134–1138, doi: 10.1111/j.1471-0528.2005.00646.x, indexed in Pubmed: 16045530.
14. DeLancey JO. Structural anatomy of the posterior pelvic compartment as it relates to rectocele. Am J Obstet Gynecol. 1999; 180(4): 815–823, doi: 10.1016/s0002-9378(99)70652-6, indexed in Pubmed: 10203649.
15. Teleman P, Stenzelius K, Iorizzo L, et al. Validation of the Swedish short forms of the Pelvic Floor Impact Questionnaire (PFIQ-7), Pelvic Floor Distress Inventory (PFDI-20) and Pelvic Organ Prolapse/Urinary Incontinence Sexual Questionnaire (PISQ-12). Acta Obstet Gynecol Scand. 2011; 90(5): 483–487, doi: 10.1111/j.1600-0412.2011.01085.x, indexed in Pubmed: 21306343.
16. Lau HH, Sun FY, Wang H, et al. Cutoff score of the traditional Chinese version of the short form of the pelvic organ prolapse/urinary incontinence sexual questionnaire (PISQ-12). Taiwan J Obstet Gynecol. 2020; 59(2): 227–230, doi: 10.1016/j.tjog.2020.01.009, indexed in Pubmed: 32127142.
17. Zhu L, Yu S, Xu T, et al. Chinese validation of the Pelvic Floor Impact Questionnaire Short Form. Menopause. 2011; 18(9): 1030–1033, doi: 10.1097/gme.0b013e31820fbcbe, indexed in Pubmed: 21587092.
18. Haylen BT, Vu D, Birrell W, et al. A preliminary anatomical basis for dual (uterosacral and sacrospinous ligaments) vaginal vault support at colporrhaphy. Dual-balanced vaginal vault support at colporrhaphy. Int Urogynecol J. 2012; 23(7): 879–882, doi: 10.1007/s00192-011-1633-7, indexed in Pubmed: 22212715.
19. Sullivan ES, Longaker CJ, Lee PY. Total pelvic mesh repair: a ten-year experience. Dis Colon Rectum. 2001; 44(6): 857–863, doi: 10.1007/BF02234709, indexed in Pubmed: 11391148.
20. Oh S, Choi S, Lee SoY, et al. Posterior repair versus no posterior repair for posterior vaginal wall prolapse resolved under simulated apical support at the time of native tissue apical suspension. Int Urogynecol J. 2021; 32(8): 2203–2209, doi: 10.1007/s00192-021-04728-8, indexed in Pubmed: 33635351.
21. Wong V, Guzman Rojas R, Shek KL, et al. Laparoscopic sacrocolpopexy: how low does the mesh go? Ultrasound Obstet Gynecol. 2017; 49(3): 404–408, doi: 10.1002/uog.15882, indexed in Pubmed: 26877210.
22. Gluck O, Blaganje M, Veit-Rubin N, et al. Laparoscopic sacrocolpopexy: A comprehensive literature review on current practice. Eur J Obstet Gynecol Reprod Biol. 2020; 245: 94–101, doi: 10.1016/j.ejogrb.2019.12.029, indexed in Pubmed: 31891897.
23. Gadonneix P, Ercoli A, Salet-Lizée D, et al. Laparoscopic sacrocolpopexy with two separate meshes along the anterior and posterior vaginal walls for multicompartment pelvic organ prolapse. J Am Assoc Gynecol Laparosc. 2004; 11(1): 29–35, doi: 10.1016/s1074-3804(05)60006-0, indexed in Pubmed: 15104827.
24. Liang S, Zhu L, Song X, et al. Long-term outcomes of modified laparoscopic sacrocolpopexy for advanced pelvic organ prolapse: a 3-year prospective study. Menopause. 2016; 23(7): 765–770, doi: 10.1097/GME.0000000000000628, indexed in Pubmed: 27138745.
25. Ramanah R, Ballester M, Chereau E, et al. Anorectal symptoms before and after laparoscopic sacrocolpoperineopexy for pelvic organ prolapse. Int Urogynecol J. 2012; 23(6): 779–783, doi: 10.1007/s00192-011-1657-z, indexed in Pubmed: 22258718.
26. Fox SD, Stanton SL. Vault prolapse and rectocele: assessment of repair using sacrocolpopexy with mesh interposition. BJOG. 2000; 107(11): 1371–1375, doi: 10.1111/j.1471-0528.2000.tb11650.x, indexed in Pubmed: 11117764.
27. Grimes C, Lukacz E, Gantz M, et al. What happens to the posterior compartment and bowel symptoms after sacrocolpopexy? Evaluation of 5-year outcomes from E-CARE. Female Pelvic Med Reconstr Surg. 2014; 20(5): 261–266, doi: 10.1097/spv.0000000000000085.
28. Thibault F, Costa P, Thanigasalam R, et al. Impact of laparoscopic sacrocolpopexy on symptoms, health-related quality of life and sexuality: a medium-term analysis. BJU Int. 2013; 112(8): 1143–1149, doi: 10.1111/bju.12286, indexed in Pubmed: 24007194.
29. Baines G, Price N, Jefferis H, et al. Mesh-related complications of laparoscopic sacrocolpopexy. Int Urogynecol J. 2019; 30(9): 1475–1481, doi: 10.1007/s00192-019-03952-7, indexed in Pubmed: 31041499.
30. Unger CA, Paraiso MF, Jelovsek JE, et al. Perioperative adverse events after minimally invasive abdominal sacrocolpopexy. Am J Obstet Gynecol. 2014; 211(5): 547.e1–547.e8, doi: 10.1016/j.ajog.2014.07.054, indexed in Pubmed: 25088866.

31. Nygaard IE, McCreery R, Brubaker L, et al. Pelvic Floor Disorders Network. Abdominal sacrocolpopexy: a comprehensive review. Obstet Gynecol. 2004; 104(4): 805–823, doi: 10.1097/01.AOG.0000139514.90897.07, indexed in Pubmed: 15458906.
32. Ganatra A, Rozet F, Sanchez-Salas R, et al. The current status of laparoscopic sacrocolpopexy: a review. Eur Urol. 2009; 55(5): 1089–1103, doi: 10.1016/j.eururo.2009.01.048.
33. Vandendriessche D, Sussfeld J, Giraudet G, et al. Complications and reoperations after laparoscopic sacrocolpopexy with a mean follow-up of 4 years. Int Urogynecol J. 2017; 28(2): 231–239, doi: 10.1007/s00192-016-3093-6, indexed in Pubmed: 27549223.
34. Ennemoser S, Schönfeld M, von Bodungen V, et al. Clinical relevance of occult stress urinary incontinence (OSUI) following vaginal prolapse surgery: long-term follow-up. Int Urogynecol J. 2012; 23(7): 851–855, doi: 10.1007/s00192-012-1765-4, indexed in Pubmed: 22581237.
35. van der Ploeg JM, Oude Rengerink K, van der Steen A, et al. Dutch Urogynaecology Consortium, Dutch Urogynaecology Consortium. Prolapse surgery with or without stress incontinence surgery for pelvic organ prolapse: a systematic review and meta-analysis of randomised trials. BJOG. 2014; 121(5): 537–547, doi: 10.1111/1471-0528.12509, indexed in Pubmed: 24382099.

VIA MEDICA

ORIGINAL PAPER / GYNECOLOGY

Ginekologia Polska
2025, vol. 96, no. 2, 96–101

ISSN 0017–0011, e-ISSN 2543–6767

DOI: 10.5603/gpl.101029

Investigation of lower urinary system symptoms in patients with isolated posterior compartment prolapsus: a cross-sectional study

Burcu Serhanoğlu, Mustafa Cengiz Dura, Şükrü Yıldız, Zınar Serhanoğlu, Berk Gürsoy, Murat Ekin

Bakırkoy Dr. Sadi Konuk Education and Research Hospital, Department of Gynecology, Istanbul, Türkiye

ABSTRACT

Objectives: The effects of posterior vaginal wall prolapse on pelvic floor function have not been adequately investigated, particularly for lower urinary tract symptoms (LUTS). We aimed to investigate the effects of isolated posterior compartment prolapse on LUTS.

Material and methods: The study was conducted as a prospective cross-sectional study with female patients with isolated posterior prolapse who presented with any LUTS. All patients were evaluated according to the POP-Q system. A total of 41 patients with stage 2–3 isolated pelvic organ prolapse were included in the study group. The control group consisted of a total of 41 patients without significant pelvic organ prolapse. Study and control groups were compared in terms of demographic data and UDI-6, IIQ-7, ICIQ-FLUTS, LUTS QoL, FLUT Sex Scales.

Results: The incidence of SUI, UI, frequency, nocturia, abnormal evacuation, difficulty in passage and vaginal farting in the study group was found to be statistically significantly higher than the control group. In the study group, the total scores on the UDI-6, IIQ-7, and LUTS QoL measures were significantly higher. While the total scores of the ICIQ-FLUTS Scale "Filling" and "Incontinence" subgroups were significantly higher in the study group, no significant difference was found in the "voiding" subgroup. There was no statistically significant difference between the two groups in terms of their total FLUT Sex Scores.

Conclusions: It has been shown that isolated posterior prolapse may be associated with an increase in lower urinary tract system symptoms and a decrease in quality of life.

Keywords: isolated posterior vaginal prolapse; lower urinary tract sympto; urogynecology

Ginekologia Polska 2025; 96, 2: 96–101

INTRODUCTION

The pelvic floor is a holistic anatomical system that works in a certain harmony. Any damage to any component of the pelvic floor can disrupt this alignment [1]. Pelvic organ prolapse (POP) is the protrusion of one or more female pelvic organs outside the pelvis through the vagina, including the uterus, bladder, and intestines, which causes the pelvic organs to descend toward the vaginal wall [2]. The main symptoms associated with posterior POP are pelvic pressure sensation, constipation, defecation with reduction, faecal incontinence, sexual dysfunction. The most specific, but rare, sign of posterior prolapse is a need to apply pressure on the vagina, rectum, or perineum to complete defecation [3, 4].

The relationship between anterior vaginal wall prolapses and lower urinary tract symptoms (LUTS) has been known for a long time, and data on the effect of the posterior vaginal wall prolapses on LUTS are scarce [5]. Posterior compartment defects are present in 76% of women with pelvic organ prolapse [6]. Despite the high prevalence of posterior compartment defects, isolated posterior

Corresponding author:
Berk Gürsoy
Bakırkoy Dr. Sadi Konuk Education and Research Hospital,Department of Gynecology,
Istanbul, 34173 Istanbul, Türkiye
e-mail: berk.gursoy.93@gmail.com

Received: 06.06.2024 Accepted: 30.08. 2024 Early publication date: 24.10.2024

compartment defects are extremely rare and their effects on pelvic floor function have not been adequately studied, particularly for lower urinary tract symptoms (LUTS) [7]. On the consequences of isolated posterior compartment abnormalities on voiding, there is limited available data. In the study of Cole et al. [8] based on the hypothesis that posterior compartment defects may cause lower urinary tract symptoms due to changes in functional anatomy, they reported that 7 patients' symptoms improved after the repair of the posterior defect in 8 symptomatic patients.

Objectives

In this study, we aimed to investigate the effects of isolated posterior compartment prolapse on LUTS. We postulated, based on our clinical experience, that in cases of severe posterior abnormalities, vaginal mass effects could contribute to voiding obstruction via vaginal compression.

MATERIAL AND METHODS

The study was conducted with female patients aged between 30–70 years who applied to urogynecology outpatient clinic in Bakırkoy Dr. Sadi Konuk Training and Research Hospital, Gynecology and Obstetrics Clinic between March 2021 and August 2022. After the approval of the local ethics review board with decision number 2021-07-11 on 05.04.2021, the study was started. Informed consent was obtained from the patients. The patients were examined prospectively. Demographic data and past medical and surgical histories (age, parity, menopausal status, tobacco use, obstetric history, body mass index (BMI), accompanying comorbidities) were recorded. All patients were evaluated by a specialist experienced in urogynecology.

Evaluation of the patients included a standard clinical examination and a urogynecological examination with detailed evaluation of the anterior, apical, and posterior vaginal compartments. Prolapse was assessed and recorded using the POP-Q staging system. Forty-one patients with isolated posterior prolapse without clinically significant anterior and apical compartment defects, classified as stage 2 in 20 patients and stage 3 in 21 patients were included in the study. The control group consisted of 41 patients without significant pelvic organ prolapse. Women with stage 2 and above anterior and apical defects, women with a history of urogynecological surgery or any treatment for LUTS, and women with diseases that may cause lower urinary tract symptoms such as neurological disease, myoma uteri, endometriosis, and adnexal mass were excluded from the study.

To assess LUTS and sexual well-being, patients were administered the Urinary Distress Inventory (UDI-6), Incontinence Impact Questionnaire (IIQ-7), ICIQ-FLUTS, LUTS QoL, and FLUTS Sex Scale questionnaires. The UDI-6 was evaluated on a percentile basis, with a minimum score of 0 and a maximum score of 100. The IIQ-7 questionnaire scoring ranged from a minimum of 0 to a maximum of 21, while the ICIQ-FLUTS questionnaire was assessed using three subscales that examined different symptoms. These subscales were categorized as "Filling", "Voiding", and "Incontinence" based on the corresponding questions, with scoring ranges of 0–16, 0–12, and 0–20, respectively. Additionally, the LUTS QoL survey focused on the impact of incontinence on quality of life by assessing social consequences, with scores ranging from 19 to 76. To evaluate the effect of urinary incontinence on sexual function and its impact on quality of life in women, the FLUTS Sex Scale was used, with scores ranging from 0 to 14. Higher scores across all questionnaires indicate increased symptom severity and a decline in quality of life. Responses to the LUTS questionnaire, which is part of the urogynecological evaluation, were also evaluated. LUTS surveys examined questions from these aspects; stress urinary incontinence (SUI), urge incontinence (UI), frequency, nocturia, intermittent flow, abnormal voiding, as well as passage strain, vaginal farting, dyspareunia, and pelvic pain were also recorded.

To examine the impact of urine incontinence on QOL, the incontinence impact questionnaire (IIQ) and the urogenital distress inventory (UDI) were created and combined [9]. The Second International Consultation on Incontinence suggests the use of both surveys [10]. The Sixth International Consultation on Incontinence (ICI) advises using questionnaires from the International Consultation on Incontinence Questionnaire (ICIQ) modules when evaluating LUTS in clinical practice and for research [11].

For the evaluation of LUTS and sexual functions, Turkish validated urogenital distress inventory (UDI-6) and incontinence impact questionnaire (IIQ-7) were compared between study and control groups using ICIQ-FLUTS, LUTS QoL, FLUT Sex Scales [12, 13].

After the effect power was calculated as 0.41 with the G-Power sample number calculation program, it was calculated that it would be appropriate to include a total of 77 patients in the study with a confidence interval of 80% and a sensitivity of $p < 0.05$.

While evaluating the findings obtained in the study, NCSS (Number Cruncher Statistical System) 2020 Statistical Software (NCSS LLC, Kaysville, Utah, USA) program was used for statistical analysis. While evaluating the study data, quantitative variables were shown with mean, standard deviation, median, min and max values, and qualitative variables were shown with descriptive statistical methods such as frequency and percentage. Shapiro Wilks test and Box Plot graphics were used to evaluate the conformity of the data to the normal distribution.

Student's t-test was used for quantitative two-group evaluations with normal distribution. The Mann-Whitney-U test

was used to evaluate the non-normally distributed variables according to two groups. Logistic regression analysis was used in multivariate assessments. Chi-square test, Yates Continuity Correction and Fisher's Exact test were used to compare qualitative data. The results were evaluated at the 95% confidence interval and the significance level of $p < 0.05$ (Fig. 1).

RESULTS

The ages of the cases ranged from 31 to 68, with an average of 49.20 ± 7.71 years. The mean age of the study and control groups did not show a statistically significant difference ($p > 0.05$). The BMI values of the study group were found to be statistically significantly higher ($p = 0.018$; $p < 0.05$) (Tab. 1).

The increasing numbers of delivery, especially vaginal delivery and traumatic vaginal delivery in cases with isolated posterior prolapse were found to be statistically significantly higher than the control group ($p = 0.001$; $p < 0.01$). The number of cesarean deliveries in cases with isolated posterior prolapse was found to be statistically significantly lower than the control group ($p = 0.001$; $p < 0.01$) (Tab. 1).

In cases with isolated posterior prolapse, the incidence of SUI, UI, frequency, nocturia, abnormal evacuation, difficulty in passage, and vaginal farting was found to be statistically significantly higher than the control group (respectively; $p = 0.004$; $p = 0.001$; $p = 0.001$; $p = 0.015$; $p = 0.43$, $p = 0.026$, $p = 0.001$, $p < 0.05$ (Tab. 3). Intermittent flow and pelvic pain complaints in the study and control groups did not show a statistically significant difference ($p > 0.05$) (Tab. 2).

The total scores of the cases with isolated posterior prolapse in the ICIQ-FLUTS Scale "Filling" and "Leakage" sub-dimensions were found to be statistically significantly higher than the control group ($p = 0.001$; $p = 0.001$; $p < 0.01$). There was no statistically significant difference between the total scores of the two groups in the ICIQ-FLUTS Scale "Voiding" sub-dimension ($p > 0.05$). The total scores of the patients with isolated posterior prolapse from the LUTS QoL Scale were found to be statistically significantly higher than the control group ($p = 0.001$; $p < 0.01$). There was no statistically significant difference between the total scores

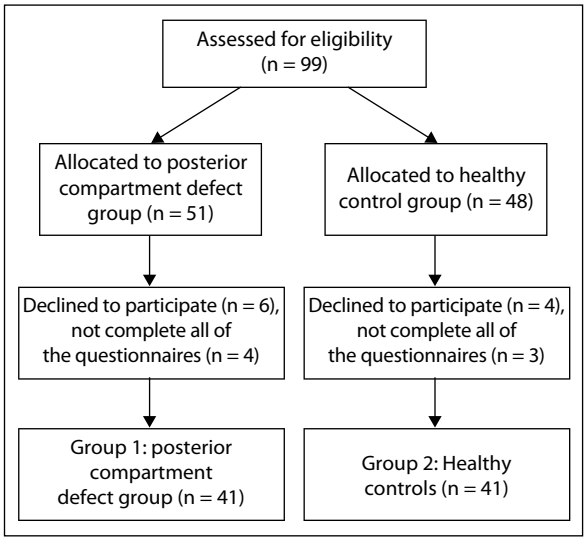


Figure 1. Flow chart of the study

Table 1. Distribution of complementary features of cases according to the presence of isolated posterior prolapse

		Posterior prolapse		p value
		None (n = 41)	Yes (n = 41)	
Age	Mean ± SD	49.02 ± 6.06	49.37 ± 9.15	[a]0.843
	Median (min–max)	49 (36–61)	48 (31–68)	
BMI	Mean ± SD	27.72 ± 5.18	30.48 ± 5.13	[a]0.018*
	Median (min–max)	26.7 (18.7–40.1)	30.8 (19.5–44.4)	
	Normal	11 (26.8)	5 (12.2)	
	Overweight	19 (46.3)	14 (34.1)	
	Obese	11 (26.8)	22 (53.7)	
Parity (birth number)	Mean ± SD	2.10 ± 1.14	3.00 ± 1.00	[d]0.001**
	Median (min–max)	2 (0–5)	3 (1–6)	
Number of CS	Mean ± SD	0.59 ± 0.84	0.24 ± 0.58	[d]0.001**
	Median (min–max)	0 (0-3)	0 (0–2)	
Vaginal delivery number	Mean ± SD	1.56 ± 1.34	2.78 ± 1.11	[a]0.001**
	Median (min–max)	1 (0–5)	3 (1–6)	
Traumatic vaginal delivery history	No	35 (85.4)	17 (41.5)	[c]0.001**
	Yes	6 (14.6)	24 (58.5)	

[a] Student -t Test; [c] Pearson Chi-Square Test; [d] Mann Whitney -U Test; **p < 0.01; BMI — body mass index; CS — cesarean section; min — minimum, max — maximum; SD — standard deviation

Table 2. Comparison of the complaints of the cases according to the presence of isolated posterior prolapse

		Posterior prolapse		p value
		None (n = 41)	Yes (n = 41)	
Complaints	SUI	11 (26.8)	24 (58.5)	[b]0.004**
	UI	7 (17.1)	22 (53.7)	[b]0.001**
	Frequency	5 (12.2)	22 (53.7)	[b]0.001**
	Nocturia	17 (41.5)	28 (68.3)	[b]0.015*
	Discontinuous flow	3 (7.3)	8 (19.5)	[b]0.105
	Abnormal discharge	2 (4.9)	8 (19.5)	[b]0.043*
	Passage strain	4 (9.8)	12 (29.3)	[b]0.026*
	Pelvic pain	2 (4.9)	1 (2.4)	[e]1.000
	Vaginal farting No	31 (75.6)	10 (24.4)	[b]0.001**
	Yes	6 (14.6)	25 (61.0)	
	Non-sexually active	4 (9.8)	6 (14.6)	

[b]Fisher freeman Halton Test; [c]Pearson Chi-Square Test; [e]Fisher Exact Test; *p < 0.05; **p < 0.01; SUI — stress urinary incontinence; UI — urge incontinence

Table 3. Comparison of all scales according to the presence of isolated posterior prolapse

		Posterior prolapse		p value
		None (n = 41)	Yes (n = 41)	
Filling (ICIQ-FLUTS)	Mean ± SD	2.17 ± 2.26	5.76 ± 3.64	[d]0.001**
	Median (min–max)	1 (0–10)	6 (0–13)	
Voiding (ICIQ-FLUTS)	Mean ± SD	0.15 ± 0.53	0.32 ± 0.99	[d]0.663
	Median (min–max)	0 (0–3)	0 (0–5)	
Incontinence (ICIQ-FLUTS)	Mean ± SD	1.76 ± 2.9	6.17 ± 4.99	[d]0.001**
	Median (min–max)	0 (0–13)	4 (0–17)	
FLUT Sex Scale score	Mean ± SD	0.43 ± 0.5	0.75 ± 0.73	[d]0.068
	Median (min–max)	0.3 (0–1.8)	0.8 (0–2.8)	
LUTS QoL Score	Mean ± SD	1.08 ± 0.22	1.73 ± 0.72	[d]0.001**
	Median (min–max)	1 (0.9–1.9)	1.4 (1–3.5)	
IIQ-7 Score	Mean ± SD	0.73 ± 1.88	5.56 ± 6.40	[d]0.001**
	Median (min–max)	0 (0–9)	3 (0–21)	
UDI-6 Score (%)	Mean ± SD	6.64 ± 10.63	30.35 ± 18.80	[d]0.001**
	Median (min–max)	0 (0–44.4)	27.8 (0–72.2)	

[d]Mann Whitney-U Test; **p < 0.01

of the cases with isolated posterior prolapse from the FLUT Sex Scale (p > 0.05) (Tab. 3).

The total scores of patients with isolated posterior prolapse from the Incontinence Impact Questionnaire (IIQ-7) and Urogenital Distress Inventory (UDI-6) Scale were found to be statistically significantly higher than the control group (p = 0.001; p < 0.01), (p = 0.001; p < 0.01).

To determine the effect of the BMI parameter, which was found to be significantly different between the study and control groups, on statistics, on the grounds that it might be a confounding factor, we evaluated the effects of BMI and IIQ-7, UDI-6, ICIQ-FLUTS filling score and leakage score subgroups, LUTS QoL score, and FLUT sex score using logistic regression analysis.

While the regression results of the confounding variable BMI parameter and UDI-6 and LUTS QoL scores remained statistically significant, no significant difference was found in the ICIQ-FLUTS scale filling and leakage sub-dimensions.

DISCUSSION

The relationship between anterior vaginal wall prolapses and LUTS has been known for a long time, and data on the effect of isolated posterior vaginal wall prolapses on LUTS are scarce. Isolated posterior compartment defects are rare and

often coexist with other compartment defects. Therefore, the relationship between LUTS and posterior compartment defects can easily be overlooked. There are also several reasons for this. First, there is a misconception that lower urinary tract symptoms are limited to anterior defects and therefore a detailed posterior compartment evaluation is skipped in patients presenting with LUTS; second is the difficulties in estimating the direct effects of posterior defects on LUTS. The integrity of the pelvic floor is made up of a static and dynamic structure formed by the interplay of all the many parts that make up the pelvis according to the Integral Theory, prolapse and the majority of pelvic floor symptoms, such as urinary stress, urge and abnormal bowel and bladder emptying, as well as certain types of pelvic pain, result from laxity in the vagina or its supporting ligaments as a result of altered connective tissue [14–16]. As a result, even a mild prolapse that compromises its integrity might cause serious discomfort [17].

Kilic et al. [18] retrospectively evaluated 60 patients with isolated posterior compartment prolapse, including 8 stage 1, 33 stage 2, and 19 stage 3 isolated posterior compartment prolapse, using the LUTS and UDI-6 questionnaires. They noted significant elevations in UDI-6 total scores in the study group, indicating that isolated posterior compartment prolapse may be associated with LUTS [18]. Based on this study, we aimed to investigate the effects of isolated posterior compartment prolapse on LUTS. As a result of our study, despite the regression analysis of BMI, which is thought to be a confounding factor, we found a significant increase in the UDI-6 total score, and we obtained results similar to those of Kilic et al. [18] In our study, unlike Kilic et al. [18], we aimed to evaluate the negative effects of isolated posterior prolapses on quality of life and sexual functions by also examining the parameters of UDI-6, ICIQ-FLUTS, LUTS QoL and FLUT Sex Scale.

Cole et al. [8] evaluated 23 patients with isolated posterior compartment prolapse in terms of LUTS and urodynamic parameters. Fifteen women had stage 3 and 8 women had stage 2 defects. They grouped lower urinary tract symptoms as storage, voiding, and mixed symptoms. Nine of the patients reported storage only, 1 voiding only, 12 mixed symptoms, while only 1 patient reported no LUTS [8]. In our study, we compared a total of 41 patients with isolated posterior prolapse, stage 2 in 20 patients and stage 3 in 21 patients, with 41 patients without prolapse. We grouped the lower urinary system symptoms under 3 titles as filling, voiding and incontinence. While we found the filling and incontinence symptoms to be statistically significantly higher in patients with isolated posterior prolapse, we did not detect a significant difference between the two groups in terms of voiding symptoms. When we subjected the statistical results to regression analysis, we did not find statistical significance in all three subgroups.

Myers et al. [19] examined urodynamic parameters in patients with posterior defects to assess whether isolated posterior prolapses mask SUI. They reported that stage 3 posterior prolapse may increase the maximum urethral closure pressure and mask SUI [19]. Since we built the hypothesis of our study on symptomatology, we did not examine urodynamic parameters, which are mechanical findings. However, the study can be improved by examining the urodynamic parameters in patients with a high score in the UDI-6 scale UDI-S subgroup. One of the limitations of our study is the lack of urodynamic evaluation to compare with the existing literature.

There are few studies in the literature on posterior compartment prolapse, and there is no research on the effect of posterior compartment prolapse on quality of life and sexual functions. The original aspect of our study is that it is the only study in literature examining the effect of isolated posterior prolapse on LUTS, quality of life and sexual functions. Although BMI is a confounding factor, we determined the social and psychological negative effects of isolated posterior prolapse by regression analysis. Although there was no statistically significant difference between the total scores of the FLUT Sex Scale between the two groups, the high score in the study group and the level of significance of the 'p' value suggest that this variable may also be significant in a larger series.

With the elimination of the BMI confounding variable that may affect the aforementioned symptoms, the significance between the two groups in terms of ICIQ-FLUTS filling and incontinence subgroups and sexual functions disappeared. However, more studies with larger series are needed to make a more precise interpretation.

The strength of our study is that it reveals the relationship between LUTS and isolated posterior compartment defects, which are rarely studied in the literature but frequently encountered in clinical practice. In terms of standardization of the evaluation, all patients are examined and evaluated in a single center by a single experienced urogynecologist. One of the limitations of our study is the lack of urodynamic evaluation to compare with the existing literature. The presence of BMI as a confounding variable between groups is another limitation, even though regression analysis was to be done.

CONCLUSIONS

Women with posterior prolapse may be asymptomatic or present to the clinician with anorectal, urinary or sexual symptoms. In our study, it was shown that isolated posterior prolapses may be associated with urinary system symptoms as well as anorectal symptoms. This relationship may be overlooked by the clinician. These women should be examined in more detail in terms of lower urinary tract symptoms.

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

All procedures performed in studies involving human participants were accordance with the ethical standards of institutional and/or national research committees and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Ethical approval for this study was obtained from the Ethical Committee of Health Sciences University, Bakirkoy Dr. Sadi Konuk Training and Research Hospital (Approval number: 2021-07-11). A detailed informed consent was obtained from all patients.

Authors contributions

Conceptualization — ME, BG, SY, BS; data curation — ME, ZS, MCD, BG; formal analysis — BS, MCD, ZS, SY; methodology — ME, BG, SY, BS; software — ZS, MCD, SY, ME; validation — BG, SY, BS; visualization — ME, MCD, BS, BG, ZS; writing, original draft — ME, SY, BG, BS, MCD; writing, review, editing — BS, BG, MCD, ZS; supervision — BS, SY, BG; project administration — ME, BG, MCD, SY, BS, ZS. All authors agree with the content of the manuscript. The authors have no financial or non-financial conflicts of interest regarding this article to disclose.

Funding

None.

Acknowledgments

None.

Conflict of interest

All authors are in agreement with the content of the manuscript. The authors have no financial or non-financial conflicts of interest regarding this article to disclose.

REFERENCES

1. Nieuwoudt EM Pelvic organ prolapse and pelvic floor muscle strength. University of the Free State; 2006. https://scholar.ufs.ac.za/server/api/core/bitstreams/7f61d516-fea6-4cf9-a072-b354caf0981d/content.
2. Chung SH, Kim WB. Various Approaches and Treatments for Pelvic Organ Prolapse in Women. J Menopausal Med. 2018; 24(3): 155–162, doi: 10.6118/jmm.2018.24.3.155, indexed in Pubmed: 30671407.
3. Ellerkmann RM, Cundiff GW, Melick CF, et al. Correlation of symptoms with location and severity of pelvic organ prolapse. Am J Obstet Gynecol. 2001; 185(6): 1332–7; discussion 1337, doi: 10.1067/mob.2001.119078, indexed in Pubmed: 11744905.
4. Burrows LJ, Meyn LA, Walters MD, et al. Pelvic symptoms in women with pelvic organ prolapse. Obstet Gynecol. 2004; 104(5 Pt 1): 982–988, doi: 10.1097/01.AOG.0000142708.61298.be, indexed in Pubmed: 15516388.
5. Vitale SG, Laganà AS, Noventa M, et al. Transvaginal Bilateral Sacrospinous Fixation after Second Recurrence of Vaginal Vault Prolapse: Efficacy and Impact on Quality of Life and Sexuality. Biomed Res Int. 2018; 2018: 5727165, doi: 10.1155/2018/5727165, indexed in Pubmed: 29675427.
6. Guiahi M, Kenton K, Brubaker L. Sacrocolpopexy without concomitant posterior repair improves posterior compartment defects. Int Urogynecol J Pelvic Floor Dysfunct. 2008; 19(9): 1267–1270, doi: 10.1007/s00192-008-0628-5, indexed in Pubmed: 18496636.
7. Davis K, Kumar D. Posterior pelvic floor compartment disorders. Best Pract Res Clin Obstet Gynaecol. 2005; 19(6): 941–958, doi: 10.1016/j.bpobgyn.2005.08.010, indexed in Pubmed: 16198148.
8. Cole EE, Kaufman MR, Scarpero HM, et al. The effects of isolated posterior compartment defects on lower urinary tract symptoms and urodynamic findings. BJU Int. 2006; 97(5): 1024–1026, doi: 10.1111/j.1464-410X.2006.06130.x, indexed in Pubmed: 16643484.
9. Shumaker SA, Wyman JF, Uebersax JS, et al. Health-related quality of life measures for women with urinary incontinence: the Incontinence Impact Questionnaire and the Urogenital Distress Inventory. Continence Program in Women (CPW) Research Group. Qual Life Res. 1994; 3(5): 291–306, doi: 10.1007/BF00451721, indexed in Pubmed: 7841963.
10. Rathod SR, Vyas N, Sorani DM. Validation of Gujarati Version of International Physical Activity Questionnaire. Int J of Health Sci Res 2018, 8(1):122-128. https://www.ijhsr.org/IJHSR_Vol.8_Issue.1_Jan2018/18.pdf (2018).
11. Abrams P, Cardozo L, Wagg A, et al. Incontinence: 6th International Consultation on Incontinence, Tokyo, September 2016. In: 2017: International Continence Society; 2017.
12. Cam C, Sakalli M, Ay P, et al. Validation of the short forms of the incontinence impact questionnaire (IIQ-7) and the urogenital distress inventory (UDI-6) in a Turkish population. Neurourol Urodyn. 2007; 26(1): 129–133, doi: 10.1002/nau.20292, indexed in Pubmed: 17083117.
13. Gungor Uğurlucan F, Yasa C, Yuksel Ozgor B, et al. Validation of the Turkish version of the ICIQ-FLUTS, ICIQ-FLUTS long-form, ICIQ-LUTS quality-of-life, and ICIQ-FLUTS sexual functions. Neurourol Urodyn. 2020; 39(3): 962–968, doi: 10.1002/nau.24302, indexed in Pubmed: 32032453.
14. Petros PE, Ulmsten UI. An integral theory of female urinary incontinence. Experimental and clinical considerations. Acta Obstet Gynecol Scand Suppl. 1990; 153: 7–31, doi: 10.1111/j.1600-0412.1990.tb08027.x, indexed in Pubmed: 2093278.
15. Petros PEP, Woodman PJ. The Integral Theory of continence. Int Urogynecol J Pelvic Floor Dysfunct. 2008; 19(1): 35–40, doi: 10.1007/s00192-007-0475-9, indexed in Pubmed: 17968480.
16. Liedl B, Inoue H, Sekiguchi Y, et al. Update of the Integral Theory and System for Management of Pelvic Floor Dysfunction in Females. European Urology Supplements. 2018; 17(3): 100–108, doi: 10.1016/j.eursup.2017.01.001.
17. Petros PE, Ulmsten U. Tests for ‚detrusor instability' in women. These mainly measure the urethral resistance created by pelvic floor contraction acting against a premature activation of the micturition reflex. Acta Obstet Gynecol Scand. 1993; 72(8): 661–667, doi: 10.3109/00016349309021161, indexed in Pubmed: 8259755.
18. Kilic D, Guler T, Gokbel I, et al. Effects of isolated posterior vaginal wall prolapse on lower urinary tract symptoms. J Gynecol Obstet Hum Reprod. 2021; 50(4): 102095, doi: 10.1016/j.jogoh.2021.102095, indexed in Pubmed: 33592348.
19. Myers DL, Lasala CA, Hogan JW, et al. The effect of posterior wall support defects on urodynamic indices in stress urinary incontinence. Obstet Gynecol. 1998; 91(5 Pt 1): 710–714, doi: 10.1016/s0029-7844(98)00049-0, indexed in Pubmed: 9572216.

VIA MEDICA

ORIGINAL PAPER / GYNECOLOGY

Ginekologia Polska
2025, vol. 96, no. 2, 102–108

ISSN 0017–0011, e-ISSN 2543–6767

DOI: 10.5603/gpl.98199

Effect of video-based exercise on premenstrual symptoms: a randomized controlled trial

Şeyma Aykut, Ömer Şevgin

Üsküdar Unıversity, İstanbul, Türkiye

ABSTRACT

Objectives: This study aims to investigate the impact of Pilates exercises on premenstrual syndrome (PMS) symptoms, perceived stress levels, and pain intensity.

Material and methods: Forty-six women with PMS participated in this study and were assigned to the intervention and control groups based on their willingness to participate. The intervention group undertook Pilates practices via video recording twice a week for 8 weeks, while the control group did not engage in regular exercise during the same period. PMS symptoms were assessed using the Premenstrual Syndrome Scale (PMSS), premenstrual stress levels were evaluated using the Perceived Stress Scale (PSS), and premenstrual pain levels were assessed using the McGill Melzack Pain Questionnaire (MPQ) at both the beginning and end of the study.

Results: There was a significant difference observed in the PMSS, PSS and MPQ evaluations of the intervention group following their participation in Pilates practices ($p < 0.05$). Conversely, no significant difference was observed in the PMSS, PSS and MPQ evaluations of the control group at the end of the study ($p > 0.05$). There was no statistically significant difference between the two groups in PMSS evaluation ($p > 0.05$) at the end of the study. However, a statistically significant difference was detected in PSS and MPQ evaluations ($p < 0.05$).

Conclusions: Pilates exercise can affectively decrease the perceived stress level and pain severity in PMS affected women. This study highlights the efficacy of Pilates for physiotherapists in PMS symptom reduction. Moreover, the implementation of a self-guided video-based home exercise program could provide patients with practical and time-efficient alternatives.

Keywords: premenstrual syndrome; pilates; stress; pain

Ginekologia Polska 2025; 96, 2: 102–108

INTRODUCTION

Premenstrual disorders include a spectrum of conditions, including premenstrual syndrome, premenstrual dysphoric disorder, and the premenstrual exacerbation of an existing medical condition [1]. The premenstrual phase occurs 7–10 days before the onset of menstruation. Premenstrual syndrome (PMS) is a prevalent issue amongst women today, and it has physical and psychological effects on women [2].

Several evaluation methods are utilized to examine the physical and psychological alterations women undergo from the premenstrual phase through to menstrual bleeding. One commonly employed scale is the Premenstrual Syndrome Scale (PMSS), which encompasses various aspects and inquiries. The PMSS scores can indicate the intensity of premenstrual reactions experienced [3]. There are various pharmacological and non-pharmacological strategies available to manage premenstrual symptoms. The most important of the non-pharmacological methods are exercise interventions. Specifically, aerobic, swimming, yoga-based, and Pilates-based exercises have demonstrated efficacy in mitigating premenstrual symptoms [4]. Pilates exercises have been shown to manage posture disorders and balance problems effectively [5]. Moreover, positive effects have been observed in pain reduction, enhanced quality of life, and mitigation of premenstrual syndrome symptoms [6, 7]. Employing modalities that decrease premenstrual symptoms for women and increasing their awareness in this domain may alleviate discomforts including pain, stress, and mood disturbances encountered before menstrual bleeding. This, in turn, could establish a zone of comfort for women during the premenstrual phase.

Corresponding author:
Ömer Şevgin
Üsküdar Unıversity, İstanbul, Türkiye
e-mail: omer.sevgin@uskudar.edu.tr

Received: 12.11.2023 Accepted: 22.07.2024 Early publication date: 29.10.2024

The objective of this investigation was to examine the impact of Pilates routines on symptoms of premenstrual syndrome, levels of perceived stress, and severity of pain.

MATERIAL AND METHODS

Study design

This study was conducted between February 2023 and October 2023, following ethical approval from the Non-Interventional Research Ethics Committee of Üsküdar University (61351342). The study was carried out as a randomized controlled parallel-group study, adhering to the principles of human experimentation outlined in the Declaration of Helsinki and receiving approval from the ethics committee. This study's clinical trial number is NCT05998044.

Sample size calculation

The power analysis of the study determined a sample size within a 95% confidence interval for an effect size of 0.05 and a 5% level of error. Consequently, the intervention and control groups were planned to have a minimum of 23 participants each. Statistical procedures were performed using G*Power 3.1.9.4 software.

Randomization

The research was conducted as a parallel-group study with randomized controlled manner. The names of the female volunteers who met the inclusion criteria for the study were listed on slips of paper and placed into a bag. The slips were then randomized by an evaluator using the lottery method to form groups.

Participants were given information about the objectives, duration, assessment methods and procedures of the study. Before completing the questionnaires and necessary assessments the informed consent forms were obtained from participants. Fifty-five participants were initially approached to participate in the study. However, five participants were excluded due to failure to meet the inclusion criteria, and four participants were unable to regularly complete the exercises. The participants were randomly allocated to two groups of equal size in accordance with a controlled procedure. The study sample comprised 46 individuals, with 23 subjects in both the intervention and control groups. None of the 46 participants dropped out, and all were included in the final analysis (Fig. 1).

Inclusion criteria of the study were determined as being a woman between the ages of 18–35, not having an obstacle to exercise (not having orthopedic, cardiopulmonary, mental diseases, etc. that would prevent exercise), not having given birth, having a score above the mild level in the PMSQ score, and having a normal menstrual cycle. Exclusion criteria were being on regular medication, being pregnant, being in a menopausal period, and having any gynecological disease (endometriosis, ovarian cyst, pelvic infection, fibroid/uterine tumors, *etc.*). Also, individuals who were regular drug users were not included in the study and were therefore excluded from the study.

Research groups

At the beginning and end of the study, all participants completed evaluation questionnaires using Google Surveys (through the link provided via email and WhatsApp applications) or paper questionnaires to establish the intervention and control groups. The participants' sociodemographic characteristics were evaluated using the sociodemographic information form. The scoring of premenstrual symptoms was determined with the Premenstrual Syndrome Scale (PMSS), stress levels were scored with the Perceived Stress Scale (PSS), and pain status was assessed and scored using the McGill Melzack Pain Scale (MPQ).

Control group: Participants in the control group were instructed to refrain from engaging in regular exercise activities for a period of eight weeks. At the conclusion of the eight-week interval, the assessment surveys were re-administered.

Intervention group: Before beginning the intervention exercises, we conveyed general information about Pilates to participants through face-to-face meetings or online communication via WhatsApp and Zoom. After completing the evaluation questionnaires, participants were sent a Google Drive link to access a video recording of the Pilates exercises. This enabled the patients to be informed about how to perform the exercises correctly. They were instructed to perform the exercises twice a week for 8 weeks. The physiotherapist provided written, practical, and verbal explanations for all exercises in the video recording and instructed the participants to perform them. Weekly contact was made via phone to confirm exercise completion.

The participants engaged in the prescribed exercise regimen two times per week for eight weeks. This was a mandatory requirement. Given that the participants were permitted to determine the days on which they exercised, they were able to avoid any potential issues associated with exercising during their menstrual periods.

In the Pilates exercise program, the warm-up phase lasted 10 minutes, the stretching phase 5 minutes, and the average duration of the exercises was 30–40 minutes. The initial four exercises were allocated for the warm-up phase while the final four exercises were designated for the stretching phase. Each exercise entailed performing a single set of 8 repetitions, except for the Hundred exercise which had 10 sets of 10 repetitions. The number of repetitions was gradually raised every two weeks to 10, 12, and 14 repetitions, correspondingly. Participants were instructed to activate the video recording every time they carried out

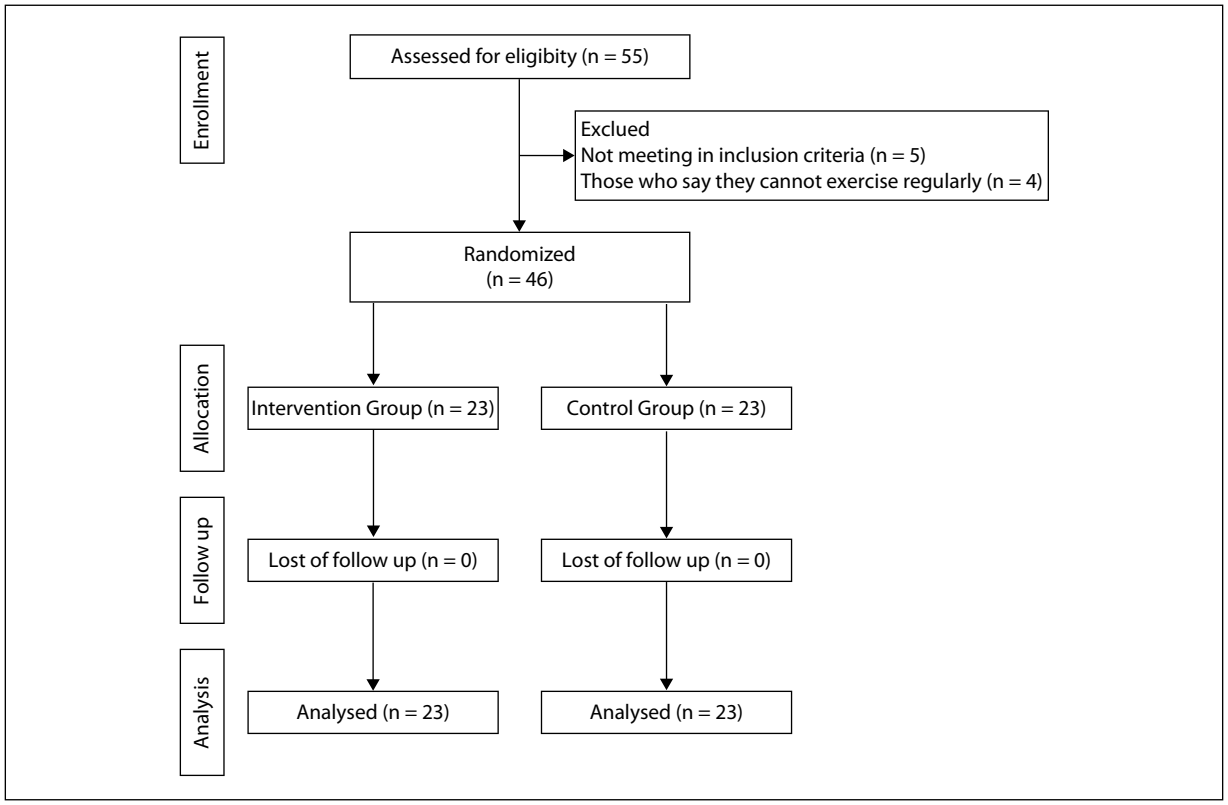


Figure 1. CONSORT diagram of the study

the exercises and then perform the exercises according to the video demonstrations. After eight weeks, participants completed reevaluation questionnaires. The exercise program consisted of Arm Circles, Toe Touch, Bridge, Shoulder Bridge, Chest, Lift Hundred, Roll Up, Leg Circles Chris Cross, Side Kick, Side Leg Circles, one leg kick, double leg kick, Swan, Single leg Stretch, Double leg Stretch, Saw and Spine Stretch (Fig. 2 A–R).

Outcome measures

Sociodemographic Information Form

To identify the personal and menstrual period traits of participants, the sociodemographic information form included questions on age, height, weight, age at menarche (in years), menstruation length (in days), menstrual cycle duration (in weeks), employment status, smoking habits, marital status, and level of education.

Premenstrual Syndrome Scale (PMSS)

The PMSQ is a 44-item, five-point Likert scale (never, very rarely, sometimes, often, always). The scoring is done by taking into account the condition "within one week before menstruation". In the scoring of the scale, "Never" option is evaluated as 1 point, "Very rarely" option as 2 points, "Sometimes" option as 3 points, "Frequently" option as 4 points and "Continuously" option as 5 points [8].

Perceived Stress Scale (PSS)

The Perceived Stress Scale, developed by Cohen et al. in 1983, has been extensively tested for validity and reliability in many studies. Comprised of 14 five-point Likert-type items, the scale offers response options ranging from "never (0)" and "almost never (1)" to "sometimes (2)," "often (3)," and "very often (4)." Items 4–7, 9, 10 and 13 are reverse-scored on this 14-item form [9]. The scale can yield scores from 0 to 56. A high total score on the Perceived Stress Level Scale indicates elevated levels of stress. Scores between 0 and 35 indicate a positive stress level, with participants demonstrating effective stress coping strategies or functional coping mechanisms. Participants who scored between 36 and 56 on the stress coping scale were found to use ineffective methods to manage stress.

McGill Melzack Pain Questionnaire (MPQ)

The MPQ is composed of four sections. The initial section comprises two depictions of the body, which depict the front and rear aspects to identify the regions of the body that have been affected by the patient's pain. Following that, the patient is requested to indicate the site of the pain on the body drawing, and if the pain is deep or on the surface of the body, mark it with the letter 'D' or 'S', correspondingly. In the subsequent part, the patient is queried about the pain's similarity to other sensations. There are 20 sets

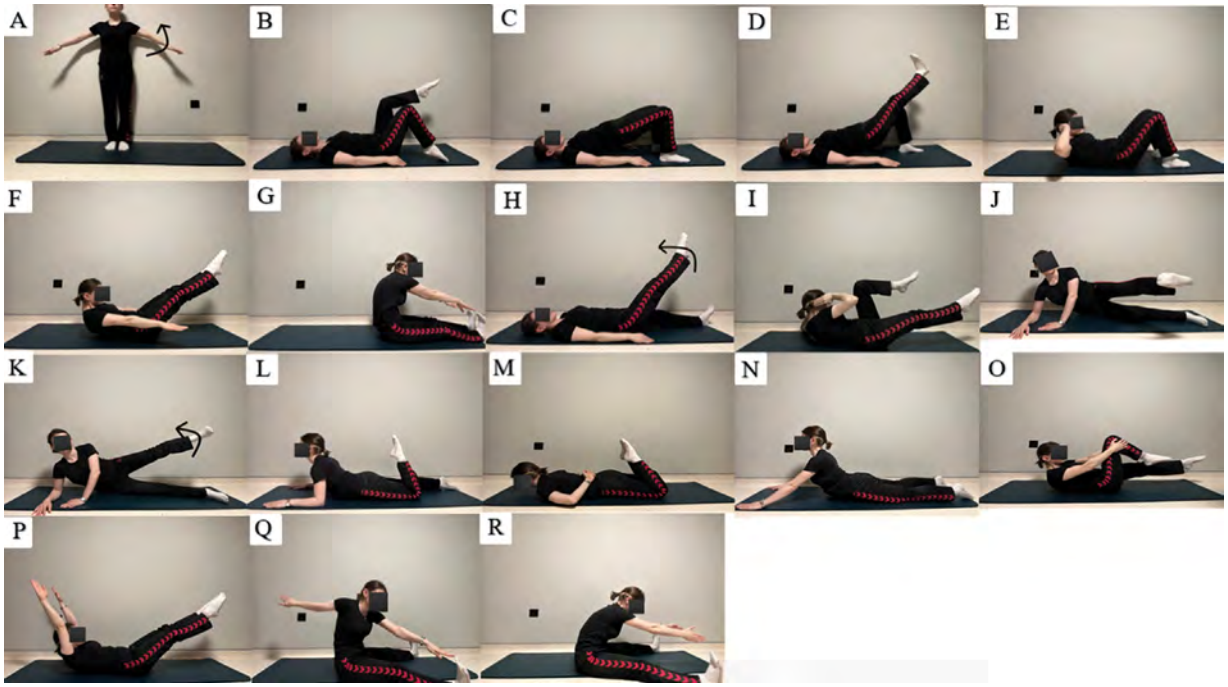


Figure 2. The Pilates exercise program

of 2 to 6 descriptive words which delineate the various aspects of pain objectively, including the sensory, perceptual, and evaluative dimensions. The initial 10 sets relate to the sensory dimension, followed by 5 sets relating to the perceptual dimension. The 16th set relates to evaluation and the concluding 4 sets relate to the multidimensional aspects of pain. The patient selects the suitable words from the respective category. Part three inquiries about the connection between pain and time. The fourth section consists of questions intended to gauge the intensity of pain, and a rating scale utilizing descriptive words is used to evaluate this [10].

Analyzing the data

Statistical analysis was performed using SPSS 28.0.1.1.1. The Shapiro-Wilk and Kolmogorov-Smirnov tests were used to assess the conformity of the variables to the normal distribution. The continuous variables were reported as mean ± standard deviation if they conformed to normal distribution, while median (minimum–maximum) values were reported for those that did not correspond to normal distribution. Categorical variables were presented as n (%). Independent group comparisons were conducted using the Mann-Whitney U test following a normality test, whilst comparisons between dependent groups were undertaken with the Wilcoxon Signed Ranks test. Results were interpreted as $p < 0.05$ indicating a statistically significant difference and $p > 0.05$ indicating no significant difference.

RESULTS

Demographic characteristics of the participants

Table 1 provides the sociodemographic and menstrual characteristics of the participants, including their age, height, weight, age at menarche, duration of menstruation, and menstrual cycle length. Upon comparison of the intervention and control groups, there was no statistically significant difference between the two groups in terms of age, age at menarche, duration of menstruation, and menstrual cycle length ($p > 0.05$), indicating homogenous distribution between the groups.

Between group and within group pre and post intervention measurements

Table 2 displays the pre- and post-questionnaire data of the MPQ for the intervention group. Although a statistically significant difference was found between pre- and post-exercise evaluations, no such difference was observed in the control group ($p > 0.05$). Additionally, statistically significant difference in PMSS scores was observed between the pre- and post-exercise assessments of the intervention group ($p < 0.05$). Conversely, no statistically significant difference in PMSS scores was observed between the pre- and post-exercise assessments of the control group ($p > 0.05$). The intervention group exhibited a significant increase in PSS scores, whereas no significant difference was observed in the control group ($p > 0.05$) during the pre- and post--exercise evaluations.

Table 1. Sociodemographic and menstrual characteristics of the participants

Variables	Intervention mean ± SD	Control mean ± SD	p value
Age [years]	25.69 ± 1.94	25.69 ± 1.84	0.982
Age at menarche [years]	13.26 ± 0.23	12.78 ± 0.39	0.073
Duration of menstruation [day]	6.56 ± 0.33	6.47 ± 0.25	0.973
Menstrual cycle duration [week]	4.04 ± 0.14	4.26 ± 0.26	0.923

*p < 0.05; SD — standard deviation

Table 2. Pre- and post-exercise measurements of the PSS, PMSS and PSS measurements

Parameters		Pretreatment mean ±SD	Posttreatment mean ± SD	p value
MPQ	Intervention	72.34 ± 8.27	67.34 ± 10.25	0.031*
	Control	72.26 ± 10.1	69.82 ±12.15	0.348
PMSS	Intervention	139 ± 29.89	118.13 ± 30.34	0.002*
	Control	122.91 ± 37.2	128.39 ± 38.91	0.285
PSS	Intervention	27.3 ± 8.88	23.17 ± 6.54	0.008*
	Control	27.82 ± 5.15	26.78 ± 6.31	0.420

*p < 0.05; MPQ — McGill Pain Questionnaire; PSS — Perceived Stress Scale; PMSS — Premenstrual Syndrome Scale

Table 3 outlines the PMSS, PSS, and MPQ findings for both the intervention and control groups. The PMSS total score showed no significant difference post-exercise (p > > 0.05). However, PSS and MPQ total scores were found to differ significantly between groups before and after exercising (p < 0.05).

DISCUSSION

The majority of women experience symptoms of PMS. These symptoms can affect people's quality of life, causing stress, pain and mood disorders. Exercise has been proven to effectively reduce the severity of such symptoms and improve quality of life [11–13]. There is limited number of research in the area of exercise therapy for PMS. Our study is the first randomized controlled study to compare the functional and patient-reported outcomes of PMS affected women who underwent the There is a paucity of research in the field of exercise therapy for PMS. Our study represents the first randomized controlled study to examine the functional and patient-reported consequences of PMS in women who performed the Pilates exercises. The main findings of this study were: (I) There was a significant decrease in symptom severity as determined by the PSS subsequent to the intervention in comparison to the initial evaluation; (II) Upon comparison of the two groups, it was discovered that the intervention group exhibited significantly lower PSS scores than the control group; (III) Despite a significant reduction in PMSS scores in the intervention group, the post treatment results showed no significant difference between the two cohorts in statistical terms; (IV) Participants in the intervention group were shown to have lower MPQ scores than those in the control group.

PMS symptoms may vary depending on the age at which menarche occurs and the length of menstruation. Thus, the impact of these variables on PMS symptoms could differ among individuals, making a personalized evaluation necessary. This outcome indicates that PMS is a multifaceted syndrome with interactions among numerous variables [13–17]. A study investigated the impact of yoga exercises on PMS symptoms in employed women and found that the symptoms were lower compared to those who were unemployed [11]. In our research, we found no significant difference between the average PMSS scores of employed and unemployed women. Furthermore, the nature of one's occupation could influence PMS symptoms, which may vary across different occupational groups. Hence, it is necessary to investigate the impact of work experiences on the PMSS score of individuals. A study involving 40 university students experiencing PMS symptoms observed a decrease in symptoms when Pilates exercises were combined with vitamin E. Another study investigating the effects of Pilates exercises on university students with PMS symptoms reported a reduction in symptoms after three months of exercising [13, 18]. Upon analysis of the PSS evaluation of the intervention group in our study, a notable reduction in symptom severity was observed compared to the initial evaluation. Compared to controls, the intervention group showed more decrease in all 9 PSS sub parameters, including depressed affect, anxiety,

Table 3. PMSS, PSS, and MPQ results of the intervention and control groups post treatment

Parameters	Intervention group mean ± SD	Control group mean ± SD	p value
MPQ	67.34 ± 10.25	69.82 ± 12.15	0.030*
PMSS	118.13 ± 30.34	128.39 ± 38.91	0.080
PSS	23.17 ± 6.54	26.78 ± 6.31	0.007*

*p < 0.05; MPQ — McGill Pain Questionnaire; PSS — Perceived Stress Scale; PMSS — Premenstrual Syndrome Scale

fatigue, irritability, depressive thoughts, pain, appetite changes, sleep changes and bloating. Although there was a reduction in the PMSS score in the intervention group, the results did not show a statistically significant difference between the two groups. Therefore, it cannot be clearly concluded that the intervention group was more successful in reducing symptoms than the control group. This may be due to factors such as the small sample size, the duration of the exercises and the length of the intervention period.

Pilates may reduce stress in PMS, with studies suggesting that it is more effective than aerobic exercise at reducing both stress and psychological symptoms [19, 20]. In our study, there was a significant decrease in PSS scores in the intervention group at the final assessment in comparison to the first assessment. In other words, people's perceived stress levels decreased as a result of doing Pilates. Comparing both groups, it was found that the intervention group had statistically significant lower PSS scores than the control group. In this context, the reduction in stress levels can also be associated with the Pilates exercises and therefore the Pilates principles.

Regular exercise helps to strengthen muscles, increase flexibility, improve circulation and increase the release of endorphins. Endorphins act as the body's natural painkillers and happiness hormones, so an increase in endorphin levels through exercise helps to reduce pain. Our investigation revealed a substantial reduction in the intervention group's MPQ scores at the final assessment in contrast to the first assessment, with statistical significance recorded. Conversely, no significant score reduction was observed in the control group at the last assessment in comparison to the first. It was also shown that people in the intervention group experienced a greater reduction in pain than those in the control group. It is encouraging that the intervention group showed a reduction in PMS symptoms. This can allow individuals to exercise at their leisure, unrestricted by time or space. These results showed that Pilates exercise programs recorded via video for women with PMS symptoms have no adverse effects, making for a safe and easily accessible treatment approach.

This study provides an opportunity to further understand the beneficial effects of exercise on PMS management for gynecologists, physiotherapists, and other healthcare professionals involved in PMS management. Increasing awareness of the potential health benefits of exercise for people with PMS may increase referrals to exercise-based physiotherapy programs. The present research provides valuable objective findings regarding the functional and self-reported results of various exercise programs for women with PMS. These observations could effectively assist physiotherapists in determining the most suitable exercise regimen to enhance selective patient outcomes.

The current randomized controlled trial is a novel contribution to the field of exercise therapy for PMS. This study presents the first evaluation of Pilates exercise programs in women with PMS, analyzing both functional and patient-reported outcomes. Recognizing the significance of limitations in this study, the utilization of general PSS and MPQ questionnaires instead of a condition-specific questionnaire could have introduced external factors like psychosocial or life stressors that may have affected the study's outcomes. Expanding the intervention technique and evaluating different exercise modalities or extending the intervention duration of the Pilates exercise studies are prospective focuses for future research.

CONCLUSIONS

Pilates practice resulted in a significant reduction in PMSS, PSS and MPQ scores. Notably, while no meaningful variance between the intervention and control groups' PMSS score was perceived during the post-intervention data comparison, there was a discernible difference in PSS and MPQ scores. We demonstrated that correct muscle usage and improved muscle awareness through Pilates may effectively alleviate the symptoms of PMS. The results suggest that individuals suffering from PMS symptoms may gain advantages from non-pharmacological interventions. Therefore, in order to guide patients towards these interventions, health professionals are advised to educate patients about some exercise modalities such as home or video-based exercises.

Article information and declarations

Data availability statement

The data is available upon request.

Ethics statement

The ethical approval was taken from the Non-Interventional Research Ethics Committee of Üsküdar University (61351342). This study's clinical trial number is NCT05998044.

Author contributions

Şeyma Aykut — conceptualization, methodology, data curation, writing — original draft preparation, visualization, investigation; Ömer Şevgin — conceptualization, methodology, data curation, writing — rriginal draft preparation, supervision, validation, writing — reviewing and editing.

Funding

None.

Acknowledgments

None.

Conflict of interest

The authors declare no conflict of interest.

Supplementary material

None.

REFERENCES

1. Yonkers KA, Simoni MK. Premenstrual disorders. Am J Obstet Gynecol. 2018; 218(1): 68–74, doi: 10.1016/j.ajog.2017.05.045, indexed in Pubmed: 28571724.
2. Gudipally PR, Sharma GK. Premenstrual Syndrome. StatPearls. Treasure Island. 2023.
3. Kahyaoglu Sut H, Mestogullari E. Effect of Premenstrual Syndrome on Work-Related Quality of Life in Turkish Nurses. Saf Health Work. 2016; 7(1): 78–82, doi: 10.1016/j.shaw.2015.09.001, indexed in Pubmed: 27014495.
4. Yesildere Saglam H, Orsal O. Effect of exercise on premenstrual symptoms: A systematic review. Complement Ther Med. 2020; 48: 102272, doi: 10.1016/j.ctim.2019.102272, indexed in Pubmed: 31987230.
5. Li F, Omar Dev RD, Soh KG, et al. Effects of Pilates on Body Posture: A Systematic Review. Arch Rehabil Res Clin Transl. 2024; 6(3): 100345, doi: 10.1016/j.arrct.2024.100345, indexed in Pubmed: 39372244.
6. Sanchez B, Kraemer W, Maresh C. Premenstrual Syndrome and Exercise: A Narrative Review. Women. 2023; 3(2): 348–364, doi: 10.3390/women3020026.
7. Çitil ET, Kaya N. Effect of pilates exercises on premenstrual syndrome symptoms: a quasi-experimental study. Complement Ther Med. 2021; 57: 102623, doi: 10.1016/j.ctim.2020.102623, indexed in Pubmed: 33246104.
8. Çitil ET, Çitil Canbay F. Premenstrual syndrome severity in Turkey: a meta-analysis study. Psychol Health Med. 2023; 28(7): 1783–1794, doi: 10.1080/13548506.2022.2105914, indexed in Pubmed: 35903865.
9. Vannuccini S, Clemenza S, Cassioli E, et al. Uterine Fibroids, Perceived Stress, and Menstrual Distress: a Key Role of Heavy Menstrual Bleeding. Reprod Sci. 2023; 30(5): 1608–1615, doi: 10.1007/s43032-022-01126-3, indexed in Pubmed: 36471219.
10. Puto G, Repka I, Brzyski P. Pain measurement in the older people: evaluation of the psychometric properties of the Geriatric Pain Measure (GPM-24) - polish version. BMC Geriatr. 2021; 21(1): 560, doi: 10.1186/s12877-021-02495-1, indexed in Pubmed: 34663222.
11. Tsai SY. Effect of Yoga Exercise on Premenstrual Symptoms among Female Employees in Taiwan. Int J Environ Res Public Health. 2016; 13(7), doi: 10.3390/ijerph13070721, indexed in Pubmed: 27438845.
12. El-Lithy A, El-Mazny A, Sabbour A, et al. Effect of aerobic exercise on premenstrual symptoms, haematological and hormonal parameters in young women. J Obstet Gynaecol. 2015; 35(4): 389–392, doi: 10.3109/01443615.2014.960823, indexed in Pubmed: 25279689.
13. Çitil ET, Kaya N. Effect of pilates exercises on premenstrual syndrome symptoms: a quasi-experimental study. Complement Ther Med. 2021; 57: 102623, doi: 10.1016/j.ctim.2020.102623, indexed in Pubmed: 33246104.
14. Goker A, Artunc-Ulkumen B, Aktenk F, et al. Premenstrual syndrome in Turkish medical students and their quality of life. J Obstet Gynaecol. 2015; 35(3): 275–278, doi: 10.3109/01443615.2014.948820, indexed in Pubmed: 25140580.
15. Sahin S, Ozdemir K, Unsal A. Evaluation of premenstrual syndrome and quality of life in university students. J Pak Med Assoc. 2014; 64(8): 915–922, indexed in Pubmed: 25252518.
16. Alpaslan AH, Avcı K, Soylu N, et al. Association between premenstrual syndrome and alexithymia among Turkish University students. Gynecol Endocrinol. 2014; 30(5): 377–380, doi: 10.3109/09513590.2014.887066, indexed in Pubmed: 24512608.
17. Raval CM, Panchal BN, Tiwari DS, et al. Prevalence of premenstrual syndrome and premenstrual dysphoric disorder among college students of Bhavnagar, Gujarat. Indian J Psychiatry. 2016; 58(2): 164–170, doi: 10.4103/0019-5545.183796, indexed in Pubmed: 27385849.
18. Omidali F. Effects of Pilates and Vitamin E on Symptoms of Premenstrual Syndrome. Journal of Research Development in Nursing and Midwifery. 2016; 13(1): 1–9, doi: 10.18869/acadpub.jgbfnm.13.1.1.
19. ERBAŞ N, ALTUNBAŞ N. According to Some Variables in Girls A High School Determining the Premenstrual Syndrome Violence and Perceped Stress Level. Acibadem Universitesi Saglik Bilimleri Dergisi. 2021; 12(2), doi: 10.31067/acusaglik.849971.
20. Samadi Z, Zeinab T, Valiani M. Effects of Pilates and Aerobic Exercise on Symptoms of Premenstrual Syndrome in Non-Athlete Girls. Journal of Isfahan Medical School. 2013; 30: 1880–1891.

VIA MEDICA

ORIGINAL PAPER / GYNECOLOGY

Ginekologia Polska
2025, vol. 96, no. 2, 109–118

ISSN 0017–0011, e-ISSN 2543–6767

DOI: 10.5603/gpl.96519

Assessment of the impact of *VDR* polymorphisms on selected hormonal, metabolic and mineral balance markers in young women with hyperandrogenism

Izabela Uzar[1], Anna Bogacz[2], Elzbieta Sowinska-Przepiera[3], Anhelli Syrenicz[3], Adam Kaminski[4], Marlena Wolek[2], Boguslaw Czerny[1, 2]

[1]*Department of General Pharmacology and Pharmacoeconomics, Pomeranian Medical University in Szczecin, Poland*
[2]*Department of Stem Cells and Regenerative Medicine, Institute of Natural Fibers and Medicinal Plants, Plewiska, Poland*
[3]*Department of Endocrinology, Metabolic Diseases, and Internal Diseases, Pomeranian Medical University in Szczecin, Poland*
[4]*Department of Pediatric Orthopedics and Musculosceletal Oncology, Pomeranian Medical University in Szczecin, Poland*

ABSTRACT

Objectives: Hyperandrogenism is a frequently recognized endocrine imbalance in which there is excessive production of androgens. The purpose of the study was to investigate the impact of vitamin D receptor (*VDR*) gene polymorphisms on chosen bone metabolism and biochemical parameters in women with hyperandrogenism.

Material and methods: Eighty young females with hyperandrogenism were enrolled in the study, in whom selected parameters of bone turnover, endocrine and metabolic parameters were determined. Two polymorphisms of the *VDR* gene were analyzed: rs731236 (*TaqI*) and rs1544410 (*BsmI*), using real-time polymerase chain reaction (PCR). Statistical tests were performed in this research with the program SPSS Statistics 17.0 for Windows.

Results: The rs731236 and rs1544410 polymorphisms of the *VDR* gene turned out to be statistically significantly related to the concentration of insulin determined in the 60'glucose tolerance test. There was no relationship between the studied polymorphisms of the *VDR* gene and the determined parameters of bone metabolism and other biochemical parameters.

Conclusions: The research presented that *VDR* gene variants may influence disturbances in carbohydrate metabolism in young women with hyperandrogenism.

Keywords: hyperandrogenism; *VDR* polymorphisms; bone metabolism; biomarkers; hormonal parameters

Ginekologia Polska 2025; 96, 2: 109–118

INTRODUCTION

Hyperandrogenism is characterized by excessive production of androgenic hormones in women and is their most common endocrine disorder, affects up to 10% of females of reproductive age [1]. In about 80% of cases, hyperandrogenism accompanies polycystic ovary syndrome (PCOS). Other causes of excessive androgenization include non-classical congenital adrenal hyperplasia (NCAH), ovarian tumors, and menopause. Idiopathic hyperandrogenemia or idiopathic hirsutism can affect 3.9–15.8% of women [1–3]. In healthy women, androgens are produced in almost equal amounts by the ovaries and adrenal glands. Determining the origin of androgens in hyperandrogenism may be useful in understanding the type and specificity of disorders accompanying hyperandrogenization. The ovaries are the main source of androgens in idiopathic hyperandrogenism and PCOS, and the adrenal glands in NCAH [4]. Hyperandrogenism in women is characterized by progressive defeminization and the appearance of androgenization symptoms such as seborrhea, acne, hirsutism, androgenic alopecia and metabolic changes [1, 5]. Hyperandrogenism in young females is associated with a wide variation in the degree of expression of individual symptoms, and the degree of their intensity and type do not indicate a specific cause. The symptoms of hyperandrogenization may also appear when the serum concentration of androgens is normal [6, 7].

Corresponding author:
Izabela Uzar
Department of Pharmacology and Pharmacoeconomics, Pomeranian Medical University in Szczecin, 48 Żołnierska St., 71–230 Szczecin, Poland
e-mail: uzari@wp.pl

Received: 14.07.2023 Accepted: 2.07.2024 Early publication date: 18.12.2024

The active form of vitamin D_3 with hormonal properties is an important factor regulating the calcium-phosphate balance in the human body. However, the role of vitamin D_3 is not limited to its influence on bone metabolism; it is also an important parameter influencing the hormonal balance, and its deficiency plays an important role in the pathogenesis of many endocrine and autoimmune diseases and cancers [8, 9]. It is also known that vitamin D_3 is important for fertility in both women and men by influencing the expression of VDR receptors for vitamin D_3 in such organs as ovaries, uterus, placenta, testes, pituitary and hypothalamus [9, 10]. It has been shown that low vitamin 25 (OH) D levels in women aged 35–51 may be associated with high levels of follicle stimulating hormone (FSH), which leads to lower estrogen levels [10]. The presence of VDR receptor polymorphisms is also associated with metabolic and endocrine disorders in PCOS and hyperandrogenism [11]. Vitamin D_3 plays a role in the synthesis of sex hormones by affecting the expression and activity of enzymes involved in steroidogenesis, and its deficiency may contribute to the occurrence of endometriosis due to its immunomodulatory and anti-inflammatory properties. It has been shown that the active form of vitamin D_3 — calcitriol — increases the production of progesterone by 13%, estradiol by 9%, and estrone by 21% [12]. Calcitriol may also affect the activity of aromatase catalyzing the conversion of androgens to estrogens [9].

The effect of vitamin D on various tissues is modulated by its receptor — VDR. By combining with the VDR receptor, vitamin D activates the transcription of genes dependent on it [11]. The vitamin D receptor gene is highly polymorphic. The *BsmI* polymorphism (rs1544410) seems to be related to metabolic and hormonal disorders in PCOS, but not all authors agree on this. However, it is believed that the presence of this polymorphism increases the risk of PCOS as well as influences the level of vitamin D [11, 13, 14].

In the case of *TaqI* polymorphism of the VDR receptor (rs731236), most authors show its relationship with an increased risk of PCOS and significantly affect the levels of hormonal and metabolic parameters, as well as an increase in the prevalence of hirsutism and its severity in PCOS [13]. In numerous publications to date, the relationships between *VDR* polymorphisms and metabolic and hormonal parameters in PCOS have been analyzed [13]. There is no similar research on disorders in young women with idiopathic hyperandrogenism.

Hyperandrogenism is a complex disorder with a genetic basis involving natural and epigenetic variables. The explanation of the hereditary background aims to improve diagnosis and treatment options. The aim of this project was to analyze the relationship between the occurrence of rs731236 (*TaqI*) and rs1544410 (*BsmI*) polymorphisms and selected biochemical, hormonal and bone metabolism parameters in young females with hyperandrogenism.

MATERIAL AND METHODS

Patients

The research included 80 young females aged 18 to 35 years with hyperandrogenism examined in 2013 and 2015 in the Department of Endocrinology, Metabolic Diseases and Internal Medicine at the Pomeranian Medical University in Szczecin, Poland.

The following were the inclusion criteria for the study: Caucasian race, absence of menstruation for at least six months followed by at least three months of oligomenorrhea, clinical symptoms of masculinization: acne, seborrhea, hirsutism, without long-term medications, and without significant abnormalities on physical examination. The exclusion criteria were: PCOS, congenital adrenal hyperplasia or premature ovarian failure, low birth weight, prematurity, nutritional disorders, abnormal nutrition during childhood or adolescence, growth and weight gain diseases, intensive sport, metabolic diseases, chronic use of stimulants or drugs that affect bone metabolism, and bone disease in the family. All patients also had a concentration of androstenedione (a precursor of androgens), leptin and body mass index (BMI) above reference values. Patients with idiopathic hyperandrogenism (the presence of clinical and biochemical hyperandrogenism in the absence of PCOS features), were included in the study [15, 16].

The severity of hirsutism was determined according to the Ferriman–Gallwey scale (≥ 8 points). We selected two single nucleotide polymorphisms (SNPs): rs731236, rs1544410 on the basis of the following criteria: minor allele frequency > 0.2, functional relevance and importance, SNPs significantly associated with bone mineral density (BMD) in previous studies (Fig. 1).

The research was approved by the Bioethics Committee of the Pomeranian Medical University, number KB-0012/115/15 of 16 November 2015. The study was performed in accord with the Helsinki Declaration (1975, corrected 2000).

Analysis of serum concentrations for selected factors

Each patient had fasting blood collection at 8 am and centrifuged. Immunoenzymatic tests (ELISA — DRG International, Inc.) were used to determine sRANKL (free and bound RANKL), osteoprotegerin (OPG) and 25-OH vitamin D total concentrations. Serum parathormone and calcitonin concentrations were measured with a chemiluminescent assay (Immulite 1000, Siemens). Electrochemiluminescent tests (Cobas, Roche Diagnostic) were used to determine luteinizing hormone (LH), folliculotropic hormone

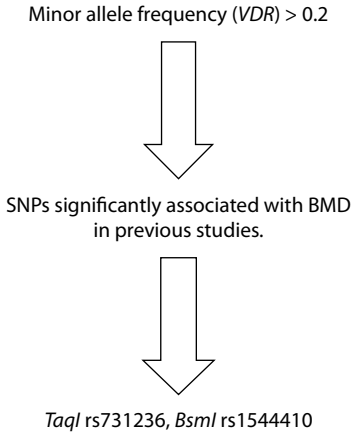


Figure 1. Selection of rs for the study

(FSH), 17-hydroxyprogesterone, estradiol, prolactin (PRL), testosterone (T), androstenedione, dehydroepiandrosterone sulfate (DHEA-SO4), sex hormone binding globulin (SHBG). Free testosterone concentration was calculated from the free androgen index ((FAI = TT/SHBG × 100%). The analytical sensitivities of the assays were: calcitonin — 2.0 pg/mL, parathormone — 3.1 pg/mL, 25-OH vitamin D total — 5.6 nmol/L, sRANKL — 0.5 pmol/L, OPG — 0.14 pmol/L, leptin — 2.0 ng/mL. Tests were conducted according to the manufacturer's instructions and subjected to quality control using the manufacturer's two-level control set. Samples were performed in duplicate. The microplate reader and microplate washer used for ELISA assays and the precision of the assays were checked using Pathozyme ELISA Sure kit (Omega Diagnostics, UK).

Bone mineral density (BMD) analysis

Bone mineral density (BMD) analysis was performed at the Department of Endocrinology, Metabolic Diseases and Internal Medicine at the Pomeranian Medical University in Szczecin, Poland. BMD was analyzed in the lumbar spine from L2 to L4 vertebrae using Dual Energy X-ray Absorptiometry (DEXA) method with the LUNAR DPX 100 (Lunar Corp., Madison, USA). The quantitative body mass composition (*i.e.* total body fat — BF), android, gynoid fat, visceral adipose tissue (VAT) and lean body mass were measured in all participants by DEXA using an automatic whole body scanning method. The original manufacturer's software (Body Composition) was used to determine the individual areas of measurements (female, male and visceral region). All patients were imaged using the same DEXA Lunar device to minimize inter-device variability. Quality assurance on this device was performed as recommended by the International Society for Clinical Densitometry (ISCD) [17].

Analysis of the rs731236 and the rs1544410 polymorphisms of the *VDR* gene

Analysis of *VDR* gene polymorphisms was conducted in the Clinical Laboratory at the Department of Endocrinology, Metabolic Diseases, and Internal Medicine at Pomeranian Medical University. Genomic DNA was isolated from peripheral blood using a QIAamp Blood Mini Kit (Qiagen GmbH, Hilden, Germany) according to the manufacturer's procedure. *VDR* genetic variants: rs731236 (*TaqI*), rs1544410 (*BsmI*) were selected for the study according to the NCBI SNP database http://www.ncbi.nlm.nih.gov/SNP. Genotyping was conducted RT-PCR with TaqMan® SNP Genotyping Assays (Thermo Fisher Scientific, Waltham, USA) on a LightCycler 480 according manufacturer's procedure: initial denaturation at 95°C for 10 min, followed by 40 cycles of 95°C for 15 s, 60°C for 1 min, 40°C for 30 s (20 µL reaction mixture).

Statistical analysis

The results of the study were analyzed statistically using SPSS Statistics 17.0 for Windows. Hardy–Weinberg equilibrium of the polymorphisms was analyzed by the chi-square test. We analyzed the frequency of the studied SNPs and the association with selected biochemical and clinical factors using one-way analysis of variance (ANOVA). Values with normal distribution were presented as means ± SEM (standard error of the mean).

RESULTS

We compared the distribution of genotypes frequencies for the rs731236 and rs1544410 polymorphisms of the *VDR* gene in women with hyperandrogenism. For the rs731236 polymorphism, the *AG* was more common (53.8%) compared to the *AA* (32.5%) and *GG* (13.8%) genotypes was observed. In patients with the *VDR* rs1544410 polymorphism, a higher frequency of the *CT* genotype (52.5%) compared to *CC* (32.5%) and *TT* (15.0%) was observed (Tab. 1).

Analysis of the *VDR* polymorphism rs731236 showed a higher concentration of insulin 60' and insulin 120' in women with the *GG* genotype (insulin 60': *GG* — 172.10 ± 36.29 mg/dL vs *AA* — 156.59 ± 16.48 mg/dL, *AG* — 102.74 ± 9.44 mg/dL, p = 0.008; insulin 120': *GG* — 119.65 ± 42.56 mg/dL vs *AA* — 100.79 ± 13.78 mg/dL, *AG* — 67.76 ± 7.94 mg/dL, p = 0.063) (Tab. 4). Vitamin D and vitamin 25 (OH) D measurements showed a higher concentration in women with the *AA* genotype (vitamin D: *AA* — 19.32 ± 3.58 ng/mL vs *AG* — 14.98 ± 1.68 ng/mL, *GG* — 8.06 ± 0.68 ng/mL, p = 0.081; vitamin 25 (OH) D: *AA* — 23.82 ± 1.73 ng/mL vs *AG* — 21.56 ± 0.97 ng/mL, *GG* — 17.38 ± 2.39 ng/mL, p = 0.067) (Tab. 5).

Table 1. The frequency of alleles and genotypes of the *VDR* polymorphisms in women with hyperandrogenism

VDR TaqI rs731236			VDR BsmI rs1544410		
Genotype	**Observed value, n [%]**	**Expected value [%]**	**Genotype**	**Observed value, n [%]**	**Expected value [%]**
AA	26 (32.5)	35.3	*CC*	26 (32.5)	34.5
AG	43 (53.8)	48.2	*CT*	42 (52.5)	48.5
GG	11 (13.8)	16.5	*TT*	12 (15.0)	17.0
Total	80 (100)	100	**Total**	80 (100)	100
Allele			**Allele**		
A	95 (59.38)	–	*C*	94 (58.75)	–
G	65 (40.62)	–	*T*	66 (41.25)	–
Total	160 (100)	–	**Total**	160 (100)	–

Table 4. Analysis of biochemical factors vs *VDR* gene variants in women with hyperandrogenism

Parameter	VDR Taq I rs731236	Mean ± SEM	p value	VDR Bsm I rs1544410	Mean ± SEM	p value
Glucose 0′ [mg/dL]	*AA*	90.64 ± 1.89	0.449	*CC*	90.64 ± 1.89	0.449
	AG	89.88 ± 2.17		*CT*	89.88 ± 2.17	
	GG	96.89 ± 9.53		*TT*	96.89 ± 9.53	
Glucose 60′ [mg/dL]	*AA*	130.61 ± 6.44	0.843	*CC*	130.61 ± 6.44	0.843
	AG	135.20 ± 5.41		*CT*	135.20 ± 5.41	
	GG	135.21 ± 9.80		*TT*	135.21 ± 9.80	
Glucose 120′ [mg/dL]	*AA*	109.31 ± 5.55	0.949	*CC*	109.31 ± 5.55	0.949
	AG	107.16 ± 3.92		*CT*	107.16 ± 3.92	
	GG	109.13 ± 11.40		*TT*	109.13 ± 11.40	
Insulin 0′ [µIU/mL]	*AA*	22.49 ± 2.77	0.722	*CC*	22.49 ± 2.77	0.722
	AG	24.55 ± 6.56		*CT*	24.55 ± 6.56	
	GG	31.48 ± 7.71		*TT*	31.48 ± 7.71	
Insulin 60′ [µIU/mL]	*AA*	156.59 ± 16.48	**0.008**	*CC*	156.59 ± 16.48	**0.008**
	AG	102.74 ± 9.44		*CT*	102.74 ± 9.44	
	GG	172.10 ± 36.29		*TT*	172.10 ± 36.29	
Insulin 120′ [µIU/mL]	*AA*	100.79 ± 13.78	0.063	*CC*	100.79 ± 13.78	0.063
	AG	67.76 ± 7.94		*CT*	67.76 ± 7.94	
	GG	119.65 ± 42.56		*TT*	119.65 ± 42.56	
AG	*AA*	1.05 ± 0.06	0.855	*CC*	1.05 ± 0.06	0.655
	AG	1.08 ± 0.05		*CT*	1.09 ± 0.05	
	GG	1.03 ± 0.07		*TT*	1.01 ± 0.07	
VF	*AA*	969.80 ± 242.17	0.701	*CC*	969.80 ± 242.17	0.909
	AG	843.70 ± 146.86		*CT*	872.12 ± 149.74	
	GG	1114.71 ± 347.58		*TT*	988.50 ± 326.40	

*p < 0.05 — comparison between genotypes and the parameters analyzed (one-way ANOVA test); values normally distributed are expressed as means ± SEM; AG — distribution of android and gynoid fat; VF — visceral fat indication

Concentrations of the other parameters analyzed: estradiol, FEI (Free Estradiol Index), prolactin, 17-OH-progesterone, LH, FSH, SHGB, testosterone, BAT, FAI, androstendione, DHEA-SO4, glucose 0′, glucose 60′, glucose 120′, insulin 0′, calcitonin, parathormone, OPG, sRANKL, BMD L1-L4, T-score, Z-score, BMD total, BMI, BMC, AG, VF and TBS in context of the of the rs731236 showed no significant associations (Tab. 2–5).

Analysis of the second *VDR* polymorphism rs1544410 showed higher concentrations of insulin 60′ and insulin 120′ in women with the *TT* genotype

Table 5. Analysis of bone metabolism and biochemical factors vs *VDR* gene variants in women with hyperandrogenism

Parameter	VDR Taq I rs731236	Mean ± SEM	p value	VDR Bsm I rs1544410	Mean ± SEM	p value
Vitamin D [ng/mL]	*AA*	19.32 ± 3.58	0.081	*CC*	19.32 ± 3.58	0.081
	AG	14.98 ± 1.68		*CT*	14.98 ± 1.68	
	GG	8.06 ± 0.68		*TT*	8.06 ± 0.68	
Vitamin 25 [OH] D [ng/mL]	*AA*	23.82 ± 1.73	0.067	*CC*	23.82 ± 1.73	0.153
	AG	21.56 ± 0.97		*CT*	21.28 ± 0.95	
	GG	17.38 ± 2.39		*TT*	18.84 ± 2.61	
Calcitonin [pg/mL]	*AA*	3.30 ± 2.13	0.563	*CC*	3.30 ±2.13	0.565
	AG	1.73 ± 0.21		*CT*	1.64 ± 0.20	
	GG	1.47 ± 0.31		*TT*	1.82 ± 0.45	
PTH [pg/mL]	*AA*	38.60 ± 3.96	0.875	*CC*	38.60 ± 3.96	0.822
	AG	41.46 ± 3.64		*CT*	41.97 ± 3.69	
	GG	41.13 ± 6.62		*TT*	39.36 ± 6.29	
OPG [pmol/L]	*AA*	3.40 ± 0.24	0.127	*CC*	3.4 ± 0.24	0.171
	AG	3.57 ± 0.15		*CT*	3.57 ± 0.16	
	GG	4.37 ± 0.72		*TT*	4.27 ± 0.66	
sRANKL [pmol/L]	*AA*	243.18 ± 48.12	0.603	*CC*	243.18 ± 48.12	0.641
	AG	196.99 ± 23.21		*CT*	199.70 ± 23.64	
	GG	221.65 ± 37.99		*TT*	209.56 ± 36.42	

BMI — body mass index; OPG — osteoprotegerin, PTH — parathyroid hormone

(insulin 60′: *TT* — 172.10 ± 36.29 mg/dL vs *CC* — 156.59 ± 16.48 mg/dL, *CT* — 102.74 ± 9.44 mg/dL, p = 0.008; insulin 120′: *TT* — 119.65 ± 42.56 mg/dL, CC — 100.79 ± 13.78 mg/dL, *CT* — 67.76 ± 7.94 mg/dL, p = 0.063) (Tab. 4). The concentration of vitamin D was higher in women with the *CC* genotype (*CC* — 19.32 ± 3.58 ng/mL vs *CT* — 14.98 ± 1.68 ng/mL, *TT* — 8.06 ± 0.68 ng/mL, p = 0.081) (Tab. 5).

Measurements of the other parameters analyzed: estradiol, FEI, prolactin, 17-OH-progesterone LH, FSH, SHGB, testosterone, BAT, FAI, androstendione, DHEA-SO4, glucose 0′, glucose 60′, glucose 120′, insulin 0′, calcitonin, parathyroid hormone, osteoprotegerin, sRANKL, BMD L1-L4, T-score, Z-score, BMD total, BMI, BMC, AG, VF and TBS in women with hyperandrogenism in relation to the *VDR* rs1544410 polymorphism distribution of genotypes did not show any significant differences (Tab. 2–5).

Moreover, the statistical power for the two only statistically significant comparisons was 0.2396 for *AA* vs *GG* and 0.2592 for *CC* vs *TT*, respectively. These are preliminary results to be confirmed in a larger group. Nevertheless, the highly significant p value (p = 0.008) for both comparisons indicates that such differences may exist.

DISCUSSION

The analysis of the *VDR* gene polymorphisms showed a relationship for the *TaqI* rs731236 and BsmI rs1544410 polymorphisms and the insulin concentration determined at 60 minutes (insulin 60′) in the glucose tolerance test. In the case of the rs731236 *VDR* polymorphism, *GG* homozygotes showed a significantly higher concentration of 60′ insulin compared to *AA* homozygotes and *AG* heterozygotes. For the rs1544410 *VDR* polymorphism, a significantly higher concentration of 60′ insulin was observed in *TT* homozygotes compared to *CC* and *CT* genotypes. For both polymorphisms, a significant trend was observed in relation to the insulin concentration determined in the 120′ glucose tolerance test (insulin 120′). For the rs731236 *VDR* polymorphism, the 120′ insulin concentration was higher for the *GG* genotype compared to the *AA* and *AG* genotypes. In the case of the rs1544410 *VDR* polymorphism, the 120′ insulin concentration was higher for the *TT* genotype compared to the *CC* and *CT* genotypes. In addition, the *GG* homozygotes of the rs731236 polymorphism occurred with a similar frequency to the *TT* homozygotes of the rs1544410 polymorphism, which may enhance carbohydrate disturbances in patients. In all the patients with hyperandrogenism, the 60′ and 120′ insulin concentration in the glucose tolerance test was above the reference range. In the literature, Xavier et al. [18] indicate that the rs731236 and rs1544410 polymorphisms of the *VDR* gene are related to PCOS, in which carbohydrate disorders are frequent. It has been shown that vitamin D deficiency may be related to insulin resistance.

Table 2. Analysis of female hormonal factors vs *VDR* gene variants in women with hyperandrogenism

Parameter	VDR Taq I rs731236	Mean ± SEM	p value	VDR Bsm I rs1544410	Mean ± SEM	p value
Estradiol [pg/mL]	*AA*	50.11 ± 7.78	0.794	*CC*	50.11 ± 7.78	0.608
	AG	53.43 ± 7.23		*CT*	51.79 ± 7.29	
	GG	59.57 ± 10.40		*TT*	63.02 ± 10.11	
FEI [pmol/nmoL]	*AA*	7.30 ± 1.29	0.330	*CC*	7.30 ± 1.29	0.330
	AG	5.96 ± 1.09		*CT*	5.96 ± 1.09	
	GG	9.06 ± 1.56		*TT*	9.06 ± 1.56	
Prolactin [ng/mL]	*AA*	14.78 ± 1.91	0.290	*CC*	14.78 ± 1.91	0.290
	AG	20.31 ± 3.09		*CT*	20.31 ± 3.09	
	GG	16.78 ± 2.20		*TT*	16.78 ± 2.20	
17-OH-Progesterone [ng/mL]	*AA*	1.57 ± 0.45	0.481	*CC*	1.57 ± 0.45	0.529
	AG	1.19 ± 0.11		*CT*	1.19 ± 0.11	
	GG	1.60 ± 0.32		*TT*	1.54 ± 0.29	
LH [mIU/mL]	*AA*	9.79 ± 1.21	0.133	*CC*	9.79 ± 1.21	0.336
	AG	12.18 ± 1.94		*CT*	11.86 ± 1.10	
	GG	5.97 ± 1.25		*TT*	7.51 ± 1.89	
FSH [mIU/mL]	*AA*	5.60 ± 0.33	0.168	*CC*	5.60 ± 0.33	0.397
	AG	12.02 ± 3.53		*CT*	10.47 ± 3.29	
	GG	5.54 ± 0.61		*TT*	10. 20 ± 4.69	

FEI — Free Estradiol Index; FSH — follicle stimulating hormone; LH — luteinizing hormone

Table 3. Analysis of male hormonal factors vs *VDR* gene variants in women with hyperandrogenism

Parameter	VDR Taq I rs731236	Mean ± SEM	p value	VDR Bsm I rs1544410	Mean ± SEM	p value
Testosterone [ng/mL]	*AA*	0.54 ± 0.05	0.379	*CC*	0.54 ± 0.05	0.368
	AG	0.46 ± 0.04		*CT*	0.46 ± 0.04	
	GG	0.45 ± 0.07		*TT*	0.44 ± 0.06	
BAI [%]	*AA*	45.47 ± 2.89	0.182	*CC*	45.47 ± 2.89	0.182
	AG	39.01 ± 2.44		*CT*	39.01 ± 2.44	
	GG	45.56 ± 4.65		*TT*	45.56 ± 4.65	
FAI [%]	*AA*	1.94 ± 0.12	0.183	*CC*	1.94 ± 0.12	0.183
	AG	1.66 ± 0.10		*CT*	1.66 ± 0.10	
	GG	1.94 ± 0.20		*TT*	1.94 ± 0.20	
Androstendione [ng/mL]	*AA*	4.32 ± 0.37	0.574	*CC*	4.32 ± 0.37	0.574
	AG	3.95 ± 0.36		*CT*	3.95 ± 0.36	
	GG	3.68 ± 0.25		*TT*	3.68 ± 0.25	
DHEA-SO4 [µg/dL]	*AA*	271.77 ± 31.34	0.785	*CC*	271.77 ± 31.34	0.959
	AG	252.86 ± 26.67		*CT*	260.63 ± 26.35	
	GG	284.13 ± 29.67		*TT*	261.46 ± 35.32	
SHBG [nmol/L]	*AA*	35.49 ± 4.88	0.442	*CC*	35.49 ± 4.89	0.442
	AG	48.18 ± 6.88		*CT*	48.18 ± 6.88	
	GG	41.99 ± 15.81		*TT*	41.99 ± 15.81	

BAI — Body Adiposity Index; DHEA-SO4 — dehydroepiandrosterone sulfate; FAI — Free Androgen Index; SHGB — sex hormone binding globulin

Insulin secretion by pancreatic beta cells is regulated by the concentration of calcium. Vitamin D, by regulating calcium concentration and polymorphisms of the *VDR* gene for vitamin D, may influence insulin secretion by pancreatic beta cells [8]. It has been shown that low vitamin D levels are also associated with type 2 diabetes in PCOS, although the mechanism is not fully known [19]. In a study on the Brazilian population, Rodrigues et al. [20] also observed an association of type 2 diabetes with low 25(OH)D levels. However, they did not observe an association between the frequency of the genotype or alleles of the rs1544410 and rs731236 polymorphisms, and type 2 diabetes. This study included 101 patients of the Brazilian population with type 2 diabetes. However, many publications showed an association between *VDR* polymorphisms and carbohydrate disorders [20]. Mayer et al. [21] indicate that low vitamin D levels are often associated with altered glucose metabolism. They observed a significant relationship between the level of 25(OH)D and fasting blood glucose and insulin sensitivity. They also described the relationship of low vitamin 25(OH)D level and decreased insulin resistance with the rs2228570 polymorphism of the VDR receptor. Shaat et al. 22] demonstrated the relationship between the rs1544410 *VDR* polymorphism and the increase in insulin secretion in women after pregnancy complicated by gestational diabetes mellitus (GDM). In studies on 13-year-olds (72% of girls) living in tropical countries, Rahmadhani et al. [23] noticed a relationship between the rs1544410 *VDR* polymorphism and the risk of vitamin D deficiency, and that the AA genotype shows a significantly lower level of vitamin 25 (OH) D compared to other genotypes. This was also observed in our study, but it was not statistically significant. The AA genotype was associated with a higher risk of vitamin D deficiency and insulin resistance compared to the GG genotype. In the meta-analysis by Han et al. [24] presented the relationship between the rs1544410 *VDR* polymorphism and the metabolic syndrome (MetS) and the rs731236 *VDR* polymorphism with PCOS. In addition, they observed an association of *BsmI* and *Taq1* polymorphisms with diseases associated with insulin resistance in Caucasians with dark pigmentation. Many studies show that vitamin D deficiencies are higher in dark-pigmented Caucasians and Asians because of the lower ability to produce this vitamin in the skin. On the other hand, Apaydin et al. [25] studied *BsmI* and *TaqI* polymorphisms in pregnant Turkish women and found no relationship between them and gestational diabetes melitus. Thus, the results of studies on the effect of *VDR* polymorphisms on carbohydrate metabolism are not always unambiguous and not always easy to interpret, due to the multitude of factors affecting glycemia and diseases dependent on insulin resistance. However, it is known that vitamin D, via the VDR receptor, plays a key role in the insulin metabolic pathway and insulin secretion both by controlling calcium levels and affecting pancreatic beta cells, and it also inhibits the immune response in type 2 diabetes [20, 25]. Therefore, it seems justified to focus research on metabolic disorders also in young women with hyperandrogenism. Because their early diagnosis would enable the prevention of more serious disorders. As indicated by the previously cited publications, this is also important during pregnancy, which may be complicated by diabetes [22, 25]. The results of our research, although requiring confirmation on a larger group of patients, seem to be consistent with the earlier observations of many authors and indicate a possible relationship between *VDR* polymorphisms and disturbances in carbohydrate metabolism also in young women with hyperandrogenism. They open up a new aspect of interest in a group of women who have not been studied so often in this area. It is likely that vitamin D supplementation may increase insulin sensitivity in hyperandrogenemia and PCOS [26]. It is known that insulin resistance is common in PCOS, and that hyperandrogenism itself is associated with insulin resistance [27–29]. Insulin also enhances LH-stimulated androgen production. On the other hand, androgens may reduce insulin sensitivity [29]. Hyperinsulinemia and insulin resistance, as suggested by Talaei et al. [30], may be associated with the occurrence of hirsutism in patients with PCOS and idiopathic hirsutism. Vitamin D concentration is also associated with clinical hyperandrogenism in women [18]. A trend was observed for vitamin D concentration for both polymorphisms. For the rs731236 *VDR* polymorphism, this concentration was higher for the *AA* genotype compared to the *AG* and *GG* genotypes. For the rs1544410 *VDR* polymorphism, the vitamin D concentration was higher in carriers of the *CC* genotype compared to the *CT* and TT genotypes. For the rs731236 *VDR* polymorphism, a trend was also shown for the vitamin 25 (OH) D concentration, which was higher in *AA* homozygotes compared to *AG* heterozygotes and *GG* homozygotes. In all the participants with hyperandrogenism, vitamin D concentration was below the reference value range in deficit (< 20 ng/mL). These results may indicate a relationship of vitamin D concentration to the *TaqI* and *BsmI* polymorphisms of the *VDR* gene in young women with hyperandrogenism, but this requires further research. It has been proven in numerous studies that the effect of vitamin D is not limited only to the regulation of mineral balance but is also of great importance for hormonal and carbohydrate metabolism. Vitamin D interacts through VDR receptors located in various tissues and organs involved in the regulation of calcium and carbohydrate metabolism and reproductive functions and modulates their functions. *VDR* gene polymorphisms have been identified as affecting androgen secretion disorders in PCOS [31]. Vitamin D is also of key importance in bone metabolism in

Table 6. Analysis of bone metabolism and biochemical factors vs *VDR* gene variants in women with hyperandrogenism

Parameter	VDR Taq I rs731236	Mean ± SEM	p value	VDR Bsm I rs1544410	Mean ± SEM	p value
BMD total	*AA*	1.18 ± 0.03	0.488	*CC*	1.18 ± 0.03	0.780
	AG	1.19 ± 0.02		*CT*	1.19 ± 0.02	
	GG	1.23 ± 0.04		*TT*	1.21 ± 0.05	
BMD L1-L4	*AA*	1.20 ± 0.03	0.622	*CC*	1.20 ± 0.03	0.465
	AG	1.23 ± 0.02		*CT*	1.24 ± 0.02	
	GG	1.24 ± 0.07		*TT*	1.20 ± 0.07	
T score	*AA*	0.12 ± 0.32	0.506	*CC*	0.12 ± 0.32	0.263
	AG	0.59 ± 0.20		*CT*	0.69 ± 0.17	
	GG	0.53 ± 0.58		*TT*	0.18 ± 0.61	
Z score	*AA*	0.16 ± 0.27	0.652	*CC*	0.16 ± 0.27	0.219
	AG	0.32 ± 0.20		*CT*	0.40 ± 0.19	
	GG	0.11 ± 0.48		*TT*	0.39 ± 0.50	
BMI	*AA*	30.84 ± 2.32	0.312	*CC*	30.84 ± 2.32	0.513
	AG	27.93 ± 1.44		*CT*	28.18 ± 1.46	
	GG	32.54 ± 3.04		*TT*	30.99 ± 3.06	
BMC [g]	*AA*	2338.44 ± 67.51	0.281	*CC*	2338.44 ± 67.51	0.341
	AG	2446.16 ± 36.65		*CT*	2442.55 ± 37.69	
	GG	2361.57 ± 89.25		*TT*	2386.13 ± 81.10	
TBS	*AA*	1.40 ± 0.03	0.327	*CC*	1.40 ± 0.03	0.452
	AG	1.34 ± 0.03		*CT*	1.34 ± 0.03	
	GG	1.40 ± 0.06		*TT*	1.37 ± 0.06	

BMC — bone mineral content; BMD L1-L4 — bone mineral density L1-L4; BMD total — bone mineral density total; TBS — Trabecular Bone Score; T-score — the ratio of the bone mineral density (BMD) of the test person to the average bone density of the young person; Z score — bone mineral density index

PCOS patients [32]. However, the results regarding the relationship between *VDR* gene polymorphisms and the risk of PCOS are not clear [33]. Some authors confirm this relationship [34], while others do not show it [31, 35, 36]. Vitamin D deficiency may also be associated with an increased risk of PCOS, and vitamin D alone may protect PCOS patients against osteoporosis [26]. No statistically significant relationship between the rs731236 and rs1544410 *VDR* gene polymorphisms and bone mineral density and other parameters of bone metabolism was found in the studies carried out in women with hyperandrogenism, similarly to the studies by Bander et al. [37] or Seremak-Mrozikiewicz et al. [38] for the *TaqI* polymorphism. This may be related to the relatively small group of women and their young age. Also, the results of a meta-analysis by Shen et al. [39] did not confirm the relationship between the *VDR* gene polymorphisms *BsmI, TaqI* as well as *ApaI* and FokI with the risk of fractures in postmenopausal women. On the other hand, Stathopolou et al. [40] did not observe an association of the *BsmI* and *TaqI* polymorphisms with BMD, osteoporosis, and the risk of osteoporotic fractures in Greek postmenopausal women. The results of many studies are often ambiguous because osteoporosis is a disorder with a complex etiopathogenesis and influenced by numerous factors, for example, the type of population studied, ethnic and geographical differences, as found in the meta-analysis of Zintzaras et al. [41]. However, many authors confirm the relationship of *VDR* gene polymorphisms with bone mineral density, for example Banjabi et al. [42], who showed a significantly higher risk of developing osteoporosis for *TaqI* polymorphism carriers. Similarly, Ahmad et al. [43] point to the *TaqI* polymorphism as an important risk factor for the development of osteoporosis and significantly associated with BMD in menopausal women. Douroudis et al. [44] indicate a significant correlation between *VDR* polymorphisms and lower bone mineral density in postmenopausal women.

In this project, no relationship between the rs731236 and rs1544410 polymorphisms of the *VDR* gene was found with other determined biochemical and clinical parameters. On the other hand, Ranjzad et al. [45] demonstrated the association of *VDR* gene polymorphisms with the concentration of LH and SHBG in women with PCOS. Women with the *GG* variant of the *VDR* gene rs1544410 SNP had a lower level of SHBG in relation to the *AA* variant. In contrast, the *GG* genotype

turned out to be a likely risk factor for PCOS because it was associated with an increase in bioavailable androgens in women with PCOS. In this study, a correlation between the *CC* genotype of the *VDR* gene rs731236 polymorphism and the LH concentration was also observed [45]. Earlier studies showed an association between insulin resistance and hyperandrogenism, and that PCOS was associated with a significant decrease in insulin sensitivity, independent of obesity. The influence of the active form of vitamin D — calcitriol — on FSH secretion has also been suggested [42]. Jukic et al. [10] observed that a low concentration of vitamin 25 (OH) D leads to an increase in FSH secretion and a decrease in the concentration of estrogen in premenopausal women aged 30–49, and that the concentration of vitamin 25 (OH) D is positively correlated with the concentration of anti-Müllerian hormone (AMH), which is an ovarian reserve marker.

This study was designed to determine the effects of VDR receptor variants on bone metabolism, metabolic and hormonal factors in young females with hyperandrogenizm. Our research also has limitations. The main potential limitation is a relatively small number of participants without a control group. More studies involving more women are needed as idiopathic hyperandrogenization is an increasingly common disorder contributing to metabolic and mineral imbalances and to social problems. There are few reports on this in the literature, as the focus of interest is hyperandrogenization associated with PCOS. This project is part of the search for the relationship between genetic conditions and the type of disorders observed, as well as the possibility of using molecular tests in the diagnosis and therapy of hyperandrogenism and coexisting disorders and their prevention.

CONCLUSIONS

The research presents that *VDR* gene polymorphisms may be related to disturbances in carbohydrate metabolism in young women with hyperandrogenism. The rs731236 and rs1544410 polymorphisms of the *VDR* gene turned out to be statistically significantly related to the concentration of insulin determined in the 60 'glucose tolerance test. This may suggest the possibility of changes in carbohydrate metabolism, but more research is needed on a larger group of patients. The relationship of these polymorphisms with the parameters of bone turnover and other biochemical and clinical parameters has not been demonstrated.

Article information and declarations

Ethics statement

The study was approved by the Ethical Committee of the Pomeranian Medical University (no. KB-0012/115/15 of 16 November 2015).

Author contributions

Conceptualization, methodology, preparation of the manuscript — IU; validation and formal analysis — AB; writing: review and editing — ESP; validation and formal analysis — AS; writing: review — AK; analysis of data — MW; supervision, project administration — BC.

Funding

The study was supported by statutory projects from the Institute of Natural Fibers and Medicinal Plants in Poznań and Pomeranian Medical University in Szczecin, Poland.

Conflict of interest

All authors declare no conflict of interest.

REFERENCES

1. Sowińska-Przepiera E, Niedzielska M. Hiperandrogenism in women as a clinical diagnosthic and therapeutical problem. Prz Lek. 2018; 75(8): 405–410.
2. Carmina E, Rosato F, Jannì A, et al. Extensive clinical experience: relative prevalence of different androgen excess disorders in 950 women referred because of clinical hyperandrogenism. J Clin Endocrinol Metab. 2006; 91(1): 2–6, doi: 10.1210/jc.2005-1457, indexed in Pubmed: 16263820.
3. Sanchón R, Gambineri A, Alpañés M, et al. Prevalence of functional disorders of androgen excess in unselected premenopausal women: a study in blood donors. Hum Reprod. 2012; 27(4): 1209–1216, doi: 10.1093/humrep/des028, indexed in Pubmed: 22343706.
4. Carmina E. Ovarian and adrenal hyperandrogenism. Ann N Y Acad Sci. 2006; 1092: 130–137, doi: 10.1196/annals.1365.011, indexed in Pubmed: 17308139.
5. Ajmal N, Khan SZ, Shaikh R. Polycystic ovary syndrome (PCOS) and genetic predisposition: a review article. Eur J Obstet Gynecol Reprod Biol X. 2019; 8(3): 100060, doi: 10.1016/j.eurox.2019.100060, indexed in Pubmed: 31403134.
6. Unluhizarci K, Kaltsas G, Kelestimur F. Non polycystic ovary syndrome-related endocrine disorders associated with hirsutism. Eur J Clin Invest. 2012; 42(1): 86–94, doi: 10.1111/j.1365-2362.2011.02550.x, indexed in Pubmed: 21623779.
7. Rosenfield RL, Ehrmann DA. The pathogenesis of polycystic ovary syndrome (PCOS): the hypothesis of PCOS as functional ovarian hyperandrogenism revisited. Endocr Rev. 2016; 37(5): 467–520, doi: 10.1210/er.2015-1104, indexed in Pubmed: 27459230.
8. Wehr E, Trummer O, Giuliani A, et al. Vitamin D-associated polymorphisms are related to insulin resistance and vitamin D deficiency in polycystic ovary syndrome. Eur J Endocrinol. 2011; 164(5): 741–749, doi: 10.1530/EJE-11-0134, indexed in Pubmed: 21389086.
9. Muscogiuri G, Altieri B, de Angelis C, et al. Shedding new light on female fertility: the role of vitamin D. Rev Endocr Metab Disord. 2017; 18(3): 273–283, doi: 10.1007/s11154-017-9407-2, indexed in Pubmed: 28102491.
10. Jukic AM, Steiner AZ, Baird DD. Association between serum 25-hydroxyvitamin D and ovarian reserve in premenopausal women. Menopause. 2015; 22(3): 312–316, doi: 10.1097/GME.0000000000000312, indexed in Pubmed: 25093721.
11. Song DoK, Lee H, Hong YS, et al. Vitamin D receptor and binding protein polymorphisms in women with polycystic ovary syndrome: a case control study. BMC Endocr Disord. 2019; 19(1): 145, doi: 10.1186/s12902-019-0477-x, indexed in Pubmed: 31870342.
12. Parikh G, Varadinova M, Suwandhi P, et al. Vitamin D regulates steroidogenesis and insulin-like growth factor binding protein-1 (IGFBP-1) production in human ovarian cells. Horm Metab Res. 2010; 42(10): 754–757, doi: 10.1055/s-0030-1262837, indexed in Pubmed: 20711952.
13. Vulcan T, Filip GA, Lenghel LM, et al. Polymorphisms of vitamin D receptor and the effect on metabolic and endocrine abnormalities in polycystic ovary syndrome: a review. Horm Metab Res. 2021; 53(10): 645–653, doi: 10.1055/a-1587-9336, indexed in Pubmed: 34544196.
14. Al Thomali A, Daghestani MH, Daghestani MH, et al. Polymorphic variations in VDR gene in saudi women with and without polycystic ovary syndrome (PCOS) and significant influence of seven polymorphic sites on

anthropometric and hormonal parameters. J Med Biochem. 2018; 37(4): 415–425, doi: 10.2478/jomb-2018-0007, indexed in Pubmed: 30584400.
15. Ortiz-Flores AE, Martínez-García MÁ, Nattero-Chávez L, et al. Iron overload in functional hyperandrogenism: in a randomized trial, bloodletting does not improve metabolic outcomes. J Clin Endocrinol Metab. 2021; 106(4): e1559–e1573, doi: 10.1210/clinem/dgaa978, indexed in Pubmed: 33462622.
16. Luque-Ramírez M, Ortiz-Flores AE, Martínez-García MÁ, et al. Effect of iron depletion by bloodletting vs. observation on oxidative stress biomarkers of women with functional hyperandrogenism taking a combined oral contraceptive: a randomized clinical trial. J Clin Med. 2022; 11(13): 3864–3880, doi: 10.3390/jcm11133864, indexed in Pubmed: 35807149.
17. Shuhart CR, Yeap SS, Anderson PA, et al. Executive summary of the 2019 ISCD position development conference on monitoring treatment, DXA cross-calibration and least significant change, spinal cord injury, peri-prosthetic and orthopedic bone health, transgender medicine, and pediatrics. J Clin Densitom. 2019; 22(4): 453–471, doi: 10.1016/j.jocd.2019.07.001, indexed in Pubmed: 31400968.
18. Xavier LB, Gontijo NA, Rodrigues KF, et al. Polymorphisms in vitamin D receptor gene, but not vitamin D levels, are associated with polycystic ovary syndrome in Brazilian women. Gynecol Endocrinol. 2019; 35(2): 146–149, doi: 10.1080/09513590.2018.1512966, indexed in Pubmed: 30182771.
19. Pittas AG, Lau J, Hu FB, et al. The role of vitamin D and calcium in type 2 diabetes. A systematic review and meta-analysis. J Clin Endocrinol Metab. 2007; 92(6): 2017–2029, doi: 10.1210/jc.2007-0298, indexed in Pubmed: 17389701.
20. Rodrigues KF, Pietrani NT, Bosco AA, et al. Lower vitamin D levels, but not VDR polymorphisms, influence type 2 diabetes mellitus in brazilian population independently of obesity. Medicina (Kaunas). 2019; 55(5): 188, doi: 10.3390/medicina55050188, indexed in Pubmed: 31121922.
21. Mayer O, Seidlerová J, Černá V, et al. Serum vitamin D status, vitamin D receptor polymorphism, and glucose homeostasis in healthy subjects. Horm Metab Res. 2018; 50(1): 56–64, doi: 10.1055/s-0043-122144, indexed in Pubmed: 29183090.
22. Shaat N, Katsarou A, Shahida B, et al. Association between the rs1544410 polymorphism in the vitamin D receptor (VDR) gene and insulin secretion after gestational diabetes mellitus. PLoS One. 2020; 15(5): e0232297, doi: 10.1371/journal.pone.0232297, indexed in Pubmed: 32407388.
23. Rahmadhani R, Zaharan NL, Mohamed Z, et al. The associations between VDR BsmI polymorphisms and risk of vitamin D deficiency, obesity and insulin resistance in adolescents residing in a tropical country. PLoS One. 2017; 12(6): e0178695, doi: 10.1371/journal.pone.0178695, indexed in Pubmed: 28617856.
24. Han FF, Lv YL, Gong LL, et al. VDR Gene variation and insulin resistance related diseases. Lipids Health Dis. 2017; 16(1): 157, doi: 10.1186/s12944-017-0477-7, indexed in Pubmed: 28822353.
25. Apaydın M, Beysel S, Eyerci N, et al. The VDR gene FokI polymorphism is associated with gestational diabetes mellitus in Turkish women. BMC Med Genet. 2019; 20(1): 82, doi: 10.1186/s12881-019-0820-0, indexed in Pubmed: 31096931.
26. Guraya SS, Alhussaini KA, Shaqrun FM, et al. Correlation of clinical, radiological and serum analysis of hypovitaminosis D with polycystic ovary syndrome: A systematic review and meta-analysis. J Taibah Univ Med Sci. 2017; 12(4): 277–283, doi: 10.1016/j.jtumed.2017.02.005, indexed in Pubmed: 31435252.
27. Zeng X, Xie YJ, Liu YT, et al. Polycystic ovarian syndrome: correlation between hyperandrogenism, insulin resistance and obesity. Clin Chim Acta. 2020; 502: 214–221, doi: 10.1016/j.cca.2019.11.003, indexed in Pubmed: 31733195.
28. Otto-Buczkowska E, Grzyb K, Jainta N. Polycystic ovary syndrome (PCOS) and the accompanying disorders of glucose homeostasis among girls at the time of puberty. Pediatr Endocrinol Diabetes Metab. 2018; 24(1): 40–44, doi: 10.18544/PEDM-24.01.0101, indexed in Pubmed: 30083660.
29. Rosenfield RL, Ehrmann DA. The pathogenesis of polycystic ovary syndrome (PCOS): the hypothesis of PCOS as functional ovarian hyperandrogenism revisited. Endocr Rev. 2016; 37(5): 467–520, doi: 10.1210/er.2015-1104, indexed in Pubmed: 27459230.
30. Talaei A, Adgi Z, Mohamadi Kelishadi M. Idiopathic hirsutism and insulin resistance. Int J Endocrinol. 2013; 2013: 593197, doi: 10.1155/2013/593197, indexed in Pubmed: 24228029.
31. Santos BR, Lecke SB, Spritzer PM. Apa-I polymorphism in VDR gene is related to metabolic syndrome in polycystic ovary syndrome: a cross-sectional study. Reprod Biol Endocrinol. 2018; 16(1): 38, doi: 10.1186/s12958-018-0355-9, indexed in Pubmed: 29669566.
32. Di Bari F, Catalano A, Bellone F, et al. Vitamin D, bone metabolism, and fracture risk in polycystic ovary syndrome. Metabolites. 2021; 11(2), doi: 10.3390/metabo11020116, indexed in Pubmed: 33670644.
33. Krul-Poel YHM, Snackey C, Louwers Y, et al. The role of vitamin D in metabolic disturbances in polycystic ovary syndrome: a systematic review. Eur J Endocrinol. 2013; 169(6): 853–865, doi: 10.1530/EJE-13-0617, indexed in Pubmed: 24044903.
34. Niu YM, Wang YD, Jiang GB, et al. Association between vitamin D receptor gene polymorphisms and polycystic ovary syndrome risk: a meta-analysis. Front Physiol. 2019; 10(9): 1902, doi: 10.3389/fphys.2018.01902, indexed in Pubmed: 30687119.
35. Jedrzejuk D, Łaczmański Ł, Milewicz A, et al. Classic PCOS phenotype is not associated with deficiency of endogenous vitamin D and VDR gene polymorphisms rs731236 (TaqI), rs7975232 (ApaI), rs1544410 (BsmI), rs10735810 (FokI): a case-control study of lower Silesian women. Gynecol Endocrinol. 2015; 31(12): 976–979, doi: 10.3109/09513590.2015.1062865, indexed in Pubmed: 26422783.
36. Dasgupta S, Dutta J, Annamaneni S, et al. Association of vitamin D receptor gene polymorphisms with polycystic ovary syndrome among Indian women. Indian J Med Res. 2015; 142(3): 276–285, doi: 10.4103/0971-5916.166587, indexed in Pubmed: 26458343.
37. Bander D, Parczewski M, Urbańska A, et al. Osteoporosis associated selected single nucleotide polymorphisms frequency in HIV-infected and non-infected Polish population. Endokrynol Pol. 2017; 68(5): 541–549, doi: 10.5603/EP.a2016.0043.
38. Seremak-Mrozikiewicz A, Drews K, Mrozikiewicz PM, et al. Correlation of vitamin D receptor gene (VDR) polymorphism with osteoporotic changes in Polish postmenopausal women. Neuro Endocrinol Lett. 2009; 30(4): 540–546, indexed in Pubmed: 20010502.
39. Shen H, Xie J, Lu H. Vitamin D receptor gene and risk of fracture in postmenopausal women: a meta-analysis. Climacteric. 2014; 17(4): 319–324, doi: 10.3109/13697137.2013.856401, indexed in Pubmed: 24156276.
40. Stathopoulou MG, Dedoussis GVZ, Trovas G, et al. The role of vitamin D receptor gene polymorphisms in the bone mineral density of Greek postmenopausal women with low calcium intake. J Nutr Biochem. 2011; 22(8): 752–757, doi: 10.1016/j.jnutbio.2010.06.007, indexed in Pubmed: 21115334.
41. Zintzaras E, Rodopoulou P, Koukoulis GN. BsmI, TaqI, ApaI and FokI polymorphisms in the vitamin D receptor (VDR) gene and the risk of osteoporosis: a meta-analysis. Dis Markers. 2006; 22(5–6): 317–326, doi: 10.1155/2006/921694, indexed in Pubmed: 17264402.
42. Banjabi AA, Al-Ghafari AB, Kumosani TA, et al. Genetic influence of vitamin D receptor gene polymorphisms on osteoporosis risk. Int J Health Sci (Qassim). 2020; 14(4): 22–28, indexed in Pubmed: 32694969.
43. Ahmad I, Jafar T, Mahdi F, et al. Association of vitamin D receptor gene polymorphism (TaqI and Apa1) with bone mineral density in North Indian postmenopausal women. Gene. 2018; 659(4): 123–127, doi: 10.1016/j.gene.2018.03.052, indexed in Pubmed: 29559350.
44. Douroudis K, Tarassi K, Ioannidis G, et al. Association of vitamin D receptor gene polymorphisms with bone mineral density in postmenopausal women of Hellenic origin. Maturitas. 2003; 45(3): 191–197, doi: 10.1016/s0378-5122(03)00148-8, indexed in Pubmed: 12818464.
45. Ranjzad F, Mahban A, Shemirani AI, et al. Influence of gene variants related to calcium homeostasis on biochemical parameters of women with polycystic ovary syndrome. J Assist Reprod Genet. 2011; 28(3): 225–232, doi: 10.1007/s10815-010-9506-4, indexed in Pubmed: 21082232.

VIA MEDICA

ORIGINAL PAPER / GYNECOLOGY

Ginekologia Polska
2025, vol. 96, no. 2, 119–125

ISSN 0017–0011, e-ISSN 2543–6767

DOI: 10.5603/gpl.101325

Cost-effectiveness of nonavalent vs bivalent HPV vaccine in Polish setting

Michal Jakubczyk[1, 2], Joanna Bieganska[1], Katarzyna Kowalczuk[1], Rafal Jaworski[3], Marcin Czech[4], Andrew Pavelyev[5], Vincent Daniels[5], Maciej Niewada[1, 6]

[1]*HealthQuest, Warsaw, Poland*
[2]*SGH Warsaw School of Economics, Warsaw, Poland*
[3]*MSD, Poland*
[4]*Institute of Mother and Child, Warsaw, Poland*
[5]*Center for Observational and Real World Evidence (CORE), Merck & Co., United States*
[6]*Department of Experimental and Clinical Pharmacology, Medical University of Warsaw, Poland*

ABSTRACT

Objectives: Human papillomavirus (HPV) is a prevalent sexually transmitted infection with significant implications for public health. In Poland, a nationwide vaccination program offers a choice between the 9-valent (9v) and 2-valent (2v) HPV vaccines. We aimed to assess the cost-effectiveness of the 9v vs 2v vaccine from the public payer perspective in Poland.

Material and methods: A cost-effectiveness analysis was conducted to compare the public health and economic benefits of using 9v vs 2v vaccine in Poland over 100-year horizon using a previously published deterministic dynamic transmission model. A target population of girls and boys aged 12–13 years was considered. The model was populated with local epidemiological inputs, utilities, and costs, including vaccine and administration costs, as well as costs related to medical procedures for HPV-related diseases.

Results: The 9v vaccine reduced the prevalence of HPV infections and HPV-related diseases substantially more than 2v vaccine when both are compared to no vaccination strategy. The total discounted cost savings of using the 9v vaccine instead of 2v, excluding the vaccine costs, amounted to EUR 66 million. The incremental cost-effectiveness ratio amounted to 8094 EUR per quality-adjusted life year, much below the official cost-effectiveness threshold in Poland set up at the three times the annual gross domestic product per capita. 9v cost-effectiveness ratio remained unchanged when shorter time-horizons of 20, 40, 60, or 80 years were considered.

Conclusions: Using 9v HPV vaccine in Poland is highly cost-effective compared to the 2v vaccine.

Keywords: vaccine; human papillomavirus, cost-effectiveness, Poland

Ginekologia Polska 2025; 96, 2: 119–125

INTRODUCTION

Human papillomavirus (HPV) is the most common infection transmitted sexually [1]. The lifetime probability of being HPV-infected, assuming having at least one sexual partner of the opposite sex, has been estimated in the United States at 84.6% for women (95% confidence interval, 95% CI, equal to 53.6%–95%) and at 91.3% for men (95% CI = 69.5%–97.7%) [2]. The worldwide prevalence of HPV was estimated at 11.7% in women and at 21% in men in 2017 [3].

While about 90% of HPV infections clear up on their own, occasionally these infections persist and may result in various types of cancer, including the cervical, anal, vulva, oropharyngeal, oral cavity, or laryngeal cancer [4, 5]. In view of how widespread HPV is, it is responsible for a large share of cervical cancer (CC): the most carcinogenic types, HPV-16 and 18 cause almost 70% of CC worldwide, while the HPV types 31, 33, 45, 52, and 58 together account for an additional 15% of CC [3]. There are local differences in genotypes distribution, for example, in Poland HPV types

Corresponding author:
Maciej Niewada
HealthQuest, 63 Mickiewicza St., 01–625 Warsaw and Department of Experimental and Clinical Pharmacology, Medical University of Warsaw, 1b Banacha St., 02–097 Warsaw, Poland
e-mail: maciej.niewada@gmail.com

Received: 26.06.2024; Accepted: 20.09.2024; Early publication date: 7.10.2024

31 and 52 are both more prevalent than HPV 18 [6]. CC is the fourth most common cancer type in women and the second most common cancer type in women aged 15–44 [1]. The annual numbers of CC cases and related deaths were estimated at > 600 000 and > 340 000 in 2020, respectively [5]. Other types of HPV are also responsible for numerous disease cases. HPV types 6 and 11 are claimed to cause more than 90% of cases genital warts (GW) and recurrent respiratory papillomatosis (RRP) [7].

Meanwhile, HPV is a vaccine-preventable infection and HPV vaccines are available since 2006. The currently available vaccines in Poland protect against 2 types of HPV (16 and 18) or 9 types (6, 11, 16, 18, 31, 33, 45, 52, and 58). The high efficacy, effectiveness, and safety of the vaccines have been demonstrated [8]. The vaccination coverage (as measured by the first dose received) varies substantially between the parts of the world (as defined by the World Health Organization [WHO] regions).

In Poland, the nation-wide program of HPV vaccination started in 2023. The program targets 12- and 13-year-old boys and girls and offers a choice between two doses of fully reimbursed either a bivalent (2v) or a nonavalent (9v) vaccine. As part of the free HPV vaccination program in Poland, from June 1 to November 29, 2023, 138,155 girls and boys aged 12 and 13 were vaccinated (about 90% with 9v vaccine), which constitutes around 17% vaccine coverage rate, far below the targeted 90% proposed by EU Beating Cancer Plan [9–11].

To help inform decision on choosing one vaccination strategy over another, additional evidence including cost-effectiveness is warranted.

Objectives

We aimed to assess the cost effectiveness of using 9v vs 2v HPV vaccine in Poland from the public payer perspective.

MATERIAL AND METHODS

Study design and model description

We conducted a cost-effectiveness analysis (CEA) to assess the public health and economic consequences under 9v and 2v HPV vaccination strategies targeting 12–13-year-old boys and girls in Poland. To provide a wider context for this comparison, also the public health consequences of no vaccination are presented. Incremental costs and quality adjusted life years (QALYs) were estimated based on the number of cases, morality rate, and costs associated with each vaccination strategy. We accounted for multiple types of cost incurred for public payer, including vaccine acquisition costs and administration as well as cost of medical procedures associated with managing HPV-related diseases (details follow). The indirect cost related to productivity loss has not been included.

We used a previously published and described CEA model [12, 13]: a population-based, deterministic, dynamic transmission model which reflects the natural history of HPV infection and HPV-related diseases. The model captures the clinical and financial consequences of using of either 2v or 9v HPV vaccines. The consequences are accrued over time using a system of equations that describe the spread of HPV in the population, the incidence of HPV-related diseases, and their consequences on the mortality, health-related quality of life, and cost. The model or its previous versions has been used previously in CEA of the 9v HPV vaccine. The present iteration of the model includes also considerations for infections associated with HPV types 31, 33, 45, 52, and 58, adding significant relevance to our research inquiries. The details of the previous version were published [14]. The model was populated with Polish-specific data on epidemiology, cost, and health state utilities.

To fully account for life-time clinical benefits of vaccines, we used a 100-year time horizon. However, the results were also presented in shorter horizons. The future costs and effects were discounted using the annual rate of 5% and 3.5% as required in CEA in Poland. In sensitivity analysis, the undiscounted results were presented.

In subsections below, we present how the parameters of the model were set, focusing on population size and mortality, sexual behaviour, clinical and screening information, vaccine efficacy, vaccination coverage rate, costs, and health state utility values. More detailed information was placed in the Supplementary Material.

Demographic and sexual behaviour

The demographic inputs on population size and age and gender structure were derived from the Demographic Yearbook 2022 from the Statistics Poland (Główny Urząd Statystyczny, GUS) [15]. Polish life tables were used to account for overall mortality [16]. In view of the lack of Polish-specific data, the information on sexual activity was based on a British study [17]. To describe sexual mixing, the model uses the standard approach in which partnership data and assumptions about the structure of gender mixing are used to calculate the number of partners in different age and sexual activity groups [18]. The inputs for sexual mixing were based on the US population study [19].

Clinical and screening inputs

The number of women receiving hysterectomy was estimated using the GUS demographic data and data from the National Health Fund (NFZ) on procedures M11, M12, M13, M20, and M21 [20]. Parameters related to CC and other cancer types of mortality were derived from the National Cancer Registry [21].

The proportion of women receiving a follow-up screening test after abnormal Pap Smear test result was based on the data on CC prevention program provided on the

government website and MoH information on the National Oncological Strategy in 2021 [19, 22]. The report also included information on the approximate number of women who reported for further diagnostics after receiving abnormal cytological test results. These data allowed us to calculate the percentage of women with an abnormal result who underwent further diagnostics for cervical cancer (see Supplementary Material).

The data on the proportion of women screened for CC were derived from the report on the health status of the Polish population [23]. Polish-specific data were used for the diagnostic performance of CC Pap screening and colposcopy while French data were used on the diagnostic performance of cervical intraepithelial neoplasia PAP screening [24, 25].

Vaccine efficacy and vaccination coverage rate

The vaccine efficacy was assumed as in studies presenting the model. The vaccination coverage rates in females and males in different age groups for subsequent years of the analysis ranged from 20% to 60% and were derived from various publications, both Polish and foreign, depending on data availability. Vaccination rate model inputs along with the sources are described in detail in the Appendix. The proportion of both females and males aged 12–13 years who receive the 2nd dose of vaccine after receiving the 1st dose was assumed as 85%.

Costs

We assumed the cost of the vaccines proposed in public tender. The administration cost of vaccines has also been included into total vaccination cost (Tab. A6 in the Supplementary Material).

Costs per episode of care for individual health states such as cervical intraepithelial neoplasia, CC and vaginal cancer, entailing the costs of diagnosing and treating the case, were derived from the available 2021 economic analysis for 2v HPV vaccine [26]. The same source was used to inform the model on costs of cytological examination, colposcopy and biopsy.

The costs of treatment of penile, head and neck cancer and viral pharyngeal warts were calculated using NFZ tariffs and claims data [27].

Prices given in PLN were converted into EUR at the exchange rate of approx. 4.59 PLN per EUR (as of 28th April 2023).

More cost-specific information is presented in the Supplementary Material.

Utilities

The health state utility values for the Polish population without HPV-related diseases come were based on the published population norms [28]. Due to the lack of Polish data, default decrements of the health status utility values for the non-Polish population suffering from HPV infection were used in the model input.

Model outputs

We present the results in terms of the number of HPV infections and related diseases. Regarding the cost, we present the total discounted cost over the time horizon of analysis separately for the cost of vaccines and the cost of treatment of the HPV-related diseases. As a sensitivity analysis, we also present the results over various time horizons shorter than 100 years.

RESULTS

Clinical outcomes

HPV-vaccination with 9v vaccine — as compared to no vaccination — results approx. in a reduction of the HPV infections prevalence in females by 34% and in males by 26%. Vaccination with 2v vaccine resulted in approx. a 18% and a 10% reduction, respectively. It is important to note that the reduction is somewhat diminished by the conservative assumptions regarding the vaccination rate. The reduction mostly happens in the first 15 years of the analysed time horizon (Fig. B1 and B2 in the Supplementary Material). In consequence, the incidence of HPV-related diseases is reduced as shown in Table 1. The decrease mostly follows the decrease in HPV infections and mostly occurs between 30 and 60 years of the considered time horizon (Fig. B3 in the Supplementary Material)

The largest relative benefit of 9v over 2v was observed for the cumulative percentage reduction in the incidence of HPV 6/11 related CIN 1, CIN2/3, genital warts (in women and man), and RRP.

It was estimated that using 9v vs 2v HPV vaccine reduced the number of deaths from HPV-related causes over given horizon by 6210 (CC), 130 (vaginal cancer) 224 (vulvar cancer), 101 and 60 (anal cancer in women and men, respectively), 126 (penile cancer), 1244 and 1122 (RRP in women and men, respectively).

In total, using 9v vs 2v yielded additional 163 QALYs per 100 000 people (in the whole population, not only in the vaccinated people).

Cost

The estimated cost savings related to HPV-related diseases avoided over time using 9v vaccine vs 2v vaccine are presented in Figure 1. In total, using a 9v vs 2v results in a discounted savings of approximately EUR 66 million (excluding the vaccine cost). In view of the discounting, in present value terms, the savings mostly occur between 10 and 30 years since the start of the analysed time horizon. The additional results are presented in Table B1 in Supplementary Material.

The total number of people receiving any dose in the analysed time horizon amounted to approx. 31.3 million

Table 1. Cumulative reduction and cumulative percent reduction (in parentheses) of the disease incidence cases for 9v vs 2v depending on the time horizon of analysis

	Time horizon			
	5 years	25 years	50 years	100 years
Cervical				
Cancer	0 (0.0)	156 (0.2)	2 557 (2.1)	14 346 (7.3)
CIN 1	491 (0.7)	63 317 (21.1)	167 330 (29.4)	373 190 (33.6)
CIN 2/3	349 (0.5)	39 975 (13.6)	105 059 (19.6)	234 332 (22.8)
Vaginal				
Cancer	0 (0.0)	0 (0.0)	23 (0.8)	358 (8.1)
VAIN 1	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
VAIN 2/3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Vulvar				
Cancer	0 (0.0)	0 (0.0)	18 (0.5)	317 (5.6)
VIN 1	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
VIN 2/3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Genital Warts and HPV 6/11-related CIN 1				
Genital Warts (female)	1 961 (1.8)	108 798 (20.3)	341 398 (31.9)	860 129 (40.1)
Genital Warts (male)	926 (1.3)	62 055 (17.6)	196 514 (27.8)	495 326 (35.0)
CIN 1	1029 (0.7)	150 101 (19.6)	502 593 (32.8)	1 283 883 (41.8)
Anal				
Cancer (female)	0 (0.0)	0 (0.0)	12 (0.2)	177 (1.6)
Cancer (male)	0 (0.0)	0 (0.0)	5 (0.2)	85 (1.8)
Penile Cancer	0 (0.0)	1 (0.0)	35 (1.3)	362 (10.6)
RRP				
RRP (female)	18 (0.5)	2 437 (12.9)	10 015 (26.5)	27 763 (36.8)
RRP (male)	13 (0.4)	2 137 (12.2)	8 989 (25.7)	25 093 (35.9)

Cases are rounded to the nearest 1, and percentages are rounded to the nearest 0.1

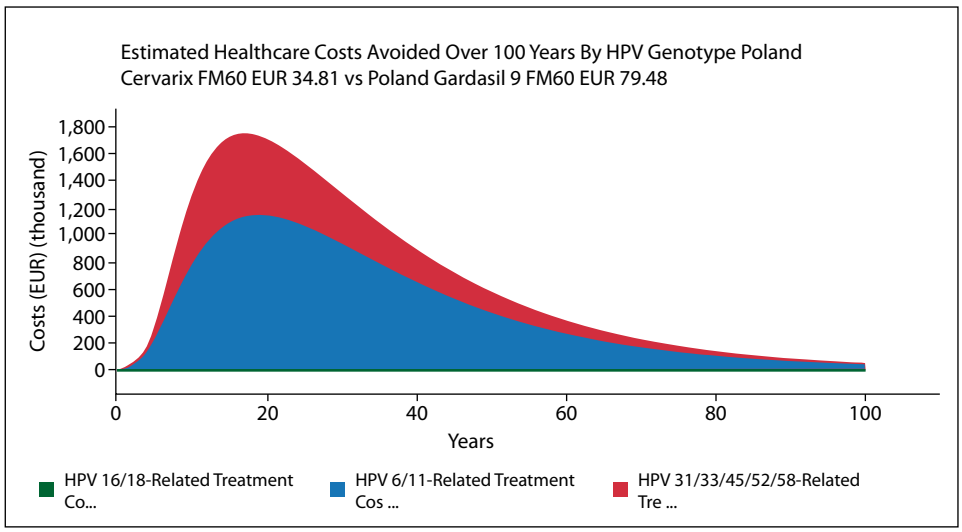


Figure 1. The estimated avoided healthcare cost by HPV genotype as generated over time within the considered time horizon (discounted)

people, for both 9v or 2v vaccine. The estimated incremental total discounted cost of using 9v vs 2v vaccine amounted to approx. EUR 569 million.

Cost-effectiveness results with sensitivity analysis

Accounting for both the incremental cost of vaccination and the avoided cost of diseases, the total additional cost of using 9v instead of 2v amounts to approx. EUR 503 million in the base-case in 100-year time horizon.

The incremental cost and QALY gains per person amount to EUR13.26 and 0.00164, respectively. In consequence, the incremental cost-effectiveness ratio (ICER) equals 8094 EUR/QALY.

When shorter time horizons are considered, the results do not account for the benefits accrued over time, which reduces the cost-effectiveness of 9v vaccine. For the time horizons equal to 20, 40, 60, and 80 years, the ICER coefficients amount to approx. 38,481, 16,638, 11,253, and 9077 EUR/QALY, respectively, which is still substantially below the official acceptability threshold in Poland.

Conversely, when the future cost and effects are not discounted, the benefits obtained in the future gain more weight, and the cost-effectiveness of the 9v vaccine increases. For the 100-year time horizon, the ICER amounts to only 4583 EUR/QALY.

In the base-case analysis, the impact of 9v on head and neck cancer was not included. When the impact of 9v on this type of cancer is accounted for in the modelling, the ICER changes to 8022 EUR/QALY, with discounting and in the 100-year time horizon.

DISCUSSION

In the paper, we compared the cost and effects of two HPV vaccines — the 2v and the 9v one — currently offered in Poland within the national, non-mandatory vaccination program. The effects were expressed as QALYs, by far the most widely used measure of clinical effects in CEA. Using QALYs allows for measuring the benefits of improving both the survival and the health-related quality of life and also for the aggregation of health benefits across a multitude of possible clinical conditions resulting from HPV infection.

In Poland, there is a precisely defined threshold for the cost per QALY to be used in health technology assessment in public decision-making process (for most of the countries the thresholds are estimated based on historical decisions or are only indicated as ranges [29, 30]). The value of the threshold in Poland is defined as three times the annual Gross Domestic Product per capita, and as of 31st October 2023, it amounts to 190,380 PLN/QALY, or approx. 41 500 EUR/QALY as per exchange rate used in all calculations for the present paper. The obtained ICER is well below this threshold, which clearly indicates that using the 9v instead of 2v vaccine is well justified from an economic point of view. From a purely clinical perspective, the 9v vaccine allow for preventing more cases of HPV-related diseases and deaths than the 2v vaccine.

Nevertheless, we understand the rationale for how the prevention program is currently organised, *i.e.*, the possibility for the person to choose the vaccine they feel matches their medical needs and preferences most. This is especially the case if the public having a choice may decrease the vaccine hesitancy and in consequence increase the overall vaccination coverage, which currently seems below expectations [9]. From the perspective of the person being offered the vaccine, the results support the continued provision of the 9v vaccine in the national program free of charge, even more so that it is currently being chosen by approx. 90% of the program participants.

Our study is subject to additional limitations. First, for many parameters, Polish-specific values were lacking. Seeing that public decisions need to be made nonetheless; we think it is warranted to use best available source of data instead. For this reason, we decided to use foreign data, for instance, the British and US data on the sexual behaviour. Obtaining credible Polish-specific data would require large samples and be challenging in view of how sensitive aspects these data relate to. For this reason, such efforts go beyond the scope of the present study and constitute an important area of further research.

Another limitation is that the actual cost of the vaccines is subject to non-disclosure agreements between the pharmaceutical companies and Ministry of Health. In view of this limitation, we decided to calculate the vaccines cost for the National Immunization Program based on the data derived from the public tender platform where the exact prices are not listed.

The public-payer perspective has been adopted to reflect the preferred approach for cost-effectiveness studies run in Poland for the sake of the decision making. The societal perspective including indirect cost would highly likely increase the cost-effectiveness outcomes.

Regarding the modelling assumptions, we see how using a 100-year horizon may be challenged, as it differs from the time-horizons typically used in CEA of other, non-vaccine health technologies, where often life-time horizons are used but the age of patients effectively implies that at most a couple of decades are accounted for. The reason for using the 100-year horizon is that the effects of any prophylactic health technologies are only observed in the longer horizon than for curative medical technologies. While it might be deemed somewhat simplistic to believe that the assumptions used in the analysis will hold valid in such long a time horizon, the results of the analysis allow to understand the

justification for using the 9v vaccine in the present setting. Moreover, it is important to notice that the impact of future cost and effects is diminished by the discounting. Finally, the results obtained for limited time-horizons continue to demonstrate the cost-effectiveness of 9v vs 2v HPV vaccine delivering the ICER below the official cost-effectiveness threshold in Poland. It is of great importance to monitor the impact of the current vaccination program over the long term in terms of the health and cost utility outcomes.

Our results resemble those obtained with the same economic model in other countries. In Norway, the ICER of 9v vs 2v for a 100-year horizon amounted to approx. 10,000 EUR, which only slightly exceeds the value obtained in the present study [12]. Importantly, our results tend to correspond with those using other modelling approaches than we applied. For instance, in a study in India using different economic model, all types of vaccines, 2v, quadrivalent, and 9v, were found to be cost-effective as compared to no-vaccination, with ICERs as low as being in approx. 330–430 USD/QALY range [31]. When one compares the reported cost and disability-adjusted life years between the 2v and 9v vaccine, the 9v is dominant, *i.e.* it offers greater clinical benefit while reducing the total cost from both the health care and societal perspective. More results on the cost-effectiveness of 9v HPV vaccine against the quadrivalent vaccine or no-vaccination are available, including systematic reviews [32–34]. Most published data, as synthesized in systematic reviews, indicates less favourable cost-effectiveness outcomes for the bivalent HPV vaccine than for the other HPV vaccines [35].

It needs to be underlined that presented results are specific to the Polish setting. The results may not be directly generalizable to other countries as they may differ in terms of their healthcare systems, epidemiological profiles, and economic context.

Offering to the people the choice between different vaccines could decrease their vaccine hesitancy and boost the vaccination coverage. Nevertheless, the broadest possible protection and compatibility with the local epidemiology surveillance data need to be carefully considered.

CONCLUSIONS

Using a 9v HPV vaccine is highly cost-effective option as compared to the 2v vaccine in Poland since the calculated incremental cost per QALY (8094 EUR/QALY) amounts to less than 1 annual GDP per capita, *i.e.*, far below the official acceptability threshold in Poland set to 3 annual GDP per capita (41 500 EUR/QALY). Our study provides insights that can inform reimbursement allocation decisions and enhance the cost-effectiveness of resource utilization.

Article information and declarations

Data availability statement

The data presented in this study are available on reasonable request from the corresponding author.

Ethics statement

The study only used parameters found in the literature. Therefore, in our opinion, ethical committee approval was not required.

Author contributions

Michal Jakubczyk — 12.5% — concept, analysis & interpretation of data, article draft; Joanna Bieganska — 12.5% — concept, searching for data sources & preparing input parameters, critical review; Katarzyna Kowalczuk — 12.5% — concept, searching for data sources & preparing input parameters, critical review; Rafal Jaworski — 12.5% — concept, searching for data sources & preparing input parameters, critical review; Marcin Czech — 12.5% — concept, help with data sources & preparing input parameters, critical review; Andrew Pavelyev — 12.5% — model calibration & running, critical review; Vincent Daniels — 12.5% — model calibration & running, critical review; Maciej Niewada — 12.5% — concept, help with data sources & preparing input parameters, critical review, corresponding author.

Funding

This research received external funding. The sponsor of the study was MSD Poland. The data collection, analyses, and results interpretation were carried out independently by the authors.

Acknowledgments

None.

Conflict of interest

M. Niewada, J. Bieganska, K. Kowalczuk, and M Jakubczyk are employed (or were employed at the time of the analysis) by HealthQuest — a company that prepares health technology assessment reports for different entities, including MSD Poland. R. Jaworski is an employee of MSD Poland. M. Czech reports honoraria for the lectures and participation in scientific meetings for different pharmaceutical entities as a consultant. A Pavelyev is a contractor for Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, U.S.A. and owns stock in Merck & Co., Inc., Rahway, NJ, U.S.A. V Daniels is an employee of Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, U.S.A. and owns stock in Merck & Co., Inc., Rahway, NJ, U.S.A. The authors

have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or material discussed in the manuscript apart from those disclosed.

Supplementary material

Supplementary Material for publication with article is provided.

REFERENCES

1. Kombe Kombe AJ, Li B, Zahid A, et al. Epidemiology and Burden of Human Papillomavirus and Related Diseases, Molecular Pathogenesis, and Vaccine Evaluation. Front Public Health. 2020; 8: 552028, doi: 10.3389/fpubh.2020.552028, indexed in Pubmed: 33553082.
2. Chesson HW, Dunne EF, Hariri S, et al. The estimated lifetime probability of acquiring human papillomavirus in the United States. Sex Transm Dis. 2014; 41(11): 660–664, doi: 10.1097/OLQ.0000000000000193, indexed in Pubmed: 25299412.
3. https://www paho org/en/human—papillomavirus—hpv—vaccine (20.07.2023).
4. https://www who int/news—room/fact—sheets/detail/cervical—cancer (27.12.2023).
5. Bruni L, Albero G, Serrano B, et al. Human Papillomavirus and Related Diseases in the World. Summary Report 10 March 2023. ICO/IARC Information Centre on HPV and Cancer. (HPV Information Centre): 2023.
6. Przybylski M, Pruski D, Wszołek K, et al. Prevalence of HPV and Assessing Type-Specific HPV Testing in Cervical High-Grade Squamous Intraepithelial Lesions in Poland. Pathogens. 2023; 12(2), doi: 10.3390/pathogens12020350, indexed in Pubmed: 36839622.
7. Fortes HR, von Ranke FM, Escuissato DL, et al. Recurrent respiratory papillomatosis: A state-of-the-art review. Respir Med. 2017; 126: 116–121, doi: 10.1016/j.rmed.2017.03.030, indexed in Pubmed: 28427542.
8. Kamolratanakul S, Pitisuttithum P. Human Papillomavirus Vaccine Efficacy and Effectiveness against Cancer. Vaccines (Basel). 2021; 9(12), doi: 10.3390/vaccines9121413, indexed in Pubmed: 34960159.
9. https://www.termedia.pl/ginekologia/Zaszczepiono—ponad—138—tys—dzieci—przeciw—HPV,54002.html#:~:text=W%20ramach%20programu%20bezpłatnych%20szczepień,jest%20populacja%20ponad%20800%20tys. (27.12.2023).
10. Baker P, Kelly D, Medeiros R, et al. Eliminating HPV-caused cancers in Europe: Achieving the possible. J Cancer Policy. 2021; 28: 100280, doi: 10.1016/j.jcpo.2021.100280, indexed in Pubmed: 35559909.
11. https://ec europa eu/commission/presscorner/detail/en/ip_22_702 (27.12.2023).
12. Diakite I, Nguyen S, Sabale U, et al. Public health impact and cost-effectiveness of switching from bivalent to nonavalent vaccine for human papillomavirus in Norway: incorporating the full health impact of all HPV-related diseases. J Med Econ. 2023; 26(1): 1085–1098, doi: 10.1080/13696998.2023.2250194, indexed in Pubmed: 37608730.
13. Daniels V, Saxena K, Patterson-Lomba O, et al. Modeling the health and economic implications of adopting a 1-dose 9-valent human papillomavirus vaccination regimen in a high-income country setting: An analysis in the United Kingdom. Vaccine. 2022; 40(14): 2173–2183, doi: 10.1016/j.vaccine.2022.02.067, indexed in Pubmed: 35232593.
14. Elbasha EH, Dasbach EJ, Insinga RP. Model for assessing human papillomavirus vaccination strategies. Emerg Infect Dis. 2007; 13(1): 28–41, doi: 10.3201/eid1301.060438, indexed in Pubmed: 17370513.
15. Demographic Surveys Department. Demographic Yearbook of Poland, Statistics Poland, 2022. https://stat.gov.pl/obszary—tematyczne/roczniki—statystyczne/roczniki—statystyczne/rocznik—demograficzny—2022,3,16.html (26.10.2023).
16. Poland. National Accounts Statistics: Main Aggregates and Detailed Tables. 2023: 3514–3554, doi: 10.18356/9789213584552c153.
17. Mercer CH, Tanton C, Prah P, et al. Changes in sexual attitudes and lifestyles in Britain through the life course and over time: findings from the National Surveys of Sexual Attitudes and Lifestyles (Natsal). Lancet. 2013; 382(9907): 1781–1794, doi: 10.1016/S0140-6736(13)62035-8, indexed in Pubmed: 24286784.
18. Garnett GP, Anderson RM. Factors controlling the spread of HIV in heterosexual communities in developing countries: patterns of mixing between different age and sexual activity classes. Philos Trans R Soc Lond B Biol Sci. 1993; 342(1300): 137–159, doi: 10.1098/rstb.1993.0143, indexed in Pubmed: 7904355.
19. The social organization of sexuality: sexual practices in the United States. Choice Reviews Online. 1995; 32(08), doi: 10.5860/choice.32-4802a.
20. https://statystyki nfz gov pl/Benefits/1a (27.12.2023).
21. https://pacjent gov pl/program—profilaktyczny/profilaktyka—raka—szyjki—macicy (27.12.2023).
22. https://www gov pl/web/zdrowie/narodowa—strategia—onkologiczna—nso (27.12.2023).
23. https://stat.gov.pl/obszary—tematyczne/zdrowie/zdrowie/stan—zdrowia—ludnosci—polski—w—2019—r—,26,1.html (27.12.2023).
24. Rokita W. Wartość diagnostyczna cytologii i kolposkopii u kobiet ze śródnabłonkową neoplazją szyjki macicy. Ginekol Pol. 2011; 82: 607–611.
25. National Agency for Accreditation and Evaluation of Health (ANAES). Recommadations pour la pratique clinique: conduite à tenir devant un frottis anormal du col de l'utérus. 1998 et actualisation 2002. https://www.has—sante.fr/?id=c_272243 (27.12.2023).
26. Analiza ekonomiczna. Szczepionka przeciw wirusowi brodawczaka ludzkiego Cervarix® w profilaktyce zmian przednowotworowych narządów płciowych i odbytu (szyjki macicy, sromu, pochwy i odbytu) oraz raka szyjki macicy i raka odbytu. Pracownia HTA, 2021. https://bipold.aotm.gov.pl/assets/files/zlecenia_mz/2021/041/AW/41_AW_OT.4230.6.2021_Cervarix_AE.pdf (27.12.2023).
27. Order No. 21/2023/DSOZ of the President of the National Health Fund of 31.01. 2023. https://baw.nfz.gov.pl/NFZ/document/1669/Zarzadzenie—21_2023_DSOZ (27.12.2023).
28. Golicki D, Niewada M. EQ-5D-5L Polish population norms. Arch Med Sci. 2017; 13(1): 191–200, doi: 10.5114/aoms.2015.52126, indexed in Pubmed: 28144271.
29. Iino H, Hashiguchi M, Hori S. Estimating the range of incremental cost-effectiveness thresholds for healthcare based on willingness to pay and GDP per capita: A systematic review. PLoS One. 2022; 17(4): e0266934, doi: 10.1371/journal.pone.0266934, indexed in Pubmed: 35421181.
30. Gandjour A. Willingness to pay for new medicines: a step towards narrowing the gap between NICE and IQWiG. BMC Health Serv Res. 2020; 20(1): 343, doi: 10.1186/s12913-020-5050-9, indexed in Pubmed: 32321496.
31. Arora S, Tuffaha H. Cost-effectiveness analysis of human papillomavirus vaccines for the prevention of cervical cancer in India. Asia Pac J Clin Oncol. 2024; 20(1): 55–62, doi: 10.1111/ajco.13962, indexed in Pubmed: 37132538.
32. Mahumud RA, Alam K, Afroz S, et al. Correction: Cost-effectiveness evaluations of the 9-Valent human papillomavirus (HPV) vaccine: Evidence from a systematic review. PLoS One. 2023; 18(11): e0294379, doi: 10.1371/journal.pone.0294379, indexed in Pubmed: 37943757.
33. Ng SS, Hutubessy R, Chaiyakunapruk N. Systematic review of cost-effectiveness studies of human papillomavirus (HPV) vaccination: 9-Valent vaccine, gender-neutral and multiple age cohort vaccination. Vaccine. 2018; 36(19): 2529–2544, doi: 10.1016/j.vaccine.2018.03.024, indexed in Pubmed: 29625764.
34. Wondimu A, Postma MJ, van Hulst M. Cost-effectiveness analysis of quadrivalent and nonavalent human papillomavirus vaccines in Ethiopia. Vaccine. 2022; 40(14): 2161–2167, doi: 10.1016/j.vaccine.2022.02.080, indexed in Pubmed: 35248423.
35. Kostaras D, Karampli E, Athanasakis K. Vaccination against HPV virus: a systematic review of economic evaluation studies for developed countries. Expert Rev Pharmacoecon Outcomes Res. 2019; 19(2): 147–158, doi: 10.1080/14737167.2019.1555039, indexed in Pubmed: 30501434.

VIA MEDICA

ORIGINAL PAPER / GYNECOLOGY

Ginekologia Polska
2025, vol. 96, no. 2, 126–135

ISSN 0017–0011, e-ISSN 2543–6767

DOI: 10.5603/gpl.101419

The role of selected cytokines from the interleukin-1 family in the peritoneal fluid of women with endometriosis

Marta Smycz-Kubanska[1], Dominika Wendlocha[1], Andrzej Witek[2], Aleksandra Mielczarek-Palacz[1]

[1]Department of Immunology and Serology, Faculty of Pharmaceutical Sciences in Sosnowiec, Medical University of Silesia, Katowice, Poland

[2]Department of Gynecology and Obstetrics, Faculty of Medical Sciences in Katowice, Medical University of Silesia, Katowice, Poland

ABSTRACT

Objectives: Endometriosis is a complex, chronic inflammatory disease in which immune system disorders play an important role. Soluble mediators of the immune and inflammatory response, including cytokines, are involved in these processes. Therefore, the aim of the conducted research was to understand the role of selected cytokines belonging to the Interleukin-1(IL-1) family, including IL-36α, IL-36β, IL-36γ, IL-36R, IL-37 and IL-38, in the onset and development of endometriosis by analysing the concentration of the tested molecules and to determine whether their concentration depends on the stage of the disease.

Material and methods: The study group included 60 women who had pelvic endometriosis diagnosed during laparoscopy and subsequently confirmed by histopathology. The reference group consisted of 20 women who had no endometriosis or other pelvic lesions during laparoscopy.

Results: Immunoenzymatic assays were used to determine the concentration of the cytokines studied. In the peritoneal fluid of women with endometriosis, a statistically significant increase in the concentrations of all parameters tested was observed: IL-36α, IL-36β, IL-36γ, IL-36R, IL-37 and IL-38. The concentration of these cytokines depended on the severity of the disease.

Conclusions: Disturbances of the immune system involving the network of cytokines belonging to the IL-1 family occurring in the peritoneal fluid environment testify to the involvement of these molecules in the development of the disease and are one of many factors involved in the pathogenesis of endometriosis. The use of some of them in the treatment of endometriosis may be a hope for effective causal treatment of this disease, but this requires further, more advanced research.

Keywords: endometriosis; cytokines; peritoneal fluid; inflammation

Ginekologia Polska 2025; 96, 2: 126–135

INTRODUCTION

Endometriosis is an estrogen-dependent inflammatory gynecological disease characterized by the presence of endometrial tissue outside the uterine cavity. The most common location of endometrial lesions is the peritoneum of the sinus of Douglas and the vesico-uterine fold, the ovaries and fallopian tubes, the sacro-uterine ligaments and the outer membrane of the uterus and the rectovaginal septum [1]. More distant and unusual locations are also worth mentioning, such as the pericardium, lungs, pleura, diaphragm, brain, lower limbs, navel, as well as the caesarean section scar [2–4].

About 5–15% of women of reproductive age suffer from endometriosis, however, due to the non-specific symptoms and difficult diagnosis, the actual number of patients is unknown. The main clinical symptom of the disease is pain

Corresponding author:
Marta Smycz-Kubanska
Department of Immunology and Serology, Faculty of Pharmaceutical Sciences in Sosnowiec Medical University of Silesia, Katowice, Poland
e-mail: mkubanska@sum.edu.pl

Received: 2.07.2024 Accepted: 9.07.2024 Early publication date: 4.10.2024

located in the pelvic area accompanied by prolonged and heavy menstruation. An important problem is infertility accompanying endometriosis, because 40–60% of affected women have problems with getting pregnant [5–7].

The classification created by the American Society for Reproductive Medicine (ASRM) determines the advancement of the disease, taking into account the extent and depth of endometriosis foci and the involvement of the peritoneum, fallopian tubes and ovary, as well as the presence and type of adhesions. ASRM has distinguished four stages of the disease, which are marked from I to IV [8, 9].

Despite numerous studies conducted over the years, the pathogenesis of endometriosis is still not fully understood. Even though there are many theories trying to explain the possibility of developing the disease, none of them fully explains the mechanisms involved in the formation and development of endometriosis. One of the oldest is Sampson's theory from 1927 [10], which assumes that the source of cells may be endometrial fragments that move with the retrograde flow of menstrual blood through the fallopian tubes to the ovaries and peritoneal cavity, where they implant and then proliferate and vascularize. Many researchers are paying attention to the fact that an important element in the pathogenesis of endometriosis are disorders in the functioning of the immune system. In the early 1980s, Professor Dmowski [11] formulated the hypothesis that this disease occurs in women who have disorders in the functioning of the immune system. According to this researcher, a properly functioning system eliminates the ectopic endometrium, while because of its dysfunction, the environment of the peritoneal cavity favors the implantation of endometrial cells in ectopic sites. Endometriosis is similar to several autoimmune diseases, in the course of which there is an increased concentration of cytokines, disorders of apoptosis and angiogenesis, or increased activity of tissue metalloproteinases. Immunological factors and angiogenesis play a key role in the pathogenesis of endometriosis, which may affect a woman's susceptibility to implantation of exfoliated endometrial cells [12, 13]. There are four stages in the development of endometriosis (Fig. 1).

An important role in the pathogenesis of endometriosis is attributed to the interleukin-1 family. Interleukins belonging to the IL-1 family play an important role in the regulation of the immune and inflammatory response, affecting almost all types of cells [17]. The interleukin-1 family consists of 11 proteins, including 7 pro-inflammatory agonists (IL-1α, IL-1β, IL-18, IL-33, IL-36α, IL-36β, IL-36γ) and 4 anti-inflammatory antagonists (IL-1Ra, IL-36Ra, IL-37 and IL-38) [18, 19]. The characteristics of the interleukin-1 family are listed in Table 1 [16]. IL-1 family cytokines are released at the earliest stage of the immune response and act as a signal for the next cascade of pro-inflammatory cytokines [20]. The main cells secreting IL-1 are considered monocytes and macrophages, as well as T and B lymphocytes. It can also be secreted by organ-specific cells, such as keratinocytes, chondrocytes, dendritic cells, glial cells, mesangial cells, and endothelial cells [21]. Figure 2 show selected IL-1 family of cytokines.

Therefore, the aim of the conducted research was to understand the role of selected cytokines belonging to the IL-1 family, including IL-36α, IL-36β, IL-36γ, IL-36R, IL-37 and IL-38, in the onset and development of endometriosis by analyzing the concentration of the tested molecules and to determine whether their concentration depends on the stage of the disease.

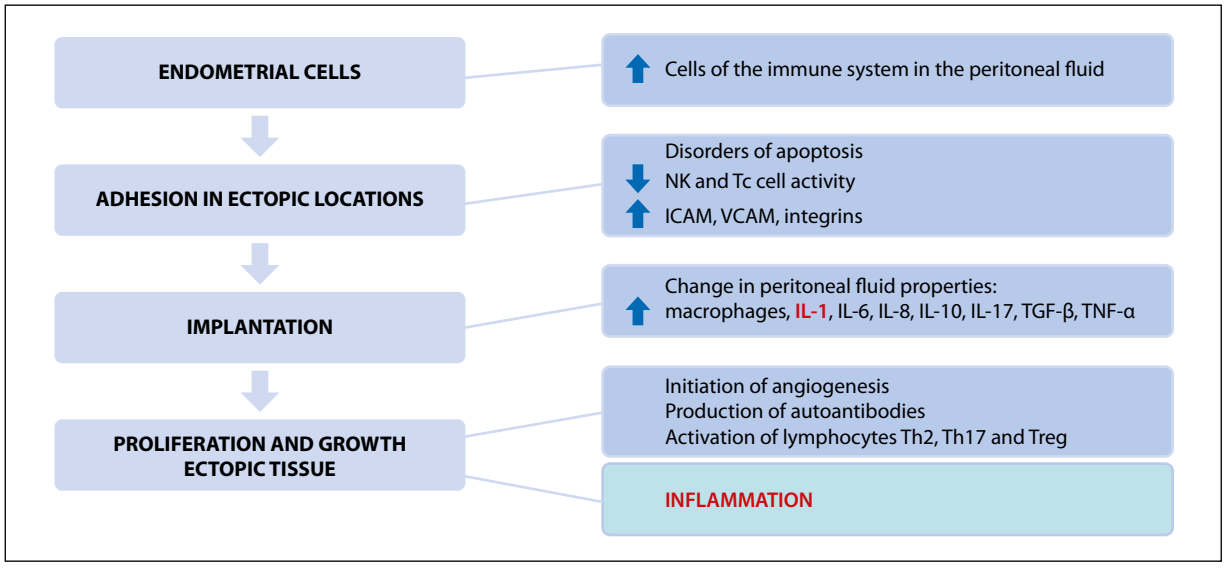


Figure 1. Stages of endometriosis development [14–16]

Table 1. The characteristics of the interleukin-1 family [14]

Interleukin-1 family	Interleukin-1 family receptor	Interleukin-1 family coreceptor	Characteristics of the interleukin-1 family
IL-1α	IL-1R1	IL-1RacP(*L-1R3*)	Pro-inflammatory
IL-1β	IL-1R1	IL-1RacP*(L-1R3)*	Pro-inflammatory
IL-1Ra	IL-1R1	–	Antagonist for IL-1α, IL-1β
IL-18	IL-18Rα*(IL-1R5)*	IL-18R(βIL1R7)	Pro-inflammatory
IL-33	IL-1R4ST2*(IL-1R4 IL-1RL1, IL-33R)*	IL-RacP	Pro-inflammatory
IL-36Ra	IL-1Rrp2*(IL-1R6)*	IL-1RacP	Antagonist for IL-36α, IL-36β, IL-36γ
IL-36α	IL-1Rrp2*(IL-1R6, IL-36R)*	IL-1RacP	Pro-inflammatory
IL-36β	IL-1Rrp2*(IL-1R6, IL-36R)*	IL-1RacP	Pro-inflammatory
IL-36γ	IL-1Rrp2*(IL-1R6, IL-36R)*	IL-1RacP	Pro-inflammatory
IL-37	IL-18Rα	IL-1R8*(SIGIRR)*	Anti-inflammatory
IL-38	IL-1R1 IL-1Rrp2	IL1RAPL1(TIGIRR-2)IL1RAPL2(TIGIRR-1)	Partial antagonist for IL-1α and β and IL-36α, β and γ

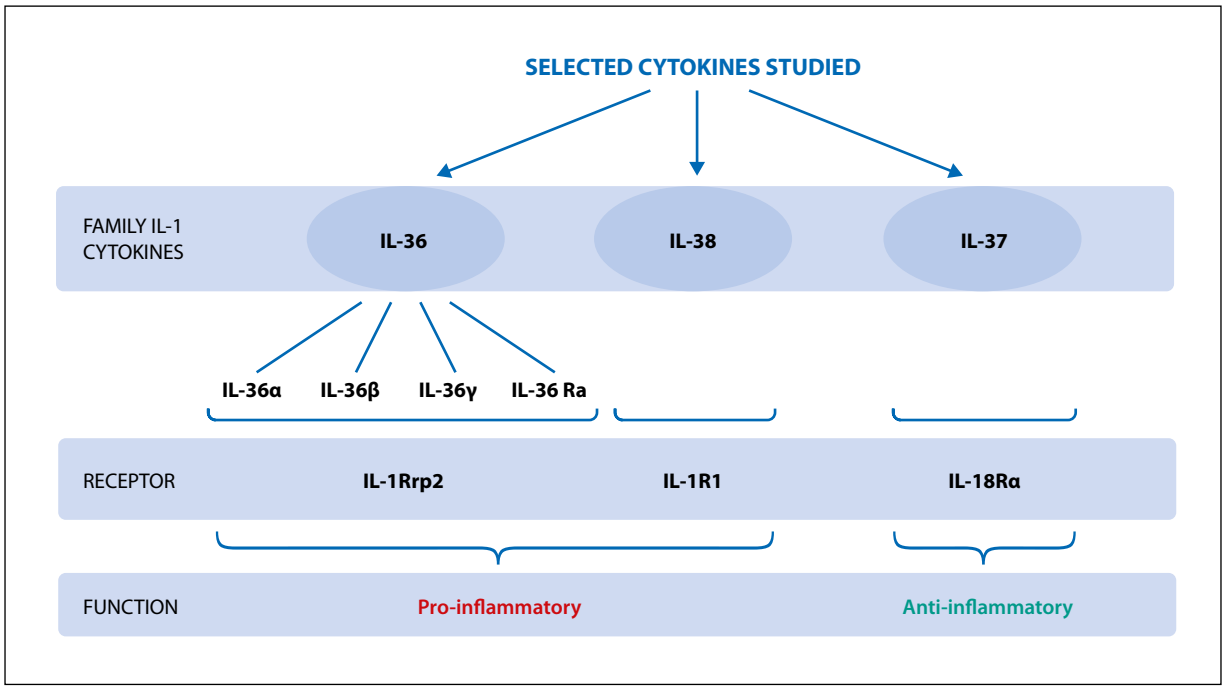


Figure 2. The IL-1 family of cytokines [22]

MATERIAL AND METHODS

The study group included 60 women aged between 21 and 49 years (mean age 32.6 ± 7.4 years) who had pelvic endometriosis diagnosed during laparoscopy and subsequently confirmed by histopathology. The research was conducted on women hospitalized at the Clinical Department of Gynecology and Obstetrics of the University Clinical Center in Katowice. Of the 60 women studied, 38 women were in the minimal/mild stage (stage I and II endometriosis) and 22 were in the moderate/severe stage (stage III and IV endometriosis). The reference group consisted of 20 women aged between 21 and 41 years (mean age 28.2 ± 5.6 years) who had no endometriosis or other pelvic lesions during laparoscopy.

Inclusion criteria for both groups were at least 2 years primary infertility, stage from I to IV ovarian endometriosis, and regular cycles. Endometriosis was diagnosed by laparoscopy and histologically confirmed and classified according to the American Society of Reproductive Medicine classification.

Peritoneal fluid collected during laparoscopy from women in the proliferative phase of the menstrual cycle was used

for the study. Immediately after collection, the peritoneal fluid was centrifuged at an acceleration of 2500 rpm for 10 minutes. The resulting fluid was divided into aliquots and stored at –80°C until assays were performed. The concentration of cytokine in peritoneal fluid was determined by sandwich ELISA. The Enzyme-linked Immunosorbent Assay Kit for Interleukin 1 Epsilon (IL1e) was used to determine the concentration of the interleukin under study, Interleukin-36α. For IL-36β Enzyme-linked Immunosorbent Assay Kit for Interleukin 1 Eta (IL1h). IL-36γ Enzyme-linked Immunosorbent Assay Kit for Interleukin 1 Family, Member 9 (IL1F9). Determination of Interleukin-36 receptor (IL-36R) levels was performed using the Enzyme-linked Immunosorbent Assay Kit for Interleukin 1 Delta (FIL1d). The Enzyme-linked Immunosorbent Assay Kit for Interleukin 1 Zeta (IL1z) was used to determine the concentration of IL-37 under study. The Enzyme-linked Immunosorbent Assay Kit for Interleukin 1 Theta (IL1q) was used to determine the concentration of test IL-38 (Tab. 2). All assays were from Cloud-Clone Corp. All results are presented as amean ± standard deviation or median and interquartile range and were examined for normality of distribution by the Shapiro-Wilk test. Parametric data were analysed using Student's t-test. For nonparametric data, Fisher's exact test (analysis of variance) was applied to indicate statistical significance because it analyses the variance relationship both within and among the groups. The correlations were tested by Spearman's rank correlation test and are presented as a correlation coefficient (r). $P < 0.05$ was considered statistically significant.

RESULTS

The study analysed the concentrations of the following cytokines IL-36α, IL-36β, IL-36γ, IL-36R, IL -37 and IL-38 in the peritoneal fluid of women with endometriosis and women from the reference group.

The results were presented in Table 3 and Figure 3–8.

Interleukin-36α, 36β, 36γ and receptor IL-36

The analysis showed a statistically significant increase in the concentration of IL-36α, 36β, 36γ and IL-36 receptor in the peritoneal fluid of women with endometriosis compared to the concentration of this parameter in the reference group. In the next step, we evaluated how the concentrations of these parameters in the peritoneal fluid developed in relation to the stage of endometriosis. For each parameter, we observed a statistically significant increase in the concentration in the group of women with moderate/severe endometriosis compared to the group of women with minimal/mild endometriosis ($p < 0.001$). The results are shown in Figure 3–6.

Table 2. A summary of the tests used in the study together with Sensitivity, Interlaboratory reproducibility, Intralaboratory reproducibility [Instruction ELISA CLOUD-CLONE]

Parameter	Test	Sensitivity	Intra-assay	Inter-assay
Interleukin-36α	Interleukin 1 Epsilon (IL1e)	< 6.3 pg/mL	CV < 10%	CV < 12%
Interleukin-36 β	Interleukin 1 Eta (IL1h)	< 2.9 pg/mL	CV < 10%	CV < 12%
Interleukin IL -36γ	Member 9 (IL1F9)	< 6.5 pg/ml	CV < 10%	CV < 12%
Interleukin-36 receptor (IL-36R)	Interleukin 1 Delta (FIL1d)	< 2.9 pg/mL	CV < 10%	CV < 12%
Interleukin-37	Assay Kit for Interleukin 1 Zeta (IL1z)	< 6.1 pg/mL	CV < 10%	CV < 12%
Interleukin-38	Interleukin 1 Theta (IL1q)	< 2.8 pg/mL	CV < 10%	CV < 12%

Table 3. Peritoneal level of studied chemokines in women with endometriosis and women from the reference group

Cytokines	Patients		p value
	Endometriosis (n = 60)	Control (n = 20)	
Interleukin-36α	256. 81 (153.48–358.25)	91.57 (73.08–124.54)	p < 0.001
Interleukin-36β	46.69 (52.62–81.56)	23.90 (18.18 – 30.20)	p < 0.05
Interleukin-36γ	88.82 (36.07–132.66)	11.49 (6.05–14.52)	p < 0.001
Receptor IL-36	47.39 (42.50–61.16)	32.35 (29.83–35.27)	p < 0.001
Interleukin-37	493.05 (314.44–595.84)	137.82 (105.38– 178.80)	p < 0.001
Interleukin-38	147.97 (102.55–238.86)	54.37 (40.90–74.87)	p < 0.01

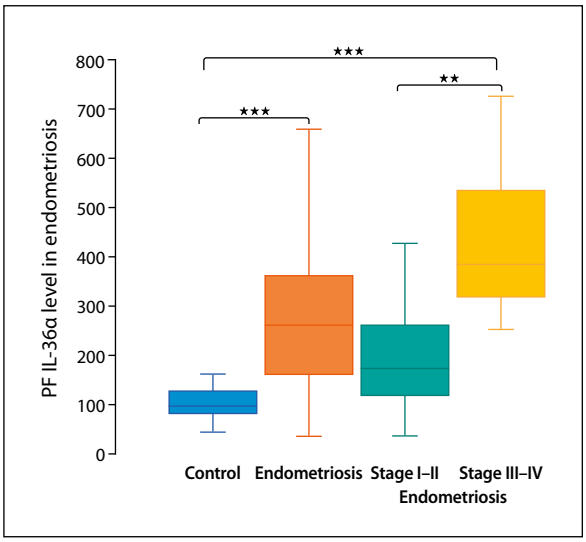


Figure 3. Comparison of IL-36α concentration in peritoneal fluid between patients and control groups according to endometriosis stage

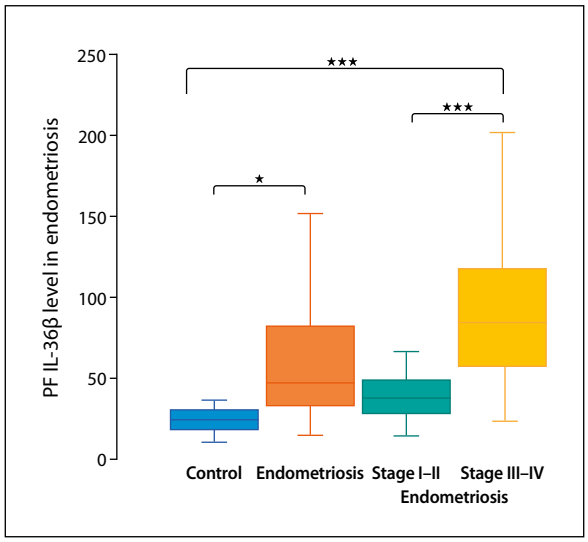


Figure 4. Comparison of IL-36β concentration in peritoneal fluid between patients and control groups according to endometriosis stage

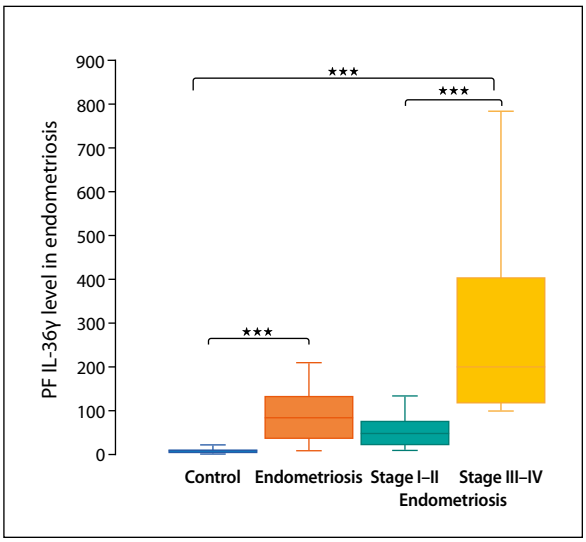


Figure 5. Comparison of IL-36γ concentration in peritoneal fluid between patients and control groups according to endometriosis stage

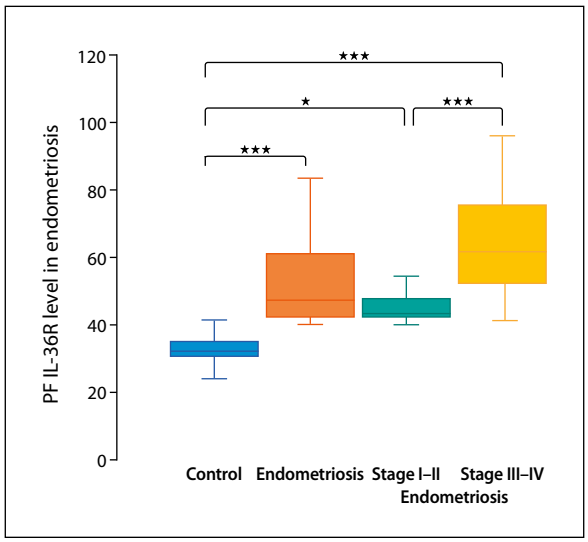


Figure 6. Comparison of IL-36R concentration in peritoneal fluid between patients and control groups according to endometriosis stage

Interleukin -37

The analysis of the results showed a statistically significant increase in the concentration of IL-37 in the peritoneal fluid of women with endometriosis compared to the concentration of this parameter in the reference group ($p < 0.001$). A statistically significant increase in the concentration of the studied parameter was observed in endometriosis with moderate/severe stage compared to the group of women with minimal/mild stage of the disease ($p < 0.001$). The results obtained are shown in Figure 7.

Interleukin -38

The analysis showed a statistically significant increase in IL-38 levels in the group of women with endometriosis compared to the levels of this cytokine in the fluid of women in the reference group ($p < 0.01$). When comparing women with moderate/severe endometriosis with those with minimal/mild endometriosis, a statistically significant increase in concentration was also observed ($p < 0.001$). The results are shown in Figure 8.

In addition, we analysed whether there was a correlation between the concentrations of IL-36α, IL-36β, IL-36γ

and IL — IL-38 showing pro-inflammatory effects and IL-37 with anti-inflammatory effects in the peritoneal fluid of women with endometriosis. The analysis showed a positive, statistically significant correlation between the concentrations of IL-36α (r = 0.8; p p < 0.0001), IL-36β, (r = 0.5; p < 0.0001) IL-36γ (r = 0.7; p < 0.0001), IL-38 (r = 0.8; p < 0.0001) which show pro-inflammatory effects and IL-37 with anti-inflammatory effects. Linear regression curves showing the above relationships are illustrated in Figure 9.

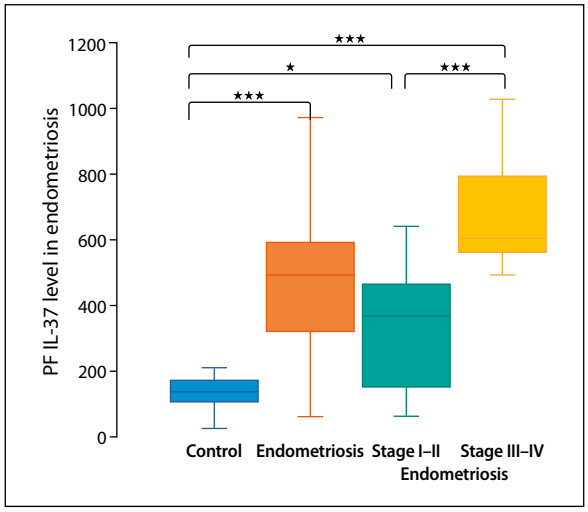


Figure 7. Comparison of IL-37 concentration in peritoneal fluid between patients and control groups according to endometriosis stage

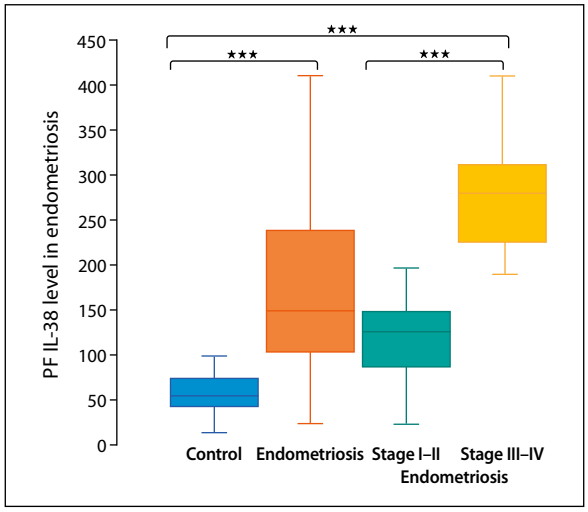


Figure 8. Comparison of IL-38 concentration in peritoneal fluid between patients and control groups according to endometriosis stage

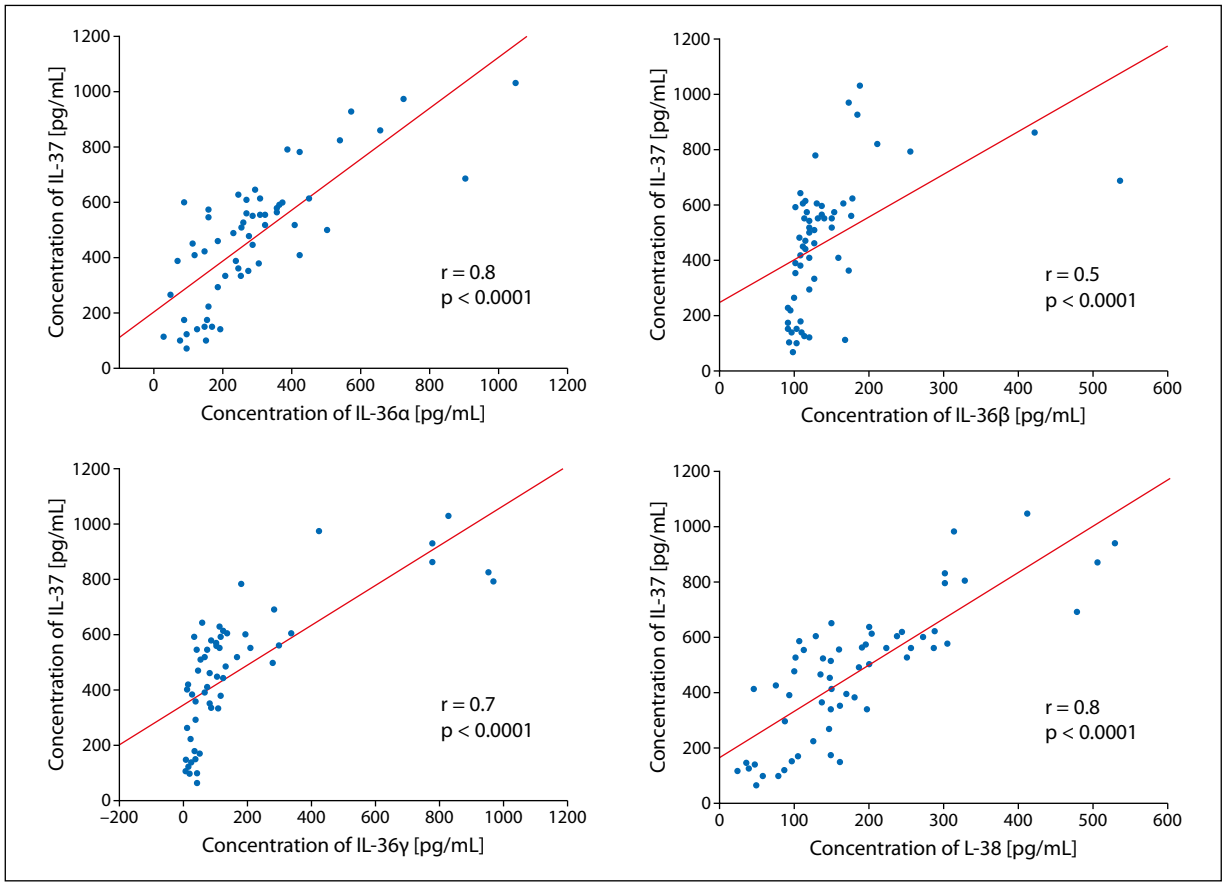


Figure 9. Linear regression curve showing the relationship between IL-36α, IL-36B, IL-36γ, IL-38 and IL-37 levels in the peritoneal fluid of women with endometriosis

DISCUSSION

Numerous studies indicate that cytokines have a significant impact on the development, course and effects of endometriosis. The effect of cytokines is noticeable already at the stage of implantation of ectopic endometrial foci. An abnormal increase in the number of activated macrophages within endometriotic lesions has been indicated, affecting the extracellular environment. Abnormal cytokine production by macrophages leads to stimulation of both epithelial and stromal cells significantly influencing the severity of the inflammatory response. Consequently, the increased interaction of differentiated cellular components in the microenvironment can lead to a continuous stimulation of inflammation, promoting the growth of endometrial lesions through increased proliferation or reduced apoptosis.

Many pieces of data confirm that cytokines contained in the peritoneal fluid of women with endometriosis stimulate the proliferation of eutopic and ectopic endometriotic lesions [23].

Studies have shown elevated expression of IL-36 in the female reproductive system during the menstrual cycle, as well as an association with immune mediator production and cell recruitment to the genital tract. The involvement of IL-36 cytokine in inflammation and the observations to date on their potential role in the development of healthy or complicated pregnancies require further research [24].

The balance and correlation between Th1 and Th2 type responses and their regulatory mechanisms, as well as their mediators, require further research to understand the functioning of the immune response during pregnancy. Information regarding the involvement of IL-36 in reproductive processes is still poorly understood, but further studies may in the future indicate how cytokines may participate in the regulation of pregnancy [24].

In the studies presented in this paper, the concentration of individual interleukins from the IL-1 family and IL-37, IL-38 in the peritoneal fluid of women with endometriosis, which is the environment for developing changes, was checked. The results of our study are comparable to those obtained by other authors. The tested material was peritoneal fluid, as was the case in previous studies. In each of the compared studies, the ELISA method was used, and the samples of the test material were stored in an analogous manner, and moreover, the size of the study groups in each analysis was approximate. We used the division of endometriosis into early-grade I and II and late-grade III and IV based on the rAFS system, which is an older ASRM classification system, which in turn was included in our studies [25, 26].

As a result of the tests carried out in the peritoneal fluid of women with endometriosis, changes in the concentrations of the tested interleukins: IL-36α, IL-36β, IL-36γ and IL-36R were found in comparison to the values observed in women from the reference group. Moreover, an increase in the concentration of these proteins was observed with the subsequent stages of endometriosis. The highest concentrations of IL-36α, IL-36β, IL-36γ and IL-36R were observed in women with stage IV endometriosis and the lowest in women with stage I endometriosis.

IL-36 represents 3 cytokines (IL-36α, IL-36β, IL-36γ), each of which has, pro-inflammatory effects and binds to the IL-36 receptor (IL-36R). Abnormal levels of their expression have an impact on the development of inflammation, autoimmunity, allergies and cancer [27]. Studies indicate the involvement of interleukins in inflammation. Signalling which covers IL-36, induces pro-inflammatory responses in fibroblasts, endothelium, epithelium, M2 macrophages, T cells, natural killer cells and dendritic cells (DC) [28]. Disorders associated with the IL-36 subfamily are associated with the pathogenesis of many diseases including: rheumatoid arthritis, inflammatory lung diseases, obesity, biliary obstruction and chronic glomerulonephritis [29, 30]. Studies conducted so far have shown an increase in the concentration of this cytokine in the presented diseases, which underlines the importance of this protein in chronic inflammation [31–33]. In addition, IL-36R signalling is involved in diseases such as psoriasis and colitis, mediated by pro-inflammatory cytokines and chemokines.

The level of IL-36 in the peritoneal fluid of women with endometriosis was analyzed by Heeyon Kim et al. [32] who showed that the concentration of this protein was significantly increased in the group of women with severe endometriosis. There are no unequivocal reports indicating the involvement of IL-36α, IL-36β, IL-36γ and IL-36R in this disease, however, studies covering other disease entities are available. Studies by Wang et al. [34] indicate the participation of IL-36γ, (an IL-36R agonist) in the proliferation and progression of lung cancer [34]. Similar conclusions were drawn by Yang et al. [35] indicating a strong association between IL-36γ and IL-36Ra with the development of intestinal inflammation and the development of intestinal cancer [35]. This is consistent with our study, which showed an increase in IL-36γ and IL-36R in women with endometriosis accompanied by a chronic inflammation. Moreover, these concentrations correlated with the progression of the disease, the highest concentration was observed in women with stage IV endometriosis and the lowest in women with stage I endometriosis. The concentration of IL-36α was higher in women with late endometriosis than in women with early endometriosis, which may reflect the increased production of this cytokine as the disease progresses [31, 33]. Li et al. [36] indicate a new mechanism of action of pro-inflammatory IL-36α with suppressed IL-36RA and IL-38 antagonists, thanks to which hyperosmolarity induces inflammation in a culture model and dry eye disease [36]. IL-36β is produced by the innate immune system cells and lymphocytes, inducing

the production of pro-inflammatory cytokines, chemokines and co-stimulatory molecules, thus promoting the polarization of Th1 and Th17 cells. There is evidence that IL-36β is involved in innate immunity and inflammation of the skin and lungs, where epithelial cells may be the source of this cytokine. IL-36β is involved in pathological states of min. psoriasis and A. fumigatus infection [31]. In our study, we have shown an increase in the level of IL-36β in the peritoneal fluid of women with endometriosis, which correlated with an increase in patients' inflammation.

IL-37 is a new member of the IL-1 family that can reduce, inhibit inflammation and also affect immunity. In addition, IL-37 can inhibit macrophage proliferation, apoptosis, migration and expression of pro-inflammatory cytokines such as IL-1β, IL-6, and IL-10, and inhibit the occurrence and development of endometriosis by targeting multiple signalling pathways. Recent studies indicated that IL-37 expression in ectopic and eutopic endometrium and serum levels in patients with endometriosis were higher than in patients without endometriosis. IL-37 expression correlates with disease severity, but discrepancies still exist regarding the concentration of this parameter in peritoneal fluid [37, 38].

The analysis showed a statistically significant change in the concentration of IL-37 in the peritoneal fluid in women with endometriosis compared to women from the reference group.However, the mechanism of action of IL-37 is not fully known.Despite the ethnic differences in the women included in the study, the results of studies by Fan et al. [39] and Jiang et al. [40] also showed an increase in the concentration of IL-37 in the peritoneal fluid in women with endometriosis, which indicates a significant participation of this interleukin in the inflammatory processes associated with endometriosis.

Interleukin 37 has been identified as a natural suppressor of the innate inflammatory response. IL-1β can increase IL-37 expression, the most effective stimulant identified so far is transforming growth factor β (TGFβ), which is produced by peritoneal mesothelial cells and increased in areas close to endometriosis lesions. All studies conducted so far have shown higher concentrations of IL-37 in women with late endometriosis (stage III and IV) than in women with early endometriosis, suggesting increased secretion of IL-37 in more advanced stages of the disease. Considering that IL-37 is an anti-inflammatory cytokine, its increased expression in women with endometriosis is surprising. However, it is probably related to the inhibition of early pathogenic clearance of foreign tissue and facilitates lesion formation.

According to the researchers, the obtained results indicate the use of IL-37 as a potential diagnostic tool in endometriosis [39, 40]. In addition, Fan et al. [39] suggested that IL-37 should also be considered in future studies using different estrogen concentrations, given that endometriosis is a hormone-dependent disease. Therefore, it seems important to direct research to clarify the mechanism by which IL-37 affects the eutopic and ectopic endometrium [39].

Another evaluated cytokine parameter was IL-38. Its concentration in the peritoneal fluid of women with endometriosis was significantly increased compared to the concentration of this cytokine in the fluid of women from the reference group. An increase in concentration was also observed in stage III–IV of the disease compared to stages I–II. IL-38 is highly expressed in immune cells and plays a key role in autoimmune diseases, but the exact signalling and functional pathway is still poorly known. In the available literature, there are few studies on the occurrence of this cytokine in women with endometriosis.

Interleukin-38 (IL-38) shares structural features with the IL-1 receptor antagonist (IL-1Ra) and IL-36Ra. IL-36R is a specific IL-38 receptor, a partial antagonist of the IL-36 receptor. IL-38 inhibits the production of T cell cytokines IL-17 and IL--22. IL-38 also inhibits the production of IL-8 induced by IL-36γ, thereby suppressing inflammatory responses. IL-38-related cytokines, including IL-1Ra and IL-36Ra, are involved in the regulation of inflammation and the immune response. Study of cytokines related to IL-36 and IL-38 may provide new information to help develop anti-inflammatory therapies [41].

In addition, the study showed a positive correlation between the levels of the pro-inflammatory interleukins: IL-36α, IL-36β, IL-36γ and IL-38, and the anti-inflammatory interleukin IL-37. The demonstrated correlation between the concentrations of these parameters in a group of patients with endometriosis indicates a disturbance of the immune system taking place with the involvement of the IL-1 family of cytokine systems studied and may suggest that these proteins may directly or indirectly participate in increasing inflammation in the formation and development of the disease. The interactions taking place in the microenvironment of the peritoneal fluid may influence the direction of biological action, which is related to the severity of internalisation abnormalities in the pro/anti-inflammatory cytokine system. Understanding these mechanisms may allow us to find potential biomarkers useful for the diagnosis of endometriosis in the future, but this requires further research.

Furthermore, it is also noteworthy that changes in the concentrations of the analysed cytokines promote chronic inflammation, lesion proliferation, local hormonal imbalance, and may result in poorer oocyte quality, poor sperm motility, embryotoxicity and reduced endometrial receptivity, suggesting adverse effects on the reproductive capacity of patients. In this aspect, only increased levels of IL-1β in the peritoneal fluid have so far been indicated in women with endometriosis and associated infertility. It also seems interesting to know the role of other cytokines belonging to the IL-1 family in these patients.

CONCLUSIONS

Disturbances of the immune system involving the network of cytokines belonging to the IL-1 family occurring in the peritoneal fluid environment testify to the involvement of these molecules in the development of the disease and are one of many factors involved in the pathogenesis of endometriosis. The use of some of them in the treatment of endometriosis may be a hope for effective causal treatment of this disease, but this requires further, more advanced research.

Article information and declarations

Author contributions

Conceptualization — AMP, MSK; AW — methodology; DW, MSK — writin, original draft preparation; AMP, MSK, AW — writing, review andediting; AMP, MSK — visualization, MSK, DW, AMP — supervision;. All authors have read and agreed to the published version ofthe manuscript.

Funding

This research was funded by Medical University of Silesia in Katowice, Poland, grant number BNW-1-025/K/3/O.

Acknowledgments

Bioethics Committee of the Medical University of Silesia in Katowice (decision no. KNW/0022/KB/35/15).

Conflict of interest

The authors declare no conflict of interest.

REFERENCES

1. Parazzini F, Esposito G, Tozzi L, et al. Epidemiology of endometriosis and its comorbidities. Eur J Obstet Gynecol Reprod Biol. 2017; 209: 3–7, doi: 10.1016/j.ejogrb.2016.04.021, indexed in Pubmed: 27216973.
2. Bratu D, Chicea R, Ciprian T, et al. A rare case of ileus caused by ileum endometriosis. Int J Surg Case Rep. 2016; 26: 24–26, doi: 10.1016/j.ijscr.2016.06.023, indexed in Pubmed: 27434884.
3. Alves J, Puga M, Fernandes R, et al. Laparoscopic Management of Ureteral Endometriosis and Hydronephrosis Associated With Endometriosis. J Minim Invasive Gynecol. 2017; 24(3): 466–472, doi: 10.1016/j.jmig.2016.11.018, indexed in Pubmed: 28089810.
4. Sherif AM, Musa ER, Kedar R, et al. Subcapsular hepatic endometriosis: case report and review of the literature. Radiol Case Rep. 2016; 11(4): 303–308, doi: 10.1016/j.radcr.2016.08.004, indexed in Pubmed: 27920849.
5. Burney RO, Giudice LC. Pathogenesis and pathophysiology of endometriosis. Fertil Steril. 2012; 98(3): 511–519, doi: 10.1016/j.fertnstert.2012.06.029, indexed in Pubmed: 22819144.
6. Stratton P, Berkley KJ. Chronic pelvic pain and endometriosis: translational evidence of the relationship and implications. Hum Reprod Update. 2011; 17(3): 327–346, doi: 10.1093/humupd/dmq050, indexed in Pubmed: 21106492.
7. Hsu AL, Sinaii N, Segars J, et al. Relating pelvic pain location to surgical findings of endometriosis. Obstet Gynecol. 2011; 118(2 Pt 1): 223–230, doi: 10.1097/AOG.0b013e318223fed0, indexed in Pubmed: 21775836.
8. American Society for Reproductive Medicine (ASRM). Encyclopedia of Global Health. 2008, doi: 10.4135/9781412963855.n88.
9. Johnson NP, Hummelshoj L, Adamson GD, et al. World Endometriosis Society Sao Paulo Consortium. World Endometriosis Society consensus on the classification of endometriosis. Hum Reprod. 2017; 32(2): 315–324, doi: 10.1093/humrep/dew293, indexed in Pubmed: 27920089.
10. Sampson J. Peritoneal endometriosis due to the menstrual dissemination of endometrial tissue into the peritoneal cavity. American Journal of Obstetrics and Gynecology. 1927; 14(4): 422–469, doi: 10.1016/s0002-9378(15)30003-x.
11. Dmowski WP, Rao R, Scommegna A. The luteinized unruptured follicle syndrome and endometriosis. Fertil Steril. 1980; 33(1): 30–34, doi: 10.1016/s0015-0282(16)44473-0, indexed in Pubmed: 7351255.
12. Agic A, Djalali S, Diedrich K, et al. Apoptosis in endometriosis. Gynecol Obstet Invest. 2009; 68(4): 217–223, doi: 10.1159/000235871, indexed in Pubmed: 19729941.
13. Kaabachi W, Kacem O, Belhaj R, et al. Interleukin-37 in endometriosis. Immunol Lett. 2017; 185: 52–55, doi: 10.1016/j.imlet.2017.03.012, indexed in Pubmed: 28322860.
14. Istrate-Ofițeru AM, Berbecaru EI, Zorilă GL, et al. Specific Local Predictors That Reflect the Tropism of Endometriosis-A Multiple Immunohistochemistry Technique. Int J Mol Sci. 2022; 23(10), doi: 10.3390/ijms23105614, indexed in Pubmed: 35628423.
15. Zhang T, De Carolis C, Man GC, et al. The link between immunity, autoimmunity and endometriosis: a literature update. Autoimmun Rev. 2018; 17(10): 945–955, doi: 10.1016/j.autrev.2018.03.017, indexed in Pubmed: 30107265.
16. Miller JE, Ahn SH, Marks RM, et al. Pathophysiology and Immune Dysfunction in Endometriosis. Biomed Res Int. 2015; 2015(4): 795976, doi: 10.1155/2015/795976, indexed in Pubmed: 26247027.
17. Papathanasiou E, Conti P, Carinci F, et al. IL-1 Superfamily Members and Periodontal Diseases. J Dent Res. 2020; 99(13): 1425–1434, doi: 10.1177/0022034520945209, indexed in Pubmed: 32758110.
18. Palomo J, Dietrich D, Martin P, et al. The interleukin (IL)-1 cytokine family--Balance between agonists and antagonists in inflammatory diseases. Cytokine. 2015; 76(1): 25–37, doi: 10.1016/j.cyto.2015.06.017, indexed in Pubmed: 26185894.
19. Dinarello CA. Overview of the IL-1 family in innate inflammation and acquired immunity. Immunol Rev. 2018; 281(1): 8–27, doi: 10.1111/imr.12621, indexed in Pubmed: 29247995.
20. Fields JK, Günther S, Sundberg EJ. Structural Basis of IL-1 Family Cytokine Signaling. Front Immunol. 2019; 10: 1412, doi: 10.3389/fimmu.2019.01412, indexed in Pubmed: 31281320.
21. Zhang W, Borcherding N, Kolb R. IL-1 Signaling in Tumor Microenvironment. Adv Exp Med Biol. 2020; 1240: 1–23, doi: 10.1007/978-3-030-38315-2_1, indexed in Pubmed: 32060884.
22. Bonati L, Tang Li. Cytokine engineering for targeted cancer immunotherapy. Curr Opin Chem Biol. 2021; 62: 43–52, doi: 10.1016/j.cbpa.2021.01.007, indexed in Pubmed: 33684633.
23. Nishida M, Nasu K, Ueda T, et al. Endometriotic cells are resistant to interferon-gamma-induced cell growth inhibition and apoptosis: a possible mechanism involved in the pathogenesis of endometriosis. Mol Hum Reprod. 2005; 11(1): 29–34, doi: 10.1093/molehr/gah133, indexed in Pubmed: 15579658.
24. Martin Murrieta-Coxca . Rodríguez-Martínez S. Eugenio Cancino-Diaz M Udo R. Markert, R. Favaro R. M. Morales-Prieto D. IL-36 Cytokines: Regulators of Inflammatory Responses and Their Emerging Role in Immunology of Reproduction Int. J Mol Sci. 2019; 20: 1649.
25. Kim H, Choi YS, Kim JS, et al. Identification of Serum Biomarkers for Diagnosis of Endometriosis Using Multiplex Immunoassays. Reprod Sci. 2020; 27(5): 1139–1147, doi: 10.1007/s43032-019-00124-2, indexed in Pubmed: 32046464.
26. Han Y, Huard A, Mora J, et al. IL-36 family cytokines in protective versus destructive inflammation. Cell Signal. 2020; 75: 109773, doi: 10.1016/j.cellsig.2020.109773, indexed in Pubmed: 32898612.
27. Dong H, Hao Y, Li W, et al. IL-36 Cytokines: Their Roles in Asthma and Potential as a Therapeutic. Front Immunol. 2022; 13: 921275, doi: 10.3389/fimmu.2022.921275, indexed in Pubmed: 35903102.
28. Sun R, Gao DS, Shoush J, et al. The IL-1 family in tumorigenesis and antitumor immunity. Semin Cancer Biol. 2022; 86(Pt 2): 280–295, doi: 10.1016/j.semcancer.2022.05.002, indexed in Pubmed: 35580824.
29. Lamacchia C, Palmer G, Rodriguez E, et al. The severity of experimental arthritis is independent of IL-36 receptor signaling. Arthritis Res Ther. 2013; 15(2): R38, doi: 10.1186/ar4192, indexed in Pubmed: 23452551.
30. van Asseldonk EJP, Stienstra R, Koenen TB, et al. Treatment with Anakinra improves disposition index but not insulin sensitivity in nondiabetic subjects with the metabolic syndrome: a randomized, double-blind, placebo-controlled study. J Clin Endocrinol Metab.

2011; 96(7): 2119–2126, doi: 10.1210/jc.2010-2992, indexed in Pubmed: 21508140.
31. Neurath MF. IL-36 in chronic inflammation and cancer. Cytokine Growth Factor Rev. 2020; 55: 70–79, doi: 10.1016/j.cytogfr.2020.06.006, indexed in Pubmed: 32540133.
32. Kim H, Choi YS, Kim JS, et al. Identification of Serum Biomarkers for Diagnosis of Endometriosis Using Multiplex Immunoassays. Reprod Sci. 2020; 27(5): 1139–1147, doi: 10.1007/s43032-019-00124-2, indexed in Pubmed: 32046464.
33. Chelvanambi M, Weinstein AM, Storkus WJ. IL-36 Signaling in the Tumor Microenvironment. Adv Exp Med Biol. 2020; 1240: 95–110, doi: 10.1007/978-3-030-38315-2_8, indexed in Pubmed: 32060891.
34. Wang P, Yang W, Guo H, et al. IL-36γ and IL-36Ra Reciprocally Regulate NSCLC Progression by Modulating GSH Homeostasis and Oxidative Stress-Induced Cell Death. Adv Sci (Weinh). 2021; 8(19): e2101501, doi: 10.1002/advs.202101501, indexed in Pubmed: 34369094.
35. Yang W, Dong HP, Wang P, et al. IL-36γ and IL-36Ra Reciprocally Regulate Colon Inflammation and Tumorigenesis by Modulating the Cell-Matrix Adhesion Network and Wnt Signaling. Adv Sci (Weinh). 2022; 9(10): e2103035, doi: 10.1002/advs.202103035, indexed in Pubmed: 35119210.
36. Li JM, Lu R, Zhang Y, et al. IL-36α/IL-36RA/IL-38 signaling mediates inflammation and barrier disruption in human corneal epithelial cells under hyperosmotic stress. Ocul Surf. 2021; 22: 163–171, doi: 10.1016/j.jtos.2021.08.012, indexed in Pubmed: 34428579.
37. He Y, Xiong T, Guo F, et al. Interleukin-37b inhibits the growth of murine endometriosis-like lesions by regulating proliferation, invasion, angiogenesis and inflammation. Mol Hum Reprod. 2020; 26(4): 240–255, doi: 10.1093/molehr/gaaa014, indexed in Pubmed: 32119739.
38. Li L, Liao Z, Ye M, et al. Recombinant human IL-37 inhibited endometriosis development in a mouse model through increasing Th1/Th2 ratio by inducing the maturation of dendritic cells. Reprod Biol Endocrinol. 2021; 19(1): 128, doi: 10.1186/s12958-021-00811-3, indexed in Pubmed: 34429116.
39. Fan YY, Chen HY, Chen W, et al. Expression of inflammatory cytokines in serum and peritoneal fluid from patients with different stages of endometriosis. Gynecol Endocrinol. 2018; 34(6): 507–512, doi: 10.1080/09513590.2017.1409717, indexed in Pubmed: 29308924.
40. Jiang J, Jiang Z, Xue M. Serum and peritoneal fluid levels of interleukin-6 and interleukin-37 as biomarkers for endometriosis. Gynecol Endocrinol. 2019; 35(7): 571–575, doi: 10.1080/09513590.2018.1554034, indexed in Pubmed: 30632819.
41. Yuan X, Peng X, Li Y, et al. Role of IL-38 and its related cytokines in inflammation. Mediators Inflamm. 2015; 2015: 807976, doi: 10.1155/2015/807976, indexed in Pubmed: 25873772.

VIA MEDICA

ORIGINAL PAPER / OBSTETRICS

Ginekologia Polska
2025, vol. 96, no. 2, 136–141

ISSN 0017–0011, e-ISSN 2543–6767

DOI: 10.5603/gpl.92611

Factors associated with neonatal brachial palsy in shoulder dystocia: a longitudinal study

Javier Sánchez-Romero[1, 2], Almudena Jiménez-Méndez[2], Lucía Begoña Díaz-Meca[2], Alberto Rafael Guijarro-Campillo[2], Julián Jesús Arense-Gonzalo[3], Evdochia Adoamnei[3], Aníbal Nieto-Díaz[1, 2], María Luisa Sánchez-Ferrer[1, 2]

[1]Department of Obstetrics and Gynecology, Pediatrics and Surgery, University of Murcia, Crtra. Cartagena-Madrid s/n El Palmar, Spain
[2]Department of Obstetrics and Gynecology, 'Virgen de la Arrixaca' University Clinical Hospital, Ctra. Madrid-Cartagena, Spain
[3]School of Nursing, University of Murcia, Building of the Health Sciences Campus. Ctra. Buenavista s/n, El Palmar, Spain

ABSTRACT

Objectives: The main goal is to analyze factors related to brachial plexus injury (BPI) after shoulder dystocia (SD).

Material and methods: Longitudinal prospective analysis of SD arose in a tertiary hospital from 1/1st/ 2019 to 12/31st/ /2020. A multivariable logistic regression for BPI after SD and a survival analysis for BPI recovery after SD were performed.

Results: In this period 13,414 deliveries were attended, 10,676 of those were vaginal deliveries (79.6%) reporting 69 cases of SD, with an incidence of 0.65%. SD required 102.1 seconds (SD) 10.8) as an average for solving it. Internal maneuvers were needed in 42.0% of SD reported. Neonatal BPI was suspected in 23 newborns (33.3%) at birth. Neonatal BPI at 48 hours of life was statistically associated with maternal BMI above 30 kg/m^2 (OR = 7.91; CI 95% 1.3–47.7; p = 0.024), > 120 seconds for solving SD (OR = 14.4; CI 95% 1.7–121.82; p = 0.014) and operative delivery (OR = 6.8; CI 95% 1.2–37.6; p = 0.028). The BPI recovery was statistically associated with clavicle fracture (HR = 0.31 CI 95% 0.10–0.96 p = 0.042) and specific rehabilitation treatment (HR = 9.2 CI 95% 1.87–45.23 p = 0.006).

Conclusions: The following factors were associated with neonatal BPI at 48 hours of life: maternal BMI above 30 kg/m^2, operative delivery, or shoulder dystocia that requires more than 120 seconds for solving it. The BPI recovery was associated with clavicle fracture and specific rehabilitation treatment.

Keywords: shoulder dystocia; brachial palsy; brachial plexus; dystocia

Ginekologia Polska 2025; 96, 2: 136–141

INTRODUCTION

Shoulder dystocia (SD) is an obstetric emergency, with potentially devastating consequences, that occurs in 0.2–3% of all cephalic vaginal deliveries [1, 2]. Around two and a half percent of early perinatal mortality is caused by SD [3, 4]. In fact, SD is considered an "obstetric nightmare" [5]. Neonatal morbidity associated with SD is quite important, being brachial palsy the most prevalent injury. The brachial plexus injury (BPI) is the main lesion causing long-term disability, and it may appear up to 10% of all deliveries complicated with SD [4].

Certain maternal features such as gestational diabetes, obesity, fetal macrosomia, post-term pregnancy, and previous SD are associated with SD [6–10]. Other intrapartum characteristics such as excessively extended or rapid second stage of delivery [6, 10] or operative delivery [6] should also be taken into account. However, in general, risk factors associated with SD are yet poorly known, and its prediction is still challenging nowadays [1, 5]. For example, a few factors such as Diabetes Mellitus, neonatal weight above 4,000 g, or SD solving time above 120 seconds have been associated with BPI [11]. However, all predictive models evaluating SD, failed to properly foresee BPI associated with SD [11].

The main objective of this study is to analyze factors related to BPI after SD. The description of neonatal brachial palsy evolution is proposed as a secondary objective.

Corresponding author:
Javier Sánchez-Romero
Department of Obstetrics and Gynecology, Pediatrics and Surgery, University of Murcia, Crtra. Cartagena-Madrid s/n El Palmar, 30120 Murcia, Spain and Department of Obstetrics and Gynecology, 'Virgen de la Arrixaca' University Clinical Hospital, Ctra. Madrid-Cartagena, s/n, 30120 El Palmar, Murcia, Spain
e-mail: javier.sanchez14@um.es

Reccieved: 11.07.2022 Accepted: 21.07.2024 Early publication date: 11.10.2024

MATERIAL AND METHODS

This is a longitudinal prospective analysis of SD that arose in 'Virgen de la Arrixaca' University Hospital between 1st of January of 2019 and 31st of December of 2020. This study was approved by the Institutional Reviews Boards (2022-7-1-HCUVA). The principles of the Declaration of Helsinki were followed throughout the study. This center is the largest maternity department in Spain with above 7,500 births per year. In this period 13,414 deliveries were attended, 10,676 of those were vaginal deliveries (79.6%).

A new SD notification system was introduced in January 2019, including the following information: the health professional who attends SD and their categories, the time at it occurs, the second stage duration, onset of labor, the time needed to solve SD, the maneuvers required, the need of episiotomy, head position, neonatal weight, APGAR score, cord blood gasometry, neonatal reanimation, and neonatal fracture. Third-trimester weight, height, and ultrasound parameters such as cephalic circumference (HC), abdominal circumference (AC), estimated fetal weight [12] were retrospectively recorded. Newborns were followed-up at 3, 6, and 12 months. When a BPI was suspected, a pediatric orthopedic evaluation before the discharge was required.

The diagnosis of neonatal brachial palsy was established based on clinical findings, which included arm weakness consistent with a brachial plexus injury. Electromyography was performed as needed to determine the localization and severity of nerve injury when neonatal brachial palsy persisted for more than 3 months after birth. All newborns were followed up by a pediatrician, infant orthopedic surgeon, or pediatric physiatrist. The strength in the upper limbs was assessed using the Medical Research Council (MRC) muscle strength testing scale, which classifies strength into five categories. When physical rehabilitation was required, the pediatric physiatrist provided intensive follow-up.

The primary outcome variable was neonatal brachial palsy at 48 hours of life. *A priori* statistical power of 48.49% was calc based on sample size. A descriptive analysis of all the variables analyzed was performed. Normality and homoscedasticity were assessed for all continuous variables with Shapiro-Wilk test and Levene test, respectively. All continuous variables respected the principles of normality and homoscedasticity. Proportions were compared using Pearson's chi-squared test and Fisher correction when applied. Obstetric history, anthropometric measurements, diabetes mellitus, cephalic circumference, abdominal circumference, AC/HC ratio, AC-HC difference, estimated fetal weight at 3rd trimester, the time needed to solve SD, and type of delivery underwent bivariate analysis using Student's t-test or Pearson's chi-squared test for to compare the characteristics of each group. Afterward, all variables above mentioned with p value < 0.2 in bivariate analysis were considered using a multivariate analysis logistic regression model. In common with all logistic regression analyses, this produced a model applicable to the dataset from which it was generated. A survival analysis of neonatal brachial palsy recovery was performed, and it was also adjusted by Cox regression. All tests were two-tailed, and the level of statistical significance was set at 0.05. Data analysis was performed using SPSS version 25.0 (SPSS Inc., Chicago, Illinois), RStudio version 1.2.5033: Integrated Development for R (RStudio, Inc., Boston, Massachusetts), R version 3.6.2 (https://www.r-project.org/. Accessed February 13, 2021) and STATA BE-Basic Edition version 17.0 (StataCorp, College Station, Texas).

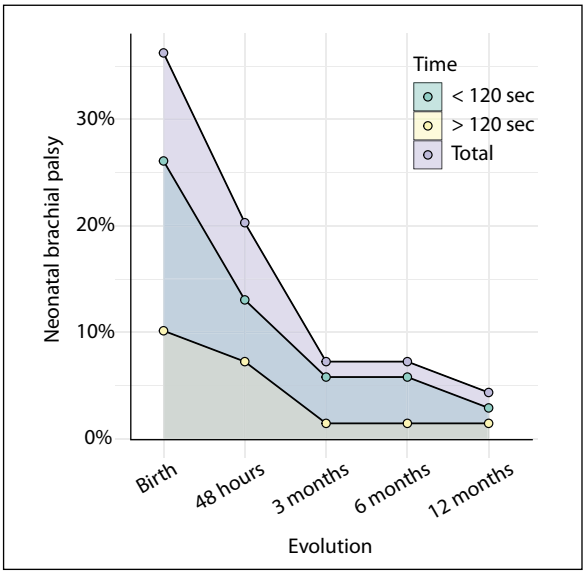


Figure 1. Neonatal brachial palsy evolution compared by the duration of shoulder dystocia

RESULTS

A total of 69 SD was reported during the recruitment period. Of 13.414 deliveries that were attended, 2.738 were cesarean section (20.4%) and 10,676 vaginal deliveries (79.6%). The SD incidence was 0.65%. BPI at birth was suspected in 25 newborns (36.2%) whose birth was complicated with SD. However, this diagnosis was confirmed at 48 hours of life just in 14 babies (20.3%). These newborns were followed-up at 3, 6, and 12 months. Brachial palsy remained in five babies (7.2%) at 3 months, but only three babies (4.3%) suffered BPI finally (Fig. 1). Six newborns (24%) underwent conservative treatment with physiotherapy and specific rehabilitation treatment, and just one baby (4%) needed surgery. The specific rehabilitation treatment was prescribed by the pediatric physiatrist and includes passive range-of-motion exercises, supportive splints (to prevent

finger flexion or elbow contractures), and the promotion of muscle strengthening.

The 26 pregnant women were nulliparous (37.7%), and just three (4.3%) had a previous cesarean section. 11.6% of the patients suffered from diabetes mellitus (DM). Pregestational diabetes was reported in five patients (7.2%) and three pregnancies (4.3%) resulted complicated with gestational diabetes mellitus. Regarding DM, 25.0% of them were managed with diet and exercise and 75.0% required insulin therapy. Two patients opted for insulin pump therapy.

The mean head circumference (HC) at 3rd trimester ultrasound scan was 326.6 mm (standard deviation 1.7). The mean abdominal circumference (AC) and the mean estimated fetal weight was 345.5 mm (standard deviation 3.3) and 3349.0 g (standard deviation 73.0) respectively. The mean difference AC-HC was 18.9 mm (standard deviation 2.8).

The labor onset as an average at 40.1 (standard deviation 0.2) gestation weeks. Delivery was attended by a midwife in 95.7% of the cases. Meanwhile, an obstetrician was present at delivery just in 66.7% of the births.

A right mediolateral episiotomy was required in 40 deliveries (58.0%). The obstetrics outcomes are shown in Table 1. Regarding operative deliveries, vacuum was required in 86.2%, Kjelland's forceps in 10.3%, and Thierry's Spatulas in 3.4%. The mean duration of the second stage of labor was 80.6 minutes (standard deviation 9.0). SD required 102.1 seconds (standard deviation 10.8) as an average for solving it.

The neonatal outcomes are resumed in Table 1. The mean pH in the artery and venous umbilical cord blood was 7.25 and 7.23 (Standard Deviation 0.0 and 0.1) respectively. The mean lactic acid concentration in umbilical cord blood

Table 1. Obstetrics outcomes compared by the duration of shoulder dystocia

		Shoulder dystocia duration				
				> 120 seg (n = 12)		p value
		n	Relative frequency	n	Relative frequency	
Age	< 20 years	2	3.5%	1	8.3%	0.392
	20–35 years	35	61.4%	9	75.0%	
	≥ 35 years	20	35.1%	2	16.7%	
Primary maneuvers		57	100%	12	100%	
Mc Roberts		57	100%	12	100%	
Suprapubic pressure		49	86%	12	100%	0.334
Posterior arm		21	36.8%	8	66.7%	0.057
Rotational maneuvers		6	10.5%	4	33.3%	**0.041**
Clavicle fracture		7	12.3%	4	33.3%	0.090
BMI	< 30 kg/m^2	23	40.4%	7	58.3%	0.253
	> 30 kg/m^2	34	59.6%	5	41.7%	
Diabetes mellitus		5	8.8%	3	25%	0.137
Labor onset	Spontaneous	29	50.9%	7	58.3%	0.638
	Induced	28	49.1%	5	41.7%	
Delivery	Spontaneous	33	57.9%	8	66.7%	0.749
	Operative	24	42.1%	4	33.3%	
Episiotomy		32	56.1%	8	66.7%	0.502
APGAR at birth ≤ 6		7	12.3%	4	33.3%	0.070
APGAR at 5 minutes ≤ 6		1	1.8%	3	25%	**0.002**
APGAR at 10 minutes ≤ 6		0	0%	2	16.7%	**0.002**
Neonatal care unit admission		7	12.3%	5	41.7%	**0.015**
NICU admission		4	7.0%	4	33.3%	**0.010**

BMI — body mass index; NICU — neonatal intensive care unit

was 5.49 mmol/L (standard deviation 0.7). The neonatal mean weight was 3988.3 grams (standard deviation 53.4). The mean HC at birth was 35.2 cm (standard deviation 0.2) and the mean height was 52.6 cm (standard deviation 0.2). Twelve babies (17.4%) required neonatal care unit (NCU) admission. Furthermore, other eight newborns (11.6%) were admitted to the neonatal intensive care unit (NICU).

SD was solved before 120 seconds in 57 cases (82.6%). Meanwhile, 29.8% of SD that required < 120 seconds (s) experimented neonatal brachial palsy, 41.7% of SD that required > 120 suffered from BPI. However, these differences increased at 48 hours of life when neonatal brachial palsy stilled in the 15.8% of SD that required < 120 s, whereas palsy persisted in 41.7% of SD that required > 120 s (p = 0.057).

The BPI at 48 hours of life incidence was statistically associated with the following variables in multivariant analysis: maternal BMI above 30 kg/m^2 (OR = 7.91; CI 95% 1.31–47.69; p = 0.024), > 120 seconds for solving SD (OR = 14.4; CI 95% 1.7–121.82; p = 0.014) and operative delivery (OR = 6.79; CI 95% 1.22–37.64; p = 0.028). No statistically significant association were found between neonatal brachial palsy at 48 hours of life and diabetes mellitus (OR = 2.36; CI 95% 0.32–17.4; p = 0.399) nor ratio AC/HC > 1.1 (OR = 2.15; CI 95% 0.24–19.36; p = 0.495).

Table 2. Multivariate Cox regression analysis of neonatal brachial palsy recovery

Variable	HR	CI 95%	p value
Newborn weight > 4000 g	1.01	0.38-2.71	0.979
Operative delivery	0.51	0.17-1.51	0.221
Posterior arm maneuvers	2.62	0.80-8.62	0.113
Rotational maneuvers	0.70	0.20-2.38	0.564
Clavicle fracture	0.31	0.10-0.96	**0.042**
Specific rehabilitation treatment	9.2	1.87-45.23	**0.006**
Surgery	6.58	0.44-99.51	0.174

When a BPI was confirmed, the recovery occurred with a median time of 3.4 days (CI 95% 0.29–13.71). Kaplan-Meier curves for required time for solving shoulder dystocia are shown in Figure 2. No statistically significant differences were found in BPI recovery at survival analysis for required time for solving shoulder dystocia (log-rank p = 0.07). The BPI recovery was statistically associated with the following variables in multivariant Cox regression analysis (Tab. 2): Clavicle fracture (HR = 0.31 CI 95% 0.10-0.96 p = 0.042) and specific rehabilitation treatment (HR = 9.2 CI 95% 1.87–45.23 p = 0.006).

DISCUSSION

This study revealed the prevalence and evolution of brachial plexus injury in deliveries complicated with shoulder dystocia. Neonatal brachial palsy at 48 hours of life was statistically associated with maternal BMI above 30 kg/m^2, > 120 seconds for solving SD and operative delivery. The BPI recovery was associated with specific rehabilitation treatment and clavicle fracture. A SD requiring more than 120 seconds for solving it was associated with the necessity of

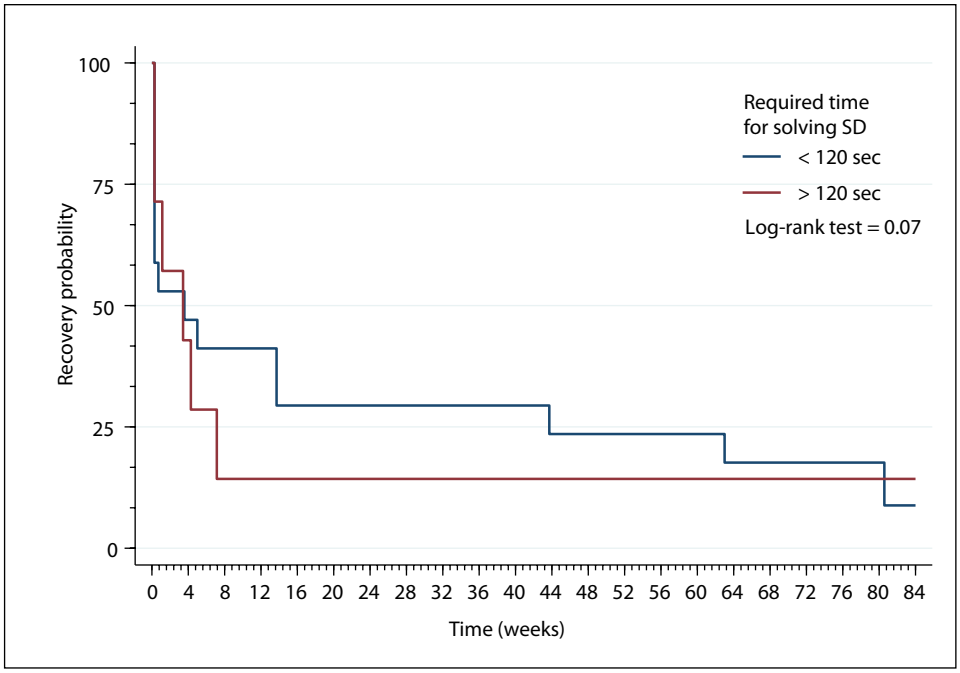


Figure 2. Neonatal brachial palsy recovery: Kaplan-Meier curves for required time for solving shoulder dystocia

internal maneuvers, a score below 7 in the APGAR test at 5 and 10 minutes after birth and with NICU admission.

Previous publications associated an increasing number of maneuvers and also a larger amount of time for solving SD with more neonatal morbidity [13, 14]. Hoffman et al. [13] reported a brachial palsy rate of about 5% when just a maneuver is required. However, this rate increases up to 15% when four maneuvers are needed. Rotational maneuvers are associated with a higher risk of neonatal plexus injury [13]. Leung et al. [15] found that 95% of SD requiring three or fewer maneuvers have a lower neonatal plexus injury rate than that SD requiring four or more maneuvers.

Primary (Mc Roberts and suprapubic pressure) and internal (Posterior arm and rotational maneuver) maneuvers were required in 100% and 42.0% respectively of SD reported in our study. Other authors reported a primary maneuvers success rate of 25.8% [15]. We hypothesized that not all SD, especially minor dystocia, are registered in the notification form system causing this difference.

This study has at least one year of follow-up. The neonatal brachial palsy evolution is similar to that reported by other authors [11, 16]. At birth and at 48 hours of life, the neonatal brachial palsy rate is high. Although, at 3–6 months most of the neonatal brachial palsy solved, from this point on, the recovery is more unlikely.

Neither AC at 3rd trimester ultrasound scan, HC, ratio AC/HC nor difference AC-HC are associated with neonatal brachial palsy. Other authors also revealed this difficult to predict neonatal brachial palsy with clinical or ultrasound parameters [17–20].

This logistic regression model for predicting BPI at 48 hours of life after SD is not robust. Other predicting models reported in the literature also fail to predict neonatal brachial palsy [11, 14, 16]. In our regression model, neonatal brachial palsy at 48 hours of life is statistically associated with maternal BMI > 30 kg/m^2, > 120 seconds for solving SD and operative delivery. The most important factor seems to be time for solving SD, as other authors reported [14, 15]. Although maternal BMI was previously analyzed as a relevant factor for BPI after SD [14, 20], this is the first time that maternal BMI is statistically associated with neonatal BPI after SD. Therefore, obesity primary prevention during pregnancy could be crucial in preventing neonatal morbidity associated with BPI after SD.

The rate of neonatal BPI spontaneous recovery ranges between 75 and 90% [21]. In our study, a spontaneous recovery occurred in 80% of neonatal BPI (25/5) during the first three months. The short BPI recovery median time showed that the majority of BPI solved spontaneously during the first three months of life. Certain factors were associated with a BPI recovery such as clavicle fracture (HR = 0.31) and specific rehabilitation treatment (HR = 9.2). Other authors reported the operative delivery and newborn weight > 4000 grams as factors associated with neonatal BPI persistency [22, 23]. Wilson et al. [22] reported no association between clavicle or humerus fracture and neonatal BPI recovery. To the best of our knowledge, no report performing a survival analysis of neonatal BPI after SD has been published. This is the first time that clavicle fracture and specific rehabilitation treatment are associated with neonatal BPI recovery. We hypothesized that a greater force would be applied in those SD with clavicle fracture, causing severe nerve injuries that might hinder BPI recovery.

Some strengths should be highlighted. A logistic regression model for neonatal BPI after SD and a Cox regression model for neonatal BPI recovery were performed. The health care professional team that attends all deliveries in the hospital did not suffer any modification during this period. Thanks to many deliveries attended in the center, there is a relevant incidence of SD. Furthermore, it should be emphasized that an obstetrics emergency simulation-based program involving hospital attendants, nursing assistants, midwives, residents, anesthesiologists, pediatricians, and obstetricians was implemented in 2019.

An important limitation of our study is that the SD notification system is based on a self-filling paper form. Because of this, some fields are free text variables. It would be desirable a prospective multicentric analysis that includes more cases making stats analysis more robust. The medical records were not equally detailed in all the cases (*i.e.* upper and lower brachial plexus injury), what makes impossible to compare these characteristics.

In conclusion, shoulder dystocia is an obstetric emergency. Neonatal brachial palsy is a characteristic consequence of shoulder dystocia. Certain factors such as maternal BMI above 30 kg/m^2, operative delivery, or shoulder dystocia that requires more than 120 seconds for solving it are associated with neonatal brachial palsy at 48 hours of life. The BPI recovery was associated with specific rehabilitation treatment and clavicle fracture.

Article information and declarations

Data availability statement

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

Ethics statement

The local Institutional Review Board deemed the study exempt from review.

Author contributions

All authors have accepted responsibility for the entire content of this manuscript and approved its submission.

Funding

The authors do not declare any funding.

Conflict of interest

The authors declare no conflict of interest.

REFERENCES

1. Gherman R, Chauhan S, Ouzounian J, et al. Shoulder dystocia: The unpreventable obstetric emergency with empiric management guidelines. Am J Obstet Gynecol. 2006; 195(3): 657–672, doi: 10.1016/j.ajog.2005.09.007.
2. Øverland EA, Vatten LJ, Eskild A. Pregnancy week at delivery and the risk of shoulder dystocia: a population study of 2 014 956 deliveries. BJOG. 2014; 121(1): 34–42, doi: 10.1111/1471-0528.12427.
3. Baskett TF, Allen AC. Perinatal implications of shoulder dystocia. Obstet Gynecol. 1995; 86(1): 14–17, doi: 10.1016/0029-7844(95)00099-D, indexed in Pubmed: 7784010.
4. Chauhan S, Laye M, Lutgendorf M, et al. A Multicenter Assessment of 1,177 Cases of Shoulder Dystocia: Lessons Learned. Am J Perinatol. 2013; 31(05): 401–406, doi: 10.1055/s-0033-1350056.
5. Gherman RB. Shoulder dystocia: an evidence-based evaluation of the obstetric nightmare. Clin Obstet Gynecol. 2002; 45(2): 345–362, doi: 10.1097/00003081-200206000-00006, indexed in Pubmed: 12048394.
6. Acker DS, Sachs BP, Friedman EA. Risk Factors for Shoulder Dystocia. Obstetrics & Gynecology. 1985; 66(6): 762–768.
7. Dodd J, Catcheside B, Scheil W. Can shoulder dystocia be reliably predicted? Aust N Z J Obstet Gynaecol. 2012; 52(3): 248–252, doi: 10.1111/j.1479-828x.2012.01425.x, indexed in Pubmed: 22428758.
8. Ouzounian J. Shoulder Dystocia: Incidence and Risk Factors. Clin Obstet Gynecol. 2016; 59(4): 791–794, doi: 10.1097/grf.0000000000000227.
9. Tsur A, Sergienko R, Wiznitzer A, et al. Critical analysis of risk factors for shoulder dystocia. Arch Gynecol Obstet. 2012; 285(5): 1225–1229, doi: 10.1007/s00404-011-2139-8, indexed in Pubmed: 22083313.
10. Bahar A. Risk factors and fetal outcome in cases of shoulder dystocia compared with normal deliveries of a similar birthweight. BJOG. 2005; 103(9): 868–872, doi: 10.1111/j.1471-0528.1996.tb09904.x.
11. Narendran LM, Mendez-Figueroa H, Chauhan SP, et al. Predictors of neonatal brachial plexus palsy subsequent to resolution of shoulder dystocia. J Matern Fetal Neonatal Med. 2022; 35(25): 5443–5449, doi: 10.1080/14767058.2021.1882982, indexed in Pubmed: 33541167.
12. Hadlock FP, Harrist RB, Carpenter RJ, et al. Sonographic estimation of fetal weight. The value of femur length in addition to head and abdomen measurements. Radiology. 1984; 150(2): 535–540, doi: 10.1148/radiology.150.2.6691115, indexed in Pubmed: 6691115.
13. Hoffman MK, Bailit JL, Branch DW, et al. Consortium on Safe Labor. A comparison of obstetric maneuvers for the acute management of shoulder dystocia. Obstet Gynecol. 2011; 117(6): 1272–1278, doi: 10.1097/AOG.0b013e31821a12c9, indexed in Pubmed: 21555962.
14. Doty M, Chauhan S, Chang KC, et al. Persistence and Extent of Neonatal Brachial Plexus Palsy: Association with Number of Maneuvers and Duration of Shoulder Dystocia. AJP Rep. 2020; 10(01): e42–e48, doi: 10.1055/s-0040-1705140.
15. Leung TY, Stuart O, Suen SSH, et al. Comparison of perinatal outcomes of shoulder dystocia alleviated by different type and sequence of manoeuvres: a retrospective review. BJOG. 2011; 118(8): 985–990, doi: 10.1111/j.1471-0528.2011.02968.x, indexed in Pubmed: 21481159.
16. Chen HY, Blackwell SC, Yang LJS, et al. Neonatal brachial plexus palsy: associated birth injury outcomes, hospital length of stay and costs. J Matern Fetal Neonatal Med. 2022; 35(25): 5736–5744, doi: 10.1080/14767058.2021.1892066, indexed in Pubmed: 33632043.
17. Melendez J, Bhatia R, Callis L, et al. Severe shoulder dystocia leading to neonatal injury: a case control study. Arch Gynecol Obstet. 2009; 279(1): 47–51, doi: 10.1007/s00404-008-0668-6, indexed in Pubmed: 18491119.
18. Chauhan SP, Lynn NN, Sanderson M, et al. A scoring system for detection of macrosomia and prediction of shoulder dystocia: a disappointment. J Matern Fetal Neonatal Med. 2006; 19(11): 699–705, doi: 10.1080/14767050600797483, indexed in Pubmed: 17127493.
19. Miller RS, Devine PC, Johnson EB. Sonographic fetal asymmetry predicts shoulder dystocia. J Ultrasound Med. 2007; 26(11): 1523–1528, doi: 10.7863/jum.2007.26.11.1523, indexed in Pubmed: 17957046.
20. Okby R, Sheiner E. Risk factors for neonatal brachial plexus paralysis. Arch Gynecol Obstet. 2012; 286(2): 333–336, doi: 10.1007/s00404-012-2272-z, indexed in Pubmed: 22437188.
21. Foad SL, Mehlman CT, Foad MB, et al. Prognosis following neonatal brachial plexus palsy: an evidence-based review. J Child Orthop. 2009; 3(6): 459–463, doi: 10.1007/s11832-009-0208-3, indexed in Pubmed: 19885693.
22. Wilson TJ, Chang KWC, Chauhan SP, et al. Peripartum and neonatal factors associated with the persistence of neonatal brachial plexus palsy at 1 year: a review of 382 cases. J Neurosurg Pediatr. 2016; 17(5): 618–624, doi: 10.3171/2015.10.PEDS15543, indexed in Pubmed: 26799409.
23. Chang KWC, Ankumah NAE, Wilson TJ, et al. Persistence of Neonatal Brachial Plexus Palsy Associated with Maternally Reported Route of Delivery: Review of 387 Cases. Am J Perinatol. 2016; 33(8): 765–769, doi: 10.1055/s-0036-1571351, indexed in Pubmed: 26890435.

VIA MEDICA

ORIGINAL PAPER / OBSTETRICS

Ginekologia Polska
2025, vol. 96, no. 2, 142–147

ISSN 0017–0011, e-ISSN 2543–6767

DOI: 10.5603/gpl.95496

Breastfeeding myths — the prevalence among the population of Polish women

Zuzanna Tomczewska[1], Aleksandra Jaron[1], Joanna Kacperczyk-Bartnik[2], Agnieszka Dobrowolska-Redo[2], Ewa Romejko-Wolniewicz[2]

[1]Students' Scientific Group affiliated to II Department of Obstetrics and Gynecology, Medical University of Warsaw, Poland
[2]II Department of Obstetrics and Gynecology, Medical University of Warsaw, Poland

ABSTRACT

Objectives: Exclusive breastfeeding is recommended until the child is six months of age. However, there are many myths about breastfeeding. The aim of our study was to assess the knowledge of Polish women about breastfeeding.

Material and methods: A cross-sectional survey study was conducted among 1536 Polish women. A self-administered questionnaire was created using Google Forms survey management software and distributed online. The participants were asked about the most common myths in society regarding breastfeeding.

Results: The highest number of correct answers in all age groups were given to questions related to the nutritional value of breast milk (80.9–94.9%). The fewest correct answers in each age group were recorded to questions concerning the possibility of getting pregnant during the first 6 months of breastfeeding (16.1–35.3%), the safety of drinking non-alcoholic beer during lactation (24.4–37.1%), the benefits of brushing the breast while breastfeeding (16.0–37.1%), and the effectiveness of compresses made of cabbage leaves or sage infusions in relieving ailments during milk rush (6.8–12.4%). Higher education and being a mother were associated with a higher number of correct answers. Age below 25 years was associated with lower number of correct answers.

Conclusions: The results of the survey regarding breastfeeding suggest the existence of various beliefs in the population of Polish women which are not evidence based. This indicates the need for spreading adequate information about breastfeeding, especially among younger women and those who did not obtain higher education.

Keywords: breastfeeding; breast milk; lactation; nutritional value

Ginekologia Polska 2025; 96, 2: 142–147

INTRODUCTION

Breastfeeding is a special time for both the mother and the baby. The composition of breast milk is adapted to the needs of the infant and changes with the age of the child [1]. Mother's milk is rich in nutritional properties, ensuring the child's balanced growth and development, and immunological properties, protecting it against infections [2, 3]. Moreover, breastfeeding forges a psychological bond between the mother and the child [4]. It was only in 1995 that lactation care was included in the National Health Program. Currently, the World Health Organization (WHO) recommends exclusive breastfeeding until the child is six months of age and continuation of breastfeeding until the age of two and beyond with the introduction of complementary foods.

In Poland, there is not enough scientific research testing the knowledge of Polish women about breastfeeding. There is a risk of popularizing misconceptions about lactation, especially given the widespread access to the Internet today. With its help, various techniques are promoted to increase the effectiveness of breastfeeding, such as dry brushing the breast or using a pacifier to facilitate lactation.

The aim of the study was to assess the knowledge of Polish women about breastfeeding depending on the place of residence, age, level of education and having children.

MATERIAL AND METHODS

A cross-sectional survey was conducted among Polish women. The self-administered survey was created online

Corresponding author:
Ewa Romejko-Wolniewicz
II Department of Obstetrics and Gynecology, Medical University of Warsaw, 2 Karowa St., 00–315 Warsaw, Poland
e-mail: ewa.romejko-wolniewicz@wum.edu.pl

Received: 9.05.2023 Accepted: 18.08.2024 Early publication date: 30.10.2024

using Google Forms survey management software and distributed among 110 Polish Facebook groups. At the beginning of the survey, all potential participants were informed about the survey, its objectives, the manner and scope of using the data received, and the voluntary nature of participation. Anonymity and confidentiality were ensured. The only recruitment criterion was female gender.

The study group included 1536 women. The average age was 29 years (range 15 to 72 years). The respondents were divided into three age categories: below 25 years old (group A — 40.0%), between 26 and 35 years old (group B — 43.8%), above 36 years old (group C — 16.2%). Taking into account the place of residence, the respondents were divided into two subgroups: living in cities with up to 500,000 inhabitants (66.0%) and over 500,000 residents. According to the level of education the study group was divided into two subgroups: respondents with higher education (60.4%) and respondents with lower education (less than higher). The respondents were also divided into two groups according to being a mother: women with any offspring (64.8%) and women with no offspring.

The survey contained a total of 23 questions. The participants were asked about the most common myths in society regarding breastfeeding, *e.g.* giving water to the baby, using a pacifier to facilitate lactation or the benefits of using fennel. In addition, the respondents were asked about contraindications to breastfeeding, the safety of drinking non-alcoholic beer, and eating potentially allergenic food during lactation. Respondents, answering the above questions, had one of two answers to choose: "yes" and "no". The entire survey is included in the Table 1.

To compare the percentage of correct answers between the distinguished subgroups the chi-square test was used. Statistical significance was defined as a p value less than 0.05. Statistical analysis was performed using Statistica software.

Table 1. Questions included in the survey

1. Do you think that mother's milk is enough for the baby?
2. Do you think that breastfed newborns should be supplemented with water?
3. Do you think that the effectiveness of lactation depends on the size of the breasts?
4. Does the use of a pacifier in infants result in faster learning to suck and easier breastfeeding?
5. Do you think there are any contraindications to breastfeeding in the course of influenza in the mother?
6. Do you think that mastitis (with accompanying fever, chills and muscle pain) is a contraindication to breastfeeding?
7. Do you need to consume calories for two while breastfeeding?
8. Is it safe to drink non-alcoholic beer as a substitute for alcoholic beverages while breastfeeding?
9. Should the amount of breast milk given be limited when introducing solid foods?
10. Does dry brushing the breast have a positive effect on lactation?
11. Can expressed breast milk be stored on the refrigerator door?
12. Is there a chance of getting pregnant again if I follow the principles of effective breastfeeding during the first 6 months?
13. Will moms after caesarean section breastfeed as effectively as moms giving birth naturally?
14. Can previously expressed and cooled breast milk be reheated before serving, *e.g.* in a microwave, gas or electric cooker?
15. Is breast milk more cariogenic than formula milk?
16. Are dietary supplements containing fennel recommended to stimulate lactation?
17. Is milk flow present as early as on the second to fourth day after delivery an abnormal situation?
18. Are silicone breast implants a contraindication to breastfeeding?
19. Is it necessary to give additional vitamin D_3 from the first days of life while breastfeeding?
20. Can cabbage leaf compresses or sage infusions be helpful during milk rush?
21. Should a breastfeeding mother limit the consumption of potentially allergenic foods (*e.g.* gluten, nuts, products containing cow's milk protein)?
22. Can the foods the mother eats cause or worsen colic in a breastfed baby?
23. Do you agree with the statement that formula feeding and breastfeeding are equivalent?

RESULTS

The results of the survey are shown in Table 2. The group B (women between 26 and 35 years of age) gave the most correct answers to questions related to the value of breast milk as nutrition (94.9% vs 92.0% in the group C vs 80.9% in the youngest group A), and questions related to situations that may cause anxiety for a nursing mother. To the questions concerning the effectiveness of breastfeeding, the highest percentage of correct answers was also given by group B, however, when comparing groups B and C, the results turned out to be statistically insignificant. Moreover, the questions concerning the possibility of getting pregnant during the first 6 months of breastfeeding, the highest percentage of correct answers was given by the youngest group (35.3% vs 16.1% in group B vs 21.3% in the group C). The fewest correct answers in each age group were recorded to questions concerning the safety of drinking non-alcoholic beer during lactation (24.4–37.1%), the benefits of brushing the breast while breastfeeding (16.0–37.1%), storing expressed breast milk on the refrigerator door (28.8–53.1%), silicone breast implants as a contraindication to breastfeeding (32.1–40.4%), and the effectiveness of compresses made of cabbage leaves or sage infusions in relieving ailments during milk rush (6.8–12.4%).

Most women living in large cities (over 500,000 residents) gave correct answers to the questions regarding the need to eat more calories, limiting the supply of breast milk during the introduction of solid foods or supplementing with fennel to stimulate lactation: 92.5%, 64.8%, 91.0%,

Table 2. The comparison of correct answers in the surveyed women according to age, place of residence, education and having children

Question	p value	Age					
		A < 25	B 26–35	C ≥ 36	p value		
					A vs B	A vs C	B vs C
The value of mother's milk for a newborn	p < 0.001	497 (80.9%)	638 (94.9%)	229 (92.0%)	p < 0.001	p < 0.001	p < 0.05
Supplementing the newborn with water during lactation	p < 0.001	445 (72.5%)	634 (94.4%)	217 (87.2%)	p < 0.001	p < 0.001	p < 0.01
Breast size and lactation efficiency	p < 0.001	571 (93.0%)	662 (98.5%)	245 (98.4%)	p < 0.01	p < 0.01	NS
Using a pacifier	p < 0.001	349 (56.8%)	573 (85.3%)	215 (86.4%)	p < 0.001	p < 0.001	NS
Influenza in a nursing mother	p < 0.001	236 (38.4%)	593 (88.2%)	205 (82.3%)	p < 0.001	p < 0.001	p < 0.01
Breast inflammation in a nursing mother	p < 0.001	146 (23.8%)	492 (73.2%)	167 (67.1%)	p < 0.001	p < 0.001	p < 0.01
The number of calories consumed by a nursing mother	p < 0.001	546 (88.9%)	641 (95.4%)	237 (95.12%)	p < 0.01	p < 0.01	NS
The safety of drinking non-alcoholic beer	p < 0.001	228 (37.1%)	164 (24.4%)	90 (36.1%)	p < 0.01	NS	p < 0.01
Limiting the supply of breast milk	p < 0.001	254 (41.3%)	567 (84.4%)	213 (85.5%)	p < 0.001	p < 0.001	NS
Dry brushing the breast	p < 0.001	98 (16.0%)	249 (37.1%)	88 (35.3%)	p < 0.001	p < 0.001	NS
Storing expressed breast milk	p < 0.001	177 (28.8%)	357 (53.1%)	106 (42.6%)	p < 0.001	p < 0.001	p < 0.01
Possibility of getting pregnant	p < 0.001	217 (35.3%)	108 (16.1%)	53 (21.3%)	p < 0.001	p < 0.001	p < 0.01
Cesarean section and the effectiveness of lactation	p < 0.001	455 (74.1%)	612 (91.1%)	211 (84.7%)	p < 0.001	p < 0.001	p < 0.01
Warming up previously expressed milk	p < 0.001	394 (64.2%)	572 (85.1%)	215 (83.3%)	p < 0.001	p < 0.001	NS
Cariogenicity of human milk	p < 0.001	148 (24.1%)	396 (59.0%)	133 (53.4%)	p < 0.001	p < 0.001	p < 0.01
Fennel supplementation	p < 0.001	528 (86.0%)	640 (95.2%)	235 (94.4%)	p < 0.001	p < 0.01	NS
Milk rush	p < 0.001	401 (65.3%)	627 (93.3%)	228 (91.6%)	p < 0.001	p < 0.001	NS
Silicone breast implants	p < 0.001	227 (40.4%)	336 (50.0%)	80 (32.1%)	p < 0.01	p < 0.01	p < 0.01
Vitamin D_3 supplementation	p < 0.001	291 (47.4%)	581 (86.5%)	196 (78.7%)	p < 0.001	p < 0.001	p < 0.01
The use of compresses of cabbage leaves and sage infusions	p < 0.05	76 (12.4%)	59 (8.8%)	17 (6.8%)	NS	p < 0.05	NS
Limiting the consumption of potentially allergenic foods	p < 0.001	303 (49.4%)	543 (80.8%)	170 (68.3%)	p < 0.001	p < 0.001	p < 0.001
Colic in a breastfed baby	p < 0.001	205 (33.4%)	431 (64.1%)	129 (51.8%)	p < 0.001	p < 0.001	p < 0.01
The value of formulas	p < 0.001	401 (65.3%)	534 (79.5%)	209 (83.9%)	p < 0.001	p < 0.001	p < 0.05

NS — non-significant

respectively. On the other hand, the questions concerning the introduction of solid foods, the chance of getting pregnant during the first 6 months of effective breastfeeding and vitamin D_3 supplementation from the first days of life were answered correctly more often by residents from smaller towns: 68.7%, 25.3%, 70.9%, respectively.

All questions were answered correctly more often by women with higher education compared to the group of respondents with lower education (statistically significant differences). The smallest percentage of correct answers in both groups was recorded to questions concerning the possible benefits of breast brushing (33.9% in higher educated vs 19.8% in less educated), the effectiveness of using compresses of cabbage leaves or sage infusions during milk rush (9.3% vs 10.9%), respectively.

Irrespective the surveyed women had children, the answer to the question concerning the use of compresses made of cabbage leaves or sage infusions during a milk rush were mostly wrong. A greater percentage of correct answers to this question was given by childless women (13.0%) than women with offspring (8.2%). In all other questions, women being a mother gave more correct answers (statistically significant differences). Only 18% of childless women gave the correct answer to the question

	p value	Town		p value	Education		p value	Having children	
		Under 500,000	Over 500,000		Higher	Below higher		No	Yes
	p < 0.05	888 (87.8%)	476 (91.0%)	p < 0.001	857 (92.3%)	507 (83.7%)	p < 0.001	431 (80.0%)	933 (93.7%)
	NS	846 (83.6%)	450 (86.0%)	NS	834 (89.8%)	462 (76.2%)	p < 0.001	367 (68.1%)	488 (87.9%)
	NS	975 (96.3%)	503 (96.2%)	NS	910 (98.0%)	568 (93.7%)	p < 0.01	495 (91.8%)	983 (98.7%)
	p < 0.01	728 (71.9%)	409 (78.2%)	p < 0.001	759 (81.7%)	378 (62.4%)	p < 0.001	290 (53.8%)	847 (85.0%)
	NS	674 (66.6%)	360 (68.8%)	p < 0.001	715 (77.0%)	319 (52.6%)	p < 0.001	153 (28.4%)	881 (88.5%)
	p < 0.05	515 (50.9%)	290 (55.5%)	p < 0.001	596 (64.2%)	209 (34.5%)	p < 0.001	80 (14.8%)	725 (72.8%)
	NS	940 (92.9%)	484 (92.5%)	p < 0.01	878 (94.5%)	546 (90.1%)	p < 0.01	475 (88.1%)	949 (95.3%)
	p < 0.01	675 (66.7%)	378 (72.3%)	p < 0.05	660 (71.0%)	393 (64.9%)	p < 0.001	332 (61.6%)	721 (72.4%)
	p < 0.05	695 (68.7%)	339 (64.8%)	p < 0.001	706 (76.0%)	328 (54.1%)	p < 0.001	179 (33.2%)	855 (85.8%)
	p < 0.01	257 (25.4%)	178 (34.0%)	p < 0.001	315 (33.9%)	120 (19.8%)	p < 0.001	75 (13.9%)	360 (36.1%)
	NS	415 (41.0%)	225 (43.0%)	p < 0.001	443 (47.7%)	197 (32.5%)	p < 0.001	131 (24.3%)	509 (51.1%)
	p < 0.05	256 (25.3%)	122 (23.3%)	p < 0.001	744 (80.1%)	413 (68.2%)	p < 0.001	333 (61.8%)	824 (82.7%)
	p < 0.01	825 (81.5%)	453 (86.6%)	p< 0.001	820 (88.3%)	458 (75.6%)	p < 0.001	395 (73.3%)	883 (88.7%)
	NS	773 (76.4%)	408 (78.0%)	p < 0.001	763 (82.1%)	418 (69.0%)	p < 0.001	336 (62.3%)	845 (84.8%)
	p < 0.01	429 (42.4%)	248 (47.4%)	p < 0.001	494 (53.2%)	183 (30.2%)	p < 0.001	97 (18.0%)	580 (58.2%)
	NS	927 (91.6%)	476 (91.0%)	p < 0.01	866 (93.2%)	537 (88.6%)	p < 0.001	453 (84.0%)	950 (95.4%)
	NS	834 (82.4%)	422 (80.7%)	p < 0.001	820 (88.3%)	436 (72.0%)	p < 0.001	321 (59.6%)	935 (93.9%)
	p < 0.01	435 (43.0%)	260 (49.7%)	NS	426 (45.9%)	269 (44.4%)	NS	249 (46.2%)	446 (44.8%)
	p < 0.05	717 (70.9%)	351 (67.1%)	p < 0.001	721 (77.6%)	347 (57.3%)	p < 0.001	198 (36.7%)	870 (87.4%)
	NS	104 (10.3%)	48 (9.2%)	NS	86 (9.3%)	66 (10.9%)	p < 0.05	70 (13.0%)	82 (8.2%)
	p < 0.01	638 (63.0%)	378 (72.3%)	p < 0.001	689 (74.2%)	327 (54.0%)	p < 0.001	242 (45.0%)	774 (77.7%)
	p < 0.05	488 (48.2%)	277 (53.0%)	p < 0.001	542 (58.3%)	223 (36.8%)	p < 0.001	141 (26.2%)	624 (62.7%)
	NS	744 (73.5%)	400 (76.5%)	p < 0.001	749 (80.6%)	395 (65.2%)	p < 0.01	372 (69.0%)	772 (77.5%)

comparing the cariogenic properties of human milk and modified milk.

DISCUSSION

Considering the results of the study, the main factors associated with giving correct answers were having children and having higher education. The age under 25 was associated with a lower number of correct answers. The size of the place of residence had a much smaller impact on the number of incorrect answers.

It is well known that breastfeeding provides short-term and long-term health benefits to both the nursing mother and her baby [5]. Many countries have introduced programs to promote breastfeeding [6–8]. Also in Poland, under the National Health Program for 2016–2020, the Ministry of Health has taken many actions to support breastfeeding. As part of the projects, a guide on breastfeeding for mothers was created and workshops for families on breastfeeding and infant nutrition were organized [9]. The promotion of breastfeeding may be associated with the emergence of myths about lactation and doubts about the effectiveness of popular methods of feeding children who are breastfed. The widespread access to the Internet poses a risk of promoting misinformation not supported by current

evidence based medical knowledge. In the context of breastfeeding, this poses a risk of spreading inappropriate breastfeeding-related behavior.

In 2021, a study was conducted in Poland on the beliefs of both medical staff and nursing mothers regarding the principles of nutrition during lactation, and the impact of the maternal diet on the composition of breast milk and the health of the infant. The study proved that the belief that preventive dietary restrictions during lactation bring beneficial effects was still present, which supported the thesis that myths about lactation were widespread in the society [10]. An available review of the literature on the analysis of myths and beliefs regarding breastfeeding in theoretical and practical terms from 1985–2008 conducted in Brazil emphasizes the need for professional health education about lactation to verify myths and beliefs [11]. However, there is a lack of updated research assessing current level of knowledge on this topic in the world.

Lactation myths have long been the subject of scientific research. Studies clearly showed that women after caesarean section were less likely to breastfeed than women after giving birth naturally [12, 13]. They also pointed to the need to introduce additional care for women after caesarean section and education to improve the quality of breastfeeding [14, 15]. Although there are no contraindications to breastfeeding after mammoplasty with breast implants, meta-analyses and systematic reviews of studies show that women with breast implants are less likely to breastfeed than women without breast implants [16, 17]. Our survey also showed that almost half of the respondents consider breast implants as a contraindication to breastfeeding. The latest study by researchers in the Netherlands published in 2023 suggests that women with breast implants may experience an impairment in their ability to breastfeed compared to women without implants. Additionally, it points out the need for additional research on this topic to further elucidate this relationship [18].

Multiple studies proved the benefits of vitamin D_3 supplementation from the first days of life and the risk of vitamin D_3 deficiency resulting from exclusive breastfeeding [19, 20]. Despite numerous recommendations [21, 22], knowledge about the need for supplementation in society is low. A topic that raises a lot of doubts among mothers is the reduction of allergenic foods in their diet during breastfeeding. According to current medical knowledge, elimination diets for mothers during pregnancy and lactation are not recommended in the prevention of allergies [23].

To the best of our knowledge, this is the first study in Poland that examined the beliefs of Polish women regarding the rules of lactation and behavior around lactation. The results of the research confirmed that unverified beliefs still exist in society. We are aware of the limitations of our work, as the survey was only spread via social media. Therefore, the population of respondents was limited only to women with an account on social networking sites.

In general, the level of knowledge among mothers with children is high, and increasing awareness in society may reduce attachment to myths. Our study may be an introduction to myths debunking in the society, especially in the population of Polish women.

CONCLUSIONS

The results of the survey regarding breastfeeding suggest the existence of various beliefs in the population of Polish women that are not supported by current medical knowledge. Myths are still popularized, especially in the era of universal access to the Internet. That situation indicates the need for adequate information how to breastfeed among low educated women and among the youngest women. Level of education, age and being a mother are associated with different levels of knowledge about breastfeeding.

Article information and declarations

Data availability statement

Datasets are available on reviewers' request.

Ethics statement

The study was performed in accordance with the Declaration of Helsinki.

Author contributions

All authors contributed to this study, details are available in the separate Authors contribution form.

Funding

No funding was obtained for this study.

Acknowledgments

We sincerely thank all the Polish women who participated in this survey.

Conflict of interest

The authors declare no conflict of interest.

Supplementary material

None.

REFERENCES

1. Andreas NJ, Kampmann B, Mehring Le-Doare K. Human breast milk: a review on its composition and bioactivity. Early Hum Dev. 2015; 91(11): 629–635, doi: 10.1016/j.earlhumdev.2015.08.013, indexed in Pubmed: 26375355.

2. Yi DY, Kim SuY. Human breast milk composition and function in human health: from nutritional components to microbiome and microrna. Nutrients. 2021; 13(9): 3094, doi: 10.3390/nu13093094, indexed in Pubmed: 34578971.
3. Palmeira P, Carneiro-Sampaio M. Immunology of breast milk. Rev Assoc Med Bras. 2016; 62(6): 584–593, doi: 10.1590/1806-9282.62.06.584, indexed in Pubmed: 27849237.
4. Krol KM, Grossmann T. Psychological effects of breastfeeding on children and mothers. Bundesgesundheitsblatt Gesundheitsforschung Gesundheitsschutz. 2018; 61(8): 977–985, doi: 10.1007/s00103-018-2769-0, indexed in Pubmed: 29934681.
5. Sattari M, Serwint JR, Levine DM. Maternal implications of breastfeeding: a review for the internist. Am J Med. 2019; 132(8): 912–920, doi: 10.1016/j.amjmed.2019.02.021, indexed in Pubmed: 30853481.
6. Flores-Antón B, Temboury-Molina MC, Ares-Segura S, et al. Breastfeeding promotion plan in Madrid, Spain. J Hum Lact. 2012; 28(3): 363–369, doi: 10.1177/0890334412449516, indexed in Pubmed: 22689708.
7. Bettinelli ME, Chapin EM, Cattaneo A. Establishing the baby-friendly community initiative in Italy: development, strategy, and implementation. J Hum Lact. 2012; 28(3): 297–303, doi: 10.1177/0890334412447994, indexed in Pubmed: 22674964.
8. Feldman-Winter L, Procaccini D, Merewood A. A model infant feeding policy for baby-friendly designation in the USA. J Hum Lact. 2012; 28(3): 304–311, doi: 10.1177/0890334412440626, indexed in Pubmed: 22538504.
9. Akcja promocyjna Ministerstwa Zdrowia dotycząca karmienia piersią [Promotional campaign of the Ministry of Health concerning breastfeeding]. https://www.gov.pl/web/zdrowie/karmienie-piersia-akcja-promocyjna-ministerstwa-zdrowia (9.05.2023).
10. Karcz K, Lehman I, Królak-Olejnik B. The link between knowledge of the maternal diet and breastfeeding practices in mothers and health workers in Poland. Int Breastfeed J. 2021; 16(1): 58, doi: 10.1186/s13006-021-00406-z, indexed in Pubmed: 34372889.
11. Marques ES, Cotta RM, Priore SE. [Myths and beliefs surrounding breastfeeding]. Cien Saude Colet. 2011; 16(5): 2461–2468, doi: 10.1590/s1413-81232011000500015, indexed in Pubmed: 21655719.
12. Rudzinski P, Lopuszynska I, Pieniak K, et al. Feeding practices, maternal and neonatal outcomes in vaginal birth after cesarean and elective repeat cesarean delivery. Int J Environ Res Public Health. 2022; 19(13): 7696, doi: 10.3390/ijerph19137696, indexed in Pubmed: 35805350.
13. Zanardo V, Svegliado G, Cavallin F, et al. Elective cesarean delivery: does it have a negative effect on breastfeeding? Birth. 2010; 37(4): 275–279, doi: 10.1111/j.1523-536X.2010.00421.x, indexed in Pubmed: 21083718.
14. Hobbs AJ, Mannion CA, McDonald SW, et al. The impact of caesarean section on breastfeeding initiation, duration and difficulties in the first four months postpartum. BMC Pregnancy Childbirth. 2016; 16: 90, doi: 10.1186/s12884-016-0876-1, indexed in Pubmed: 27118118.
15. Beake S, Bick D, Narracott C, et al. Interventions for women who have a caesarean birth to increase uptake and duration of breastfeeding: A systematic review. Matern Child Nutr. 2017; 13(4): e12390, doi: 10.1111/mcn.12390, indexed in Pubmed: 27882659.
16. Cheng F, Dai S, Wang C, et al. Do breast implants influence breastfeeding? A meta-analysis of comparative studies. J Hum Lact. 2018; 34(3): 424–432, doi: 10.1177/0890334418776654, indexed in Pubmed: 29932861.
17. Schiff M, Algert CS, Ampt A, et al. The impact of cosmetic breast implants on breastfeeding: a systematic review and meta-analysis. Int Breastfeed J. 2014; 9: 17, doi: 10.1186/1746-4358-9-17, indexed in Pubmed: 25332722.
18. Chen J, Zhu XiM, Huynh MNQ, et al. Breastfeeding outcome and complications in females with breast implants: a systematic review and meta-analysis. Aesthet Surg J. 2023; 43(7): 731–740, doi: 10.1093/asj/sjad027, indexed in Pubmed: 36752943.
19. Tan ML, Abrams SA, Osborn DA. Vitamin D supplementation for term breastfed infants to prevent vitamin D deficiency and improve bone health. Cochrane Database Syst Rev. 2020; 12(12): CD013046, doi: 10.1002/14651858.CD013046.pub2, indexed in Pubmed: 33305822.
20. Domenici R, Vierucci F. Exclusive breastfeeding and vitamin D supplementation: a positive synergistic effect on prevention of childhood infections? Int J Environ Res Public Health. 2022; 19(5): 2973, doi: 10.3390/ijerph19052973, indexed in Pubmed: 35270666.
21. De Ronne N, De Schepper J. Société flamande de Pédiatrie. [Recommendations for vitamin D supplementation in infants and young children]. J Pharm Belg. 2013(3): 12–21, indexed in Pubmed: 24804408.
22. Szajewska H, Socha P, Horvath A, et al. Nutrition of healthy term infants. Recommendations of the Polish Society for Paediatrics Gastroenterology, Hepatology and Nutrition. Standardy Medyczne/Pediatria. 2021; 18: 805–822, doi: 10.17444/SMP2021.18.02.
23. Heine RG. Food allergy prevention and treatment by targeted nutrition. Ann Nutr Metab. 2018; 72 Suppl 3: 33–45, doi: 10.1159/000487380, indexed in Pubmed: 29631274.

VIA MEDICA

ORIGINAL PAPER / OBSTETRICS

Ginekologia Polska
2025, vol. 96, no. 2, 148–152

ISSN 0017–0011, e-ISSN 2543–6767

DOI: 10.5603/gpl.101484

Evaluation of the utility of the sFlt-1/PlGF ratio in pregnancy complicated by pre-eclampsia — single-center study. Preliminary analysis

Justyna A. Kuciel, Jagoda N. Sarad, Natalia M. Mroczek, Andrzej Jaworowski, Magdalena L. Kolak, Hubert K. Huras

Department of Obstetrics and Perinatology, Jagiellonian University Medical College, Cracow, Poland

ABSTRACT

Objectives: To evaluate relationship between soluble fms-like tyrosine kinase-1 (sFlt-1)/placental growth factor (PlGF) ratio, clinical characteristics and outcomes of pre-eclampsia.

Material and methods: Retrospective analysis of 29 pregnant women with pre-eclampsia who had measured sFlt-1/PlGF ratio was conducted using electronic medical records from Obstetrics and Perinatology ward of University Hospital in Cracow.

Results: Women median age: 33.5 years, number of pregnancies: one 52%, two 15%, three 18%,more than three 15%, number of deliveries: one 59.3%, two 37%, three 3.7%, median body mass index during hospitalization: 29.4 kg/m^2. Chronic diseases apart from hypertension: 67% of women (diabetes 37%, hypothyroidism 26%, obesity 11%). Median newborns birth weight: 1640 g, median Apgar score at 5 minutes: 8, median umbilical cord blood pH: 7.32. Fetal growth restriction: 28.6% of cases. All deliveries were by c-section. Median gestational age at delivery: 32 weeks. sFlt-1/PlGF ratio was inversely correlated with gestational age at delivery ($r = –0.42$, $p = 0.02$). The median sFlt-1/PlGF ratio was higher in women with severe pre-eclampsia ($n = 15$) than in those with mild pre-eclampsia ($n = 14$) (211 vs 57, $p < 0.001$). sFlt-1/PlGF ratio of > 85 had a sensitivity of 80% and a specificity of 71% for predicting severe pre-eclampsia.

Conclusions: sFlt-1/PlGF ratio is useful in assessing the severity and prognosis of pre-eclampsia. sFlt-1/PlGF ratio should not be used as a sole criterion for making clinical decisions, but as an adjunct to other clinical and laboratory parameters.

Keywords: pre-eclampsia; eclampsia; clinical laboratory test; sFLT-1 protein; placenta growth factor

Ginekologia Polska 2025; 96, 2: 148–152

INTRODUCTION

Preeclampsia is a complex pregnancy complication marked by elevated blood pressure and potential organ damage, notably to the liver and kidneys, posing risks to both the mother and the fetus. This condition presents a significant challenge not just to gynecologists but to a broad spectrum of medical specialists due to its role in increasing maternal morbidity and its association with severe fetal complications, such as intrauterine growth restriction [1]. Annually, preeclampsia accounts for approximately 500,000 fetal/neonatal fatalities and 70,000 maternal deaths worldwide, with a prevalence rate of 2% to 8% in pregnancies globally [2, 3]. The exact mechanisms driving preeclampsia remain elusive, highlighting the need for further research [4]. Recent theories have emphasized the critical balance between pro- and anti-angiogenic factors in understanding preeclampsia's pathogenesis. Soluble fms-like tyrosine kinase-1 (sFlt-1), an anti-angiogenic factor, disrupts vascular development by binding to and inhibiting the action of vascular endothelial growth factor (VEGF), essential for the formation and maintenance of blood vessels. Conversely, placental growth factor (PlGF), which belongs to the VEGF

Corresponding author:
Justyna A. Kuciel
Department of Obstetrics and Perinatology, Jagiellonian University Medical College, Cracow, Poland
e-mail: j.a.kuciel@gmail.com

Received: 8.07.2024 Accepted: 22.09.2024 Early publication date: 21.01.2025

family, plays a pro-angiogenic role by promoting angiogenesis by interacting with VEGF receptors on endothelial cells. An imbalance, particularly an elevated sFlt-1/PlGF ratio, has been linked to an increased risk of severe preeclampsia and adverse outcomes, underscoring the importance of this ratio as a potential marker for managing and understanding the condition [1, 5]. The cut-off points for delivery in 48 hours were proposed, but the data are limited [6]. The study aimed to evaluate the course of pregnancy complicated by preeclampsia concerning the sFlt-1/PlGF ratio, specifically focusing on the delivery timing.

Objectives

The aim of the study was to evaluate the course of pregnancy complicated by preeclampsia regarding the sFlt-1/PlGF ratio.

MATERIAL AND METHODS

Study group

A retrospective study was conducted at Jagiellonian University Hospital in the Obstetrics and Perinatology Ward from November 2022 to January 2023. The study included women diagnosed with pre-eclampsia who had their sFlt-1 and PlGF levels measured (48 hours or a maximum of 7 days before the labour). Patients with multiple pregnancies were excluded from the study.

Data regarding medical history, delivery details, and maternal and neonatal outcomes were gathered from electronic medical records. Although the patients with pre-eclampsia had their sFlt-1/PlGF ratio measured, the physicians involved in the study were kept blinded to the results.

Definition

Pre-eclampsia is categorized into early-onset (before 34 weeks) and late-onset (34 weeks or later) as per the consensus-based position statement from the Polish Society of Hypertension, Polish Cardiac Society, and Polish Society of Gynecologists and Obstetricians [7].

There were proposed sFlt-1/PlGF ratio thresholds. For early preeclampsia, a ratio higher than 655 was proposed as the cut-off for delivery, while in late preeclampsia, it was higher than 201 [8].

Statistical analysis

The statistical analysis was conducted using SPSS Statistics 9.0. The Shapiro–Wilk test was used to assess the normality of the data distribution of the quantitative variables. Due to the lack of normal distribution in the data, the median was utilized for presentation. The sFlt-1/PlGF ratio was used to determine sensitivity and specificity values for predicting severe preeclampsia. Furthermore, the correlation between the sFlt-1/PlGF ratio and gestational age at delivery was examined to check whether the ratio met the suggested cut-off values [7].

Approval for the study was obtained from the local bioethics committee (approval number 1072.6120.15.2023).

RESULTS

The retrospective study was conducted at the Jagiellonian University Hospital's Obstetrics and Perinatology Department, a tertiary referral center, from November 2022 to January 2023. It focused on 33 cases of preeclampsia, out of which 29 met the inclusion criteria and were subsequently analyzed. Exclusions included one case of twin pregnancy and three cases due to missing sFlt-1/PlGF ratios.

Participants in the study had a median age of 33.5 years and a median body mass index (BMI) of 29.4 kg/m^2 during their hospital stay. A significant (n = 20) 67% of the women had chronic conditions, with diabetes, chronic hypertension, and hypothyroidism being the most prevalent (Tab. 1). Regarding the use of hypotensive medication during pregnancy, (n = 24) 88.9% of the patients were on polytherapy, predominantly with methyldopa and nitrendipine (Tab. 2).

The newborns' median birth weight was 1640 grams, and their median Apgar score at 5 minutes was 8.

Table 1. Obstetric characteristics of the study group and data regarding chronic diseases

Characteristics	n [%]
Primigravida	14 (52%)
Primipara	16 (59.3%)
Chronic hypertension	7 (26%)
Diabetes mellitus pregestational	10 (37%)
Obesity	3 (11.1%)
Hypothyroidism	7 (26%)
Characteristics	**Median**
Age	33.5 years
BMI	29.4 kg/m^2
Gestational age of delivery	32 weeks
Neonatal birth weight	1640 g
Apgar score	8

BMI — body mass index

Table 2. Medication used during the pregnancy by the study group

Medication	The percentage of the women who used a particular medication, n [%]
Methyldopa	25 (89.3%)
Nitrendipine	18 (64.3%)
Labetalol	10 (35.7%)
Metoprolol	9 (31.1%)
Polytherapy	24 (88.9%)

The median umbilical cord blood pH stood at 7.32. Fetal growth restriction was observed in 28.6% (n = 8) of the cases. All births were via cesarean section, with the primary indications being impending eclampsia (73.1%), neonatal asphyxia risk (19.2%), labor stagnation (3.9%), planned interventions (11.7%), and other reasons (19.5%).

The study also examined the timing of delivery in relation to the sFlt-1/PlGF ratio, noting a median gestational age of 32 weeks at delivery. A notable inverse correlation between the sFlt-1/PlGF ratio and gestational age at delivery was observed (r = –0.42, p = 0.02), especially significant in the ratio category above 210, where the median gestational week dropped to 28 (details in Table 3). sFlt-1/PlGF ratio was inversely correlated with gestational age at delivery (r = –0.42, p = 0.02). The median sFlt-1/PlGF ratio was higher in women with severe pre-eclampsia (n = 15) than in those with mild pre-eclampsia (n = 14) (211 vs 57, p < 0.001). sFlt-1/PlGF ratio of > 85 had a sensitivity of 80% and a specificity of 71% for predicting severe pre-eclampsia.

Except for the sFlt-1PlGF ratio, also other laboratory tests were taken into consideration during our study. As the preeclampsia has influence on the liver and kidneys, their functions were checked (Tab. 4). To assess to severity of the preeclampsia, lactate dehydrogenase (LDH), albumins and platelet count were also regarded. Only albumin to creatinine ratio was significantly elevated.

Furthermore, the study explored proposed cut-off values for delivery, finding that most patients did not meet thresholds. The result showed that both patients with early and late preeclampsia had an emergency indication of cesarean section and sFlt-1/PlGF ratio below the proposed threshold (72% and 83%). Detailed information is in Table 5.

Table 3. The median delivery week, in the sFlt-1/PlGF ratio category

sFlt-1/PlGF ratio	Delivery (median)	The percentage of the deliveries, n [%]
< 38	34th 6 days	7 (28%)
38–85	33rd 0 days	1 (4%)
> 85	32nd 5 days	3 (12%)
> 160	34th 0 days	3 (12%)
> 210	28th 0 days	11 (44%)

sFtl-1— soluble fms-like tyrosine kinase-1; PlGF — placental growth factor

Table 4. Laboratory tests

Laboratory test	Median	Normal range
ALT	27 IU/L	< 40 IU/L
AST	30.5 IU/L	< 40 IU/L
Creatinine	59.5 µmol/L	53–115 µmol/L
Albumin to creatinine ratio	136.1 mg/g	< 30 mg/g
Platelet count	195 000/µL	150 000–450 000/µL
LDH	202 IU/L	< 480 IU/L
Albumin	30.9 g/L	35–50 g/L

LDH — lactate dehydrogenase

Table 5. Distribution of cases of cesarean section in 48 hours regarding cut-off values of sFlt-1/PlGF

Pre-eclampsia	sFlt-1/PlGF under cut-off (655 or 210)*** n [%]	sFlt-1/PlGF above cut-off n [%]
Early-onset* (< 34 weeks)	13 (72%)	5 (28%)
Late-onset** (> 34 weeks)	5 (83%)	1 (17%)

*Early-onset pre-eclampsia is defined as pre-eclampsia before 34th gestational week; **Late-onset preeclampsia is defined as pre-eclampsia after the 34th gestational week; ***The cut-off values of the sFlt-1/PlGF ratio indicate the need to deliver in early-onset preeclampsia — 655 and late-onset pre-eclampsia — 201; sFtl-1- soluble fms-like tyrosine kinase-1, PlGF — placental growth factor

DISCUSSION

The sFlt-1/PlGF ratio is a helpful tool in managing pre-eclampsia-related pregnancies [9]; however, it is not that popular to assay. This ratio can help clinicians identify patients more likely to develop severe pre-eclampsia, allowing for better management and potentially improving maternal and fetal outcomes. Our single-center study showed that the cesarean sections in pregnancies complicated by pre-eclampsia are performed earlier than the suggested cut-off values of the sFlt-1/PlGF ratio [6] (Tab. 2). The higher sFlt-1/PlGF ratio, the more intense the care of pregnant women was. The same fact was shown in other studies, which point out that the ratio level correlates with the applied therapeutic approach [10]. The results of our research are consistent with other studies on this topic, which show a correlation between the level of sFlt-1/PlGF and the clinical diagnosis of pre-eclampsia [11, 12]. Several studies have demonstrated that a higher sFlt-1/PlGF ratio is associated with an increased risk of developing severe pre-eclampsia, necessitating closer monitoring and earlier intervention [10, 13]. The study also observed that a higher median sFlt-1/PlGF ratio correlates with earlier delivery, not only due to maternal indications such as threatening eclampsia but also concerns for the child's well-being, which was previously highlighted in other research [14, 15].

In addition to predicting the severity of pre-eclampsia, the sFlt-1/PlGF ratio can also help determine the appropriate time for delivery, especially in cases with early-onset pre-eclampsia [16]. In our study, it was shown that in 72.2% (n = 13) of pregnancies complicated by early-onset preeclampsia, the sFlt-1/PlGF ratio to perform c-section were below the suggested cut-off values (cut-off value for early-onset preeclampsia — 655). In the case of late-onset preeclampsia,

the sFlt-1/PlGF ratio did not meet the proposed values in 83% (n = 5) (cut-off value for late-onset preeclampsia — 210). Threshold values for the sFlt-1/PlGF ratio may vary depending on the population studied and the specific clinical context [16]. However, some general guidelines can be applied to early-onset and late-onset pre-eclampsia for predicting adverse neonatal and maternal outcomes [16].

For early-onset pre-eclampsia, a sFlt-1/PlGF ratio of greater than or equal to 85 has been suggested as a threshold for predicting adverse outcomes [10]. In our research, the median sFlt-1/PlGF ratio in an early-onset preeclampsia group was 190. In this context, a higher ratio indicates a higher risk of complications, and clinicians may consider closer monitoring and intervention as needed. For late-onset pre-eclampsia, a sFlt-1/PlGF ratio of greater than or equal to 110 has been suggested as a threshold for predicting adverse outcomes. In our study, the median ratio in a group of late-onset preeclampsia was 131. Like early-onset pre-eclampsia, a higher ratio in late-onset pre-eclampsia may prompt increased surveillance and intervention to minimize maternal and neonatal complications. Moreover, some researchers claim that the sFlt-1/PlGF ratio of 38 or lower can be used to short-term exclude pre-eclampsia in women with clinically suspected pre-eclampsia [5]. It is essential to emphasize that these threshold values should be used in a comprehensive clinical assessment, considering other factors such as maternal and fetal well-being, gestational age, and other risk factors. The sFlt-1/PlGF ratio is a valuable tool in managing pre-eclampsia, but it should be interpreted in the context of the overall clinical picture [17].

Strength and limitations

The study's strength is its novel approach to pre-eclampsia. The sFlt-1/PlGF ratio is a new indicator that is not commonly studied. However, the biggest limitation is the low number of cases.

CONCLUSIONS

The sFlt-1/PlGF ratio is a valuable tool for assessing the severity and prognosis of preeclampsia. It can help identify women at high risk of developing complications and who may benefit from early delivery or intensive monitoring. It is worth introducing these angiogenic factors into clinical practice, but the index should be interpreted in the context of other laboratory methods (Tab. 4) and the overall clinical picture. However, the utility of the sFlt-1/PlGF ratio has been shown in our study, further research in clinical practice setting would be beneficial especially as a multicenter, prospective study.

Article information and declarations

Data availability statement

Original contributions presented in the study are included in the article. Any further inquiries can be directed to the corresponding author.

Ethics statement

Approval for the study was obtained from the local bioethics committee (approval number 1072.6120.15.2023).

Author contributions

JK — concept of the article, corresponding author; JS — data acquisition; NM — article draft; AJ — interpretation of the data; MK — analysis of the data; HH — revised article, corrections.

Funding

The article had no external funders.

Acknowledgments

Not applicable.

Conflict of interest

There was no conflict of interest.

Supplementary material

None.

REFERENCES

1. Tataru-Copos AF, Popescu MI, Murvai R, et al. Efficiency of sFlt-1/PlGF ratio in preeclampsia diagnosis. Medicina (Kaunas). 2022; 58(9), doi: 10.3390/medicina58091196, indexed in Pubmed: 36143873.
2. Rana S, Lemoine E, Granger JP, et al. Preeclampsia: pathophysiology, challenges, and perspectives. Circ Res. 2019; 124(7): 1094–1112, doi: 10.1161/CIRCRESAHA.118.313276, indexed in Pubmed: 30920918.
3. Stepan H, Galindo A, Hund M, et al. Clinical utility of sFlt-1 and PlGF in screening, prediction, diagnosis and monitoring of pre-eclampsia and fetal growth restriction. Ultrasound Obstet Gynecol. 2023; 61(2): 168–180, doi: 10.1002/uog.26032, indexed in Pubmed: 35816445.
4. Verlohren S, Brennecke SP, Galindo A, et al. Clinical interpretation and implementation of the sFlt-1/PlGF ratio in the prediction, diagnosis and management of preeclampsia. Pregnancy Hypertens. 2022; 27: 42–50, doi: 10.1016/j.preghy.2021.12.003, indexed in Pubmed: 34915395.
5. Zeisler H, Llurba E, Chantraine F, et al. Predictive value of the sFlt-1:PlGF ratio in women with suspected preeclampsia. N Engl J Med. 2016; 374(1): 13–22, doi: 10.1056/NEJMoa1414838, indexed in Pubmed: 26735990.
6. Kumar N, Das V, Agarwal A, et al. Correlation of sFlt/PlGF ratio with severity of preeclampsia in an Indian population. AJOG Glob Rep. 2023; 3(2): 100177, doi: 10.1016/j.xagr.2023.100177, indexed in Pubmed: 36911235.
7. Prejbisz A, Dobrowolski P, Kosiński P, et al. Management of hypertension in pregnancy: prevention, diagnosis, treatment and longterm prognosis. Kardiol Pol. 2019; 77(7-8): 757–806, doi: 10.33963/KP.14904, indexed in Pubmed: 31322138.
8. Verlohren S, Herraiz I, Lapaire O, et al. The sFlt-1/PlGF ratio in different types of hypertensive pregnancy disorders and its prognostic potential in preeclamptic patients. Am J Obstet Gynecol. 2012; 206(1): 58.e1–58.e8, doi: 10.1016/j.ajog.2011.07.037, indexed in Pubmed: 22000672.

9. Lecarpentier E, Tsatsaris V. Angiogenic balance (sFlt-1/PlGF) and preeclampsia. Ann Endocrinol (Paris). 2016; 77(2): 97–100, doi: 10.1016/j.ando.2016.04.007, indexed in Pubmed: 27130072.
10. Jeon HR, Jeong DH, Lee Y, et al. sFlt-1/PlGF ratio as a predictive and prognostic marker for preeclampsia. J Obstet Gynaecol Res. 2021; 47(7): 2318–2323, doi: 10.1111/jog.14815, indexed in Pubmed: 33973302.
11. Bednarek-Jędrzejek M, Kwiatkowski S, Ksel-Hryciów J, et al. The sFlt-1/PlGF ratio values within the <38, 38-85 and >85 brackets as compared to perinatal outcomes. J Perinat Med. 2019; 47(7): 732–740, doi: 10.1515/jpm-2019-0019, indexed in Pubmed: 31339858.
12. Valenzuela FJ, Pérez-Sepúlveda A, Torres MJ, et al. Pathogenesis of preeclampsia: the genetic component. J Pregnancy. 2012; 2012: 632732, doi: 10.1155/2012/632732, indexed in Pubmed: 22175024.
13. Skjaerven R, Vatten LJ, Wilcox AJ, et al. Recurrence of pre-eclampsia across generations: exploring fetal and maternal genetic components in a population based cohort. BMJ. 2005; 331(7521): 877, doi: 10.1136/bmj.38555.462685.8F, indexed in Pubmed: 16169871.
14. Sun Y, Meng C, Yu L. Correlation of serum IGF-1 and sFlt-1 levels with adverse pregnancy outcomes in patients with severe preeclampsia. Altern Ther Health Med. 2023; 29(5): 364–369, indexed in Pubmed: 37171953.
15. Nóbrega L, Katz L, Lippo L, et al. Association of sFlt-1 and C-reactive protein with outcomes in severe preeclampsia: a cohort study. Medicine (Baltimore). 2022; 101(11), doi: 10.1097/MD.0000000000029059, indexed in Pubmed: 35356925.
16. Graupner O, Lobmaier SM, Ortiz JU, et al. sFlt-1/PlGF ratio for the prediction of the time of delivery. Arch Gynecol Obstet. 2018; 298(3): 567–577, doi: 10.1007/s00404-018-4840-3, indexed in Pubmed: 29968165.
17. Burwick RM, Rodriguez MH. Angiogenic Biomarkers in Preeclampsia. Obstet Gynecol. 2024; 143(4): 515–523, doi: 10.1097/AOG.0000000000005532, indexed in Pubmed: 38350106.

VIA MEDICA

CLINICAL VIGNETTE

Ginekologia Polska
2025, vol. 96, no. 2, 153–154

ISSN 0017–0011, e-ISSN 2543–6767

DOI: 10.5603/gpl.100984

Clinical application of synthetic osmotic cervical dilator in labor pre-induction: departmental protocol and literature review

Maisa Manasar-Dyrbus, Katarzyna Wilk, Maja Zieba-Domalik, Jakub Staniczek, Rafal Stojko

Chair and Clinical Department of Gynecology, Obstetrics and Gynecological Oncology, Medical University of Silesia, Katowice, Poland

ABSTRACT

Labor induction is a common obstetric procedure, performed in approximately 30–40% of pregnancies in developed countries. This intervention is typically employed to stimulate uterine contractions before spontaneous labor begins, especially when there are maternal or fetal health concerns. Hygroscopic dilators, used for cervical ripening in these cases, have demonstrated high success rates in achieving adequate cervical dilation. Their usage can reduce the need for pharmacological agents, thereby minimizing the risk of hyperstimulation and other side effects associated with labor induction drugs [1–2].

DEPARTMENTAL PROTOCOL

In our department, we employ osmotic dilators for cervical ripening as part of preinduction labor procedures. Prior to the application of dilators, patients undergo transvaginal ultrasound of the cervix and gynecological examination. Additionally, fetal wellbeing is assessed using ultrasound and cardiotocography (CTG). Patients with a Bishop score below 3 are eligible for osmotic cervical dilators. The standard protocol involves inserting three Dilapan-S dilators into the cervix for 24 hours (Fig. 1 A, B). After insertion, a transvaginal ultrasound is performed to ensure proper placement (Fig. 1 C, D). During the 24-hour period, fetal heart rate is monitored every two hours through standard auscultation, without the need for additional supervision. The dilators are removed if labor contractions begin, if the rupture of membranes or after 24 hours, followed by a reassessment of the cervix through a gynecological examination (Fig. 1 E, F).

LITERATURE REVIEW

Mechanical methods for cervical ripening, such as hygroscopic dilators, are considered safer compared to prostaglandins. They are widely accepted among patients due to their higher safety profile. Various studies have compared the use of hygroscopic cervical dilators (Dilapan-S) with other mechanical and pharmacological methods of labor induction. Patients undergoing induction with Dilapan-S reported higher satisfaction rates, and the method was associated with reduced risks of hyperstimulation and pain during cervical ripening, enhancing its safety profile compared to pharmacological induction [2, 4].

A randomized controlled trial in 2022 compared osmotic cervical dilators and misoprostol in a cohort of 307 women, with 151 treated with osmotic dilators and 152 with misoprostol. Results indicated that patients using hygroscopic dilators experienced less abdominal and vaginal pain and improved sleep quality. Moreover, a higher percentage of these patients had vaginal deliveries compared to those using misoprostol (61.6% vs 59.2%) [5]. Induction with Dilapan-S can be performed in an outpatient setting and does not require continuous electronic fetal monitoring, thereby improving patient comfort and reducing hospitalization duration. Shorter hospital stays correlate with higher patient satisfaction and lower healthcare costs. The use of Dilapan-S for labor induction has yielded satisfactory results, with cervical maturity significantly improving from a Bishop score. Patients did not report any discomfort, gastric issues, or pain during the procedure [6]. Dilapan-S offers a similar cervical preparation time for vaginal delivery compared to misoprostol but provides a better safety profile, greater patient comfort, and a lower risk of myometrial hyperstimulation. The U.S. Food

Corresponding author:
Jakub Staniczek
Chair and Clinical Department of Gynecology, Obstetrics and Gynecological Oncology, Medical University of Silesia, Katowice, Poland
e-mail: jstaniczek@sum.edu.pl

Received: 6.06.2024 Accepted: 10.06.2024 Early publication date: 8.11.2024

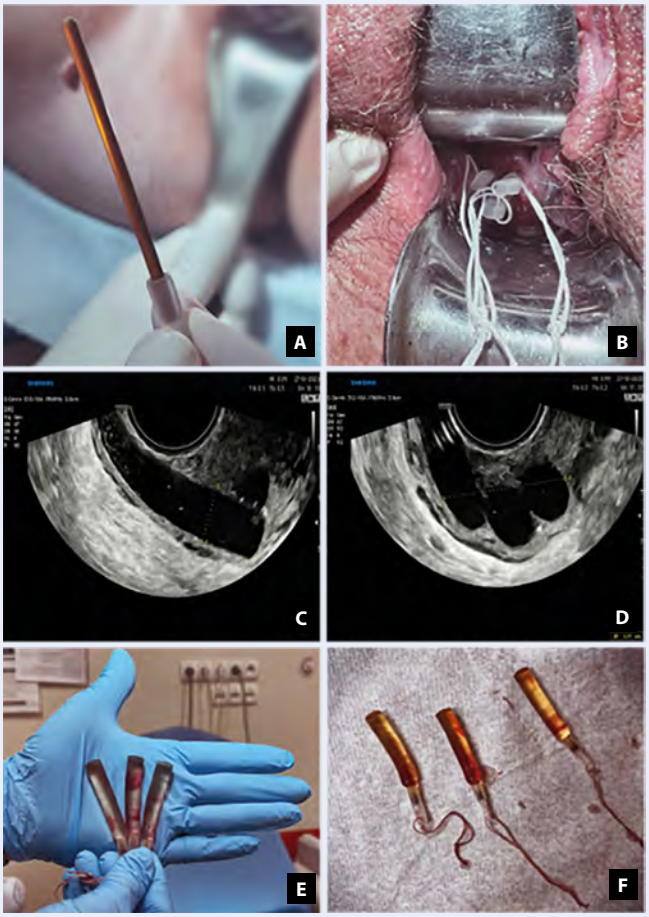


Figure 1. A. Synthetic osmotic cervical dilator (Dilapan-S), **B.** 3 synthetic osmotic cervical dilators (Dilapan-S) in cervix, **C, D.** Synthetic osmotic cervical dilators (Dilapan-S) in cervix after 24 h in transvaginal ultrasound, **E, F.** Synthetic osmotic cervical dilator (Dilapan-S) after 24 h

and Drug Administration approved his method for labor induction in 2015, and it is not contraindicated for women with a history of cesarean sections [4–6].

CONCLUSION

Medical professionals should consider synthetic osmotic cervical dilators as an effective and safe method for cervical ripening, particularly in outpatient settings.

Article information and declarations

Ethics statement

None.

Author contributions

Maisa Manasar-Dyrbus 25%, Katarzyna Wilk 20%, Maja Zieba-Domalik 20%, Jakub Staniczek 25%, Rafal Stojko 10%.

Conflict of interest

Authors declare no conflict of interest.

REFERENCES

1. Bomba-Opoń D, Drews K, Huras H, et al. Polish Gynecological Society Recommendations for Labor Induction. Ginekol Pol. 2017; 88(4): 224–234, doi: 10.5603/GP.a2017.0043, indexed in Pubmed: 28509326.
2. Socha MW, Flis W, Wartęga M, et al. A Review of the Mechanism of Action and Clinical Applications of Osmotic Dilators for Cervical Ripening in the Induction of Labor and in Gynecology Procedures. Med Sci Monit. 2023; 29: e940127, doi: 10.12659/MSM.940127, indexed in Pubmed: 37368878.
3. Rath W, Kummer J, Königbauer JT, et al. Synthetic Osmotic Dilators for Pre-Induction Cervical Ripening — an Evidence-Based Review. Geburtshilfe Frauenheilkd. 2023; 83(12): 1491–1499, doi: 10.1055/a-2103-8329, indexed in Pubmed: 38046527.
4. Staniczek J, Manasar-Dyrbuś M, Stojko R. Comparing the efficacy of synthetic osmotic dilators with foley cathether and dinoprostone insert for cervical ripening in term pregnancies. Europ J Obstet Gynecol Reproduct Biol. 2024; 293: 108, doi: 10.1016/j.ejogrb.2023.08.305.
5. Gavara R, Saad AF, Wapner RJ, et al. Cervical Ripening Efficacy of Synthetic Osmotic Cervical Dilator Compared With Oral Misoprostol at Term: A Randomized Controlled Trial. Obstet Gynecol. 2022; 139(6): 1083–1091, doi: 10.1097/AOG.0000000000004799, indexed in Pubmed: 35675605.
6. Saad AF, Gavara R, Senguttuvan RN, et al. Outpatient Compared With Inpatient Preinduction Cervical Ripening Using a Synthetic Osmotic Dilator: A Randomized Clinical Trial. Obstet Gynecol. 2022; 140(4): 584–590, doi: 10.1097/AOG.0000000000004942, indexed in Pubmed: 36083097.

VIA MEDICA

CLINICAL VIGNETTE

Ginekologia Polska
2025, vol. 96, no. 2, 155–156

ISSN 0017–0011, e-ISSN 2543–6767

DOI: 10.5603/gpl.102089

Transvaginal single posterior incision extraperitoneal bilateral sacrospinous ligament suspension combined with reconstruction of pericervical ring through cervical cerclage

Puying Luo[1]*, Sijie Yi [2]*, Wenqun Luo[2], Yuanhuan Xiong[1]

[1]Department of Gynecology, Jiangxi Maternal and Child Health Hospital, Nanchang, China
[2]Department of Obstetrics and Gynecology, Jiangxi Provincial People's Hospital, The First Affiliated Hospital of Nanchang Medical College, Nanchang, China
**These authors contributed equally to the manuscript*

Transvaginal sacrospinous ligament suspension (SSLS) is a minimally invasive transvaginal procedure that aims to correct apical prolapse [1, 2]. It is highly effective, but its success often depends on the performing surgeon's skill. The most difficult steps in SSLS include the approach to the pararectal fossa and the dissection of the sacrospinous ligament (SSL). The SSL is located deep in the pelvis. As such, dissecting and exposing the ligament during traditional transvaginal surgery is quite challenging, especially for beginning surgeons. Recurrence is likely if there is unstable cervical anchoring. Considering the above, we have optimized the existing technique for SSLS. We hope that this report can promote its widespread application.

A 36-year-old G4P4 woman was referred to our clinic for pelvic organ prolapse (POP). The gynecological evaluation demonstrated a stage III anterior, stage III apical, and stage I posterior POP. She had no known co-morbids and no previous history of cesarean section. She desired surgical correction with uterine conservation. After obtaining informed consent, the patient was admitted for optimized transvaginal SSLS according to the described technique.

The procedure was done under spinal anesthesia in the dorsal lithotomy position.

Step 1: The posterior vaginal wall was exposed, and a water pad with a maximum volume of 100 mL was positioned in place. (Fig. 1A). Step 2: A vertical incision was made in the posterior vaginal wall up to the pouch of Douglas (Fig. 1B). Step 3: The bilateral pararectal space was bluntly separated to expose the SSLs (Fig. 1C). Step 4: Full exposure of the SSL was attained using a capio suturing device. One 2-0 Ethicon X519 suture was placed through each SSL, approximately 2 to 3 cm medial to the ischial spine (Fig. 1D, E). Step 5: Reconstruction of the pericervical ring at the junction of the sacral ligament and cervix was performed (Fig. 2A, B). Step 6: A nylon suture was passed through and suspended in the pericervical ring (Fig. 2D, E). Step 7: The vaginal wall was closed by tightening the existing sutures. The SSLs were maintained approximately 2.5 cm away from the pericervical ring (Fig. 2C). Step 8: The anatomical position of all relevant structures was confirmed.

The patient was seen at two weeks, three months, seven months, and eleven months post-operatively. She demonstrated good results at each follow-up and remains satisfied with her surgical outcomes to date and reports no recurrence of any of her presenting symptoms.

Apical vaginal support is thought to be the keystone of pelvic organ support [3, 4]. Good cervical anchoring significantly increases success [5]. As such, permanent tissue fixation between the anchoring point and the target tissue is integral to maximizing post-operative results. Our technique utilizes a non-absorbable suture to construct the pericervical ring. The technique avoids excessive tension and suture bridge formation. Compared to a unilateral SSLS, a bilateral SSLS provides more symmetry to the vaginal cavity. It also addresses the dorsal-caudal deviation of the vaginal axis by providing durable apical and midline support for the prolapsed organ. This case demonstrates that using a single posterior vaginal incision to perform extraperitoneal anterior uterus-sparing prolapse repair is feasible, minimally invasive, safe, and effective. Future surgeons may also find that the technique provides easily identifiable anatomical landmarks. As such, it may be easier for novice surgeons to master. Our approach is a good alternative option for apical suspension.

Corresponding author:
Yuanhuan Xiong, Department of Gynecology, Jiangxi Maternal and Child Health Hospital, Nanchang, 330006, P.R. China; e-mail: 491651347@qq.com

Received: 15.08.2024 Accepted: 9.09.2024 Early publication date: 8.10.2024

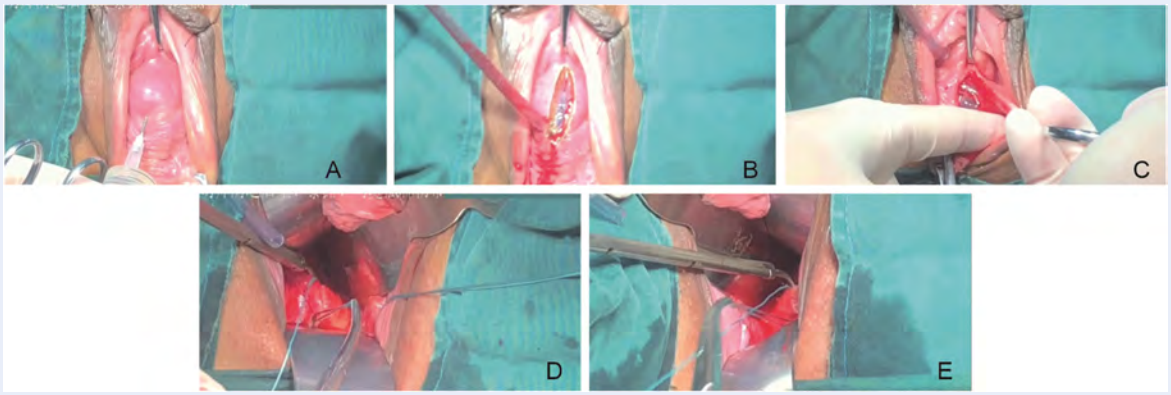


Figure 1. Posterior vaginal wall was exposure, infiltration (mix of 30 mL xylocaine 1% and 30 mL SSI) and incised through a posterior midline incision five centimeter up to posteror fornix. Then, recto-vaginal fascia was blunt dissected from vaginal mucosa. Right and left sacrospinous ligaments were exposure. After that, one non-absorbable sutures were placed two centimeter bilateral medial to the ischial spine by a Capio (Boston Scientific, Marlborough, MA, USA)

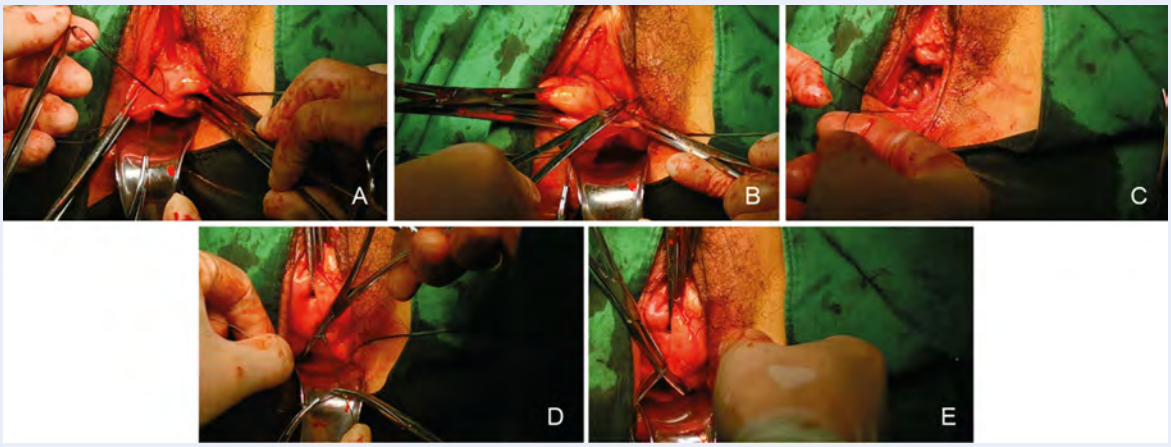


Figure 2. Reconstruction of pericervical ring with cervical cerclage. The other end of the non-absorbable line passess through the pericervical ring. closure of the posterior vaginal wall and fixation of the uterine to the sacrospinous ligaments bilaterally

Article information and declarations

Ethics statement

Institutional Review Board approval was not required.

Author contributions

Puying Luo: concept, concept, assumptions, study design, acquisition of data, analysis and interpretation of data, article draft; Sijie Yi: concept, assumptions, study design, analysis and interpretation of data, article draft, revised article critically; Wenqun Luo: acquisition of data; Yuanhuan Xiong: corresponding author, revised article critically.

Acknowledgments

Written informed consent was obtained from the patient for publication of the case report and accompanying image.

Conflict of interest

The authors declare that they have no conflicts of interest.

REFERENCES

1. Larouche M, Belzile E, Geoffrion R. Surgical Management of Symptomatic Apical Pelvic Organ Prolapse: A Systematic Review and Meta-analysis. Obstet Gynecol. 2021; 137(6): 1061–1073, doi: 10.1097/AOG.0000000000004393, indexed in Pubmed: 33957652.
2. Pelvic Organ Prolapse: ACOG Practice Bulletin, Number 214. Obstet Gynecol. 2019; 134(5): e126–e142, doi: 10.1097/AOG.0000000000003519, indexed in Pubmed: 31651832.
3. Szymczak P, Grzybowska M, Sawicki S, et al. Laparoscopic Pectopexy — CUSUM Learning Curve and Perioperative Complications Analysis. J Clin Med. 2021; 10(5): 1052, doi: 10.3390/jcm10051052.
4. Yilmaz ET, Yapca O, Topdagi Y, et al. Comparison of two natural tissue repair-based surgical techniques; sacrospinous fixation and uterosacral ligament suspension for pelvic organ prolapse treatment. J Gynecol Obstet Human Reproduct. 2021; 50(4): 101905, doi: 10.1016/j.jogoh.2020.101905.
5. Dietz V, van der Vaart CH, van der Graaf Y, et al. One-year follow-up after sacrospinous hysteropexy and vaginal hysterectomy for uterine descent: a randomized study. Int Urogynecol J. 2010; 21(2): 209–216, doi: 10.1007/s00192-009-1014-7, indexed in Pubmed: 19834635.

VIA MEDICA

CLINICAL VIGNETTE

Ginekologia Polska
2025, vol. 96, no. 2, 157–159

ISSN 0017–0011, e-ISSN 2543–6767

DOI: 10.5603/gpl.100723

Stroke in twin pregnancy: a rare case of acute ischemic stroke management

Aleksandra Pawlucka[1], Magdalena Kolak[2], Andrzej Jaworowski[2], Hubert Huras[2]

[1]Obstetrics and Perinatology Circle, Jagiellonian University, Medical College, Cracow, Poland
[2]Jagiellonian University, Medical College, Department of Obstetrics and Perinatology Cracow, Poland

CASE PRESENTATION

A 35-year-old patient at 33 weeks of a dichorionic diamniotic twin pregnancy presented with a complex medical history, including a previous cesarean section, hypothyroidism, gestational hypertension treated with methyldopa from the 28th week of gestation, and a mild COVID-19 infection at 25 weeks of gestation. She developed sudden onset aphasia, right-sided hemianopia, and coordination disorders on the right side. She was urgently transported to the emergency room at the University Hospital in Cracow with a negative COVID-19 antigen test, and she was suspected of having an ischemic stroke. An MRI without contrast revealed diffusion restriction in the left medial temporal and occipital lobes, thalamus, and pulvinar nucleus, indicating an acute ischemic stroke in the territory of the left posterior cerebral artery (Fig. 1). Angio-MRI showed an asymmetrically reduced flow signal in the left posterior cerebral artery. The patient was conscious but exhibited sensory-motor aphasia, right-sided hemianopia, a less pronounced right nasolabial fold, and bilateral positive Babinski reflexes, with an NIHSS (National Institutes of Health Stroke Scale) score of 7, suggesting a moderate stroke. Treatment with intravenous alteplase — a 6.5 mL bolus (0.01 g, 0.02 g, and 0.05 g) was initiated, followed by a 69 mL hourly infusion. Since no large vessel occlusion was present, she was not eligible for endovascular treatment. Fetal well-being was monitored three hours after the alteplase infusion, showing normal ultrasound and Doppler velocimetry results. The obstetric examination revealed no pathologies. Rehabilitation began the following day, and her headache responded to intravenous paracetamol. The gynecological reconsultation was unremarkable. Neurological reassessment showed improvement, with a decrease in NIHSS score to 2. Ultrasound Doppler of the lower limbs revealed only varicose vein dilatation, more pronounced on the left side. A follow-up brain MRI identified a small hemorrhagic focus within the ischemic lesion (Fig. 2), and echocardiography revealed left atrial enlargement. Angio-MRI showed a slight narrowing of the left posterior cerebral artery. Neck ultrasound showed no abnormalities. Aspirin therapy was recommended in doses of 150 mg after returning home and later adjusted to 75 mg. The patient also underwent a hematological consultation due to a low fibrinogen concentration resulting from the fibrinolytic treatment. Tests for congenital thrombophilia and antiphospholipid syndrome were ordered, and the results obtained were normal. The patient was transferred to the Pregnancy Pathology Department. Routine cardiotocography monitoring showed normal results. She received steroid therapy for fetal lung maturation, iron supplementation for anemia, and the gradual administration of enoxaparin. The patient was discharged one week after the stroke event and readmitted at 37 weeks of gestation for a scheduled cesarean section due to the AIS episode and previous cesarean history caused by arrested progress of labor — as recommended by the Polish Society of Gynecologists and Obstetricians. The surgery, performed under spinal anesthesia, resulted in the delivery of healthy newborns. Postoperative recovery was stable. Neurological follow-up revealed persistent right-sided hemianopia and a positive Babinski reflex on the left, necessitating ongoing observation and further investigations.

DISCUSSION

This case highlights the complexity of AIS management in pregnancy, especially with multiple gestations and pre-existing conditions [1]. The patient's hypothyroidism, gestational hypertension, and recent COVID-19 infection

Corresponding author:
Aleksandra Pawlucka
Obstetrics And Perinatology Circle, Jagiellonian University, Medical College, Cracow, Poland
e-mail: aleksandra.pawlucka@student.uj.edu.pl

Received: 16.05.2024 Accepted: 16.07.2024 Early publication date: 3.10.2024

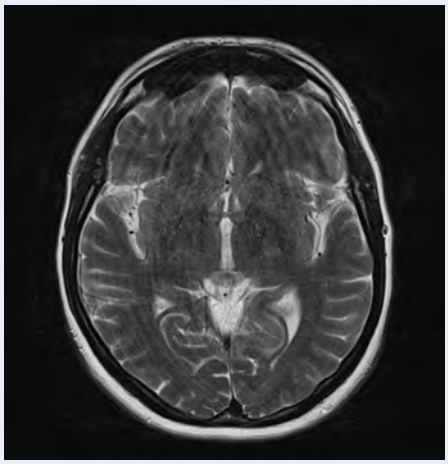


Figure 1. MRI showing stroke of left hemisphere in a day of admission

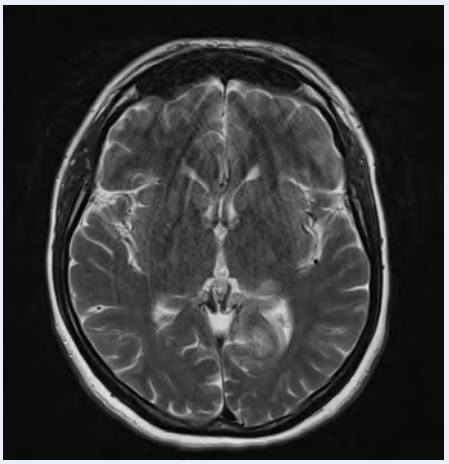


Figure 2. MRI showing resolving the lesion after alteplase treament

significantly contributed to her elevated stroke risk, as observed in other studies [2, 4]. The hypercoagulability associated with COVID-19 during pregnancy amplifies stroke risks, particularly in the third trimester and among those with diabetes, hypothyroidism, and hypertension [4]. The risk persists for several weeks post-infection, with the initial week post-COVID-19 seeing a significantly heightened risk (HR of 23) compared to later weeks (HR of 1.62 at week 49) [5]. Even before COVID-19, viral infections like influenza, VZV, HCV, or HSV have been linked to increased short-term stroke risk [6, 7]. However, COVID-19 increases the risk of thrombotic events threefold compared to influenza [8].

In this case MRI facilitated the timely diagnosis, and the treatment with intravenous alteplase aligned with current guidelines [3]. IVT is recognized as both effective and safe treatment option for AIS in pregnancy [9, 10]. Experts recommend applying the same stroke qualification criteria to pregnant and postpartum women as to other patients, albeit with a tailored assessment of the risk-benefit ratio. The treatment choice hinges on the time elapsed from symptom onset to diagnosis and the presence of a large vessel occlusion; thrombectomy is preferable if the latter is present and hemorrhagic risk postpartum is considered [3]. The complication rates for thrombolysis in pregnant women are similar to those in non-pregnant populations. Out of 20 published cases of childbearing women receiving IVT for AIS (alone or in combination with EVT), two cases of intracranial hemorrhage (with favorable outcomes) and one intrauterine hematoma were reported [1].

In this case, a multidisciplinary approach involving neurology, obstetrics, and radiology was crucial for ensuring maternal and fetal safety. The decision to proceed with cesarean delivery at 37 weeks was based on individualized care considerations, following the recommendations of the Polish Society of Gynecologists and Obstetricians. The patient's recovery, marked by an improvement in the NIHSS score and successful delivery, underscores the effectiveness of timely and coordinated care. However, the persistence of neurological deficits highlights the need for continuous monitoring and rehabilitation.

CONCLUSIONS

This case underscores the need for prompt recognition of stroke symptoms, the utility of neuroimaging in diagnosis, and the effectiveness of a multidisciplinary approach to treatment in pregnancy. The interaction of COVID-19 with pregnancy-related changes exacerbates the likelihood of thrombotic complications, underscoring the need for heightened vigilance and proactive management in these patients. Moreover, the successful use of intravenous thrombolysis in this case illustrates this treatment's potential safety and efficacy in pregnant patients, providing a valuable reference for managing similar cases. Future research and updated clinical guidelines are vital for optimizing management strategies for AIS in pregnant patients, ensuring the best possible outcomes for both mother and child.

Article information and declarations

Ethics statement

The patient's informed consent was obtained.

Author contributions

AP— 40% — concept, assumptions, corresponding author, analysis and interpretation of data, article draft; MK — 20% — acquisition of data, revised article critically; AJ — 30% — acquisition of data, revised article critically, analysis and interpretation of data; HH — 10% — acquisition of data.

Conflict of interest

All authors declare no conflict of interest.

REFERENCES

1. Wiącek M, Oboz-Adaś A, Kuźniar K, et al. Acute Ischemic Stroke in Pregnancy. Clin Neuroradiol. 2022; 33(1): 31–39, doi: 10.1007/s00062-022-01215-5.
2. Wiszniewska M. Stroke in Pregnancy and Perinatal Period. J Med Clinic Res Rev. 2020; 4(6), doi: 10.33425/2639-944x.1149.
3. Kremer C, Gdovinova Z, Bejot Y, et al. European Stroke Organisation guidelines on stroke in women: Management of menopause, pregnancy and postpartum. Eur Stroke J. 2022; 7(2): I–XIX, doi: 10.1177/23969873221078696, indexed in Pubmed: 35647308.
4. Skalska-Swistek M, Kolak M, Jaworowski AP, et al. SARS-CoV-2 infection during pregnancy — single-center retrospective study. Ginekol Pol. 2023; 94(10): 831–838, doi: 10.5603/gpl.95565, indexed in Pubmed: 37599571.
5. Knight R, Walker V, Ip S, et al. CVD-COVID-UK/COVID-IMPACT Consortium and the Longitudinal Health and Wellbeing COVID-19 National Core Study. Association of COVID-19 With Major Arterial and Venous Thrombotic Diseases: A Population-Wide Cohort Study of 48 Million Adults in England and Wales. Circulation. 2022; 146(12): 892–906, doi: 10.1161/CIRCULATIONAHA.122.060785, indexed in Pubmed: 36121907.
6. Belani P, Schefflein J, Kihira S, et al. COVID-19 Is an Independent Risk Factor for Acute Ischemic Stroke. AJNR Am J Neuroradiol. 2020; 41(8): 1361–1364, doi: 10.3174/ajnr.A6650, indexed in Pubmed: 32586968.
7. Zerangian N, Erabi G, Poudineh M, et al. Venous thromboembolism in viral diseases: A comprehensive literature review. Health Sci Rep. 2023; 6(2): e1085, doi: 10.1002/hsr2.1085, indexed in Pubmed: 36778773.
8. Ward A, Sarraju A, Lee D, et al. COVID-19 is associated with higher risk of venous thrombosis, but not arterial thrombosis, compared with influenza: Insights from a large US cohort. PLoS One. 2022; 17(1): e0261786, doi: 10.1371/journal.pone.0261786, indexed in Pubmed: 35020742.
9. Pacheco LD, Hankins GDV, Saad AF, et al. Acute Management of Ischemic Stroke During Pregnancy. Obstet Gynecol. 2019; 133(5): 933–939, doi: 10.1097/AOG.0000000000003220, indexed in Pubmed: 30969218.
10. Dicpinigaitis AJ, Sursal T, Morse CA, et al. Endovascular Thrombectomy for Treatment of Acute Ischemic Stroke During Pregnancy and the Early Postpartum Period. Stroke. 2021; 52(12): 3796–3804, doi: 10.1161/STROKEAHA.121.034303, indexed in Pubmed: 34538088.

VIA MEDICA

OD PONAD 30 LAT
AKTYWNIE UCZESTNICZYMY W ROZWOJU NAUKI I EDUKACJI MEDYCZNEJ.

- W ciągu roku wydajemy ponad 800 publikacji
- Publikujemy blisko 50 czasopism
- Organizujemy ponad 300 konferencji i webinariów rocznie
- Udostępniamy około 3000 godzin filmów edukacyjnych
- Prowadzimy księgarnię medyczną Ikamed
- Obsługujemy 40 serwisów internetowych, oferujemy aplikacje mobilne

www.viamedica.pl

@ViaMedicaMedicalInformation

VIRTUAL MEETING

VIA MEDICA

Virtual Meeting

Endometrioza. Standardy postępowania

■ **8 kwietnia 2025 roku**

Przewodnicząca Komitetu Naukowego
prof. dr hab. n. med. Małgorzata Kędzia

SZCZEGÓŁY

www.endometrioza.viamedica.pl

PATRONAT MEDIALNY

PARTNER

PATRONAT

VIA MEDICA

Top of the Top
Ginekologia i Położnictwo 2025

Gdańsk, 23–24 maja 2025 roku

Przewodniczący Komitetu Naukowego
prof. dr hab. n. med. Piotr Sieroszewski

SZCZEGÓŁY

www.topofthetopginekologia.viamedica.pl

PATRONAT MEDIALNY tvmed

PARTNER ikamed.pl

Konferencja jest skierowana tylko do osób uprawnionych do wystawiania recept lub osób prowadzących obrót produktami leczniczymi — podstawa prawna: ustawa z dnia 6 września 2001 r. Prawo farmaceutyczne (t.j. Dz.U. z 2020 r. poz. 944).