POLISH GYNECOLOGY

GINEKOLOGIA POLSKA

Edited since 1922

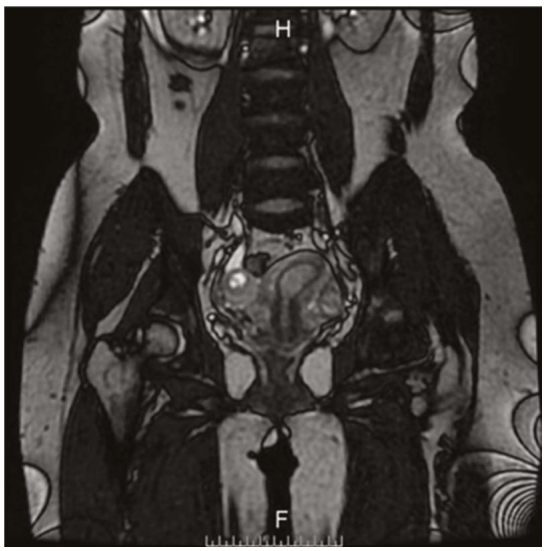
no **8**/vol **93**/**2022**

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

IF: **1.216**, MEiN: **40**

GINEKOLOGIA POLSKA 2022, VOL 93, NO 8, PAGES 603–678

ORIGINAL PAPERS



ISSN 0017–0011
e-ISSN 2543–6767

VIA MEDICA

VIII Konferencja Ginekologia onkologiczna

VIRTUAL MEETING

30 września 2022 roku

Przewodniczący Komitetu Naukowego:
dr hab. n. med. Radosław Mądry

Szczegółowe informacje oraz rejestracja na stronie:

www.onkogin.viamedica.pl

ORGANIZATOR
VIA MEDICA

PATRONAT MEDIALNY
tvmed

PARTNER
ikamed.pl
internetowa księgarnia medyczna

Virtual Meeting jest skierowany 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 2019 r. poz. 499).

22-3122.001.004

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 sp. z o.o. VM Group sp.k.,
73 Świętokrzyska St, 80–180 Gdańsk, Poland, phone: (+48 58) 320 94 94, fax: (+48 58) 320 94 60,
e-mail: redakcja@viamedica.pl, marketing@viamedica.pl, http://www.viamedica.pl

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

Indexed in: CrossRef, DOAJ, Index Copernicus, Polish Ministry of Education and Science (40), POL-Index, Polish Medical Bibliography, PubMed, Science Citation Index Expanded (1.216), Scimago Journal Rank, 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: marketing@viamedica.pl

Subscription. Printed institutional subscription — 12 issues for 300 EUR.
More details at: https://journals.viamedica.pl/ginekologia_polska/user/subscriptions

21-0520.009.001

POLISH GYNECOLOGY

GINEKOLOGIA POLSKA

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

CONTENTS

VIA MEDICA

EDITORIAL

Ginekologia Polska
2022, vol. 93, no. 8, 603–604

ISSN 0017–0011, e-ISSN 2543–6767

DOI 10.5603/GP.2022.0087

Editorial

Sebastian Kwiatkowski

Pomeranian Medical University in Szczecin, Poland

Modern perinatal medicine is an increasingly specialized field that makes use of state-of-the-art technological and diagnostic inventions. The developments increase our ability to assess how the pregnancy is progressing, predict pathologies, and intervene during gestation. This progress requires that all of us should keep up with the frequent discoveries. At the same time, even within the maternal-fetal medicine domain, individual specialists tend to focus rather on some selected pathologies, as it is otherwise extremely difficult to keep abreast of the dozens of new reports and publications that appear each week on scientific and publisher websites. Reading their paper editions is slowly becoming a thing of the past, as most articles are first made available online. Thus, medicine — like other disciplines — is witnessing an accelerated pursuit of knowledge.

One of the topics that have been the subject of intense research in recent years is the so-called utero-placental compartment. The way in which trophoblast development and invasion progresses can lead to either success or (frequently) failure of pregnancy. Beginning in the first weeks after embryo implantation, the trophoblast develops the villous tree and penetrates deep into the maternal tissues, thus creating a unique system that allows the fetus to grow in the intrauterine environment for months to come. Disorders of this process can be diverse and multifactorial. Among the main factors impeding the development of this compartment are chronic maternal diseases on the one hand, and immunological disorders on the other. Understanding the causes and the exact mechanisms behind them will certainly be a challenge for us to face up to in the coming decades. We are now at the stage of properly selecting the group of patients burdened with an increased likelihood of developing preeclampsia or hypotrophy caused by placental abnormalities. Both the conditions, although with completely different clinical presentations, share impaired placental development that manifests itself most often in the second half of pregnancy. Our success in understanding the common pathomechanism has led to a tremendous transformation over the last two decades of how preeclampsia is defined. The traditional diagnosis based on hypertension and proteinuria presented in 2003 by the National Heart, Lung and Blood Institute (NHLBI) [1], which is widely recognized, was modified in 2013 by American College of Obstetricians and Gynecologists (ACOG) [2] to include other organ changes, as well. In 2018, The International Society for the Study of Hypertension in Pregnancy (ISSHP) [3] supplemented the diagnosis by adding utero-placental compartment dysfunction with the clinical presentation of fetal growth restriction and/or umbilical artery flow abnormalities. The definition announced this year [4] includes, beside the aforementioned aspects, also placental abruption and, most interestingly, abnormalities of the placental angiogenesis parameters (sFlt/PlGF). Our improved insight into the causes of the condition moves us away from defining it as a disease to perceiving it rather as a syndrome with a wide variety of clinical presentations, where supervision requires the assessment of both perinatal and neonatal outcomes [5].

Accurate selection of pregnant patients at risk of developing placental pathologies is therefore increasingly important. An excellent set of tools has been provided by the Aspirin to prevent preeclampsia (ASPRE) study [6], the efficiency of which is still the subject of research [7]. The algorithm it proposes, which takes into account both ultrasound and biochemical parameters, as well as medical history, has proven highly useful as a basis for the preventive introduction of acetylsalicylic acid. Currently, most researchers are convinced that similar predictive efficacy can also be achieved in the second trimester of pregnancy [8, 9]. However, the greatest challenges that lie ahead are in monitoring gestation and deciding whether to terminate pregnancy in women demonstrating the various clinical forms of placental insufficiency [10]. My belief is that a combination of the traditional physical examination methods such as blood pressure measurement, cardiotocography, ultrasound, and amniotic fluid volume assessment [11] with modern methods for assessing placental function will be crucial in ensuring proper management.

Corresponding author:
Sebastian Kwiatkowski
Pomeranian Medical University in Szczecin, 1 Rybacka St, 70-204 Szczecin, Poland
e-mail: sebastian.kwiatkowski@pum.edu.pl

This new definition of placental insufficiency that accounts for its varied severity pertains to nearly 10% of all pregnancies. This large proportion of women at risk of developing this pathology requires the care of a very highly trained staff of specialists. It is also extremely important to educate the patients themselves.

Raising awareness by educating both gynecologists and our patients regarding pregnancy-related issues is the task that we assigned to the PRENATALPROJEKT platform, which I was the initiator of. The rise in significance of the modern means of communication and social media has provided opportunities for us to communicate with our target audiences regardless of what time of day it is or where on the globe we live. Language barriers are also less and less of an obstacle. Our meetings are open to the public, and the content conveyed is carefully selected to suit the audiences. More and more (not only academic) centers in Poland are joining the Project, which helps us to get to know each other and integrate our community. So far, we have organized more than a dozen meetings over the past two years, attracting an audience of several thousand people. The training courses and lectures that originally focused on issues of placental insufficiency now cover a variety of problems of perinatal medicine in general. Our cooperation, also realized through the Perinatology Section of the Polish Society of Gynecologists and Obstetricians (PTGiP), is growing in scope and now involves dozens of excellent specialists from all over the country. Our plans go as far into the future as 2023. In the coming years, we would like to go beyond the borders of Poland and establish cooperation in educating women with colleagues from Europe, with a special focus on Central and Eastern Europe. We would also like to encourage the younger generation of doctors to extend their research interests and become involved in educating women. In cooperation with the PRENATALPROJEKT Foundation, we are developing appropriate tools to assist us in achieving these goals.

In the meantime, I wish to encourage you to read the next issue of the journal "Ginekologia Polska" which, thanks to the efforts of the Society, but above all of the Editor-in-Chief, is increasingly well-recognized in the Community.

Conflict of interest

All authors declare no conflict of interest.

REFERENCES

1. Roberts J, Pearson G, Cutler J, et al. Summary of the NHLBI Working Group on Research on Hypertension During Pregnancy. Hypertension. 2003; 41(3): 437–445, doi: 10.1161/01.hyp.0000054981.03589.e9.
2. Hypertension in Pregnancy. Obstetrics & Gynecology. 2013; 122(5): 1122–1131, doi: 10.1097/01.aog.0000437382.03963.88.
3. Brown M, Magee L, Kenny L, et al. The hypertensive disorders of pregnancy: ISSHP classification, diagnosis & management recommendations for international practice. Pregnancy Hypertension. 2018; 13: 291–310, doi: 10.1016/j.preghy.2018.05.004.
4. Magee L, Brown M, Hall D, et al. The 2021 International Society for the Study of Hypertension in Pregnancy classification, diagnosis & management recommendations for international practice. Pregnancy Hypertension. 2022; 27: 148–169, doi: 10.1016/j.preghy.2021.09.008.
5. Stefanska KA, Zielinski M, Jassem-Bobowicz J, et al. Perinatal and neonatal outcome in patients with preeclampsia. Ginekol Pol. 2021 [Epub ahead of print], doi: 10.5603/GP.a2021.0101, indexed in Pubmed: 34105747.
6. Rolnik D, Wright D, Poon L, et al. Aspirin versus Placebo in Pregnancies at High Risk for Preterm Preeclampsia. New England Journal of Medicine. 2017; 377(7): 613–622, doi: 10.1056/nejmoa1704559.
7. Tousty P, Czuba B, Borowski D, et al. Effectiveness of Different Algorithms and Cut-off Value in Preeclampsia First Trimester Screening. Journal of Pregnancy. 2022; 2022: 1–11, doi: 10.1155/2022/6414857.
8. Litwinska M, Litwinska E, Astudillo A, et al. Stratification of pregnancy care based on risk of pre-eclampsia derived from biophysical and biochemical markers at 19–24 weeks' gestation. Ultrasound in Obstetrics & Gynecology. 2021; 58(3): 360–368, doi: 10.1002/uog.23640.
9. Nowacka U, Papastefanou I, Bouariu A, et al. Second-trimester contingent screening for small-for-gestational-age neonate. Ultrasound in Obstetrics & Gynecology. 2022; 59(2): 177–184, doi: 10.1002/uog.23730.
10. Kwiatkowski S, Bednarek-Jędrzejek M, Kwiatkowska E, et al. Diagnosis of placental insufficiency independently of clinical presentations using sFlt-1/PLGF ratio, including SGA patients. Pregnancy Hypertension. 2021; 25: 244–248, doi: 10.1016/j.preghy.2021.07.245.
11. Özgen G, Dincgez Cakmak B, Özgen L, et al. The role of oligohydramnios and fetal growth restriction in adverse pregnancy outcomes in preeclamptic patients. Ginekol Pol. 2021 [Epub ahead of print], doi: 10.5603/GP.a2021.0094, indexed in Pubmed: 34105748.

VIA MEDICA

ORIGINAL PAPER / GYNECOLOGY

Ginekologia Polska
2022, vol. 93, no. 8, 605–613

ISSN 0017–0011, e-ISSN 2543–6767

DOI 10.5603/GP.a2022.0002

A self-developed contained bag for laparoscopic myomectomy morcellation

Ying Wei[1*], Xuelan Zhou[2*], Qiong-Zhen Ren[1], Qi Ma[3], Xiaomin Tao[1], Minfang Shao[1], Suhong Jia[1]

[1]Department of Obstetrics and Gynecology, The Second Affiliated Hospital of Soochow University, Suzhou, China
[2]Department of Anesthesiology, The Second Affiliated Hospital of Soochow University, Suzhou, China
[3]Department of Ultrasonography, The Second Affiliated Hospital of Soochow University, Suzhou, China
**These authors contributed equally to this study*

ABSTRACT

Objectives: Open power morcellation during a laparoscopic myomectomy (LM) can result in the dissemination of benign or occult malignant tumor cells in the abdominopelvic cavity. The development of a new contained collection bag for power morcellation is now favored by gynecologic surgeons worldwide.

Material and methods: This study was a single-arm trial comprising 20 women who consecutively underwent an LM involving the use of a newly designed contained collection bag for power morcellation between November 3rd 2017 and April 31st 2018. There was also a historical control group consisting of 30 women who underwent open power morcellation during an LM between May 1st 2017 and October 31st 2017. All the essential information concerning the patients and surgically related data, including the myoma size, the operation duration, and the cell count of the intraperitoneal irrigating fluid, were collected and analyzed.

Results: The uterus size and the maximum diameters of the uterus and the myoma of the two groups were not significantly different ($p = 0.65$, $p = 0.71$, and $p = 0.31$, respectively). Pseudopneumoperitoneum was established and clear visualization was guaranteed in all 20 cases in the experimental group. The remaining fragment tissue amount (mean ± SD) and weight (mean ± SD) in the collection bag after morcellation in the experimental group were 5.00 ± 1.48 and 3.87 ± 1.31 (g). All the collection bags were routinely examined after the LM using normal saline, and no leaks or lesions were found. The cell counts of the intraperitoneal irrigating fluid both before and after morcellation were less than 10^5–10^6/L. The pathology of all the tissues confirmed that there were no malignant tumors. The operation of the experimental group was 18 mins longer than that of the historical control group ($p = 0.00$).

Conclusions: This newly designed collection bag system for LM morcellation is effective, feasible, and safe.

Key words: contained morcellation; laparoscopic myomectomy; parasitic myoma; uterine sarcoma

Ginekologia Polska 2022; 93, 8: 605–613

INTRODUCTION

Laparoscopic myomectomy (LM) has lower intraoperative and postoperative morbidity than hysteromyomectomy, and it has become the first choice for most women who wish to preserve their uterus. During the traditional operation, open power morcellation is used in the abdominopelvic cavity to facilitate removal of uterine myomas, but this can lead to the spread of tumor cells and greatly reduces the patient's chances of survival [1–4]. The US Food and Drug Administration (FDA) issued a safety notice in 2014 to discourage the use of power morcellators in gynecology [5]. Afterwards, there was a worldwide reduction in LM surgery [6].

A preliminary attempt was made to address the above problems. After the enucleation of the myoma during the laparoscopic surgery, all the tissue was loaded into a contained bag, and then the myoma was disintegrated in this same contained bag in order to prevent the tumor tissue from

Corresponding author:
Qiong-Zhen Ren
Department of Obstetrics and Gynecology, the Second Affiliated Hospital of Soochow University, No.1055 of Sanxiang Road, Gusu District, Suzhou 215004, China
phone: +86 13912646986, e-mail: rqz102238@163.com
and
Suhong Jia
Department of Obstetrics and Gynecology, The Second Affiliated Hospital of Soochow University, No.1055 of Sanxiang Road, Gusu District, Suzhou 215004, China
phone: +86 15950002238, e-mail: jiasuhongjsh@163.com

Received: 17.12.2021 Accepted: 22.01.2022 Early publication date: 3.03.2022

spreading into the pelvic cavity [7]. In 2014, Chou et al. [8] first reported the Sydney Contained in Bag Morcellation technique, which involves puncturing the inflated bag. Although the design of a contained morcellation system has progressed, there have been no reports of a single bag system that can accommodate the morcellator, with an assistant grasping the forceps, nor one that does not risk needing to change the surgery to single port laparoscopic surgery or puncturing the inflated bag. The purpose of this study is to evaluate the effectiveness, feasibility, and safety of a newly developed contained collection bag for use during an LM.

MATERIAL AND METHODS

This study was a single-arm trial involving 20 women who consecutively underwent an LM with a newly designed contained collection bag for power morcellation between November 3rd 2017 and April 31st 2018. All the eligible subjects were in the experimental group. The historical control group consisted of 30 women who underwent open power morcellation during an LM between May 1st 2017 and October 31st 2017. The patients all had routine follow-ups at three months, six months, one year, and two years after the operation. The chief complaints were recorded, and physical and ultrasonic examinations were performed. This study was approved by the ethics committee of the Second Affiliated Hospital of Soochow University and registered in the Chinese Clinical Trial Registry (registration number: ChiCTR-INR-16009840; 2016/11/13). Both the historical control group patients and the experimental group patients underwent open power morcellation with fully informed consent.

The main inclusion criteria were as follows: patients with a uterine myoma who met the surgical indications; patients wishing to retain their uterus; patients planning to undergo an LM; women aged 20–45 years with a sexual history; patients willing to cooperate with follow-ups and to sign informed consent and with no major visceral diseases. The main exclusion criteria were as follows: patients who could not have the operation because of a serious cardiopulmonary disease; patients who had a procedure besides the LM during the same operation; and patients whose follow-ups could not be maintained.

Bag design

The self-developed collection bag (patent No. ZL 201520384022.2), designed by Dr.Ren Qiongzhen, was produced by Jiangsu Maslech Medical Technology Co., Ltd. It was made of thermoplastic polyurethane membrane, and it was biocompatible and transparent and non-flammable, non-melting, and non-expanding at high temperatures. The average maximum burst pressure was 4.4 kPa (33 mmHg) at a temperature of 23.1°C and a humidity of 50% RH (Reference standard: YY/T0681.3-2010, tested by Shanghai Microspectrum Technology Service Co., Ltd.). The bag was sterilized with ethylene oxide, and the residual amount of ethylene oxide was less than 10 μg/g.

The collecting bag was composed of a main bag body, four pocket ports, and threading wires (Fig. 1). The volume of the main bag body was 1000–3000 mL. The circumference of the first port was 320 mm (equivalent to the circumference of a 100 mm diameter circle), and this port was used to enter the lesion tissue. The edge of the first port could be thread with threading wire. The diameter of the second, the third, and the fourth ports was 16–20 mm, and the neck length was 80–120 mm. The latter three ports could be pulled out of the abdominal cavity through a puncture hole, and a 5–15 mm trocar could be passed inside. The ports were designed with a conical shape to prevent the sheath from slipping. These three ports were used for the morcellator, the optical lens, and the forceps held by the assistant. The whole bag could be entered into the abdominal cavity through a 10 mm trocar after being folded over. Different color bands were used in different ports to facilitate the rapid establishment of a false pneumoperitoneum.

Preoperative preparation

A ThinPrep cytologic test and a human papillomavirus test were performed to exclude cervical lesions. Patients with menstrual disorders, including increased menstrual volume and prolonged menstruation, were treated with diagnostic curettage to exclude endometrial lesions. Ultrasonography and/or pelvic computerized tomography (CT)/magnetic resonance imaging (MRI) were performed to determine the size of the uterus and the size, number, location, and character of the myomas. The operation was performed during the follicular phase after menstruation. The patients were informed of the risks and gave signed consent. Preoperative vaginal sterilizing was performed once a day for three consecutive days before surgery, and unreserve clyster was used for bowel preparation one day beforehand.

Surgical technique

All the operations were performed by the same four experienced senior physicians. The patient was placed in lithotomy position under general anesthesia. Pneumoperitoneum at a pressure of 13–15 mmHg was established with a CO_2 insufflator (KARL STORZ, Germany). A 4-trocar system was used in all the operations: a 10 mm trocar on the umbilicus point for the optical lens; a 5 mm trocar on the right Mc Burney point for the assistant grasping forceps; a 10 mm trocar on reverse Mc Burney point; and a 5 mm trocar on supra-pubic point for the chief surgeon. The LM was performed in a routine manner, and 1–0 synthetic suture was used to suture the uterine wound to stop any bleeding.

The reverse Maxwell's port was extended to 15 mm in order to accommodate the morcellator (KJ-301) (Hangzhou Kangji Medical Instrument Co., Ltd). Before the morcellation, the abdominal cavity and pelvic cavity were rinsed with normal saline, and once all the rinse solution was absorbed a cell count was made. The folded collection bag was inserted into the abdominal cavity through the reverse McDonald's point sheath. Under direct vision, the bag was opened by the assistant, and the tissue was moved into the bag though the first port, which was then tightened and knotted with 2–0 absorbable suture to prevent air leakage. Under direct vision, the second port was pulled out of the reverse Maxwell's point puncture hole, the third port was pulled out of the umbilical puncture hole, the fourth port was pulled out of the Maxwell's point puncture hole, and the sheath was put into the bag mouth. The optical lens was then put into the umbilical trocar, and the morcellator was pushed through the reverse Maxwell's point trocar and the forceps through the Maxwell's point trocar. After all the ports were sealed, a pseudopneumoperitoneum was established using a CO_2 insufflator at the same pressure of 13–15 mmHg. Tissue morcellation and removal were performed under direct vision, with the assistant fixing the myoma in place with the forceps.

After the main tumors were morcellated, the remaining fragments of tissue in the bag were counted under laparoscopy, removed one by one, and weighed. After the morcellation, the air in the bag was discharged. The second and fourth ports were inverted and knotted to prevent tumor contamination, and the collection bag was removed through the umbilical puncture point. The abdominal and pelvic cavity was washed with normal saline and all the rinsing fluid absorbed before a cell count. The collection bag was carefully examined for leakage using normal saline. A cell count was conducted after the red blood cells were lysed using FACS Lysing Solution [Sangon Biotech (Shanghai) Co., Ltd].

Statistical indicators and statistical analysis

The baseline statistical indicators concerning the patients were age, body mass index (BMI), fertility history, and previous abdominal surgery history. The main surgically related indicators were success rate of bag inflation, leakage rate, visual field clarity, operation time, remaining tissue fragment weight and amount, intraperitoneal irrigating fluid before and after morcellation, intraoperative bleeding, intraoperative complications (penetration of intima, injury of important vascular and nerve organs, etc.), post-operative complications, and the amount of hemoglobin before and after the operation. The secondary observation indexes were postoperative morbidity, blood transfusion rate, postoperative hospitalization days and hospitalization expenses,

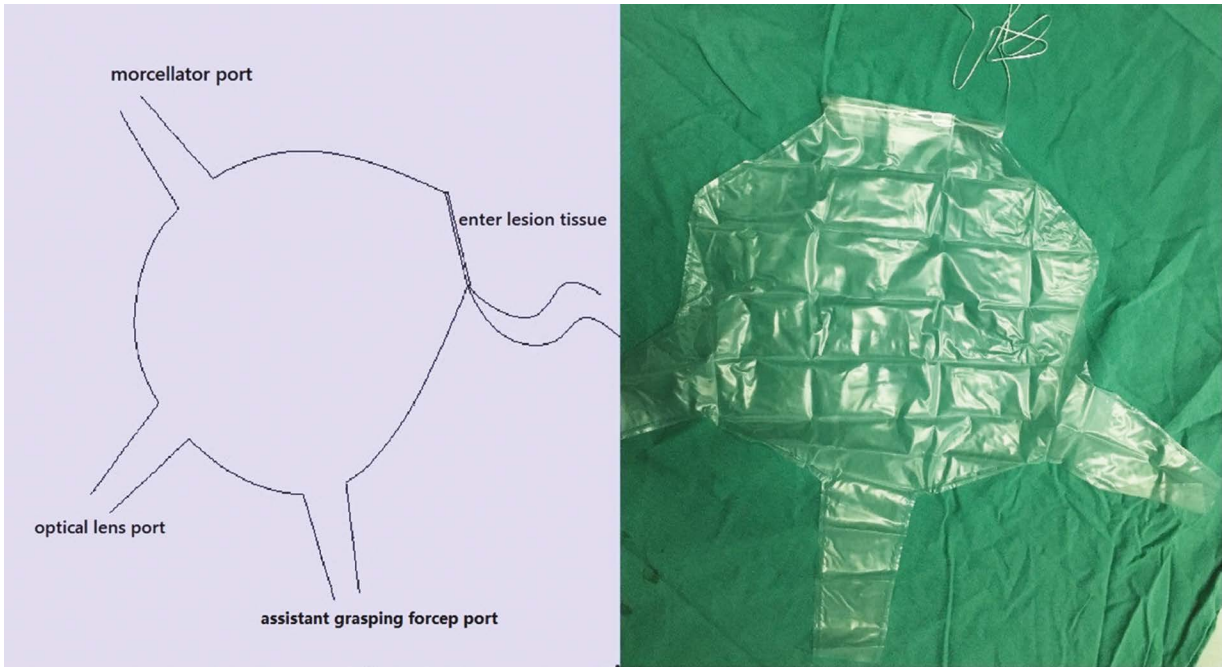


Figure 1. Contained collection bag. The volume of the main bag body is 1000–3000 mL. The circumference of the first port is 320 mm (equivalent to the circumference of a 100 mm diameter circle), which was used for entering the lesion tissue. The edge of the first port could be thread by threading wires. The diameter of the second, the third and the fourth ports was 16–20 mm, and the neck length was 80–120 mm. The latter three ports can be pulled out of the abdominal cavity through puncture hole, and 5–15 mm trocar can pass through inside. The ports was designed in cone shape to prevent the sheath from slipping. The latter three ports was used for morcellator, optical lens and assistant grasping forceps, respectively. The whole bag could enter into the abdominal cavity through a 10 mm trocar after folded

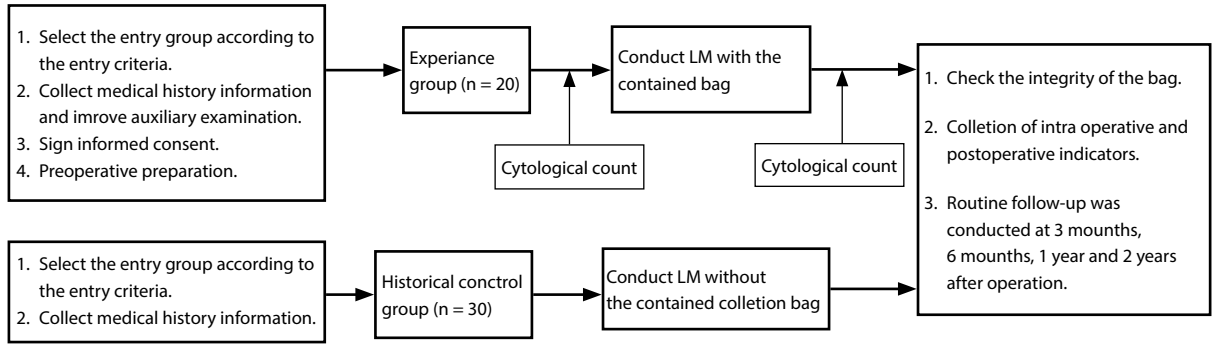


Figure 2. The study flow diagram

Table 1. Demographic and baseline characteristics of the study population

Items	Experiment group (n = 20)	Historical group (n = 30)	T/Z value	p-value
Mean age [years] (SD)	38.17 (5.57)	39.78 (6.07)	T = –0.83	0.41
Mean BMI [kg/m^2] (SD)	23.95 (2.12)	22.33 (2.25)	T = 0.79	0.19
Median number of pregnancies (IQR)	2.5 (2)	2 (3)	Z = –1.15	0.25
Median number of term pregnancies (IQR)	1.0 (0)	1 (0)	Z = –0.60	0.55

SD — standard deviation; BMI — body mass index; IQR — interquartile range

postoperative menstrual recovery, and pregnancy in previously infertile patients.

The SPSS19.0 software package (SPSS Inc., Chicago, IL, USA) was used for data analysis. A Kolmogorov–Smirnov test was used for the normality test, an independent-samples t-test was used for normally distributed data, a Mann–Whitney U test was used for data with non-normally distributed data, and a Chi square test was used for count data. Statistical significance was set at $p < 0.05$.

RESULTS

The demographic and baseline characteristics of the study population

The flow chart in Figure 2 shows that a total of 50 patients were enrolled in the study, 20 in the experimental group and 30 in the historical control group. There was no significant difference in age, BMI, birth history between the two groups (Tab. 1).

The comparison of preoperative medical history and imaging data

The preoperative rates of menorrhagia and/or prolongation of menstruation, abdominal distention and/or abdominal pain, urinary frequency, and infertility were 20%, 25%, 15%, and 5% respectively, in the experimental group, and 17%, 33%, 10%, and 10% respectively, in the historical control group. The p values were all higher than 0.05. Four cases in the experimental group and five cases in the historical control group were complicated with menorrhagia and/or prolonged menstruation. Diagnostic curettage was performed to exclude endometrial lesions before admission. Preoperative imaging (B ultrasound, CT or MRI) showed no significant difference in uterine volume, maximum uterine diameter, and maximum myoma diameter between the two groups. The history of abdominal surgery in the two groups was 50.0% in the experimental group and 53.3% in the historical control group ($p = 0.82$) (Tab. 2).

The comparison of intraoperative and postoperative conditions

The LM was completed in all 50 patients without the need for it to be converted to a laparotomy. There were no injuries to the intestinal or urinary systems, important blood vessels, or nerves during the operations, and no other surgery was performed besides the LM. In two of the 20 cases in the experimental group and four of the 30 cases in the historical control group, the endometrium was penetrated during the LM ($p = 1.00$). These six patients were treated with antibiotics 24–48 hours after surgery to prevent infection, and mifepristone tablets 12.5 mg p.o. qd were given on the first day afterwards and for the next three months to prevent adenomyosis formation.

In the experimental group, 20 patients underwent LM with the use of a collection bag. Pseudopneumoperitoneum was successfully established in all the patients, and

the inflation success rate was 100%. The operative field was clear, and the morcellation was performed successfully (Fig. 3), with no rupture of the bag body occurring during the process of morcellation. After the main tumor was morcellated, the number of debris fragments in the bag was counted under laparoscopy. The average number of remaining tissue fragments in the bags of the 20 patients was 5.00 (standard deviation 1.48), and the average weight of the remaining fragments was 3.87 g (standard deviation 1.31). The integrity of the bag was detected by saline injection after operation, and no bag body was damaged. The operation took significantly longer in the experimental

Table 2. A comparative analysis of preoperative complaints, auxiliary examination results and previous abdominal operation history

Items	Experiment group (n = 20)	Historical group (n = 30)	T/Z/X^2 value	p-value
AUB, No. (%)	4 (20.0)	5 (16.7)	$X^2 = 0.00$	1.00
Abdominal distention or pain, No. (%)	5 (25.0)	10 (33.3)	$X^2 = 0.39$	0.53
Frequent micturition, No. (%)	3 (15.0)	3 (10.0)	$X^2 = 0.01$	0.93
Infertility, No. (%)	1 (5.0)	3 (10.0)	$X^2 = 0.01$	0.92
Uterine size [cm^3] (Median, IQR)	144.86, 146.78	122.32, 139.08	Z = –0.50	0.65
Maximum diameter of uterus [mm] (mean ± SD)	73.25 ± 13.94	71.33 ± 16.30	T = 0.37	0.71
Maximum diameter of myoma [mm] (mean ± SD)	62.50 ± 15.07	58.24 ± 12.14	T = 1.03	0.31
Past history of abdominal surgery, No. (%)	10 (50.0)	16 (53.3)	$X^2 = 0.05$	0.82

AUB — abnormal uterine bleeding; Uterine size (B ultrasound /CT/MRI) — long diameter × wide diameter × thickness diameter * 0.523 (cm^3); SD — standard deviation; IQR — interquartile range

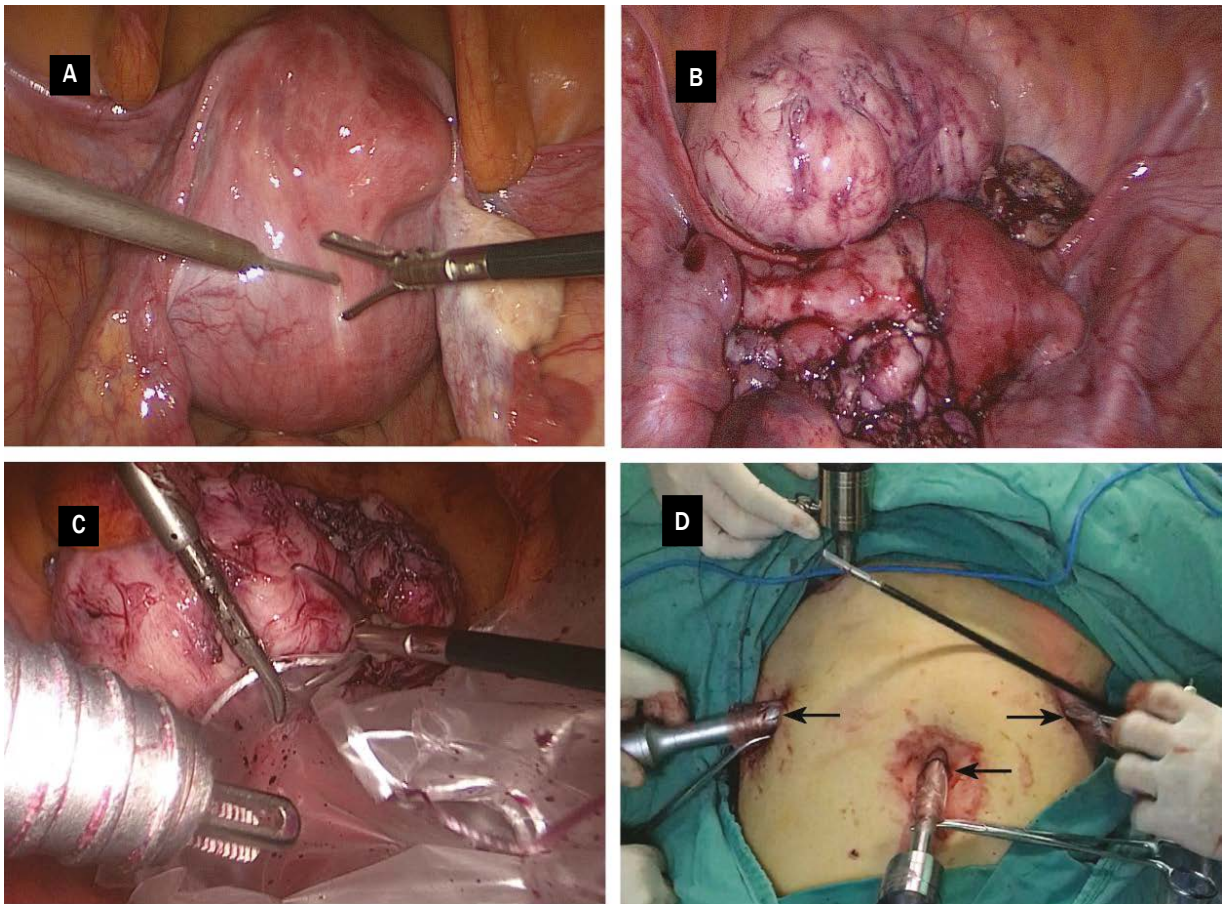


Figure 3. Clear view of contained collection bag in LM; **A.** Estimated diameter of the two myomas were 8 cm and 3 cm; **B.** The actual size of the two myomas were 10 × 8 × 6 cm and 3 × 3 × 3 cm; **C.** The folded collection bag was inserted into the abdominal cavity through the reverse McDonald's point sheath. Under direct vision, the bag was opened with the assistant and the tissue was moved into the bag though first port; **D.** Under direct vision, the second port was pulled out of the reverse Maxwell's point puncture hole, the third port was pulled out of the umbilical puncture hole, the fourth port was pulled out of the Maxwell's point puncture hole, and the sheath was put into the bag mouth respectively

→

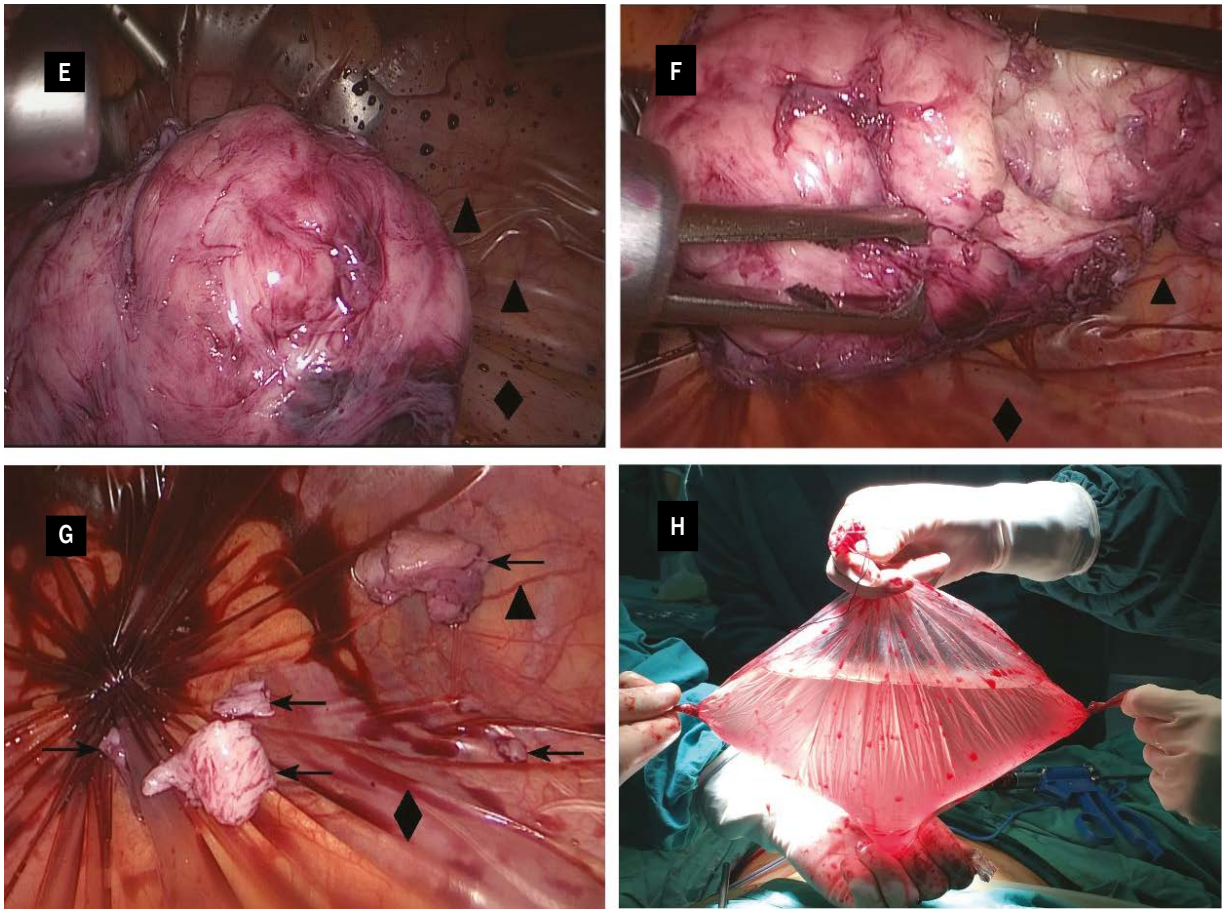


Figure 3. cont. Clear view of contained collection bag in LM; **E.** After the pseudo pneumoperitoneum was established, the intestinal tube and omentum could be pushed away, and the morcellation was performed in a clear field of vision; ▲ represents for vessels and ◆ represents for intestinal tract; **F.** The morcellation conducted with assistant fixing the tumor; **G.** The remaining fragment tissue; **H.** The collection bag were carefully examined for leakage breakage with normal saline

Table 3. Analysis of operative conditions in two groups

Items	Experiment group (n = 20)	Historical group (n = 30)	T/Z value	p-value
Successful cases of pseudo pneumoperitoneum	20/20	—	—	—
Remaining fragment tissue amount (mean ± SD)	5.00 ± 1.48	—	—	—
Remaining fragment tissue weight [g] (mean ± SD)	3.87 ± 1.31	—	—	—
Number of myoma removed during operation(mean ± SD)	1 (1, 5)	1 (1, 7)	Z = –1.19	0.23
Operation duration (min) (median, IQR)	101, 43	83, 35	Z = –3.75	0.00
Intraoperative hemorrhage [mL] (median, IQR)	110, 75	90, 50	Z = –3.55	0.17
Volume of CO_2 [L] (median, IQR)	335, 145	283, 109	Z = –4.24	0.00
Intraoperative penetrating intima, No. (%)	2 (10.0)	4 (13.3)	X^2 = 0.00	1.00
Antibiotic usage rate of class I incision, No. (%)	1 (5.6)	2 (7.7)	X^2 = 0.00	1.00

SD — standard deviation; IQR — interquartile range

group than it did in the control group (p = 0.00), and the median difference between the two groups was 18 min. The intraoperative CO_2 use in the experimental group was also significantly higher than that in the historical control group (p = 0.00), and the median difference between the two groups was 52 L (Tab. 3).

The antibiotic usage rates for class I incisions in the experimental group and the historical control group were 0.05 and 0.08, respectively (p = 1.00). The pathology results of the two groups showed that the myomas were all uterine leiomyomas. There were two cases of cellular leiomyoma in the experimental group, and one case of cellular leiomyoma,

Table 4. Postoperative analysis of two groups

Items	Experiment group (n = 20)	Historical group (n = 30)	T/Z value	p-value
Postoperative Hb decline [g/L] (mean ± SD)	23.50 ± 14.85	18.87 ± 7.54	T = 1.05	0.31
Postoperative hospital stay [d] (mean ± SD)	4.5, 2.0	5.0, 0.5	Z = –0.06	0.95
Postoperative blood transfusion, No. (%)	0	0	—	—
Postoperative morbidity, No. (%)	2 (10.0)	3 (10.0)	X^2 = 0.00	1.00
Postoperative exhaust time [d] (median, range)	2 (1, 2)	2 (1, 3)	Z = –0.14	0.89
Total hospitalization expenses (RMB) (median, IQR)	13257.49, 3102.36	13762.48, 1928.64	Z = –0.63	0.53
Menstrual recovery, No. (%)	4 (100.0)	4 (80.0)	—	1.00

Postoperative morbidity — postoperative body temperature is higher than 38.5°C. Menstrual recovery: refers to patients with preoperative menorrhea (> 80 mL) or prolonged menstrual period (> 7 d) returned to normal menstrual volume (5–80 mL) and normal menstrual period (3–7 d) after surgery. The menstrual recovery in this table was analyzed by Fisher's exact test. There was no statistic (X^2 value), and p-value was bilateral

one case of strange uterine leiomyoma, and three cases of uterine leiomyoma with degeneration in the historical control group (one case of mucinous degeneration and two cases of red degeneration), but none of them was malignant.

In the experimental group, cytological counts of lavage fluid were performed after all the red blood cells were lysed by erythrocyte lysates before and after morcellation. All the cytological counts were less than 10^5–10^6/L. No other cell culture was carried out.

There was no significant difference between the experimental group and the historical control group in postoperative hemoglobin decline, postoperative hospital stays, postoperative blood transfusion, postoperative morbidity, postoperative bowel movement time, and total hospitalization costs. There were three cases of menorrhagia (> 80 mL) and one case of prolonged menstruation (> 7 days) in the experimental group, which all returned to normal after the operation, and three cases of menorrhagia and two cases of prolonged menstruation in the historical control group, four of which returned to normal afterwards. One case of prolonged menstruation did not recover, and previous ultrasonography indicated cesarean scar diverticulum. There was no significant difference in menstrual recovery between the two groups (Tab. 4).

In this study, one patient in the experimental group was infertile, and three patients in the historical control group were infertile (Tab. 1). These patients had still not conceived four years after surgery, and so pregnancy outcome cannot be calculated at present, and further follow-up is needed.

DISCUSSION

Performing a laparoscopic myomectomy rather than a transabdominal myomectomy can reduce trauma and increase patient compliance. However, open power morcellation increases the possibility of spreading potentially malignant diseases and significantly reduces the survival of those patients [9, 10]. The rate of benign myoma is less than 0.50% (0.13–2.02%) and the incidence of potential malignant tumors during hysterectomy and morcellation is 0.10–0.25% [11, 12]. Despite these low rates of malignancy and potential malignancy, the fundamental importance of patient safety means that clinical gynecologists must balance maximum benefit with minimum harm.

There has been some exploration of the technology of improved tumor morcellation. As early as 2003, Landman et al. [13] suggested that in laparoscopic nephrectomy for renal cell carcinoma the affected tissue could be separated in vitro by expanding the body surface incision to 3 cm. The contained morcellation of a uterine myoma during LM has also been studied. This method involves accommodating the morcellation device, while also providing enough space and maintaining clear vision during surgery. The aim of this technique is to isolate and accommodate tissues considered normal before surgery, even if these tissues are subsequently diagnosed as malignant. However, at present, most of the contained morcellation systems require puncturing the bag after the pseudopneumoperitoneum is established in the abdominal cavity, which increases the possibility of bag leakage and tissue splash [14, 15].

In 2016, the FDA approved the Pneumoliner System [16]. This device consists of a sealed bag and a cylindrical plunger, which can be placed in the abdominal cavity. The umbilical incision needs to be wide enough for a cylindrical plunger to be placed in the umbilical puncture hole, as well as a 5 mm diameter fiber lens (convertible direction), a 5 mm morcellator (enhanced bipolar energy), and a pneumoperitoneum system. There is no assistance with fixing the tissue during the morcellation, as well as the More-Cell-Safe system reported in 2017 [17]. However, the Pneumoliner System is like single port laparoscopy, which increases the degree of difficulty of the operation, and it is not suitable for three or four trocars. In addition, the field of vision is relatively limited.

Morcellation techniques with assistants holding the tissue in place can guarantee quicker and safer morcellation

and avoid shaking the tumors with the morcellator, and a clear visual field can reduce the risk of damaging any surrounding vital organs. Nevertheless, it has been reported that with the contained morcellation technique, the morcellator can penetrate the bag and injure the aorta, inferior vena cava, or intestine [18], which can lead to the death of the patient [19]. In the present study, 20 patients in the experimental group had an LM that involved the use of a contained collection bag. Pseudopneumoperitoneum was successfully established in all the operations, and afterwards the intestinal tube and the omentum were pushed away. The morcellation was performed with a clear field of vision and the help of an assistant, thereby reducing the possibility of damaging nearby tissue or enabling the spread of tumor cells. It would appear that morcellation during an LM with a contained collection bag is effective, safe, and feasible.

It has been reported that the average duration of contained power morcellation is 20–26 min. longer than that of open power morcellation, but there is no significant difference in blood loss and length of hospitalization [20]. In this study, the average time increase of the experimental group operations was about 18 min. ($p = 0.00$), and the intraoperative CO_2 use was increased by about 52 L ($p = 0.00$). There was no significant difference between the experimental group and the historical control group in postoperative hemoglobin decline, postoperative hospitalization days, postoperative blood transfusion, postoperative morbidity, postoperative bowel movement time, and total hospitalization costs. The slightly prolonged operation time did not affect the postoperative recovery and total hospitalization costs of the experimental group patients. It is believed that the duration of the operation and the use of CO_2 would decrease if the sample size was increased and the contained power morcellation technique further developed.

This study involved a single-arm trial, and the sample size was relatively small. It is thus necessary to expand the sample size to confirm the validity, safety, and feasibility of the technique. Moreover, in this study, the bags were only used with tumors that were removed during an LM, and further research is necessary regarding their use in patients who are undergoing a laparoscopic hysterectomy.

In this study, the myomas of both the experimental group and the historical control group were pathologically diagnosed as benign and without any malignancy. This means that this study cannot prove that the contained bag technique can reduce the risk of spreading malignant tumors. The efficacy of this bag in preventing abdominal and pelvic dissemination of potentially malignant tumor tissue needs to be further analyzed by enlarging the sample size and increasing the follow-up time. However, this new contained collection bag should not be used in patients with known malignant tumors.

CONCLUSIONS

Morcellation with this newly designed contained collection bag during an LM can be effective, safe, and feasible. It is also economical, practical, and easy to operate. The efficacy of the contained collection bag in preventing the abdominal and pelvic dissemination of potentially malignant tumors requires confirmation.

Funding

This study was funded by the National Natural Science Foundation of China (No. 81270678); Suzhou science and technology planning project (No. SS201633, SYSD2019106, SYS2020134); Jiangsu Provincial Commission of Health and Family Planning (No. F201922) and Suzhou Wumen medical school research special scientific research fund (No.SKJYD2021190).

Ethics approval and consent to participate abstract

The study was conducted in accordance with the Declaration of Helsinki (as was revised in 2013). The study was approved by Ethics Committee of the Second Affiliated Hospital of Soochow University (No.JD-LK-2016-020-03). Written informed consent was obtained from all participants.

Conflict of interest

No potential conflict of interest was reported by the authors.

REFERENCES

1. Tan-Kim J, Hartzell KA, Reinsch CS, et al. Uterine sarcomas and parasitic myomas after laparoscopic hysterectomy with power morcellation. Am J Obstet Gynecol. 2015; 212(5): 594.e1–594.10, doi: 10.1016/j.ajog.2014.12.002, indexed in Pubmed: 25499259.
2. Istre O. Unexpected Uterine Leiomyosarcoma During Laparoscopic Hysterectomy Treated 6 Months With Ulipristal Acetate and Contained Power Morcellation. J Minim Invasive Gynecol. 2017; 24(2): 198, doi: 10.1016/j.jmig.2016.08.004, indexed in Pubmed: 27539216.
3. Park JY, Kim DY, Kim JH, et al. The impact of tumor morcellation during surgery on the outcomes of patients with apparently early low-grade endometrial stromal sarcoma of the uterus. Ann Surg Oncol. 2011; 18(12): 3453–3461, doi: 10.1245/s10434-011-1751-y, indexed in Pubmed: 21541824.
4. Ludwin A, Gawron I, Pityński K. Occult uterine leiomyosarcoma in women undergoing abdominal and minimally invasive surgeries for myomas. Ginekol Pol. 2018; 89(10): 546–552, doi: 10.5603/GP.a2018.0093, indexed in Pubmed: 30393842.
5. Food U S. Laparoscopic Uterine Power Morcellation in Hysterectomy and Myomectomy: FDA Safety Communication. Center for Devices & Radiological Health, 2014. https://xueshu.baidu.com/usercenter/paper/show?paperid=3eddca96ea9b38c1b8f9bc741523dc3c (15.12.2021).
6. Lum DA, Sokol ER, Berek JS, et al. Impact of the 2014 Food and Drug Administration Warnings Against Power Morcellation. J Minim Invasive Gynecol. 2016; 23(4): 548–556, doi: 10.1016/j.jmig.2016.01.019, indexed in Pubmed: 26827905.
7. Singh SS, Scott S, Bougie O, et al. Technical Update on Tissue Morcellation During Gynaecologic Surgery: Its Uses, Complications, and Risks of Unsuspected Malignancy. Journal of Obstetrics and Gynaecology Canada. 2015; 37(1): 68–78, doi: 10.1016/s1701-2163(15)30366-2.
8. Kanade TT, McKenna JB, Choi S, et al. Sydney contained in bag morcellation for laparoscopic myomectomy. J Minim Invasive Gynecol. 2014; 21(6): 981, doi: 10.1016/j.jmig.2014.07.005, indexed in Pubmed: 25048568.

9. Park JY, Park SK, Kim DY, et al. The impact of tumor morcellation during surgery on the prognosis of patients with apparently early uterine leiomyosarcoma. Gynecol Oncol. 2011; 122(2): 255–259, doi: 10.1016/j.ygyno.2011.04.021, indexed in Pubmed: 21565389.
10. Oduyebo T, Rauh-Hain AJ, Meserve EE, et al. The value of re-exploration in patients with inadvertently morcellated uterine sarcoma. Gynecol Oncol. 2014; 132(2): 360–365, doi: 10.1016/j.ygyno.2013.11.024, indexed in Pubmed: 24296345.
11. Brölmann H, Tanos V, Grimbizis G, et al. European Society of Gynaecological Endoscopy (ESGE) steering committee on fibroid morcellation. Options on fibroid morcellation: a literature review. Gynecol Surg. 2015; 12(1): 3–15, doi: 10.1007/s10397-015-0878-4, indexed in Pubmed: 25774118.
12. Beckmann MW, Juhasz-Böss I, Denschlag D, et al. Surgical methods for the treatment of uterine fibroids - risk of uterine sarcoma and problems of morcellation: position paper of the DGGG. Geburtshilfe Frauenheilkd. 2015; 75(2): 148–164, doi: 10.1055/s-0035-1545684, indexed in Pubmed: 25797958.
13. Landman J, Venkatesh R, Kibel A, et al. Modified renal morcellation for renal cell carcinoma: laboratory experience and early clinical application. Urology. 2003; 62(4): 632–634; discussion 635, doi: 10.1016/s0090-4295(03)00680-0, indexed in Pubmed: 14550431.
14. Lambat Emery S, Pluchino N, Petignat P, et al. Cell spillage after contained electromechanical morcellation using a specially designed in-bag system for laparoscopic myomectomy: prospective cohort pilot study. J Minim Invasive Gynecol. 2019; 26(7): 1351–1356, doi: 10.1016/j.jmig.2019.01.014, indexed in Pubmed: 30710637.
15. Cheung VYT, Pun TC. Contained morcellation for laparoscopic myomectomy within a specially designed bag. J Minim Invasive Gynecol. 2016; 23(1): 139–140, doi: 10.1016/j.jmig.2015.08.889, indexed in Pubmed: 26391058.
16. Contained Tissue Extraction System. http://medical.olympusamerica.com/products/pneumoliner (15.12.2021).
17. Szymczak P, Sawicki S, Wydra D. Laparoscopic supracervical hysterectomy with the use of the More-Cell-Safe system in a patient with uterine leiomyomas. Ginekol Pol. 2017; 88(2): 113–114, doi: 10.5603/GP.a2017.0020, indexed in Pubmed: 28326522.
18. Rechberger T, Miotła P, Futyma K, et al. Power morcellation for women undergoing laparoscopic supracervical hysterectomy - safety of procedure and clinical experience from 426 cases. Ginekol Pol. 2016; 87(8): 546–551, doi: 10.5603/GP.2016.0042, indexed in Pubmed: 27629127.
19. Milad MP, Milad EA. Laparoscopic morcellator-related complications. J Minim Invasive Gynecol. 2014; 21(3): 486–491, doi: 10.1016/j.jmig.2013.12.003, indexed in Pubmed: 24333632.
20. Vargas MV, Cohen SL, Fuchs-Weizman N, et al. Open power morcellation versus contained power morcellation within an insufflated isolation bag: comparison of perioperative outcomes. J Minim Invasive Gynecol. 2015; 22(3): 433–438, doi: 10.1016/j.jmig.2014.11.010, indexed in Pubmed: 25452122.

VIA MEDICA

ORIGINAL PAPER / GINECOLOGY

Ginekologia Polska
2022, vol. 93, no. 8, 614–619

ISSN 0017–0011, e-ISSN 2543–6767

DOI 10.5603/GP.a2022.0042

Transcervical intrauterine radiofrequency ablation of fibroids in high-risk patients with bleeding disorder

Elvin Piriyev[1], Ralf Bends[2], Sven Schiermeier[3], Thomas Romer[2]

[1]Department of Obstetrics and Gynecology, University Witten-Herdecke, Department of Obstetrics and Gynecology, Academic Hospital Cologne Weyertal University of Cologne, Germany

[2]Department of Obstetrics and Gynecology Academic Hospital Cologne Weyertal University of Cologne, Germany

[3]Department of Obstetrics and Gynecology, University Witten-Herdecke, Marien-Hospital, Witten Marienplatz, Witten, Germany

ABSTRACT

Objectives: To show the advantages of transcervical radiofrequency ablation (TRFA) in high-risk patients with bleeding disorder.

Material and methods: It is a retrospective analysis. The study included only patients with known pre-existing conditions (obesity, cardiac and neurological disease, coagulation disorder, anaemia) or post-surgical conditions who were treated with the Sonata® System for fibroid-related bleeding complaints at Academic Hospital Cologne Weyertal between January 2015 and March 2021. These patients were classified as high-risk patients. The fibroids were mostly determined due transvaginal sonography. Thirty patients were included, and 43 fibroids were determined.

Results: Therapy with the Sonata® system could be performed without complications in all cases. In our analysis, improvement of fibroid-related symptoms was observed in 89% of cases.

Conclusions: The Sonata® System is on the one hand minimally invasive, uncomplicated and fast and on the other hand a successful method of fibroid therapy, which is particularly suitable for high-risk patients with various pre-existing conditions, for whom a minimally invasive, bloodless and short surgical procedure has great advantages.

Key words: Sonata®; fibroid; ablation; high risk patients; bleeding disorder; uterus

Ginekologia Polska 2022; 93, 8: 614–619

INTRODUCTION

The estimated prevalence of uterine fibroids ranging from 4.5% to 68.6% [1]. The prevalence is age-dependent [2]. Figures in the literature vary widely, from 217 to 3745 cases per 100 000 women-years [1]. The prevalence in Germany is 48.6% in women aged 30–55 years, with the highest prevalence of 65.2% in the group with patients aged 46–50 years [2]. Fibroids cause different symptoms, and hypermenorrhoea is the main symptom with the prevalence of 40–54%. The next common symptoms are dysmenorrhea and lower abdominal pain [3, 4]. In 48% cases, fibroids are the cause of severe hypermenorrhoea with anaemia [5]. Even nowadays the most common therapy for symptomatic fibroids is a hysterectomy. The main indication for a hysterectomy is still fibroid [6–9].

The classification of fibroids is according to FIGO classification, which serves as basis [10]. The classification of fibroids is very important for prognosis and therapy recommendation. Therefore localization, size and number of fibroids should be well understood [2].

In the therapy, low effective medicament therapy, invasive and drastic therapy such as a removal of uterus are mostly used. To fill the gap between these methods, transcervical radiofrequency ablation (TRF) was developed. This method is safe and effective [11–14]. A meta-analysis of 32 studies with more than 1200 patients treated with TRF ablation showed a statistically significant and clinically relevant reduction in fibroid-related symptoms and improvement in quality of life, with low reintervention rates [11]. The benefit of TRF is that it is minimally invasive without incision, and the treatment of a broad type of fibroids is possible, especially such fibroids, which cannot be treated with a surgical hysteroscopy (FIGO 3, 4, 5, 6, and 2–5) [8].

Transcervical radiofrequency ablation has FDA (U.S. Food and Drug Administration) approval for diagnostic

Corresponding author:
Elvin Piriyev, Department of Obstetrics and Gynecology, University Witten-Herdecke, Department of Obstetrics and Gynecology, Academic Hospital Cologne Weyertal University of Cologne, Germany
e-mail: piriyev.elvins@gmail.com

Received: 3.01.2022 Accepted: 24.04.2022 Early publication date: 3.06.2022

intrauterine imaging and transcervical treatment of symptomatic uterine fibroids, including those associated with heavy menstrual bleeding. The system also has a CE mark ("Conformité Européenne" French for "European Conformity") in the European Union [14–16].

Transcervical radiofrequency ablation is performed by a gynaecologist. The instrument has a small ultrasound probe which is to insert intrauterine [17]. Before the ablation the fibroid is determined sonographically. Usually, a general anaesthesia is required for TFA. The diameter of the device is 8.3 mm. The penetration depth is less than 12 cm. The fibroid is represented due graphical navigation. After graphical visualize of fibroid the ablation is carried out. In this phase a safety zone guaranteed no thermal injury in the surrounding organs (for example bladder, bowel). It is important especially for transmural fibroids that are also located near the bladder and bowels. The procedure allows for optimization of the ablated volume in the targeted fibroid. The puncture of serosa is not necessary. The measurements are registered graphically. The ablation time is 1–7 min depending on the fibroid size (the smallest size of fibroid is 2.0 × 1.3 cm). The temperature of the electrode is about 105°C. A thermal coagulation necrosis is not caused by TFA. This method does not cause a postablation syndrome either. A good knowledge of vaginal ultrasonography and confidence in all other endoscopic fibroid therapy are required, because they can be used at the same time in combination with TRF as needed. Hospital stay time is 1–2 days [17, 18].

This technique could be of importance in the treatment of fibroids in high-risk patients (*e.g.*, obesity, cardiac disease, coagulopathy, multiple previous surgeries), as it offers the most minimally invasive and effective approach, with short surgical time. Therefore, this study was conducted to analyse the results of the Sonata® System in high-risk patients.

MATERIAL AND METHODS

Transcervical radiofrequency ablation has been performed in our department since 2011. The retrospective study included only patients with known pre-existing conditions (obesity, cardiac and neurological disease, coagulation disorder, anaemia) or post-surgical conditions who were treated with the Sonata® System for fibroid-related bleeding complaints at Academic Hospital Cologne Weyertal between January 2015 and March 2021. These patients were classified as high-risk patients. Diagnosis was mostly performed by transvaginal sonography. Thirty patients were included, and 43 fibroids were determined.

Therapy with the Sonata® System was carried out complications free in all cases. During the operations, the device could be inserted without any difficulty. First, the ablation zone and the safety zone were adjusted and then the fibroid was fixed with the central spike ("introducer"). After checking the safety zone, the electrodes were inserted. After checking the safety zone again, the fibroids were ablated with a temperature of 105°C. All patients without any complications.

RESULTS

The age of the patients ranged from 34 to 54 years (Fig. 1). All patients had abnormal uterine bleeding mostly hypermenorrhoea and two patients still had the desire to become pregnant.

A total of 43 fibroids were detected in 30 patients. Nineteen patients had one fibroid, 10 patients had two fibroids, and one patient had four fibroids.

The fibroids were classified according to FIGO classification. Figure 2 shows the number of fibroids based on FIGO classification. The majority of fibroids were classified as of FIGO 2–5 fibroids 62.8% (27 fibroids) and the minority consisted of FIGO 4 fibroids 2.3% (one fibroid).

F-fibroid

For better visualization, the fibroids were divided into six groups depending on their size. Figure 3 shows this division.

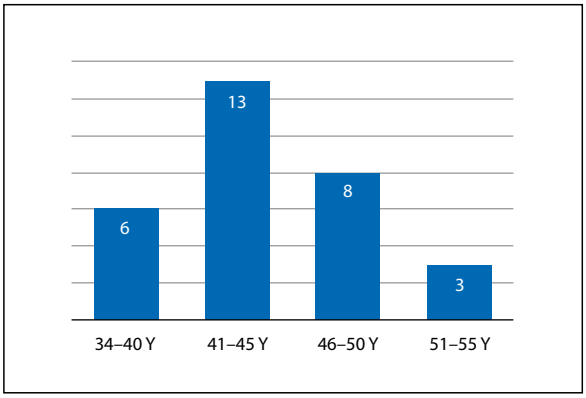


Figure 1. Overview of patients depending on age group

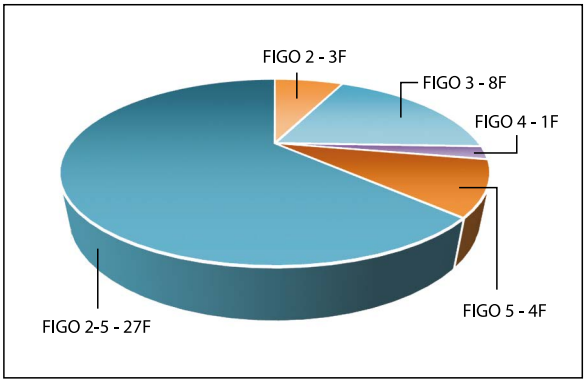


Figure 2. Number of fibroids related to FIGO classification

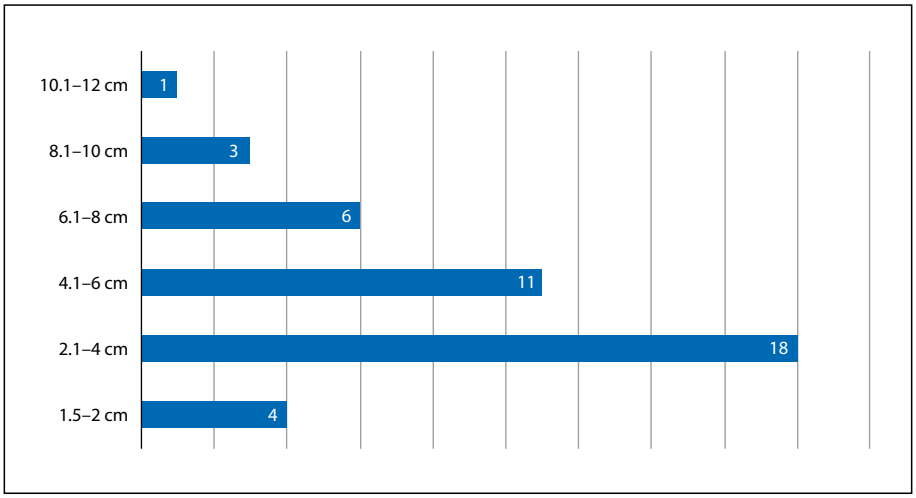


Figure 3. Myoma number related to myoma size

Table 1 shows the risks/pre-existing conditions of the patients. Twenty-two patients had one and eight patients had two risk factors/pre-existing conditions.

Three patients had third-degree-obesity: with a BMI of 45 kg/m^2 in two patients and 56 kg/m^2 in one patient. Seven patients had a large transmural fibroid of ≥ 7 cm, one patient had two fibroids of 6 cm and all these patients had strongly desired an organ-preserving minimally invasive approach. Laparoscopic fibroid removal in this case would be associated with a high risk of bleeding and a laparotomy.

Intraoperative results

The shortest ablation time of a fibroid was 1 minute 13 seconds and the longest was 25 minutes 6 seconds. Table 2 shows the ablation time of a fibroid in relation to the number of fibroids.

The ablation time and the number of ablation steps vary depending on the fibroid size. As it can be seen in Table 3, both ablation time and ablation steps increase with fibroid size.

Postoperative results

Twenty-six patients came to follow-up (Fig. 4). Twenty--three of 26 patients reported subjective improvement in symptoms, with 21 patients reporting marked improvement and two patients reporting a mild improvement. Three patients had no improvement and in one of them a hysterectomy by laparotomy was performed during follow-up. In this case the respective uterus showed four FIGO 2–5 fibroids, three of which were approximately 5 cm. The patient had already undergone two surgeries by transverse laparotomy, so the hysterectomy was also performed by laparotomy in the presence of adhesions. Therefore, an improvement of the complaints was 89%.

Special cases

Two patients with severe hypermenorrhoea still had a desire to become pregnant, of which one patient had a current desire and one had a potential desire. In both cases, significant improvement of hypermenorrhoea was observed.

The patient with the current fertility desire had a FIGO 2–5 fibroid of 7 cm. Prior to presentation at our department, a laparoscopy was performed in another hospital. A hysterectomy was recommended to the patient, due to the size of the fibroid. In our department, the ablation of the fibroid was performed using the Sonata® System. Two ablation steps were performed, 7 minutes and 5 minutes 12 seconds. After 15 months, the patient had a vaginal delivery in our department without any complications.

The second patient with a potential desire to become pregnant had the condition after midline laparotomy with the removal of 1700 g of fibroids. She had a FIGO 2 fibroid of 2.7 × 2 × 2 cm, which was ≥ 90% intramural. Transcervical radiofrequency ablation was performed with two ablation steps, 1 min. 42 seconds and 2 minutes. Transvaginal ultrasound after three months showed a significant regression to 1.7 × 1.5 × 1.4 cm. Moreover, the position of the fibroid shifted from FIGO 2 to FIGO 4 with sufficient distance from the endometrium, which is highly relevant for fertility.

DISCUSSION

For the therapy of fibroids there are a wide spectrum of options, from medicament treatment to a removal of uterus [6–9, 11–14]. Several factors must be considered in the therapy of fibroid, as a FIGO type, size, number of fibroids, severity of symptoms, patient's life stage (fertile, peri- or postmenopausal), health risk factors, medical contraindications as well the patient's wishes.

Table 1. Overview of risks in relation to number of patients

Number of patients	Risk groups	Risk subgroup	Number of patients
4	Coagulation disorder	Thrombosis	2
		Immune thrombocytopenia	1
		AT III Deficiency	1
7	Obesity	BMI 30–35 kg/m^2 (I^o)	1
		BMI 35–40 kg/m^2 (II^o)	3
		BMI > 40 kg/m^2 (III^o)	3
9	Previous operations	1 × midline laparotomy	4
		1 × LSK, 1 × midline laparotomy	1
		2 × midline laparotomy	2
		4 × midline laparotomy	1
		4 × LSK	1
6	Anaemia (Hb)	8–9 g/dL	1
		7–8 g/dL	3
		6–7 g/dL	2
2	Neurological diseases	Apoplexy cerebral vessel	1
		Brain pacemaker by strong depression	1
2	Cardiac diseases	Hypertension	1
		AVNRT	1
8	Large fibroid with a request for organ-preserving therapy	2 × 6 cm	1
		7–8 cm	4
		9–12 cm	3

AT III — antithrombin III; AVNRT — atrioventricular nodal reentrant tachycardia; BMI — body mass index; LSK — laparoscopy

Table 2. Ablation time in relation to the number of fibroids

Ablation time	Number of fibroids
1–5 minutes	26
> 5–10 minutes	8
> 10–15 minutes	3
> 15–20 minutes	4
> 20–25 minutes	2

In a study, almost a thousand women with symptomatic fibroids were asked about the therapy desire. Almost 80% of respondents did not want an invasive method and the half of respondents wanted avoid a hysterectomy [9]. In the therapy of fibroids is a need for less invasive organ-preserving therapy without incision, that is available for wide spectrums of fibroids [14–16]. For this reason, TRF was developed. This method is effective and safe [11–14]. According to the literature review as well as in our analysis, no specific intraoperative or postoperative complications were found.

In Luke's et al. [19] study, patient satisfaction with TRF was 94% (99/105) and 88% of patient had an improvement of symptoms. Toub reported an improvement in 90% of cases [14]. In our analysis, an improvement of fibroid-related symptoms was observed in 89% of cases.

The long-term results after TRF are available. The reintervention rate is 11.8% [20]. it is slightly higher than after an abdominal myomectomy (9%) and the same as with laparoscopic myomectomy (11%), but significantly lower compared to other methods (17% after uterine artery embolization, 21% after hysteroscopic fibroid resection) [21].

Bipolar operative hysteroscopy is most suitable for submucosal fibroids [2]. For large (> 3 cm), multiple (n > 3), and type-2 fibroids the hysteroscopy can be difficult. In this case there is a 20–50% chance for least one additional resection for complete treatment [2, 22, 23]. Hysteroscopy has a low intraoperative complication rate [24]. Postoperative complications in terms of intrauterine adhesions occur in 10% to 37.5% for the resection of one fibroid and up to 45% for multiple fibroids [2, 25].

Intramural and subserosal fibroids can be removed by laparoscopy and/or laparotomy. In a meta-analysis involving 576 patients, laparoscopic and abdominal removal of fibroids were compared. In the meta-analysis, the advantages of laparoscopy over laparotomy were shown, including faster postoperative recovery of patients, less blood loss

Table 3. Ablation time and number of ablation steps in relation to fibroid size

Fibroid size	Fibroid number	Ablation step	Ablation time [min]
1.5–2 cm	4	1 step	1:13–2:06
> 2–4 cm	18	12 fibroids — 1 step	1:30–5:00
		6 fibroids — 2 steps	3:13–4:06*
> 4–6 cm	11	6 fibroids — 1 step	3:00–5:42
		4 fibroids — 2 steps	5:48–7:24*
		1 fibroid — 3 steps	10:06
> 6–8 cm	6	3 fibroids — 2 steps	6:00–12:12*
		3 fibroids — 3 steps	15:18–17:00*
> 8–10 cm	3	2 fibroids — 3 steps 1 fibroid — 4 steps	13:32–18:50* 22:12*
>10–12 cm	1	4 steps	25:06*

*Total time of all ablation steps

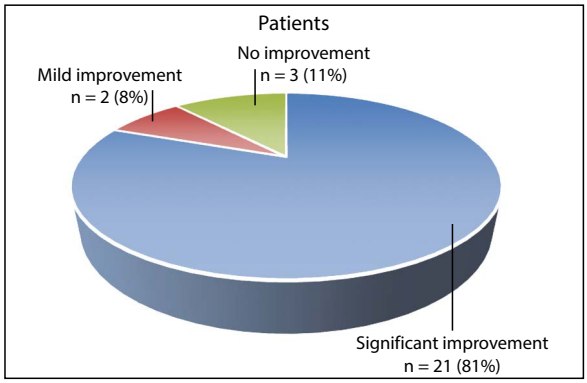


Figure 4. Postoperative results in the follow up group in percentages

and less postoperative pain. Therefore, laparotomy should be performed only in certain cases [2, 26].

Intraoperative complications of laparoscopic fibroid removal arise from inadequate hysterotomy, enucleation, haemostasis, and morcellation. Postoperative complications include hematomas after a hysterotomy, uterine adhesions, abdominal adhesions, and parasitic fibroids [27–29]. In an analysis with the laparoscopic resection of 654 fibroids (average size 5.3 cm), intraoperative complications occurred in 2.6% cases and postoperative complications in 5.7% cases [27]. Another study of 2050 laparoscopic fibroid resections showed an overall complication rate of 11.1% (225/2050) [30]. The increase of complications with laparoscopic myoma enucleation is observed [27, 31]. One possible reason for this is the increasing number of gynaecologists with lack of experience in laparoscopic fibroid removal, laparoscopic suturing, as well as electromechanical morcellation [32].

The complication rate of laparoscopy increases in patients with additional risks. Driessen et al. [33] compared two groups of patients with and without risks. Among all, BMI, number of previous surgeries and uterus size were considered. A total of 2237 laparoscopic hysterectomies were analysed. The complication rate in the group with known risks was significantly higher (10.5% vs 4.8%), blood loss 167.6 mL vs 110.1 mL and operation time 114.3 minutes vs 95.3 minutes [33].

Especially in high-risk patients with fibroids, that more difficult to reach, the therapy should be chosen very carefully. Our study shows that fibroid therapy with the Sonata® System is suitable for FIGO 2 to 5, whereas FIGO 2 to 4 fibroids are rather difficult to reach for the other surgical option. This method can also be used to treat multiple fibroids in a single session. The method is particularly suitable for patients with anaemia, as there is hardly any bleeding with the Sonata® System compared to other surgical measures.

CONCLUSIONS

Therefore, the Sonata® System is on the one hand minimally invasive, uncomplicated and fast and on the other hand a successful method of fibroid therapy, which is particularly suitable for high-risk patients with various pre-existing conditions, for whom a minimally invasive, bloodless and short surgical procedure has great advantages.

Ethical approval

According to §15 of the professional code of the North Rhine Medical Association, neither advice nor an ethics vote is necessary for a retrospective study.

Conflict of interest

Elvin Piriyev has no conflict of interest. Ralf Bends, Sven Schiermeier and Thomas Römer are consultants for the Sonata System. The authors report no other conflicts of interest in this work.

Funding

This study was not funded.

REFERENCES

1. Stewart EA, Cookson CL, Gandolfo RA, et al. Epidemiology of uterine fibroids: a systematic review. BJOG. 2017; 124(10): 1501–1512, doi: 10.1111/1471-0528.14640, indexed in Pubmed: 28296146.
2. Römer T. Medical treatment of fibroids. De Gruyter. : 2019.
3. Foth D, Röhl FW, Friedrich C, et al. Symptoms of uterine myomas: data of an epidemiological study in Germany. Arch Gynecol Obstet. 2017; 295(2): 415–426, doi: 10.1007/s00404-016-4239-y, indexed in Pubmed: 27873052.
4. Zimmermann A, Bernuit D, Gerlinger C, et al. Prevalence, symptoms and management of uterine fibroids: an international internet-based survey of 21,746 women. BMC Womens Health. 2012; 12: 6, doi: 10.1186/1472-6874-12-6, indexed in Pubmed: 22448610.
5. Nelson AL, Ritchie JJ. Severe anemia from heavy menstrual bleeding requires heightened attention. Am J Obstet Gynecol. 2015; 213(97): e1–97.e6, doi: 10.1016/j.ajog.2015.04.023 , indexed in Pubmed: 25935784.
6. Farquhar CM, Steiner CA. Hysterectomy rates in the United States 1990-1997. Obstet Gynecol. 2002; 99(2): 229–234, doi: 10.1016/s0029-7844(01)01723-9, indexed in Pubmed: 11814502.
7. Wise LA, Palmer JR, Stewart EA, et al. Age-specific incidence rates for self-reported uterine leiomyomata in the Black Women's Health Study. Obstet Gynecol. 2005; 105(3): 563–568, doi: 10.1097/01.AOG.0000154161.03418.e3, indexed in Pubmed: 15738025.
8. Downes E, Sikirica V, Gilabert-Estelles J, et al. The burden of uterine fibroids in five European countries. Eur J Obstet Gynecol Reprod Biol. 2010; 152(1): 96–102, doi: 10.1016/j.ejogrb.2010.05.012, indexed in Pubmed: 20598796.
9. Borah BJ, Nicholson WK, Bradley L, et al. The impact of uterine leiomyomas: a national survey of affected women. Am J Obstet Gynecol. 2013; 209(4): 319.e1–319.e20, doi: 10.1016/j.ajog.2013.07.017, indexed in Pubmed: 23891629.
10. Munro MG, Critchley HOD, Broder MS, et al. FIGO Working Group on Menstrual Disorders. FIGO classification system (PALM-COEIN) for causes of abnormal uterine bleeding in nongravid women of reproductive age. Int J Gynaecol Obstet. 2011; 113(1): 3–13, doi: 10.1016/j.ijgo.2010.11.011, indexed in Pubmed: 21345435.
11. Bradley LD, Pasic RP, Miller LE. Clinical Performance of Radiofrequency Ablation for Treatment of Uterine Fibroids: Systematic Review and Meta-Analysis of Prospective Studies. J Laparoendosc Adv Surg Tech A. 2019; 29(12): 1507–1517, doi: 10.1089/lap.2019.0550, indexed in Pubmed: 31702440.
12. Iversen H, Dueholm M. Radiofrequency Thermal Ablation for Uterine Myomas: Long-term Clinical Outcomes and Reinterventions. J Minim Invasive Gynecol. 2017; 24(6): 1020–1028, doi: 10.1016/j.jmig.2017.05.021, indexed in Pubmed: 28662989.
13. Lin L, Ma H, Wang J, et al. Quality of Life, Adverse Events, and Reintervention Outcomes after Laparoscopic Radiofrequency Ablation for Symptomatic Uterine Fibroids: A Meta-Analysis. J Minim Invasive Gynecol. 2019; 26(3): 409–416, doi: 10.1016/j.jmig.2018.09.772, indexed in Pubmed: 30253997.
14. Toub DB. A New Paradigm for Uterine Fibroid Treatment: Transcervical, Intrauterine Sonography-Guided Radiofrequency Ablation of Uterine Fibroids with the Sonata System. Curr Obstet Gynecol Rep. 2017; 6(1): 67–73, doi: 10.1007/s13669-017-0194-2, indexed in Pubmed: 28357157.
15. Bongers M, Brölmann H, Gupta J, et al. Transcervical, intrauterine ultrasound-guided radiofrequency ablation of uterine fibroids with the VizAblate® System: three- and six-month endpoint results from the FAST-EU study. Gynecol Surg. 2015; 12(1): 61–70, doi: 10.1007/s10397-014-0873-1, indexed in Pubmed: 25774122.
16. Chudnoff S, Guido R, Roy K, et al. Ultrasound-Guided Transcervical Ablation of Uterine Leiomyomas. Obstet Gynecol. 2019; 133(1): 13–22, doi: 10.1097/AOG.0000000000003032, indexed in Pubmed: 30531573.
17. Römer T, Bends R, Christoffel L, et al. The significance of transcervical ultrasound-guided radiofrequency ablation in the treatment of symptomatic fibroids: results of an expert consensus from German-speaking countries. Arch Gynecol Obstet. 2022 [Epub ahead of print], doi: 10.1007/s00404-022-06516-1, indexed in Pubmed: 35316395.
18. Piriyev E, Schiermeier S, Römer T. Combined procedure of the transcervical radiofrequency ablation (TRFA) system and surgical hysteroscopy. Increased risk or safe procedure? Videosurgery and Other Miniinvasive Techniques. 2022, doi: 10.5114/wiitm.2022.113565.
19. Lukes A, Green MA. Three-Year Results of the SONATA Pivotal Trial of Transcervical Fibroid Ablation for Symptomatic Uterine Myomata. J Gynecol Surg. 2020; 36(5): 228–233, doi: 10.1089/gyn.2020.0021, indexed in Pubmed: 33061253.
20. Garza-Leal JG. Long-Term Clinical Outcomes of Transcervical Radiofrequency Ablation of Uterine Fibroids: The VITALITY Study. J Gynecol Surg. 2019; 35(1): 19–23, doi: 10.1089/gyn.2018.0051, indexed in Pubmed: 30713407.
21. Davis MR, Soliman AM, Castelli-Haley J, et al. Reintervention Rates After Myomectomy, Endometrial Ablation, and Uterine Artery Embolization for Patients with Uterine Fibroids. J Womens Health (Larchmt). 2018; 27(10): 1204–1214, doi: 10.1089/jwh.2017.6752, indexed in Pubmed: 30085898.
22. Vercellini P, Cortesi I, Oldani S, et al. The role of transvaginal ultrasonography and outpatient diagnostic hysteroscopy in the evaluation of patients with menorrhagia. Hum Reprod. 1997; 12(8): 1768–1771, doi: 10.1093/humrep/12.8.1768, indexed in Pubmed: 9308809.
23. Wamsteker K, Emanuel MH, de Kruif JH. Transcervical hysteroscopic resection of submucous fibroids for abnormal uterine bleeding: results regarding the degree of intramural extension. Obstet Gynecol. 1993; 82(5): 736–740, indexed in Pubmed: 8414318.
24. Römer T. Operative Hysteroscopy: A Practical Guide. 2 Edition. De Gruyter, https://doi.org/10.1515/9783110225006 2011.
25. Revaux A, Ducarme G, Luton D. [Prevention of intrauterine adhesions after hysteroscopic surgery]. Gynecol Obstet Fertil. 2008; 36(3): 311–317, doi: 10.1016/j.gyobfe.2007.11.014, indexed in Pubmed: 18308609.
26. Jin C, Hu Y, Chen X, et al. Laparoscopic versus open myomectomy – a meta-analysis of randomized controlled trials. Eur J Obstet Gynecol Reprod Biol. 2009; 145: 14–21.
27. Altgassen C, Kuss S, Berger U, et al. Complications in laparoscopic myomectomy. Surg Endosc. 2006; 20(4): 614–618, doi: 10.1007/s00464-004-2181-8, indexed in Pubmed: 16508820.
28. Malzoni M, Rotond M, Perone C, et al. Fertility after laparoscopic myomectomy of large uterine myomas: operative technique and preliminary results. Eur J Gynaecol Oncol. 2003; 24(1): 79–82, indexed in Pubmed: 12691325.
29. Mettler L, Schollmeyer T, Tinelli A, et al. Complications of uterine fibroids and their management, surgical management of fibroids, laparoscopy and hysteroscopy versus hysterectomy, haemorrhage, adhesions, and complications. Obstet Gynecol Int. 2012; 2012: 791248, doi: 10.1155/2012/791248, indexed in Pubmed: 22619681.
30. Sizzi O, Rossetti A, Malzoni M, et al. Italian multicenter study on complications of laparoscopic myomectomy. J Minim Invasive Gynecol. 2007; 14(4): 453–462, doi: 10.1016/j.jmig.2007.01.013, indexed in Pubmed: 17630163.
31. Milad MP, Milad EA. Laparoscopic morcellator-related complications. J Minim Invasive Gynecol. 2014; 21(3): 486–491, doi: 10.1016/j.jmig.2013.12.003, indexed in Pubmed: 24333632.
32. Tanos V, Socolov R, Demetriou P, et al. Implementation of minimal invasive gynaecological surgery certification will challenge gynaecologists with new legal and ethical issues. Facts Views Vis Obgyn. 2016; 8(2): 111–118, indexed in Pubmed: 27909568.
33. Driessen SRC, Sandberg EM, Rodrigues SP, et al. Identification of risk factors in minimally invasive surgery: a prospective multicenter study. Surg Endosc. 2017; 31(6): 2467–2473, doi: 10.1007/s00464-016-5248-4, indexed in Pubmed: 27800588.

VIA MEDICA

ORIGINAL PAPER / GYNECOLOGY

Ginekologia Polska
2022, vol. 93, no. 8, 620–628

ISSN 0017–0011, e-ISSN 2543–6767

DOI 10.5603/GP.a2021.0181

The therapeutic effect of neuromuscular electrical stimulation by different pulse widths for overactive bladder in elderly women: a randomized controlled study

Aiming Lv, Tianzi Gai, Qing Feng, Min Li, Wenhui Deng, Qiubo Iv

Department of Obstetrics and Gynecology, Beijing Hospital, National Center of Gerontology, Institute of Geriatric Medicine, Chinese Academy of Medical Sciences, China

ABSTRACT

Objectives: There have been a number of controversies about which treatment of neuromuscular electrical stimulation (NMES) is more beneficial for overactive bladder (OAB)**.** An attempt to investigate the therapeutic effect of NMES with different pulse widths for OAB in elderly women has been made in this study.

Material and methods: The postmenopausal elderly women without pelvic organ prolapse (POP) who received transvaginal NMES in Beijing Hospital from November 2020 to December 2020 were randomly divided into two groups (Group A and Group B). Patients from Group A accepted the treatment with NMES by pulse width of 300 μs and patients from Group B accepted the treatment with NMES by pulse width of 200 μs. Myoelectric potential of Type I and Type II muscle fibers at pelvic floor and overactive bladder symptom score (OABSS) were valued.

Results: There were 46 patients eligible for the study and randomly divided into Group A and Group B, 23 patients for each group. OABSS were significantly reduced in both groups after the treatment of NEMS. And OABSS in Group A (after treated by pulse width of 300 μs) were significantly decreased greater than those in Group B (after treated with pulse width of 200 μs). Both Group A and Group B had no significant difference in the mean myoelectric potential at pre-resting state when compared before and after the treatment of NEMS. Myoelectric potential of Type I muscle fiber and the maximum myoelectric potential of Type II muscle fibers were significantly increased after the treatment of NEMS than before the treatment in the two groups, respectively. And myoelectric potential of Type I muscle fiber and the maximum myoelectric potential of Type II muscle fibers in group A (after treated with pulse width of 300 μs) were increased significantly much higher than those in Group B (after treated with pulse width of 200 μs).

Conclusions: Comparing the indicators before and after the treatments of NMES, our study has preliminarily confirmed that NMES has its advantages in treating with OAB. And NMES by pulse width of 300 μs were more effective in improving pelvic floor muscle strength than NMES by pulse width of 200 μs.

Key words: neuromuscular electrical stimulation; overactive bladder; pelvic floor muscles; overactive bladder symptom score; myoelectric potential; pulse width

Ginekologia Polska 2022; 93, 8: 620–628

INTRODUCTION

According to the Definition of the International Continence Society (ICS), an overactive bladder (OAB) was recognized as a "symptom syndrome suggestive of lower urinary tract dysfunction". It is specifically defined as "urgency, with or without urge incontinence, usually with frequency and nocturia" [1]. In China, the prevalence of OAB was 6.0% (5.9% for the male and 6.0% for the female), among which a female more than 50 years old accounted for 46.3% [2]. In the United States, the prevalence of OAB was 16.5% (16.0% for the male, 16.9% for the female) and has a trend of increasing with the age growing among the female (from 2% to 19%), especially among those more than 44 years old [3]. In Europe, epidemiological data indicated that among women over 40 years old, the prevalence of OAB was 16.6% and has been increased with the age growing as well [4].

Corresponding author:
Qiubo Iv
Department of Obstetrics and Gynecology, Beijing Hospital, National Center of Gerontology, Institute of Geriatric Medicine, Chinese Academy of Medical Sciences, China
e-mail: qiubo2185@126.com

Received: 17.12.2020 Accepted: 6.04.2021 Early publication date: 5.10.2021

It can be concluded that postmenopausal women are at a great risk of OAB. Studies have shown that in healthy postmenopausal middle-aged and elderly women, the incidence of OAB was 15–37% [5], among which 20.5% needed clinical intervention [6, 7], exerting great psychological pressure on patients. The pathogenesis of OAB mainly includes non-neurogenic detrusor instability, overactive bladder, dysfunctions of urethra and pelvic floor muscles, abnormal hormone metabolisms and so on. In addition to screening tests, overactive bladder symptom score (OABSS) has been proved to be highly sensitive to the diagnosis of OAB [8]. Traditional treatments for OAB include bladder training, pelvic floor muscle training (PRMT), anticholinergic drug, sacral nerve stimulation (SNS) and surgery. RCT studies have identified that bladder training [9], PRMT [10, 11] and drug therapy [10] could improve the symptoms of OAB. However, the side effects of drug therapy, such as constipation and dry mouth, has affected the medication adherence, with only 10–30% of the OAB population taking the medication as prescribed for at least one year [12]. SNS and surgery are invasive treatments, with limits in the clinical practice. As a noninvasive treatment, some studies [13–16] have found that neuromuscular electrical stimulation (NMES) could inhibit unstable muscle contractions and spastic musculature, regulate the hypoxic state of the muscles and strengthen the pelvic floor muscle, to improve pelvic floor disorders, such as pelvic organ prolapsed (POP), urinary incontinence and sexual dysfunction. However, there have been a number of controversies about which treatment of NMES is more beneficial for OAB.

Objectives

Our study is aiming to compare the therapeutic effect of NMES with different pulse width for OAB in elderly women, providing evidence for the treatments.

MATERIAL AND METHODS

Subjects

Postmenopausal women with OAB as chief complaint in Beijing Hospital from November 2020 to December 2020 were selected.

Inclusion criteria

1. More than 12 months from the last menstrual period;
2. Score of "urgent urination" on OABSS questionnaire of overactive bladder (OABSS) ≥ 2 points, and total score ≥ 3 points. Patients both meet the above two criteria can be enrolled.

Exclusion criteria

1. Routine urine test suggested urinary tract infection or ultrasound suggested vesical calculus;
2. Pelvic organ prolapse quantification system (POP-Q) suggested the lowest extent in the vagina was ≥ 0 cm from the hymenal ring;
3. Patients had taken anticholinergic drugs or received behavioral therapy for OAB such as bladder training three months before the enrollment;
4. Patients with a pacemaker implanted;
5. Patients in the acute stage of vaginal inflammation;
6. Patients with malignant tumors;
7. Patients suffering from mental illness and unable to cooperate with treatments;
8. Transabdominal ultrasound indicated that the residual volume of urine in the bladder was > 50 mL;
9. Urination diary indicated that daily water intake was > 2000 mL in average;
10. Patients with nervous system diseases;
11. Patients with massive space-occupying lesions in pelvis cavity and abdominal cavity;
12. patients with a history of urological surgery. Patients meeting any of the exclusion criteria would be excluded.

Pre-treatment evaluation

The same doctor conducted the consultation, gynecological examination, POP-Q examination, and OABSS investigation for both groups. Two other operators were assigned to measure the pelvic floor myoelectric potential for the patients through the Pelvic Floor SEMG Analysis and Biological Feedback Training System (MID A2, Medlander, Nanjing City, China). Four symptoms addressing day-time frequency, night-time frequency, urgency, and urgency incontinence are scored in the Homma OABSS questionnaire (Appendix 1) [17]. The total score is the sum of the four parts.

Randomization

Eligible patients were randomly assigned based on balanced treatment assignments with a computerized randomization allocation sequence via using blocks of 46 opaque, sealed envelopes to include the information of the treatments of NMES with different pulse width (300 μs or 200 μs) and divided into two groups. Both the patients and the physician in the pre-treatment evaluation were blind to the treatments.

Treatments of NMES

Neuromuscular stimulation Therapy Systems (MID B6, Medlander, Nanjing City, China) was applied in the treatment by two designated operators. With the patient in supine position, an electrode is placed into the vagina (the electrode is placed completely within the hymenal ring). Group A received the treatments with the frequency of 5Hz, pulse width of 300 μs, rampe time of 0 second and the duration of 30 minutes. Group B received the treatments with the frequency

of 5Hz, pulse width of 200 μs, rampe time of 0 second, the duration of 30 minutes. The treatments were performed in both groups once every 2–3 days for a total of 10 times. The therapeutic magnitude of the current is determined by the patients' feeling of strong muscle contraction or tingling without pain. The maximum safe current was 100 mA.

Post-treatment evaluation

Two of the same operators in the pre-treatment evaluation were assigned to measure the pelvic floor myoelectric potential with the Pelvic Floor SEMG Analysis and Biological Feedback Training System (MID A2, Medlander, Nanjing City, China) and finish the OABSS questionnaire for the second time within two days after all the treatments performed for the patients.

Statistical analysis

The software of EpiData 3.1 was used to input research data and SPSS 32.0 was used for statistical analysis. The quantitative variables within each group were described using means, medians and standard deviations. In addition, the Shapiro-Wilk normality test was applied. For variables with normal distribution in the two groups, Student's t-test was used to compare between the groups; otherwise, the Mann-Whitney test was used. For paired data in the pre- and post- treatment with normal distribution, paired t-test was used; otherwise, Wilcoxon signed rank test was used. The qualitative variables were described with frequencies and percentages and analyzed with Chi-square test. All tests were two sided, and p-values < 0.05 were considered statistically different. According to the principle of intent-to-treat analysis (ITT), all the subjects were included in the statistical analysis, whether they received all treatments or not.

RESULTS

Study design

There were 46 patients eligible for the study and randomly divided into two groups, 23 patients for each group. Group A received treatment of NMES by pulse width of 300 μs, and Group B received treatment of NMES by pulse width of 200 μs. respectively. A total of five patients (1 from Group A and 4 form Group B) did not complete all the treatments and withdrew from the study, among which three patients (1 from Group A and 2 from Group B) were not able to reach the outpatient department during the scheduled time, one patient (from Group B) was hospitalized for lung infection, one patient (from Group B) had impaired glucose tolerance (IGT) during the treatments. Finally, 22 patients of Group A and 19 patients of Group B completed all the treatments. The five patients who withdrew from the study also finished post-treatment evaluation within the scheduled time.

During the treatments of NMES, there were three patients (2 from Group A and 1 from Group B) suffered from slight abdominal pain, which disappeared spontaneously 1–3 days later; there was another one patient (from Group A) suffered from increased vaginal secretions, which was confirmed to have bacterial vaginosis later by laboratory tests and recovered after treated with oral metronidazole for one week. All four patients continued the original treatments after the symptoms disappeared. There were no other complaints from the patients.

According to the principle of ITT analysis, all the 46 patients were analyzed statistically, as shown in Figure 1.

Comparison of the baseline between Group A and Group B

As shown in Table 1, there was no significant difference in baseline between Group A and Group B, including age ($U = 211.000$, $p = 0.237$), BMI ($t = 0.377$, $p = 0.708$), delivery times ($U = 253.000$, $p = 0.713$), cesarean section rate, and forceps delivery rate ($U = 1.095$, $p = 0.295$).

Comparison of the indicators before and after the treatments of NMES by pulse width of 300 μs in Group A

As shown in Table 2, in Group A, OABSS ($Z = -4.221$, $p < 0.001$) and mean myoelectric potential at pre-resting state ($Z = -4.198$, $p < 0.001$) were significantly decreased after the treatments of NMES by pulse width of 300 μs in comparison with those before the treatments. The myoelectric potential of Type I muscle fibers ($Z = -3.407$, $p = 0.001$) and the maximum myoelectric potential of Type II muscle fibers ($t = -4.577$, $p < 0.001$) were significantly increased after the treatments of NMES in comparison with those before the treatments.

Comparison of the indicators before and after the treatments of neuromuscular electrical stimulation by pulse width of 200 μs in Group B

As shown in Table 3, in Group B, OABSS ($Z = -4.217$, $p < 0.001$) and mean myoelectric potential at pre-resting state ($Z = -4.198$, $p < 0.001$) were significantly decreased after the treatments of NMES by pulse width of 200 μs in comparison with those before the treatments. However, mean myoelectric potential of Type I muscle fibers ($Z = -0.396$, $p = 0.692$) and the maximum myoelectric potential of Type II muscle fibers ($t = 0.107$, $p = 0.915$) were both not significantly different after the treatments of NMES in comparison with those before the treatments.

Comparison of the differences of the indicators before and after the treatments of NMES with different pulse widths between Group A and Group B.

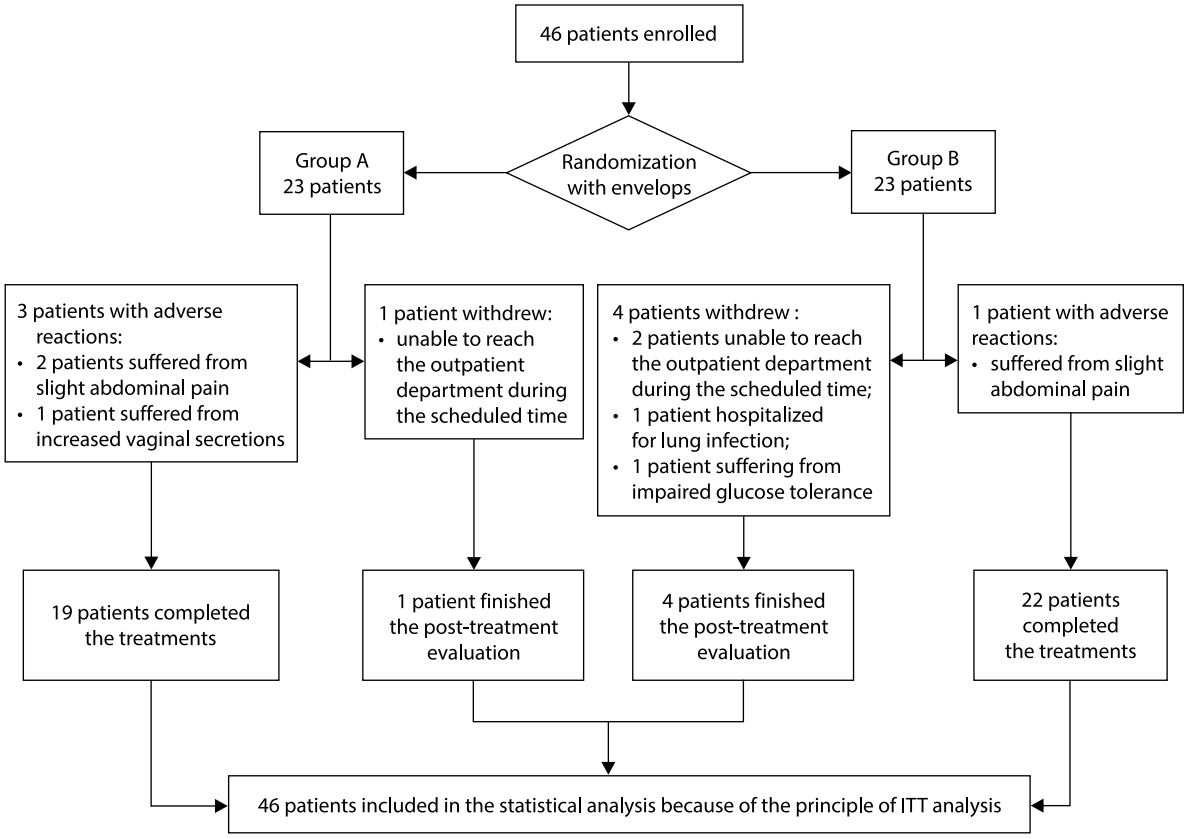


Figure 1. Flow diagram

Table 1. Comparison of the baseline between Group A and Group B

Baseline	Group A	Group B	U	p-value
No.	23	23	–	–
Age [years old]	57 (55.58)	56 (54.58)	211.000[&]	0.237
BMI [kg/m^2]	24.34 ± 2.46	24.08 ± 2.37	0.377[*]	0.708
Delivery times	1 (1.1)	1 (1.1)	253.000[&]	0.713
Cesarean section rate (%)	7/23	7/23	–	–
Forceps delivery rate (%)	3/23	1/23	1.095[#]	0.295

BMI — body mass index; *referred to student's t test; [#]referred to chi-square test; [&]referred to Mann-Whitney U

Table 2. Comparison of the indicators before and after the treatments of neuromuscular electrical stimulation by pulse width of 300 μs in Group A

Indicators	Pre-treatment	Post-treatment	Z	p-value
OABSS	8 (7, 9)	2 (1, 4)	–4.221[&]	< 0.001
mean myoelectric potential at pre-resting state [μv]	4.45 (2.06, 6.88)	1.10 (0.80, 2.00)	–4.198[&]	< 0.001
Mean myoelectric potential of Type I muscle fibers (slow-twitch) [μv]	13.12 (11.23, 18.66)	25.02 (22.37, 27.95)	–3.407[&]	0.001
Maximum myoelectric potential of Type II muscle fibers (fast-twitch) [μv]	25.48 ± 13.81	34.25 ± 13.00	–4.577[*]	< 0.001

OABSS — overactive bladder symptom score; *referred to paired t test; [&]referred to Wilcoxon rank-sum test

Table 3. Comparison of the indicators before and after the treatments of neuromuscular electrical stimulation in Group B

Indicators	Pre-treatment	Post-treatment	Z	p-value
OABSS	9 (6, 10)	5 (2, 6)	–4.217[&]	< 0.001
mean myoelectric potential at pre-resting state [μv]	3.03 (2.18, 5.12)	1.57 (1.20, 2.29)	–4.198[&]	< 0.001
Mean myoelectric potential of Type I muscle fibers (slow-twitch) [μv]	13.40 (10.27, 20.83)	13.14 (10.34, 21.72)	–0.396[&]	0.692
Maximum myoelectric potential of Type II muscle fibers (fast-twitch) [μv]	25.99 ± 10.07	25.91 ± 10.84	0.107[*]	0.915

OABSS — overactive bladder symptom score; *referred to paired t test; [&]referred to Wilcoxon rank-sum test

Table 4. Comparison of the differences of the indicators before the treatments of neuromuscular electrical stimulation with different pulse widths between Group A and Group B

Indicators	Group A	Group B	U	p-value
OABSS	8 (7, 9)	9 (6, 10)	246.500[&]	0.689
mean myoelectric potential at pre-resting state [μv]	4.45 (2.06, 6.88)	3.03 (2.18, 5.12)	232.500[&]	0.482
Mean myoelectric potential of Type I muscle fibers(slow-twitch) [μv]	13.12 (11.23, 18.66)	13.40 (10.27, 20.83)	255.000[&]	0.835
Maximum myoelectric potential of Type II muscle fibers (fast-twitch) [μv]	25.48 ± 13.81	25.99 ± 10.07	–0.143[*]	0.887

OABSS — overactive bladder symptom score; *referred to student's t test; [&]referred to Mann-Whitney U

As shown in Table 4, before the treatments of NMES, OABSS (U = 246.500, p = 0.689), mean myoelectric potential at pre-resting state (U = 232.500, p = 0.482), mean myoelectric potential of Type I muscle fibers (U = 255.000, p = 0.835) and the maximum myoelectric potential of Type II muscle fiber (t = –0.143, p = 0.887) had no significant difference between Group A and Group B.

After the treatments of NMES, OABSS (U = 142.000, p = 0.006) in Group A (treated by pulse width of 300 μs) was significantly lower than that in Group B (treated by pulse width of 200 μs). Mean myoelectric potential at pre-resting state (U = 190.000, p = 0.101) was not significantly different between the two groups after the treatments of NMES with different pulse widths. Mean myoelectric potential of Type I muscle fibers (U = 64.000, p < 0.001) and the maximum myoelectric potential of Type II muscle fibers (t = 2.363, p = 0.023) in Group A (treated by pulse width of 300 μs) were both significantly higher than those in Group B (treated by pulse width of 200 μs), as shown in Table 5.

We also compare the differences of the indicators before and after the treatments of NMES in Group A (treated by pulse width of 300 μs) and Group B (treated by pulse width of 200 μs). As shown in Table 6, the difference of OABSS before and after the treatments of NMES in Group A were significantly greater than that in Group B (t = –3.506, p = 0.001). The differences of mean myoelectric potential at pre-resting state before and after the treatments of NMES were not significantly different between the two groups (U = 184.000, p = 0.077). The differences of myoelectric potential of Type I muscle fibers (U = 80.000, p < 0.001) and the maximum myoelectric potential of Type II muscle fibers (t = 5.256, p < 0.001) were both significantly greater in Group A than those in Group B.

DISCUSSION

In the treatments of NMES, mean myoelectric potential at pre-resting state is positively correlated with the spasm of pelvic floor muscles, which has been confirmed to be the main cause of OAB [18]. Mean myoelectric potential of Type I muscle fibers and the maximum myoelectric potential of Type II muscle fibers, as the indicators for the functions of the pelvic floor muscles, are both associated with urinary continence. Our study found that after being treated with NEMS by different pulse widths, both Group A (treated by pulse width of 300 μs) and Group B (treated by pulse width of 200 μs) had no significant difference in the mean myoelectric potential at pre-resting state, indicating that the treatments may have been no help in reducing the high tension of pelvic floor muscles. However, after being treated with NEMS by different pulse widths, myoelectric potential of Type I muscle fiber and the maximum myoelectric potential of Type II muscle fibers were significantly increased than prior to the treatment of NEMS in the two groups, respectively. And when compared the two groups having been treated with NEMS by different pulse widths, we found that myoelectric potential of Type I muscle fiber and the maximum myoelectric potential of Type II muscle fibers in group A (treated by pulse width of 300 μs) were increased much higher than those in Group B (treated by pulse width of 200 μs). In addition, after the treatments of NMES by different pulse widths, OABSS were significantly reduced than before the treatment of NEMS in the two

Table 5. Comparison of the differences of the indicators after the treatments of neuromuscular electrical stimulation with different pulse widths between Group A and Group B

Indicators	Group A	Group B	U	P-value
OABSS	2 (1, 4)	5 (2, 6)	142.000[&]	0.006
Mean myoelectric potential at pre-resting state [μv]	1.10 (0.80, 2.00)	1.57 (1.20, 2.29)	190.000[&]	0.101
Mean myoelectric potential of Type I muscle fibers(slow-twitch) [μv]	25.02 (22.37, 27.95)	13.14 (10.34, 21.72)	64.000[&]	< 0.001
Maximum myoelectric potential of Type II muscle fibers (fast-twitch) [μv]	34.25 ± 13.00	25.91 ± 10.84	2.363[*]	0.023

OABSS — overactive bladder symptom score; *referred to student's t test; [&]referred to Mann-Whitney U

Table 6. Comparison of the differences of the indicators before and after the treatments of neuromuscular electrical stimulation with different pulse widths between Group A and Group B

Indicators	Group A	Group B	U	p-value
OABSS	–5.61 ± 1.95	–3.83 ± 1.47	–3.506[*]	0.001
Mean myoelectric potential at pre-resting state [μv]	–3.45 (–5.30, –1.23)	–0.88 (–2.52, –0.61)	184.000[&]	0.077
Mean myoelectric potential of Type I muscle fibers (slow-twitch) [μv]	10.45 (2.51, 15.58)	–0.17 (–0.56, 0.85)	80.000[&]	< 0.001
Maximum myoelectric potential of Type II muscle fibers (fast-twitch) [μv]	9.71 ± 8.13	–0.08 ± 3.73	5.256[*]	< 0.001

OABSS — overactive bladder symptom score; *referred to student's t test; [&]referred to Mann-Whitney U

groups, respectively. And when compared the two groups treated with NEMS by different pulse widths, we found that OABSS in group A (treated by pulse width of 300 μs) were decreased greater than those in Group B (treated by pulse width of 200 μs), indicating that the patients treated with NEMS by pulse width of 300 μs can improve the ability of urinary continence more effectively than patients treated with NEMS by pulse width of 200 μs.

Mechanisms of NMES for OAB

OAB is composed by the symptoms of frequent, urgent urination or urge incontinence. Clinically, the etiology of OAB still keep unclear. According to the different pathogenesis, OAB can be divided into three categories: detrusor instability, detrusor hyperreflexia, and bladder hypersensitivity, i.e., the initial urine volume of the bladder is less than 100 mL. The pathophysiological changes of OAB include occulted neurogenic bladder, undetected bladder outlet obstruction, urethral-related bladder obstruction, senile urinary epithelial dysfunction, chronic bladder ischemia, chronic bladder inflammation, central sensitization, and autonomic nerve dysfunction [19]. Low-frequency electrical stimulation can increase blood supply of the muscle and its nerve, eliminate fatigue and hypoxia, inhibit excessive nerve sensitivity and reduce muscle hypertonic, so as to improve the symptoms of OAB. In a study of percutaneous electrical stimulation in the anesthetized cats, 30 minutes of electrical stimulation produced long-term post-stimulatory inhibition, and bladder volume increased significantly after treatment, reaching up to 140.5 ± 7.6% of the control. In the post-treatment period, the time of bladder contraction was significantly prolonged, reaching up to 200% of the control [20].

Analysis for the therapeutic differences with NMES treatments

With low-frequency pulse current, NMES is able to make alpha-motor unit action potentials (MUAP) in peripheral nerves, which rapidly reach the threshold. As a result, more muscle fibers can participate in the contraction, strengthen the muscle and restore the body's motor function [21]. NMES may improve muscle strength by acting on microRNa-486/PTEN/FoxO1 pathway and reducing muscle atrophy furtherly [22]. Other studies have shown that NMES could effectively increase the thickness of skeletal muscle [23] and increase muscle strength [24]. Type I muscle fibers accounts for 68–90% of deep pelvic floor muscles, characterized by tetanic contraction and relative indefatigability, whose role is to maintain the basic functions at resting state of the pelvic floor. Type II muscle fibers are mainly distributed in superficial pelvic floor muscles, characterized by periodic and quick contraction and fatigability, whose role is to cope with the exploding force from the outside. Regarding the electrophysiological characteristics of different types of muscle fibers, the pulse width of electrical stimulation should be different too.

In this study, the treatment of NMES for Group A had an analgesic effect with the release of immunoreactive β-endorphin into the cerebrospinal fluid (1–10 Hz, 300 μs, R = 0, the maximum current) [25], closer to electrophysiological characteristics of Type I muscle fibers, which could relax the muscles from the spasm, improve blood supply

of the muscle and its nerve, and had analgesia effect. Apart from improving the pelvic floor muscle strength, its main advantage lied in the therapeutic effect for urge incontinence with effectively reducing OABSS [13]. On the other hand, the treatment of NMES for Group B was a kind of analgesic treatment as well, but it was closer to electrophysiological characteristics of Type II muscle fibers with lower pulse width [26]. In conclusion, Type I muscle fibers have been playing a more important role in maintaining the stability of pelvic floor functions.

In this study, it was found that the patients having been treated with NEMS by pulse width of 300 μs had more advantages than those patients having been treated with NEMS by pulse width of 200 μs in reducing OABSS and increasing myoelectric potential of pelvic floor muscle fibers. The mechanism may be that 300μs was more suitable for OAB patients with long-term high tension, spasm and ischemia of pelvic floor muscle fibers. Therefore, the treatments of NMES should be determined according to the individual situation of the pelvic floor muscle fibers.

OABSS in China

OABSS has been recommended by ICS for evaluating the symptoms of OAB. OABSS was reported by Homma for the first time in 2006 in Japan. Nowadays, it has been adopted in many foreign clinical researches [17, 27] and validated in China as well [28]. It is a self-report questionnaire, creating a single score for all the symptoms — OAB symptom score (OABSS), to quantify the OAB symptoms and evaluate its severity. In this study, after the treatments of NMES, OABSS in Group A and Group B were both significantly reduced, indicating that NEMS may be effective for OAB.

Comparison of different treatments for OAB

The treatments for OAB in clinical practice mainly include behavior therapy (lifestyle changes, PFMT, biological feedback, etc.), drug therapy (Anticholinergic drugs, beta-3 adrenal agonists, estrogen, etc.) [29], sacral neuromodulation, et al. However, these treatments have been existed with insurmountable limitations in clinical application currently [24].

As the first-line treatment, behavior therapy could effectively improve the adherence of the OAB patients. It is usually recommended to use before or with the drugs. Lifestyle changes, such as reasonable and effective liquid management, avoiding caffeine and soft drinks, reducing fluid intake before sleep, maintaining defecate unobstructed, keeping a healthy weight and stopping smoking, can all improve the symptoms of OAB [30].

Drug therapy is the second-line treatment recommended by ICS. M cholinergic receptor blockers, by competitive inhibiting the acetylcholine in the smooth muscle of bladder and postganglionic cholinergic receptor binding sites, has been used in clinical practice for many years with its effectiveness widely confirmed. Unfortunately, about 80% of the patients had adverse effects of dry mouth. Up to 83% of the patients have stopped using the drug because of intolerance [31]. At present, the most widely studied beta-3 adrenergic agonists have been Mirabelone and Sorabelone. However, drug treatments of OAB cannot increase pelvic floor muscle strength, leaving limitations in treating comprehensive urinary incontinence or pelvic floor dysfunctions combined with the weakened pelvic floor muscle strength.

Sacral nerve stimulation (SNS) is a third-line treatment recommended by ICS. It implants an electrode in the S3 sacral foramen, which is connected to an internal pulse generator under the skin. The internal pulse generator emits pulses to release electric energy from the electrode, thereby stimulating the sacral and pudendal nerves, inhibiting the detrusor contraction and relieving the patient's symptoms. However, due to its high cost and invasion, it is only applicable to patients with severe emergent incontinence who cannot tolerate non-invasive treatments [32].

In the 1860s, Cadwell et al., began to study transvaginal electrical stimulation [33]. Subsequently, it has been proven to achieve therapeutic effects by stimulating the perineal nerve at frequencies below 12 Hz, to inhibit the detrusor muscle, regulate its involuntary contraction and reduce urination times [34]. Electrical stimulation has also been working in a passive way to help OAB patients be aware of their perineal (pelvic floor) muscle contractions, which may in turn help suppress involuntary detrusor contractions [35]. The advantage of NMES in clinical application lies in non-invasion and definite effectiveness. However, the OAB patients still have difficulty complying with the schedule of the outpatient department. Portable electrical stimulation devices that can be used at home may become popular in the future.

Limitations

In this study, the two groups of patients were not double-blind to the treatment. Fortunately, BMI, age, delivery times, OABSS and pelvic floor muscle strength between the two groups were not significantly different before the treatments, making the results of post treatment valuable. In further studies, randomized, double-blind, controlled trials should be designed to validate the therapeutic effectiveness of different treatments of NMES, and to further explore whether it's short-term or long-term effective.

CONCLUSIONS

In conclusion, OAB is a common disease that seriously affects the life quality of postmenopausal elderly women. At present, it has been a hot issue in clinical practice to

effectively improve OAB symptoms individually and comprehensively and improve the pelvic floor functions for the patients at the same time. Comparing the indicators before and after the treatments of NMES, our study has preliminarily confirmed that NMES has its advantages in treating with OAB, to improve the life quality of the patients.

Acknowledgements

We are grateful to Professor Shaowei Wang from Beijing Hospital for his theoretical guidance during the implementation of this research.

Funding

The study was financed from authors own funds.

Availability of data and materials

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

Authors' contributions

Aiming Lv designed the research, analyzed and interpreted the research data, and wrote the manuscript. Tianzi Gai, Qing Feng, Min Li, and Wenhui Deng collected the research data. Qiubo lv designed the study and guiding the writing of the manuscript.

Ethics approval and consent to participate

The present study was approved by the Ethics Committee of Beijing Hospital. Informed consent was obtained from all patients.

Patient consent for publication

Informed consent was obtained from all patients.

Conflict of interests

The authors declare that they have no competing interests. The institution does not develop products with relevant information, apply for patents, and does not provide experimental funds. The institution does not interfere with the decision to publish and share relevant research results in journals.

Supporting information

CONSORT Checklist S1 Completed "CONSORT 2010 checklist of information" to include when reporting a randomized trial in this manuscript.

Chinese Clinical Trial Registry Registration number: ChiCTR2000039585

REFERENCES

1. Haylen BT, de Ridder D, Freeman RM, et al. International Urogynecological Association, International Continence Society. An International Urogynecological Association (IUGA)/International Continence Society (ICS) joint report on the terminology for female pelvic floor dysfunction. Neurourol Urodyn. 2010; 29(1): 4–20, doi: 10.1002/nau.20798, indexed in Pubmed: 19941278.
2. Wang Y, Xu K, Hu H, et al. Prevalence, risk factors, and impact on health related quality of life of overactive bladder in China. Neurourol Urodyn. 2011; 30(8): 1448–1455, doi: 10.1002/nau.21072, indexed in Pubmed: 21826714.
3. Stewart WF, Van Rooyen JB, Cundiff GW, et al. Prevalence and burden of overactive bladder in the United States. World J Urol. 2003; 20(6): 327––336, doi: 10.1007/s00345-002-0301-4, indexed in Pubmed: 12811491.
4. Robinson D, Cardozo L, Milsom I, et al. Oestrogens and overactive bladder. Neurourol Urodyn. 2014; 33(7): 1086–1091, doi: 10.1002/nau.22464, indexed in Pubmed: 23868110.
5. Yi J, Tenfelde S, Tell D, et al. Triathlete Risk of Pelvic Floor Disorders, Pelvic Girdle Pain, and Female Athlete Triad. Female Pelvic Med Reconstr Surg. 2016; 22(5): 373–376, doi: 10.1097/SPV.0000000000000296, indexed in Pubmed: 27403753.
6. Khan AA, Eilber KS, Clemens JQ, et al. Trends in management of pelvic organ prolapse among female Medicare beneficiaries. Am J Obstet Gynecol. 2015; 212(4): 463.e1–463.e8, doi: 10.1016/j.ajog.2014.10.025, indexed in Pubmed: 25446663.
7. Brueseke TJ, Wilkins MF, Willis-Gray MG, et al. Lifetime risk of surgery for stress urinary incontinence or pelvic organ prolapse. Minerva Ginecol. 2017; 69(2): 171–177, doi: 10.23736/S0026-4784.16.04011-9, indexed in Pubmed: 28001022.
8. Malde S, Kelly S, Saad S, et al. Case-finding tools for the diagnosis of OAB in women: A narrative review. Neurourol Urodyn. 2020; 39(1): 13–24, doi: 10.1002/nau.24171, indexed in Pubmed: 31578764.
9. Wallace SA, Roe B, Williams K, et al. Bladder training for urinary incontinence in adults. Cochrane Database Syst Rev. 2004(1): CD001308, doi: 10.1002/14651858.CD001308.pub2, indexed in Pubmed: 14973967.
10. Wein A. Commentary RE: The standardisation of terminology in lower urinary tract function: report from the standardisation sub-committee of the International Continence Society. Urology. 2020; 145: 310–311, doi: 10.1016/j.urology.2020.04.064, indexed in Pubmed: 32333987.
11. Hay-Smith J, Herbison P, Ellis G, et al. Which anticholinergic drug for overactive bladder symptoms in adults. Cochrane Database Syst Rev. 2005(3): CD005429, doi: 10.1002/14651858.CD005429, indexed in Pubmed: 16034974.
12. D'Souza AO, Smith MJ, Miller LA, et al. Persistence, adherence, and switch rates among extended-release and immediate-release overactive bladder medications in a regional managed care plan. J Manag Care Pharm. 2008; 14(3): 291–301, doi: 10.18553/jmcp.2008.14.3.291, indexed in Pubmed: 18439051.
13. Lúcio A, D'ancona CA, Perissinotto MC, et al. Pelvic floor muscle training with and without electrical stimulation in the treatment of lower urinary tract symptoms in women with multiple sclerosis. J Wound Ostomy Continence Nurs. 2016; 43(4): 414–419, doi: 10.1097/WON.0000000000000223, indexed in Pubmed: 27014935.
14. Jundt K, Peschers U, Kentenich H. The investigation and treatment of female pelvic floor dysfunction. Dtsch Arztebl Int. 2015; 112(33-34): 564–574, doi: 10.3238/arztebl.2015.0564, indexed in Pubmed: 26356560.
15. Candy B, Jones L, Vickerstaff V, et al. Interventions for sexual dysfunction following treatments for cancer in women. Cochrane Database Syst Rev. 2016; 2: CD005540, doi: 10.1002/14651858.CD005540.pub3, indexed in Pubmed: 26830050.
16. Silva VR, Riccetto CL, Martinho NM, et al. Training through gametherapy promotes coactivation of the pelvic floor and abdominal muscles in young women, nulliparous and continents. Int Braz J Urol. 2016; 42(4): 779–786, doi: 10.1590/S1677-5538.IBJU.2014.0580, indexed in Pubmed: 27564290.
17. Homma Y, Yoshida M, Seki N, et al. Symptom assessment tool for overactive bladder syndrome--overactive bladder symptom score. Urology. 2006; 68(2): 318–323, doi: 10.1016/j.urology.2006.02.042, indexed in Pubmed: 16904444.
18. Robinson AJ, Snyder-Mackler L. Clinical electrophysiology: electrotherapy and electrophysiologic testing, third edition. Lippincott Williams & Wilkins, Philadelphia 1997.

19. Chen LC, Kuo HC, Chen LC, et al. Pathophysiology of refractory overactive bladder. Low Urin Tract Symptoms. 2019; 11(4): 177–181, doi: 10.1111/luts.12262, indexed in Pubmed: 30900373.
20. Yu M, Uy J, Jiang X, et al. An excitatory reflex from the superficial peroneal nerve to the bladder in cats. Am J Physiol Renal Physiol. 2017; 313(5): F1161–F1168, doi: 10.1152/ajprenal.00265.2017, indexed in Pubmed: 28855188.
21. Dumitru D, King JC, Zwarts MJ. Determinants of motor unit action potential duration. Clin Neurophysiol. 1999; 110(11): 1876–1882, doi: 10.1016/s1388-2457(99)00142-x, indexed in Pubmed: 10576482.
22. Shen J, Nie X, Huang SY, et al. Neuromuscular electrical stimulation improves muscle atrophy induced by chronic hypoxia-hypercapnia through the MicroRNA-486/PTEN/FoxO1 pathway. Biochem Biophys Res Commun. 2019; 509(4): 1021–1027, doi: 10.1016/j.bbrc.2018.12.147, indexed in Pubmed: 30654931.
23. Qiu S, Feng J, Xu J, et al. Sonomyography analysis on thickness of skeletal muscle during dynamic contraction induced by neuromuscular electrical stimulation: a pilot study. IEEE Trans Neural Syst Rehabil Eng. 2017; 25(1): 59–67, doi: 10.1109/TNSRE.2016.2556687, indexed in Pubmed: 28141512.
24. Bochkezanian V, Newton RU, Trajano GS, et al. Effect of tendon vibration during wide-pulse neuromuscular electrical stimulation (NMES) on muscle force production in people with spinal cord injury (SCI). BMC Neurol. 2018; 18(1): 17, doi: 10.1186/s12883-018-1020-9, indexed in Pubmed: 29433467.
25. Han JS. Acupuncture: neuropeptide release produced by electrical stimulation of different frequencies. Trends Neurosci. 2003; 26(1): 17–22, doi: 10.1016/s0166-2236(02)00006-1, indexed in Pubmed: 12495858.
26. Eriksen BC. Electrostimulation of the pelvic floor in female urinary incontinence. Acta Obstet Gynecol Scand. 1990; 69(4): 359–360, doi: 10.3109/00016349009036164, indexed in Pubmed: 2244472.
27. Okui N, Okui M, Horie S. Improvements in overactive bladder syndrome after polypropylene mesh surgery for cystocele. Aust N Z J Obstet Gynaecol. 2009; 49(2): 226–231, doi: 10.1111/j.1479-828X.2009.00965.x, indexed in Pubmed: 19432617.
28. Chou ECL, Hung MJ, Yen TW, et al. The translation and validation of Chinese overactive bladder symptom score for assessing overactive bladder syndrome and response to solifenacin treatment. J Formos Med Assoc. 2014; 113(8): 506–512, doi: 10.1016/j.jfma.2012.07.044, indexed in Pubmed: 25037757.
29. Jiang F, Zhu L, Xu T, et al. Efficacy and safety of solifenacin succinate tablets versus solifenacin succinate tablets with local estrogen for the treatment of overactive bladder in postmenopausal women--a multicenter, randomized, open-label, controlled comparison study. Menopause. 2016; 23(4): 451–457, doi: 10.1097/GME.0000000000000574, indexed in Pubmed: 26757270.
30. Lightner DJ, Gomelsky A, Souter L, et al. Diagnosis and Treatment of Overactive Bladder (Non-Neurogenic) in Adults: AUA/SUFU Guideline Amendment 2019. J Urol. 2019; 202(3): 558–563, doi: 10.1097/JU.0000000000000309, indexed in Pubmed: 31039103.
31. Choi H, Bae JH, Oh CY, et al. Clinical efficacy of solifenacin in the management of diabetes mellitus-associated versus idiopathic overactive bladder symptoms: a multicenter prospective study. Int Neurourol J. 2018; 22(1): 51–57, doi: 10.5213/inj.1834982.491, indexed in Pubmed: 29609421.
32. Noblett K, Siegel S, Mangel J, et al. Results of a prospective, multicenter study evaluating quality of life, safety, and efficacy of sacral neuromodulation at twelve months in subjects with symptoms of overactive bladder. Neurourol Urodyn. 2016; 35(2): 246–251, doi: 10.1002/nau.22707, indexed in Pubmed: 25546568.
33. CALDWELL KP. The electrical control of sphincter incompetence. Lancet. 1963; 2(7300): 174–175, doi: 10.1016/s0140-6736(63)92807-1, indexed in Pubmed: 14017856.
34. Messelink EJ. The overactive bladder and the role of the pelvic floor muscles. BJU Int. 1999; 83 Suppl 2: 31–35, doi: 10.1046/j.1464-410x.83.s2.7.x, indexed in Pubmed: 10210602.
35. Amaro JL, Gameiro MO, Kawano PR, et al. Intravaginal electrical stimulation: a randomized, double-blind study on the treatment of mixed urinary incontinence. Acta Obstet Gynecol Scand. 2006; 85(5): 619–622, doi: 10.1080/00016340500495058, indexed in Pubmed: 16752244.

Appendix 1. Overactive bladder symptom score (OABSS)

Item	Symptom	Frequency/times	Standardized score	Score
1. Day frequency	How many times of urination from getting up in the morning to going to sleep at night?	≤ 7	0	
		8–14	1	
		≥ 15	2	
2. Night-time frequency	How many times of urination from going to sleep at night to getting up in the morning?	0	0	
		1	1	
		2	2	
		≥ 3	3	
3. Urgency	Is there a sudden urge to urinate and an unbearable sensation occurring at the same time?	None	0	
		< 1 time per week	1	
		≥ 1 time per week	2	
		= 1 time per day	3	
		2–4 times per day	4	
		≥ 5 times per day	5	
4. Urgency incontinence	Is there a sudden urge to urinate and an intolerable incontinence?	None	0	
		< 1 time per week	1	
		≥ 1 time per week	2	
		= 1 time per day	3	
		2–4 times per day	4	
		≥ 5 times per day	5	
Total score:				

VIA MEDICA

ORIGINAL PAPER / OBSTETRICS

Ginekologia Polska
2022, vol. 93, no. 8, 629–636

ISSN 0017–0011, e-ISSN 2543–6767

DOI 10.5603/GP.a2022.0066

Risk factors associated with neonatal infectious and respiratory morbidity following preterm premature rupture of membranes

Joanna Kacperczyk-Bartnik[1], Pawel Bartnik[1], Justyna Teliga-Czajkowska[2], Aneta Malinowska-Polubiec[1], Agnieszka Dobrowolska-Redo[1], Ewa Romejko-Wolniewicz[1], Janusz Sierdzinski[3], Ksawery Golawski[4], Krzysztof Czajkowski[1]

[1]2nd Department of Obstetrics and Gynecology, Medical University of Warsaw, Poland
[2]Department of Obstetrics and Gynecology Didactics, Medical University of Warsaw, Poland
[3]Department of Medical Informatics and Telemedicine, Medical University of Warsaw, Poland
[4]Students' Scientific Group affiliated to II Department of Obstetrics and Gynecology, Medical University of Warsaw, Poland

ABSTRACT

Objectives: Preterm premature rupture of membranes (pPROM) is associated with the increased risk of chorioamnionitis, foetal exposure to inflammation, and respiratory complications in preterm neonates. The aim of the study was to identify patients at highest risk of developing neonatal infectious and respiratory morbidity following pPROM and preterm birth.

Material and methods: It was a retrospective cohort study including 299 consecutive patients in singleton pregnancies complicated by preterm premature rupture of membranes and giving birth between 22nd and 36th gestational week. Analysed factors included maternal characteristics, obstetric history, gestational age at pPROM and at delivery, latency and management. Multivariate logistic regression models were applied in order to identify risk factors for severe infectious and respiratory neonatal complications.

Results: Earlier gestational age at pPROM is associated with increased probability of developing early-onset neonatal sepsis and pulmonary hypertension. Earlier gestational age at birth and lower birth weight were independent factors associated with neonatal respiratory distress syndrome. Positive cervical culture was identified as a risk factor for acute neonatal respiratory failure.

Conclusions: Gestational age at pPROM, gestational age at birth and birth weight were the leading factors influencing the risk of developing neonatal infectious and respiratory morbidity following preterm premature rupture of membranes.

Key words: bronchopulmonary dysplasia; neonatal sepsis; pprom; premature birth; respiratory distress syndrome; respiratory insufficiency; transient tachypnea of the newborn

Ginekologia Polska 2022; 93, 8: 629–636

INTRODUCTION

Preterm premature rupture of membranes (pPROM) is associated with the increased risk of chorioamnionitis and foetal exposure to inflammation [1]. Available data shows that inflammatory intrauterine environment could have long-term effects including impact on the incidence of respiratory morbidity and cardiovascular system condition through impaired endothelial function [2–6].

There is an association between infectious and respiratory complications in preterm neonates. Neonatal infection is a documented risk factor for developing long-term respiratory morbidity including bronchopulmonary dysplasia [7–9].

At the same time, premature birth remains the most common independent risk factor for neonatal mortality and morbidity worldwide [10, 11]. Therefore, during the

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

Received: 7.01.2022 Accepted: 3.06.2022 Early publication date: 28.06.2022

management of patients with pPROM, efforts must be made in order to balance between the risk of prematurity complications and the risk of developing intrauterine infection.

Objectives

The aim of the study was to identify subgroups of patients at highest risk of developing neonatal infectious and respiratory complications following preterm premature rupture of membranes and preterm birth in singleton pregnancies.

MATERIAL AND METHODS

It was a retrospective cohort study performed in a tertiary obstetric referral centre. Study group included consecutive patients in pregnancies complicated by preterm premature rupture of membranes between 12th and 36th gestational weeks giving birth between 22nd and 36th gestational weeks in the time period between October 2016 and December 2018. Exclusion criteria were multiple pregnancy (n = 49), chromosomal and structural foetal abnormalities (n = 23) diagnosed antenatally or after birth, with the majority of structural heart defects and seven cases of fatal defects. During the study period there were 7198 births in our centre, including 755 singleton preterm births, out of which 322 were complicated by preterm premature rupture of membranes. A total of 299 women were enrolled in this analysis.

Preterm premature rupture of membranes was diagnosed based on the speculum examination, assessment of the pH level and the presence of insulin-like growth factor-binding protein 1 in the vaginal discharge. Bacterial culture from cervical canal was collected on admission from every woman. Patients were managed expectantly with strict monitoring of maternal and foetal wellbeing, antenatal corticosteroid therapy, prophylactic empirical antibiotic therapy, and regular assessment of inflammatory markers. Two doses of 12 mg betamethasone were administered after pPROM diagnosis with 24 h interval between completed 23rd and 36th gestational week. In case of latency exceeding 14 days, third dose of 12 mg betamethasone was administered after two weeks. Patients with pregestational diabetes mellitus received four doses of 6 mg betamethasone with 12 h intervals. The prophylactic antimicrobial treatment was established based on local epidemiological data and consisted of intravenous cefuroxime for 10 days. Therapy was adjusted in case of drug allergy or antimicrobial resistance detected in cervical specimen collected on admission. Analysed factors included: maternal characteristics, obstetric history, gestational age at pPROM, results of the cervical bacterial culture, latency, administered antenatal corticosteroid dose and its timing, introduction of tocolysis, delivery mode, gestational age at birth, birth weight, neonatal complications and management. Study endpoints included early-onset neonatal sepsis, pulmonary hypertension, bronchopulmonary dysplasia, acute neonatal respiratory failure, respiratory distress syndrome (RDS), and transient tachypnoea of the newborn.

Latency was counted as time between the rupture of membranes and delivery. Early-onset neonatal sepsis was diagnosed within the first 72 hours after birth based on both clinical symptoms (i.e., bradycardia, apnoea, cyanosis, lethargy) and laboratory findings — white blood cell and absolute neutrophil counts lower and upper normal limits, C-reactive protein with the cut-off value at 10 mg/L [12–14]. Positive neonatal blood culture was not required for the diagnosis as this study included in the analysis all cases of positive-culture sepsis and negative-culture clinical sepsis. Bronchopulmonary dysplasia was diagnosed in neonates requiring oxygen therapy for at least four weeks [15]. Acute neonatal respiratory failure was defined by laboratory criteria with two results from the following: $PaCO2 > 60$ mmHg, $PaO2 < 50$ mmHg or O2 saturation < 80% with an FiO2 of 1.0 and pH < 7.25 in infants requiring assisted ventilation due to acute clinical respiratory insufficiency [16, 17]. The diagnosis of respiratory distress syndrome was based on the clinical presentation of tachypnoea, retractions, expiratory grunting and cyanosis together with typical radiographic bronchogram findings [18]. Transient tachypnoea of the newborn was diagnosed based on presented symptoms, radiographic findings and exclusion of other respiratory morbidities [19]. Pulmonary hypertension was diagnosed during the hospitalization in the neonatal intensive care unit based on echocardiograms showing elevated right ventricle pressure with the estimated pulmonary pressures greater than 50% of the systemic pressure [20].

Statistical analysis was performed with the use of multivariate logistic regression models. Analysed variables included gestational age at birth, gestational age at PROM, latency, use of betamethasone, intravenous tocolysis, positive cervical culture, mode of delivery, sex of the neonate, birth weight, neonatal hypotrophy diagnosed at birth, and 1st minute Apgar score. Gestational age (at birth) stratification was performed by dividing neonates into four analysed subgroups: born before completed 28th gestational week, born between 28th and 31st gestational week, born between 32nd and 33rd gestational week, and born between 34th and 36th gestational week. In case of more than two analysed groups, the Kruskall-Wallis ANOVA analysis was performed as required. Two-tailed $p < 0.05$ was considered significant. SAS software, version 9.4 (SAS Institute, Cary, NC) was used.

The study was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Review Board of the Medical University of Warsaw (protocol code AKBE/16/2018, date of approval 6th February 2018).

RESULTS

Study group included 299 singleton patients with preterm premature rupture of membranes. Maternal characteristics, obstetric history, gestational age at PROM, latency, mode of delivery, gestational age at delivery, birth weight, 1st minute Apgar score and neonatal hospitalization duration are presented in Table 1.

Mean gestational age at birth in the subgroup with latency under 48 hours was 34 weeks and 4 days. In the subgroup with latency between 48 hours and seven days mean gestational age was 32 weeks. Mean gestational age in patients with latency exceeding 7 days was 30 weeks and 5 days. In a post hoc analysis (least square difference test) it was observed that differences in mean gestational age at birth between all three subgroups were significant (Tab. 2).

One hundred and thirty-two (44%) analysed women were primiparous. Bacterial culture from cervical swab was positive in 130 (44%) patients. Identified pathogens were: *E. coli* (n = 43), *S. agalactiae* (n = 39), *C. albicans* (n = 31), *P. bivia* (n = 19), *E. faecalis* (n = 17), *G. vaginalis* (n = 7), *K. pneumoniae* (n = 5), *E. cloacae* (n = 3), *Ureaplasma* (n = 3), *P. melan*ogenica (n = 2), *S. pyogenes* (n = 2), *B fragilis* (n = 1), *B. ovatus* (n = 1), *C crusei* (n = 1), *C glabrata* (n = 1), *C. lusitaniae* (n = 1), *C. freundii* (n = 1), *C. krosei* (n = 1), *H. influenzae* (n = 1), *P. mirabilis* (n = 1). In 200 (67%) patients latency duration was below 48 hours. Intravenous tocolysis was administered

Table 1. Study group characteristics, n = 299

Feature	Mean	SD	Ranges
Maternal age [years]	32.57	5.4	17–47
Feature	Median	Lower and upper quartile	Ranges
Gestational age at PROM [weeks]	35	31; 36	12–36
Latency [h]	17.5	7; 96	0.5–3192
Gestational age at delivery [weeks]	35	32; 36	22–36
Neonatal hospitalization [days]	10	7; 27	1–120
Birth weight [g]	2520	1950; 2880	460–4820
Feature	**n**		**%**
Primigravid	132		44
Cesarean section	145		45
Emergency cesarean section	41		14
Gestational diabetes mellitus	71		24
Pregestational diabetes mellitus	20		7
Pregnancy-induced hypertension	9		3
Pregestational hypertension	15		5
Intrahepatic cholestasis of pregnancy	9		3
Pathological cervical microbiome	130		44
1st min Apgar score 8–10	225		75
1st min Apgar score 4–7	56		19
1st min Apgar score 0–3	10		3

SD — standard deviation; PROM — premature rupture of membranes

Table 2. Mean gestational age at birth in latency subgroups ($p < 0.001$)

Analyzed subgroup	n	Latency duration	Median latency duration [hours]	Lower and upper quartile [hours]	Latency ranges [hours]	Mean gestational age at birth [weeks + days]
I	200 (67%)	Under 48 hours	9	5; 17.75	0.5–48	34 + 4*
II	47 (16%)	Between 48 hours and 7 days	96	72; 144	50–168	32*
III	52 (17%)	Over 7 days	456	288; 768	192–3192	30 + 5*

*Post hoc analysis results for subgroups: significant differences between gestational ages in subgroup I and II $p < 0.001$, I and III $p < 0.001$, and II and III $p < 0.02$

Table 3. Factors associated with neonatal morbidity — results of the multivariate logistic regression

Parameter	Wald Chi-Square	p	OR	CI 95%
Early-onset neonatal sepsis: n = 23; Chi-Square = 24.09; p < 0.0001*				
Gestational age at PROM [weeks]	12.54	**0.0004**	0.85	(0.78; 0.93)
Caesarean delivery	8.35	0.009	5.62	(1.54; 20.43)
Acute respiratory failure: n = 77; Chi-Square = 111.55; p < 0.0001*				
Gestational age at birth 22nd–27th weeks	34.56	< 0.0001	46.35	(12.9; 166.5)
Gestational age at birth 28th–31st weeks	26.7	< 0.0001	10.97	(4.42; 27.2)
Gestational age at birth 32nd –33th weeks	15.41	< 0.0001	6.26	(2.5; 15.63)
Intravenous tocolysis	9.45	0.002	3.12	(1.51; 6.44)
Positive cervical culture	5.86	0.01	2.37	(1.78; 4.75)
Male sex of the neonate	5.86	0.01	2.58	(1.2; 5.54)
Transient tachypnoea: n = 72; Chi-Square = 30.59; p < 0.0001*				
Gestational age at birth 22nd–27th weeks	0.47	0.49	0.63	(0.17; 2.35)
Gestational age at birth 28th–31st weeks	1.32	0.25	1.62	(0.71; 3.7)
Gestational age at birth 32nd –33rd weeks	7.48	0.006	3.16	(1.39; 7.2)
Intravenous tocolysis	8.1	0.004	2.48	(1.33; 4.64)
Male sex of the neonate	4.86	0.03	2.02	(1.08; 3.78)
Respiratory distress syndrome: n = 38; Chi-Square = 102.73; p < 0.0001*				
Gestational age at birth 22nd–33rd weeks	7.74	0.005	11.3	(2.05; 62.39)
Latency between 48 h and 7 days	2.02	0.15	0.37	(0.097; 1.45)
Latency over 7 days	2.84	0.09	2.46	(0.86; 6.99)
Birth weight	9.77	**0.002**	0.999	(0.998; 0.999)
Hypotrophy	4.2	0.04	9.87	(1.1; 88)
Bronchopulmonary dysplasia: n = 20; Chi-Square = 57.75; p < 0.0001*				
Birth weight	24.7	< 0.0001	0.996	(0.995; 0.998)
Use of intravenous tocolysis	6.57	0.01	7.69	(1.62; 36.52)
Pulmonary hypertension: n = 12; Chi-Square = 46.49; p < 0.0001*				
Gestational age at PROM [weeks]	20.55	**< 0.0001**	0.74	(0.69; 0.84)

*Results of the model; OR — odds ratio; CI — confidence interval; PROM — premature rupture of membranes

in 105 (35%) women. One hundred and fifty-six (52%) received two doses of antenatal corticosteroids. Thirty-eight (13%) patients received incomplete antenatal corticosteroids dose because of labour progress. One hundred and thirty-five (45%) women delivered via caesarean section and 41 (14%) had emergency caesarean section. Twenty-four (8%) women were antenatally diagnosed with the onset of intrauterine infection. Sixteen of them (67%) delivered via caesarean section. In this subgroup of patients early-onset neonatal sepsis was more prevalent in children born by a c-section than vaginal birth — 7 (44%) vs 1 (12.5%). This result, however, was not statistically significant because of subgroup size.

Early-onset neonatal sepsis was diagnosed in 23 (7.7%) children. Acute respiratory failure was present in 77 (25.8%) neonates. Thirty-eight (12.7%) newborns were diagnosed with respiratory distress syndrome. Transient tachypnoea of the neonate was present in 72 (24.2%) neonates. Bronchopulmonary dysplasia was detected in 20 (6.7%) infants. Pulmonary hypertension was diagnosed in 12 (4%) children.

Table 3 shows the results of multivariate logistic regression. Earlier gestational age at PROM was associated with increased probability of developing early-onset neonatal sepsis and pulmonary hypertension. Earlier gestational age at birth, lower birth weight and hypotrophy were independent factors associated with the risk of neonatal respiratory distress syndrome. Infants of patients requiring intravenous tocolysis and male neonates were at higher risk of developing acute respiratory failure and transient tachypnoea. Positive cervical culture was identified as a risk factor for acute neonatal respiratory failure.

Table 4 presents differences in the incidence of neonatal mortality and morbidity in different gestational age groups at birth. The highest incidence of acute respiratory failure, respiratory distress syndrome, bronchopulmonary dysplasia, pulmonary hypertension and neonatal mortality was

Table 4. Differences in the incidence of neonatal morbidity and mortality depending on the gestational age at birth: extremely preterm under 28th gestational week, very early preterm between 28th and 31st gestational week, early preterm between 32nd and 33rd gestational week, and late preterm between 34th and 36th gestational week

	Under 28th gestational week (n = 25)	28th–31st gestational week (n = 39)	32nd–33rd gestational week (n = 34)	34th–36th gestational week (n = 201)	p
Early-onset sepsis	4 (16%)	11 (28%)	2 (6%)	6 (3%)	< 0.001
Acute respiratory failure	18 (72%)	25 (64%)	17 (50%)	17 (8%)	< 0.001
Transient tachypnoea	3 (12%)	14 (36%)	18 (53%)	37 (18%)	< 0.001
Respiratory distress syndrome	15 (60%)	15 (38%)	6 (18%)	2 (1%)	< 0.001
Bronchopulmonary dysplasia	12 (48%)	8 (21%)	0	0	< 0.02
Pulmonary hypertension	5 (20%)	6 (15%)	0	1 (0.5%)	< 0.001
Neonatal mortality	5 (20%)	1 (3%)	0	0	< 0.03

observed in the extremely preterm gestational age group, born before completed 28th gestational week.

Mean median latency in the subgroup of neonates born between 22nd and 31st gestational week lasted significantly longer in case of children who developed pulmonary hypertension (n = 11) than in those who did not (n = 51) (552 hours vs 144 hours, p = 0.004). No significant differences in median latency durations were identified regarding the incidence of bronchopulmonary dysplasia, neonatal mortality, use of continuous positive airway pressure, nor use of synchronized intermittent mandatory ventilation in infants born before completed 32nd gestational week.

DISCUSSION

Main findings of our study show that birth weight and gestational age — both during the rupture of membranes and during delivery — are the leading factors associated with the risk of developing neonatal complications in pPROM population. Gestational week at PROM is a non-modifiable factor during patients' admission to the hospital. However, it could be a valuable source of information for the neonatology team about the prognosis and possible required management.

Intrauterine exposure to leakage of the amniotic fluid caused by membranes rupture is not only linked with short-term complications but also increases the risk of respiratory morbidity in later childhood. In a population-based cohort study by Imterat et al. [21] authors analysed whether pPROM was related to the number of hospitalizations for respiratory reasons. During 23 years of observation, it was found that the study group (n = 641) was burdened with higher number of respiratory hospitalizations in comparison to the control group of early preterm deliveries with intact membranes (n = 1954).

One of the partly modifiable characteristics of pPROM patients' management is the duration of amniotic fluid leakage. In the multivariate analysis we have not observed statistically significant association between latency and neonatal morbidity. Mean gestational ages were significantly different in the latency subgroups from our study (Tab. 2) — more than seven days of latency was observed in less advanced pregnancies with mean gestational age at birth of 30 weeks and 5 days. Therefore, gestational age at birth might be the leading factor influencing neonatal respiratory distress syndrome risk in this subgroup.

In a cohort study by Manuck et al. [22] the perinatal outcome of 360 patients with pPROM delivering at median of 31.4 gestational week were examined. The authors hypothesized that the incidence of severe perinatal morbidity would increase with latency duration. However, results of their multivariate models did not show any association between perinatal complications and latency. Higher incidence of severe neonatal morbidity was linked with lower gestational age and congenital sepsis. In a retrospective cohort study examining the outcome of 128 pregnancies with previable preterm premature rupture of membranes, longer latency duration, together with higher birth weight and more advanced gestational age at birth were associated with significantly lower postnatal mortality [23]. In a study by Yan et al. [24] analysing the outcome of 850 patients with pPROM, longer latency duration was a favourable factor for newborns delivered between 28th and 31st gestational week, but it was not beneficial beyond 32 weeks.

In another study examining neonatal outcome in pPROM depending on the latency duration only patients with latency exceeding 48 hours were included in the analysis (n = 206) [25]. The mean latency period in this study was 15.1 days. Authors observed that longer latency period did not contribute to higher neonatal morbidity. Conversely, in the subgroup with pPROM between completed 29th and 32nd gestational week, latency lasting more than 14 days was associated with lower incidence of neonatal complications compared to shorter latency periods (p = 0.001). After completed 32nd gestational week there was no difference

in neonatal complications incidence in latency duration subgroups: 3–7 days, 8–13 days, and 14 or more days. No statistically significant differences in the incidence of neonatal sepsis between the subgroups were identified. Similarly, to our study, latency period decreased with more advanced gestational age. However, in our analysis of the subgroup of neonates born before 32nd gestational week, longer median latency duration was observed in the subgroup of infants who developed pulmonary hypertension. This result was not confirmed in the multivariate analysis.

In a retrospective study on 159 pPROM cases by Jahromi et al. [26] authors presented the association between latency and neonatal respiratory distress syndrome incidence. There was a reverse linear relationship between latency and respiratory distress syndrome during the first 48 hours following the rupture of membranes — a gradual decrease in morbidity from 43% to 19% was observed. After 48 hours of latency the incidence of RDS increased again and reached 40%. Authors link this observation with pulmonary maturation due to antenatal corticosteroid therapy introduced shortly after PROM. However, the optimum time interval between PROM and delivery was not suggested because of big differences in leakage duration exceeding 48 hours. In another retrospective study Niesłuchowska-Hoxha et al. [27] analysed the occurrence of respiratory distress syndrome in 175 singleton pregnancies complicated by pPROM with median latency duration of 19 hours and 48 minutes. In a multivariate logistic regression authors reported association between RDS incidence and gestational age at birth, neonatal haemoglobin level, and neonatal platelet count.

We have observed association between caesarean delivery mode and the incidence of early-onset neonatal sepsis. This could be the consequence of qualifying patients with rapidly increasing inflammatory markers levels and foetal tachycardia for caesarean delivery. Results from our previous study showed that pPROM is associated with higher incidence of vaginal deliveries in comparison to preterm births with intact membranes (55% versus 35%, $p < 0.001$) [28]. It is also reported in the literature that spontaneous preterm labour is associated with higher risk of neonatal sepsis (22.9%) in comparison to patients with prolonged preterm amniotic fluid leakage without developing contractions directly afterwards (15.2%) [1]. However, in the study by Kachikis et al. [1] did not specify which type — early or late-onset sepsis — was analysed [1]. Regarding the association between caesarean delivery and neonatal sepsis, reported results vary and depend on the analysed population. In a retrospective study by Al-Lawama et al. [29] authors analysed sepsis risk factors among patients with rupture of membranes after completed 34th gestational week. Mode of delivery in the 176 analysed patients was not significant: 16 (50%) of newborns with sepsis and 65 (45%) controls were delivered via c-section, $p = 0.62$. Results of a prospective national population-based study by Lorthe et al. [30] examining the outcome of singleton pregnancies with pPROM between 24th and 32nd gestational week showed that 13 (52%) neonates with early-onset neonatal sepsis were delivered by caesarean section before labour onset compared to 253 (36%) neonates without early-onset sepsis with the same delivery mode (OR 1.9, 95% CI 0.6–6.5). In a prospective cohort study of 15926 deliveries by Zhuang et al. [31] multiple logistic models were performed in order to examine factors predisposing to the incidence of neonatal infectious diseases. Caesarean section was associated with increased risk of early-onset pneumonia in the group of term deliveries with intact membranes (OR = 1.45, 95% CI 1.05–2.02, $p = 0.03$) and term deliveries with PROM (OR = 1.83, 95% CI 1.07–3.13, $p = 0.03$). However, in this study mode of delivery was not significant in the subgroups of preterm deliveries. In a study by Polcwiartek et al. [32] analysing risk factors for early-onset sepsis in a cohort of 142,410 term infants, caesarean delivery was associated with decreased risk (OR 0.66, 95% CI 0.57–0.76, $p < 0.001$).

Our multivariate analysis did not show any association between use of intravenous tocolysis and the risk of developing neonatal infection. Similar results are presented in the literature. In a study by Lorthe et al. [30] tocolysis was used in 18 (64%) patients from the early-onset sepsis group and in 482 (73%) controls (OR 0.7, 95% CI 0.2–2.1). In a retrospective cohort study of 46968 deliveries following pPROM by Chackowicz et al. [33] it was examined whether use of tocolysis could affect the risk of neonatal septic death. Tocolysis was administered to 6264 (13.3%) patients, and it was not significantly associated with neonatal septic death at 7 days (OR 0.66, 95% CI 0.39–1.13) nor at 28 days (OR 0.85, 95% CI 0.60–1.19). However, in our study the subgroup of patients requiring intravenous tocolysis was at higher risk of developing neonatal respiratory morbidity: acute respiratory failure, transient tachypnoea of the newborn and bronchopulmonary dysplasia.

Our study identified earlier gestational age at PROM as another risk factor for neonatal morbidity**.** In a prospective cohort study by Winn et al. [34] with the incidence of pulmonary hypoplasia of 12.9% of the studied group, authors also pointed that gestational age at the rupture of membranes is the risk factors for neonatal complications. Other identified risk factors included latency duration, initial and average amniotic fluid index. According to Weiner et al. [35] increased incidence of severe neonatal respiratory morbidity following pPROM occurs in case of oligohydramnios, earlier gestational age at PROM, shorter latency, and caesarean section.

Our study showed that one of the identified independent risk factors for acute respiratory failure in neonates

was positive cervical culture. Association between vaginal dysbiosis in pPROM patients and early onset neonatal sepsis is well documented in the literature [36]. Together with the promising results of prophylactic antibiotic treatment resulting in decrease in neonatal mortality, chronic lung disease and reduced need for supplemental oxygen [37], these are the arguments standing for routine cervical culture screening and adjusted treatment based on antibiogram results in women with preterm premature rupture of membranes.

Limitations of this study include relatively high proportion of late preterm neonates and a single centre character, which determines the number of enrolled patients. This could be the reason why the gestational age at birth has not been identified as an independent risk factor for bronchopulmonary dysplasia in the presented multivariate analysis results. In a case-control study by Hernandez-Ronquillo et al. [38] identified risk factors for development of bronchopulmonary dysplasia were younger gestational age at birth, lower birth weight and neonatal infectious complications. In our study factors associated with bronchopulmonary dysplasia were lower birth weight and need for intravenous tocolysis.

CONCLUSIONS

Birth weight and gestational age at PROM and at birth are the leading factors influencing the risk of neonatal infectious and respiratory morbidity following preterm premature rupture of membranes. Another identified risk factor for neonatal morbidity was positive cervical culture, therefore collection of cervical specimen and analysis of aerobic, anaerobic, fungal, and atypical pathogens cultures results could lead to individualized and more effective management of patients resulting in fewer neonatal complications.

Conflict of interest

All authors declare no conflict of interest.

REFERENCES

1. Kachikis A, Walker CL, McAdams RM, et al. Phenotypic overlap in neonatal respiratory morbidity following preterm premature rupture of membranes versus spontaneous preterm labor. J Matern Fetal Neonatal Med. 2021; 34(12): 1941–1948, doi: 10.1080/14767058.2019.1651280, indexed in Pubmed: 31402735.
2. Liljedahl M, Martin H, Magnuson A, et al. Endothelial function in children with a history of premature prolonged rupture of membranes and bronchopulmonary dysplasia--a pilot study. Acta Paediatr. 2008; 97(7): 909–914, doi: 10.1111/j.1651-2227.2008.00802.x, indexed in Pubmed: 18430069.
3. Ogunyemi D, Murillo M, Jackson U, et al. The relationship between placental histopathology findings and perinatal outcome in preterm infants. J Matern Fetal Neonatal Med. 2003; 13(2): 102–109, doi: 10.1080/jmf.13.2.102.109, indexed in Pubmed: 12735410.
4. De Dooy J, Colpaert C, Schuerwegh A, et al. Relationship between histologic chorioamnionitis and early inflammatory variables in blood, tracheal aspirates, and endotracheal colonization in preterm infants. Pediatr Res. 2003; 54(1): 113–119, doi: 10.1203/01.PDR.0000069702.25801.D1, indexed in Pubmed: 12672904.
5. Kallapur SG, Bachurski CJ, Le Cras TD, et al. Vascular changes after intra-amniotic endotoxin in preterm lamb lungs. Am J Physiol Lung Cell Mol Physiol. 2004; 287(6): L1178–L1185, doi: 10.1152/ajplung.00049.2004, indexed in Pubmed: 15321788.
6. Kramer BW, Kaemmerer U, Kapp M, et al. Decreased expression of angiogenic factors in placentas with chorioamnionitis after preterm birth. Pediatr Res. 2005; 58(3): 607–612, doi: 10.1203/01.PDR.0000175641.39056.7A, indexed in Pubmed: 16148081.
7. Lahra MM, Beeby PJ, Jeffery HE. Intrauterine inflammation, neonatal sepsis, and chronic lung disease: a 13-year hospital cohort study. Pediatrics. 2009; 123(5): 1314–1319, doi: 10.1542/peds.2008-0656, indexed in Pubmed: 19403497.
8. Ohlin A, Björkman L, Serenius F, et al. Sepsis as a risk factor for neonatal morbidity in extremely preterm infants. Acta Paediatr. 2015; 104(11): 1070–1076, doi: 10.1111/apa.13104, indexed in Pubmed: 26118325.
9. Shah J, Jefferies AL, Yoon EW, et al. Canadian Neonatal Network. Risk factors and outcomes of late – onset bacterial sepsis in preterm neonates born at < 32 weeks' gestation. Am J Perinatol. 2015; 32(7): 675–682, doi: 10.1055/s-0034-1393936, indexed in Pubmed: 25486288.
10. Blencowe H, Cousens S, Oestergaard M, et al. National, regional, and worldwide estimates of preterm birth rates in the year 2010 with time trends since 1990 for selected countries: a systematic analysis and implications. Lancet. 2012; 379(9832): 2162–2172, doi: 10.1016/s0140-6736(12)60820-4.
11. Blencowe H, Cousens S, Chou D, et al. Born Too Soon Preterm Birth Action Group. Born too soon: the global epidemiology of 15 million preterm births. Reprod Health. 2013; 10 Suppl 1: S2, doi: 10.1186/1742-4755-10-S1-S2, indexed in Pubmed: 24625129.
12. Lim WHo, Lien R, Huang YC, et al. Prevalence and pathogen distribution of neonatal sepsis among very-low-birth-weight infants. Pediatr Neonatol. 2012; 53(4): 228–234, doi: 10.1016/j.pedneo.2012.06.003, indexed in Pubmed: 22964280.
13. Simonsen KA, Anderson-Berry AL, Delair SF, et al. Early-onset neonatal sepsis. Clin Microbiol Rev. 2014; 27(1): 21–47, doi: 10.1128/CMR.00031-13, indexed in Pubmed: 24396135.
14. Hofer N, Zacharias E, Müller W, et al. An update on the use of C-reactive protein in early-onset neonatal sepsis: current insights and new tasks. Neonatology. 2012; 102(1): 25–36, doi: 10.1159/000336629, indexed in Pubmed: 22507868.
15. Kinsella J, Greenough A, Abman S. Bronchopulmonary dysplasia. Lancet. 2006; 367(9520): 1421–1431, doi: 10.1016/s0140-6736(06)68615-7.
16. Davis PG, Hutchison AA. Acute Neonatal Respiratory Failure. In: Rimensberger P. ed. Pediatric and Neonatal Mechanical Ventilation. Heidelberg: Springer, Berlin 2015.
17. Wen SWu, Smith G, Yang Q, et al. Epidemiology of preterm birth and neonatal outcome. Semin Fetal Neonatal Med. 2004; 9(6): 429–435, doi: 10.1016/j.siny.2004.04.002, indexed in Pubmed: 15691780.
18. Fanaroff AA, Martin RJ. Neonatal-perinatal medicine: Diseases of the fetus and infant. 10th ed. Saunders, United States 2014.
19. Guglani L, Lakshminrusimha S, Ryan RM. Transient tachypnea of the newborn. Pediatr Rev. 2008; 29(11): e59–e65, doi: 10.1542/pir.29-11-e59, indexed in Pubmed: 18977854.
20. Mourani PM, Abman SH. Pulmonary vascular disease in bronchopulmonary dysplasia: pulmonary hypertension and beyond. Curr Opin Pediatr. 2013; 25(3): 329–337, doi: 10.1097/MOP.0b013e328360a3f6, indexed in Pubmed: 23615175.
21. Imterat M, Wainstock T, Sheiner E, et al. Preterm prelabor rupture of membranes prior to early preterm delivery elevates the risk of later respiratory-related hospitalizations in the offspring. Pediatr Pulmonol. 2020; 55(3): 706–712, doi: 10.1002/ppul.24649, indexed in Pubmed: 31944626.
22. Manuck TA, Maclean CC, Silver RM, et al. Preterm premature rupture of membranes: does the duration of latency influence perinatal outcomes? Am J Obstet Gynecol. 2009; 201(4): 414.e1-414.e6, doi: 10.1016/j.ajog.2009.07.045, indexed in Pubmed: 19788972.
23. Can E, Oğlak SC, Ölmez F. Maternal and neonatal outcomes of expectantly managed pregnancies with previable preterm premature rupture of membranes. J Obstet Gynaecol Res. 2022 [Epub ahead of print], doi: 10.1111/jog.15239, indexed in Pubmed: 35411577.
24. Yan C, Deng X, Hong F. Analysis of maternal and neonatal outcome of patients with preterm prelabor rupture of membranes. J Healthc Eng. 2022; 2022: 8705005, doi: 10.1155/2022/8705005, indexed in Pubmed: 35320995.
25. Baser E, Aydogan Kirmizi D, Ulubas Isik D, et al. The effects of latency period in PPROM cases managed expectantly. J Matern Fetal Neonatal

Med. 2020; 33(13): 2274–2283, doi: 10.1080/14767058.2020.1731465, indexed in Pubmed: 32089027.
26. Jahromi BN, Ardekany MS, Poorarian S. Relationship between duration of preterm premature rupture of membranes and pulmonary maturation. Int J Gynecol Obstet. 2000; 68(2): 119–122, doi: 10.1016/s0020-7292(99)00194-0.
27. Niesłuchowska-Hoxha A, Cnota W, Czuba B, et al. A retrospective study on the risk of respiratory distress syndrome in singleton pregnancies with preterm premature rupture of membranes between 24+0 and 36+6 weeks, using regression analysis for various factors. Biomed Res Int. 2018; 2018: 7162478, doi: 10.1155/2018/7162478, indexed in Pubmed: 30402491.
28. Kacperczyk-Bartnik J, Bartnik P, Teliga-Czajkowska J, et al. Comparison of maternal characteristics, pregnancy course, and neonatal outcome in preterm births with and without prelabor rupture of membranes. Ginekol Pol. 2020; 91(9): 528–538, doi: 10.5603/GP.a2020.0085, indexed in Pubmed: 33030733.
29. Al-Lawama M, AlZaatreh A, Elrajabi R, et al. Prolonged rupture of membranes, neonatal outcomes and management guidelines. J Clin Med Res. 2019; 11(5): 360–366, doi: 10.14740/jocmr3809, indexed in Pubmed: 31019631.
30. Lorthe E, Ancel PY, Torchin H, et al. Impact of latency duration on the prognosis of preterm infants after preterm premature rupture of membranes at 24 to 32 weeks' gestation: a national population-based cohort study. J Pediatr. 2017; 182: 47–52.e2, doi: 10.1016/j.jpeds.2016.11.074, indexed in Pubmed: 28081890.
31. Zhuang Lu, Li ZK, Zhu YF, et al. The correlation between prelabour rupture of the membranes and neonatal infectious diseases, and the evaluation of guideline implementation in China: a multi-centre prospective cohort study. Lancet Reg Health West Pac. 2020; 3: 100029, doi: 10.1016/j.lanwpc.2020.100029, indexed in Pubmed: 34327382.
32. Polcwiartek LB, Smith PB, Benjamin DK, et al. Early-onset sepsis in term infants admitted to neonatal intensive care units (2011-2016). J Perinatol. 2021; 41(1): 157–163, doi: 10.1038/s41372-020-00860-3, indexed in Pubmed: 33070153.
33. Chackowicz A, Czuzoj-Shulman N, Abenhaim HA. The effects of tocolysis on neonatal septic death in women with PPROM: a retrospective cohort study. Arch Gynecol Obstet. 2018; 298(5): 897–902, doi: 10.1007/s00404--018-4871-9, indexed in Pubmed: 30206736.
34. Winn HN, Chen M, Amon E, et al. Neonatal pulmonary hypoplasia and perinatal mortality in patients with midtrimester rupture of amniotic membranes--a critical analysis. Am J Obstet Gynecol. 2000; 182(6): 1638––1644, doi: 10.1067/mob.2000.107435, indexed in Pubmed: 10871491.
35. Weiner E, Barrett J, Zaltz A, et al. Amniotic fluid volume at presentation with early preterm prelabor rupture of membranes and association with severe neonatal respiratory morbidity. Ultrasound Obstet Gynecol. 2019; 54(6): 767–773, doi: 10.1002/uog.20257, indexed in Pubmed: 30834608.
36. Brown RG, Marchesi JR, Lee YS, et al. Vaginal dysbiosis increases risk of preterm fetal membrane rupture, neonatal sepsis and is exacerbated by erythromycin. BMC Med. 2018; 16(1): 9, doi: 10.1186/s12916-017-0999-x, indexed in Pubmed: 29361936.
37. Kenyon SL, Taylor DJ, Tarnow-Mordi W. Broad-spectrum antibiotics for preterm, prelabour rupture of fetal membranes: the ORACLE I randomised trial. Lancet. 2001; 357(9261): 979–988, doi: 10.1016/s0140-6736(00)04233-1.
38. Hernández-Ronquillo L, Téllez-Zenteno JF, Weder-Cisneros N, et al. Risk factors for the development of bronchopulmonary dysplasia: a case-control study. Arch Med Res. 2004; 35(6): 549–553, doi: 10.1016/j.arcmed.2004.07.001, indexed in Pubmed: 15631883.

VIA MEDICA

ORIGINAL PAPER / OBSTETRICS

Ginekologia Polska
2022, vol. 93, no. 8, 637–642

ISSN 0017–0011, e-ISSN 2543–6767

DOI 10.5603/GP.a2021.0261

Evaluation of blood transfusion rate in obstetric patients

Selim Gulucu, Kaan Eray Uzun

Department of Obstetrics and Gynaecology, Tokat Gaziosmanpasa University, Tokat, Turkey

ABSTRACT

Objectives: The aim of this study was to analyse the obstetric patients who underwent transfusion in the gynecology and obstetrics clinic.

Material and methods: Obstetric patients who underwent a blood transfusion in the peripartum period were included in the study. A total of 213 patients who needed blood transfusion were identified. Patients' age, gravida, parity, gestational week, delivery types, blood transfusion indication and time, transfusion rate, blood products used, number of transfusions, peripartum hysterectomy status, neonatal APGAR scores and hemoglobin (Hb), hematocrit (Hct), red blood cell (RBC), platelet (Plt) values which counted before and after transfusion were recorded by scanning patient files from the hospital registry system.

Results: The overall blood transfusion rate of the patients who gave birth in our clinic was 2.51%. Uterine atony (50.7%) and chronic anemia (32.9%) were found as the most frequent indications of blood transfusion in the patients included in the study. Antenatal mean Hb of all transfusion patients was 9.8; postpartum mean Hb was 8.2. Pre-transfusion mean Hb, RBC, Hct, Plt values calculated as 7, 3.9, 30.3, 245.2, respectively; post-transfusion mean Hb, RBC, Hct, Plt values were 9, 3.52, 27.5, 215.1, respectively.

Conclusions: Due to blood replacement, supply difficulties and transfusion complications, the profit-loss relationship should be individualized and clearly demonstrated before it is applied to the patient. In unpredictable obstetric situations that cause bleeding, staying up to date on current guidelines on pharmacological, hematological and surgical interventions and having an active blood transfusion center in the healthcare provider is very important in reducing maternal mortality and morbidity rates.

Key words: blood; transfusion; pregnancy; obstetrics

Ginekologia Polska 2022; 93, 8: 637–642

INTRODUCTION

Although many pregnancies and births are eventless, all pregnancies are at risk. Blood transfusions may be required during obstetric care. Blood products should be used for therapeutic purposes only if no other means are available in case of significant morbidity or mortality. Obstetric hemorrhage is the leading cause of maternal mortality and severe morbidity worldwide. Blood transfusions usually are performed inevitably due to obstetric complications like severe bleeding. There are many etiologic factors that cause obstetric hemorrhage. The most common cause of bleeding is uterine atony, abnormal placentation, genital trauma, and coagulation disorders also contribute to morbidity and mortality [1]. Although bleeding is mostly minor, transfusion is inevitable in some cases. Although the blood transfusion rate is between 0.16% and 6% in obstetrics, transfusion rates vary among countries, hospitals and doctors due to different practices [2]. Several studies in the literature have shown that the use of restrictive erythrocyte suspension (ES) transfusions has better clinical outcome benefits for patients, including reduced morbidity and mortality, shorter hospital stay, and reduced risk of intensive care unit admission [3]. Recently, there was a tendency to decrease the use of blood transfusion in obstetric practice. Researches investigating the topic showed that obstetric outcomes were better despite the decrease in blood transfusion rates [2].

Our study was conducted to determine the total of obstetric patients who received transfusions in the gynecology and obstetrics clinic, transfusion rate, transfusion time,

Corresponding author:
Selim Gulucu
Department of Obstetrics and Gynaecology, Tokat Gaziosmanpasa University, Tokat, Turkey
e-mail: selim.gulucu@gop.edu.tr

Received: 5.07.2021 Accepted: 30.12.2021 Early publication date: 6.04.2022

transfusion indications, and the presence of risk factors in patients who received transfusions.

MATERIAL AND METHODS

A total of 213 obstetric patients who received blood transfusion in the peripartum period between the date of January 2015 and August 2020 in University Faculty of Medicine Research and Practice Hospital Gynecology and Obstetrics Clinic were included in the study. The study was designed retrospectively. Ethics committee approval was obtained from the ethics committee of university before the study (approval no: 20-KAEK-271). Patients were evaluated with physical examination, routine hematologic parameters by scanning patient files from the hospital registry system, patients' age, gravity, parity, gestational week, delivery types, hemoglobin values, blood transfusion indication and time, the transfusion rate (number of transfused patients/total number of patients x 100), used blood products and neonatal APGAR scores were recorded. Hemogram parameters were analyzed in a device (Mindray BC-6800, China) with regular control and maintenance. Gestational week determined by the first day of the last menstrual period (LMP), or the first trimester ultrasonography measurements were considered in patients whose last menstrual period was unknown.

Obstetric transfusion was defined as the receipt of this blood component at any point during pregnancy from birth to discharge. Antenatal and postpartum hemogram results of all patients were recorded. Then, hemoglobin (Hb), hematocrit (Hct), red blood cell (RBC) and platelet (Plt) values were evaluated before and after transfusion. Due to the differences between blood transfusion applications; antenatal, intraoperative and postpartum periods were examined separately, and hematological parameters were evaluated in order to be more objective. Blood samples were taken and analyzed before and after transfusion of this blood and its component products. Pre-transfusion samples were accepted as controls for statistical analysis.

Statistical analyses were performed using SPSS software version 19.0 (IBM Corp., Armonk, NY, USA). It was used for statistical evaluation of demographic, transfusion and obstetric data. The data evaluation of the study was performed using descriptive statistical methods (mean, standard deviation, minimum, maximum median, ratio, frequency). Differences between groups were examined with the Dependent Sample T-Test. When p values were calculated less than 0.05, it was considered statistically significant.

RESULTS

A total of 8467 delivery records of patients who gave birth in our clinic were examined. There were 2532 vaginal deliveries in total, including 1055 primipara, 9 multiple pregnancies, and 5935 births, including 210 multiple pregnancies, were performed by cesarean section during the study period. Two hundred thirteen patients who needed blood transfusion were included in the study. The mean age of the patients was 27.44 years. Demographic characteristics and hemoglobin values of the patients are given in Table 1.

Table 1. Distribution of demographic values and hemoglobin levels (n = 213)

	Mean ± St.	Min–Max
Age [year]	27.44 ± 5.87	17–43
Gravida	2.41 ± 1.55	1–9
Parite	1.13 ± 1.26	0–6
Gestational age [week]	36.78 ± 3.72	18–41
Antenatal hemoglobin [g/dL]	9.98 ± 1.78	6.5–14.2
Postpartum hemoglobin [g/dL]	8.22 ± 1.22	5.5–11.8

The mean antenatal hemoglobin value of all transfused patients was 9.84 gr/dL, while the mean postpartum Hb values were 8.22 gr/dL. The overall blood transfusion rate was 2.51% in obstetric patients, giving birth in our clinic. Blood transfusion was needed in 2.88% and 2.35% among vaginal and cesarean delivery, respectively. Blood transfusions were performed in 73 (34.3%) patients who had vaginal delivery and 140 (65.7%) patients who had cesarean delivery. Considering parities of patients, 83 (38.9%) nulliparous and 21 (9.8%) grand multipara (5 or more pregnancies) pregnancy were seen. The mean gestational week of the patients was 36.78 ± 3.72 (18–41), and the age was 27.44 ± 5.87 (17–43) years (Tab. 1).

Blood transfusion was performed for 24 (11.3%) patients in the prenatal period, 20 (9.4%) patients during the delivery (intra-operative) and 169 (79.3%) patients in the postpartum period (Tab. 2). In total, 11 (5.1%) patients were transfused blood and blood products at different and repetitive times. The erythrocyte suspension (ES), which is one of the most blood products used in patients who underwent transfusion, was administered 2.09 ± 1.252 (0–6) units and fresh frozen plasma (FFP) 0.52 ± 1.57 (0–18) units. No one patient who developed serious complications during and after transfusion was found.

Uterine atony (n = 108, 50.7%) and chronic anemia (n = 70, 32.9%) were found as the main indications of blood transfusions in the patients included in the study. A total of 29 (13.6 %) patients needed blood transfusion due to placental anomalies [placenta previa (n = 16), ablatio placenta (n = 8), placental invasion anomaly (n = 3), retained placenta (n = 2)]. Patients transfused due to three (1.4%) episiotomy complications and one (0.5%) cervical laceration (Genital Tract Injury n = 4, 1.8%). In 2 (1%) patient,

Table 2. Distribution of qualitative values (n = 213)

		n	%
Type of delivery	Vaginal delivery	73	34.3
	Cesarean delivery	140	65.7
Pregnancy	Singleton	202	94.8
	Multiple	11	5.2
Transfusion timing	Antenatal	24	11.3
	Intra-operative	20	9.4
	Postpartum	169	79.3
Presence of hysterectomy		9	4.2
Bakri balloon placement		12	5.6
Causes of anemia	Chronic anemia	70	32.9
	Atony	108	50.7
	Placenta (previa + abruption + accreta + retained)	29	13.6
	Genital tract injury (episiotomy bleeding + cervical laceration)	4	1.8
	Adhesion-related bleeding	2	1

intraabdominal adhesion was reported as a transfusion indication. Causes of anemia leading to blood transfusion are listed in Table 2.

In order to achieve postpartum bleeding control, postpartum hysterectomy was performed in nine (4.2%) patients, while a Bakri Balloon was used in 12 (5.6%) patients. Nine of these patients had a hysterectomy because of placental anomaly (7 placenta previa, 2 placenta percreta). (Tab. 2). About APGAR scores were in 7.42 ± 1.97 (0–9) and 8.38 ± 2.02 (0–10) in a first and fifth minute, respectively, while 8 babies were accepted as stillbirths. When the blood transfusion practices of our clinic in obstetric patients are evaluated; Prenatal transfusion was observed in patients with antenatal hemoglobin level < 7. In intraoperative period, it was observed that transfusion was performed in acute bleedings that caused anemia and disrupted the hemodynamics of the patient, such as uterine atony, intra-abdominal adhesions, placental and genital system injuries.

It was observed that transfusion was given to patients with tachycardia, hypotension, hemodynamically unstable, hemoglobin value < 7g/dL, pre- and postnatal hemoglobin more than four units, and hemodynamically unstable patients in the postpartum period.

Statistically significant changes were observed in pre-transfusion and post-transfusion hematological parameters of all patients who received blood transfusion. While Hb values increased in the post-transfusion periods, Plt values decreased. In the analysis performed considering the blood transfusion administration times, the mean Hb, RBC, Hct and Plt values of the antenatal period before and after transfusion are shown in the Table 3.

DISCUSSION

Depending on surgical interventions, minor or major complications such as wound infection, pulmonary embolism, atelectasis, scar, adhesion, wound dehiscence or bleeding may occur. Bleeding may also occur during obstetric procedures. Although the blood transfusion rate in obstetrics is between 0.16% and 6%, this rate varies due to different applications [2]. During the study, the overall blood transfusion rate in patients admitted to our clinic for delivery was found to be 2.51%. In a study conducted in Canada, there were 460.370 deliveries in 44 hospitals; 3823 of the women received an obstetrical blood transfusion during pregnancy (8.3 per 1000). In this study, obstetric-related blood transfusion rate between hospitals varied 0.37–2.36%, but the average was reported as 0.83 [4]. In another study, the blood transfusion rate for obstetric reasons was found to be 4.6% [5]. Our transfer rate was compatible with the literature.

Although the number of transfusion patients who gave birth by cesarean was higher, the blood transfusion rate was found to be higher in patients who had a vaginal delivery. In the literature, studies have been shown that the blood transfusion rate is higher in patients who gave birth by cesarean section compared to those who delivered vaginally [6, 7]. Especially emergency cesarean sections have a higher risk of blood transfusion than elective cesarean sections. The low number of vaginal deliveries and the high rate of vaginal delivery blood transfusion rates were attributed to the high number of risky patients referred from other hospitals because our university hospital was a tertiary center. In a study conducted in Ireland, blood transfusion rate was

Table 3. Hematological parameters

		n	Ort ± SS	Min–Max	p-value
Antenatal	Antenatal Hb [g/dL]	24	8.16 ± 2.05	3.3–14.2	0.384
	Postpartum Hb [g/dL]	24	8.51 ± 1.33	6.6–11.4	
	PreTx Hb [g/dL]	24	7.35 ± 1.51	3.3–10.8	< 0.001*
	PostTx Hb [g/dL]	24	9.25 ± 1.02	7.6–11.6	
	PreTx RBC [millions/µL]	24	3.74 ± 0.77	0.83–4.81	0.065
	PostTx RBC [millions/µL]	24	3.99 ± 0.68	2.48–5.64	
	PreTx Hct (%)	24	26.43 ± 5.29	9.5–37.6	0.014*
	PostTx Hct (%)	24	29.12 ± 3.87	21.75–38.8	
	PreTx Plt [lakhs/mm^3]	24	280.58 ± 103.72	89–521.0	0.003*
	PostTx Plt [lakhs/mm^3]	24	236.89 ± 102.43	58.44–461.0	
Intraoperative	Antenatal Hb [g/dL]	20	9.83 ± 1.37	8.3–13.1	0.003*
	Postpartum Hb [g/dL]	20	8.5 ± 1.32	6.3–11.8	
	PreTx Hb [g/dL]	20	7.79 ± 1.15	6.3–10.5	< 0.001*
	PostTx Hb [g/dL]	20	9.02 ± 0.96	7.4–11.8	
	PreTx RBC [millions/µL]	20	3.74 ± 0.54	2.67–4.4	0.008*
	PostTx RBC [millions/µL]	20	3.33 ± 0.63	2.43–4.51	
	PreTx Hct (%)	20	30.13 ± 3.48	24.8–37.5	0.013*
	PostTx Hct (%)	20	26.74 ± 3.47	20.6–35.2	
	PreTx Plt [lakhs/mm^3]	20	244.22 ± 85.87	115.0–416.0	< 0.001*
	PostTx Plt [lakhs/mm^3]	20	189.43 ± 66.87	40–329	
Postpartum	Antenatal Hb [g/dL]	169	10.09 ± 1.88	6.4–14.2	< 0.001*
	Postpartum Hb [g/dL]	169	8.5 ± 1.32	6.3–11.8	
	PreTx Hb [g/dL]	169	7.34 ± 0.81	5.3–9.2	< 0.001*
	PostTx Hb [g/dL]	169	9.12 ± 0.92	7.0–11.5	
	PreTx RBC [millions/µL]	169	3.95 ± 0.58	2.28–6.4	< 0.001*
	PostTx RBC [millions/µL]	169	3.47 ± 0.51	2.34–5.07	
	PreTx Hct (%)	169	30.89 ± 4.88	20.0–42.9	< 0.001*
	PostTx Hct (%)	169	27.47 ± 3.41	7.3–36.0	
	PreTx Plt [lakhs/mm^3]	169	240.39 ± 80.85	50.0–495.0	< 0.001*
	PostTx Plt [lakhs/mm^3]	169	215.07 ± 81.68	34.0–710.0	
Total	Antenatal Hb [g/dL]	213	9.85 ± 1.95	3.30–14.5	< 0.001*
	Postpartum Hb [g/dL]	213	8.22 ± 1.23	5.50–11.8	
	PreTx Hb [g/dL]	213	7.38 ± 0.96	3.30–10.8	< 0.001*
	PostTx Hb [g/dL]	213	9.13 ± 0.93	7.00–11.8	
	PreTx RBC [millions/µL]	213	3.91 ± 0.61	0.83–6.4	< 0.001*
	PostTx RBC [millions/µL]	213	3.52 ± 0.57	2.34–5.64	
	PreTx Hct (%)	213	30.32 ± 5.00	9.50–42.9	< 0.001*
	PostTx Hct (%)	213	27.59 ± 3.50	7.30–38.8	
	PreTx Plt [lakhs/mm^3]	213	245.28 ± 84.67	50.00–521.0	< 0.001*
	PostTx Plt [lakhs/mm^3]	213	215.13 ± 83.32	34.00–710.0	

p-value — Dependent Sample T-Test; * Significant < 0.05; Hb —hemoglobin; Hct — hemotokrit; Plt — platelet; PostTx — after transfusion; PreTx — before transfusion; RBC — red blood cell

found 1.5% in 10-year screening in obstetric patients in 1991, and it was reported that this rate decreased to one percent in 2001 [8]. In a previous study conducted in our clinic, the blood transfusion rate in 2013 was found to be 4% [9].

The low blood transfusion rate in our study, according to the literature may attribute to the regular preconceptional follow-up and pregnancy follow-up of the patients, the appropriate treatment of iron deficiency to reduce severe anemia, the close follow-up of the patients during and after delivery, and our experience in the use of pharmacological and surgical methods. When these two studies conducted in our clinic were evaluated together, it was determined that the rate of blood transfusion could be reduced with clinical experience. Transfusion is a life-saving practice. However, an adverse reaction is observed in approximately 1% of all transfusions despite the precautions taken. Massive transfusion problems such as hemolytic reactions, infections, acute transfusion-related acute lung injury (TRALI), hypomagnesemia, hyperkalemia, hypocalcemia, hypothermia, metabolic acidosis, and coagulation abnormalities should be avoided with the use of random blood products [10, 11]. When the files of the patients included in the study were examined, no patient who developed serious complications during and after transfusion was found.

In a study conducted in Canada, it was found that there is a threefold difference in obstetric blood transfusion rates of hospitals in the same state, and this difference between hospitals shows that there is a potential for misuse of blood products in some centers [4]. It has been stated in the literature that transfusion application should be used in cases where the benefits of transfusion outweigh the risks and there are no suitable alternatives and that laboratory tests should not be the only determining factor for transfusion [12]. Similar risk factors associated with pregnancy and delivery that will require blood transfusion have been identified in the literature, including anemia, excessive uterine distention (polyhydramnios, multiple pregnancy), preterm labor, preeclampsia/eclampsia, placental pathologies (placental detachment, insertion anomaly, previa, rest placenta), includes trauma, induction of labor, operative delivery and emergency caesarean [7, 13].

Considering the blood transfusion timing in our study, generally it was performed in the postpartum period. The most common transfusion indication was uterine atony in this period. In another study, uterine atony is most common cause of postpartum hemorrhage and is responsible for 70––80% [14]. Other main reason for transfusion in our study was chronic anemia. Anemia during pregnancy is defined as the hemoglobin value below 11 g/dL in each trimester, according to the World Health Organization (WHO) [15]. Anemia is an important risk factor in postpartum bleeding [3]. This suggest that it is associated with unfollowed pregnancies that do not attend pregnancy follow-ups and do not use iron supplements. Current Swiss guidelines recommend that hemoglobin levels should be screened regularly at least once every trimester, and iron levels should be screened in the first trimester [3]. Various algorithms have been emphasized in postpartum hemorrhage, especially in massive bleeding, although the benefits of fibrinogen and tranexamic acid are shown, more studies are needed [16]. Patients should be followed carefully and closely in the postnatal period. Placental placement and invasion anomaly are important risk factors for obstetric bleeding. The location of the placenta and the invasion of the uterus should be checked as much as possible with prenatal ultrasonography. The European Perinatal Health Report states that between 0.2 and 1 peripartum hysterectomy are performed per 1000 births [17]. In the literature, uterine atonia and placental invasion anomaly were reported as the main reasons in more than 85% of patients who underwent peripartum hysterectomy [18].

In our study, the most used blood products in transfused patients were determined as erythrocyte suspension and then fresh frozen plasma. In the ACOG bulletin, it is recommended that blood products such as erythrocyte suspension, FFP and platelet suspension should be given to the patient in certain proportions in patients in whom massive blood transfusion is planned, and that this ratio should be regulated to be 1: 1: 1 [19]. In our study, the low FFP rates were attributed to different applications of different surgeons and the non-routine application of FFP after ES transfusions performed outside the postpartum period (prenatal and intraoperative period). A decrease in Plt was observed after transfusion in all periods. This decrease made us think that there was not enough FFP transfusion in addition to ES transfusion in our clinic. In our study, it was observed that the changes in hematological parameters after transfusion were consistent with previous studies [20, 21].

The strength of our study is that our clinic has evaluated the rate of obstetric blood transfusion over a period of approximately five years. However, the limitations of our study were that the study was conducted retrospectively, the duration of the operation could not be determined for this reason, there was no body mass index information, and it was not separately evaluated which blood product made how much change in hematological parameters. In addition, abortions were not included in the study and the number of deliveries was low compared to the number of cesarean sections because of our hospital is a tertiary health institution.

CONCLUSIONS

Due to supply difficulties and transfusion complications, the profit-loss relationship should be individualized and clearly demonstrated before blood transfusion is applied to the patient. In the presence of important risk factors such

as abnormal placentation, high number of previous cesarean sections, coagulation disorders, planning the delivery in tertiary centers is important for patient health. It should not be neglected to give iron supplements to women who have iron deficiency before and during pregnancy and women should be encouraged to use supplements. Early diagnosis and treatment of anemia will reduce the need for blood transfusion. In unpredictable and sudden obstetric indications that causing bleeding, staying up to date on pharmacological, hematological and surgical interventions in treatment protocols, and the presence of active blood bank in health provider are very important in reducing maternal mortality and morbidity. Evaluating blood transfusion rates and indications at certain time intervals in obstetrics clinics will be beneficial in reducing the blood transfusion rate.

Conflict of interest

The authors declared no conflict of interest.

REFERENCES

1. Baird EJ. Identification and management of obstetric hemorrhage. Anesthesiol Clin. 2017; 35(1): 15–34, doi: 10.1016/j.anclin.2016.09.004, indexed in Pubmed: 28131117.
2. Chawla S, Bal MHK, Vardhan BS, et al. Blood transfusion practices in obstetrics: our experience. J Obstet Gynaecol India. 2018; 68(3): 204–207, doi: 10.1007/s13224-018-1092-x, indexed in Pubmed: 29896000.
3. Zdanowicz JA, Schneider S, Mueller M, et al. Red blood cell transfusion in obstetrics and its implication for patient blood management: a retrospective analysis in Switzerland from 1998 to 2016. Arch Gynecol Obstet. 2021; 303(1): 121–128, doi: 10.1007/s00404-020-05744-7, indexed in Pubmed: 32813046.
4. Hutcheon JA, Chapinal N, Skoll A, et al. Inter-hospital variation in use of obstetrical blood transfusion: a population-based cohort study. BJOG. 2020; 127(11): 1392–1398, doi: 10.1111/1471-0528.16203, indexed in Pubmed: 32150336.
5. Matsunaga S, Seki H, Ono Y, et al. A retrospective analysis of transfusion management for obstetric hemorrhage in a Japanese obstetric center. ISRN Obstet Gynecol. 2012; 2012: 854064, doi: 10.5402/2012/854064, indexed in Pubmed: 22462007.
6. Balki M, Dhumne S, Kasodekar S, et al. Blood transfusion for primary postpartum hemorrhage: a tertiary care hospital review. J Obstet Gynaecol Can. 2008; 30(11): 1002–1007, doi: 10.1016/S1701-2163(16)32994-2, indexed in Pubmed: 19126281.
7. Butwick AJ, Aleshi P, Fontaine M, et al. Retrospective analysis of transfusion outcomes in pregnant patients at a tertiary obstetric center. Int J Obstet Anesth. 2009; 18(4): 302–308, doi: 10.1016/j.ijoa.2009.02.005, indexed in Pubmed: 19628384.
8. World Health Organization WHO, Maternal Health and Safe Motherhood Programme. Maternity care: what is needed for safer motherhood in the community? Safe Mother. 1992(8): 6–8, indexed in Pubmed: 12285230.
9. Çakmak B, Gülücü S, Nacar MC, et al. Obstetrikte Kan Transfüzyonu: Bir Üniversite Hastanesi Klinik Deneyimi. Gaziosmanpaşa Üniversitesi Tıp Fakültesi Dergisi. 2013; 5(3): 140–144.
10. Chhabra S, Namgyal A. Rationale use of blood and its components in obstetric-gynecological practice. Journal of Mahatma Gandhi Institute of Medical Sciences. 2014; 19(2): 93, doi: 10.4103/0971-9903.138427.
11. Ismail S, Siddiqui S, Shafiq F, et al. Blood transfusion in patients having caesarean section: a prospective multicentre observational study of practice in three Pakistan hospitals. Int J Obstet Anesth. 2014; 23(3): 253–259, doi: 10.1016/j.ijoa.2014.01.004, indexed in Pubmed: 24768302.
12. Norfolk D. Transfusion ten commandments. In: Norfolk D. ed. Handbook of transfusion medicine. TSO Publishers, Norwich 2013: 1–3.
13. Stephens B, Sethna F, Crispin P. Postpartum obstetric red cell transfusion practice: A retrospective study in a tertiary obstetric centre. Aust N Z J Obstet Gynaecol. 2018; 58(2): 170–177, doi: 10.1111/ajo.12680, indexed in Pubmed: 28776639.
14. American College of Obstetricians and Gynecologists. ACOG Practice Bulletin: Clinical Management Guidelines for Obstetrician-Gynecologists Number 76, October 2006: postpartum hemorrhage. Obstet Gynecol. 2006; 108(4): 1039–1047, doi: 10.1097/00006250-200610000-00046, indexed in Pubmed: 17012482.
15. World Health Organization (WHO). Iron Deficiency Anemia. Iron deficiency anaemia: assessment, prevention and control. A guide for programme managers. 2002: 47–52.
16. Frigo MG, Agostini V, Brizzi A, et al. Practical approach to transfusion management of post-partum haemorrhage. Transfus Med. 2021; 31(1): 11–15, doi: 10.1111/tme.12755, indexed in Pubmed: 33400316.
17. EURO-PERISTAT Project with SCPE and EUROCAT. European Perinatal Health Report. The health and care of pregnant women and babies in Europe in 2010. May 2013. https://www.europeristat.com/images/European%20Perinatal%20Health%20Report_2010.pdf (1.07.2021).
18. Jakobsson M, Tapper AM, Palomäki O, et al. NOSS study group. Emergency peripartum hysterectomy: results from the prospective Nordic Obstetric Surveillance Study (NOSS). Acta Obstet Gynecol Scand. 2015; 94(7): 745–754, doi: 10.1111/aogs.12644, indexed in Pubmed: 25845622.
19. Treml AB, Gorlin JB, Dutton RP, et al. Massive transfusion protocols: a survey of academic medical centers in the United States. Anesth Analg. 2017; 124(1): 277–281, doi: 10.1213/ANE.0000000000001610, indexed in Pubmed: 27749352.
20. Elzik ME, Dirschl DR, Dahners LE. Correlation of transfusion volume to change in hematocrit. Am J Hematol. 2006; 81(2): 145–146, doi: 10.1002/ajh.20517, indexed in Pubmed: 16432852.
21. Chauhan S, Rishi B, Tanwar P, et al. Therapeutic lessons from transfusion in pregnancy-effect on hematological parameters and coagulation profile. Am J Blood Res. 2021; 11(3): 303–316, indexed in Pubmed: 34322295.

VIA MEDICA

ORIGINAL PAPER / OBSTETRICS

Ginekologia Polska
2022, vol. 93, no. 8, 643–649

ISSN 0017–0011, e-ISSN 2543–6767

DOI 10.5603/GP.a2021.0176

Ultrasound differentiation between benign *versus* malignant adnexal masses in pregnant patients

Ewa Rabiej-Wronska[1], Marcin Wiechec[1,2,3], Kazimierz Pitynski[1,2], Ewa Wiercinska[4], Agnieszka Kotlarz[1,2]

[1]*Gynaecology and Oncology Clinical Department, University Hospital, Cracow, Poland*
[2]*Chair of Gynecology and Obstetrics, Jagiellonian University Medical College, Cracow, Poland*
[3]*Centre of Postgraduate Medical Education, Warsaw, Poland*
[4]*District Sanitary Epidemiologic Station, Wieliczka, Poland*

ABSTRACT

Objectives: The aim of this study was to assess the performance of the International Ovarian Tumor Analysis (IOTA) group ultrasound Simple Rules method in differentiating between benign and malignant ovarian tumors in pregnant patients.

Material and methods: A prospective observational study that involved pregnant patients referred to our center due to suspicions of ovarian masses between January 2015 and December 2017 was performed. The Simple Rules performance was evaluated against the histopathological results. Each of the 10 sonographic Simple Rules were computed by logistic regression to demonstrate their odds ratios in predicting malignancy.

Results: Ultrasound were conducted in 153 subjects, and 61 of those patients underwent surgery. By assigning masses presenting inconclusive picture as probably malignant, the Simple Rules method showed sensitivity of 91.67% and specificity of 69.39%. After exclusion of masses with inconclusive findings, the method showed sensitivity of 87.5% and specificity of 94.44%. The Simple Rules risk estimation method for the 1% risk cutoff showed sensitivity of 100% and specificity of 51.02%. For the 3% cutoff, sensitivity was 91.67% and specificity was 53.06%. And for 30 % cutoff, sensitivity was 91.67% and specificity 73.47 %. The logistic regression model showed that the M-rules increased the risk of malignancy while the B-rules decreased the risk.

Conclusions: Most ovarian masses in pregnant patients may be correctly categorized as benign or malignant using Simple Rules. This protocol may facilitate the management of pregnant patients presenting with adnexal masses.

Key words: pregnancy; adnexal diseases; ovarian neoplasms; ultrasonography

Ginekologia Polska 2022; 93, 8: 643–649

INTRODUCTION

The prevalence of adnexal masses during pregnancy is estimated to be 0.2–2% [1]. The majority of these masses are benign and include functional corpus luteum cysts, dermoid cysts, cystadenomas and endometriomas as the most common findings [2, 3]. Heterotopic pregnancy, tubo-ovarian abscesses, ovarian hyperstimulation and adnexal torsion should also be taken into consideration. Adnexal masses are identified during pregnancy with increasing frequency at the time of viability scans [4]. Most patients are asymptomatic, and the ovarian tumors are discovered incidentally [5].

Up to 70% of all ovarian cysts diagnosed in the first trimester resolve spontaneously later in gestation [6]. It is estimated that approximately 0.8–13% of all ovarian masses detected in pregnant women are malignant (ovarian cancer or metastatic tumors) [7, 8]. One potential reason for this incidence is increasing maternal age [9]. Primary malignant tumors seem to have no impact on neonatal outcomes, metastases to ovaries however may lead to complications of the newborn period [10].

Due to the limited application of biomarkers for ovarian malignancy screening, according to the International Ovarian Tumor Analysis (IOTA) group, sonography remains the first-line imaging modality used for this purpose, including during pregnancy [11, 12]. Several screening protocols have been described in the literature [13–16]. However, no

Corresponding author:
Ewa Rabiej-Wronska
Gynaecology and Oncology Clinical Department, University Hospital, 2 Jakubowskiego St, 30-688 Cracow, Poland
e-mail: ewa.rabiej@mailmix.pl

Received: 10.01.2021 Accepted: 28.05.2021 Early publication date: 13.10.2021

Table 1. The simple rules

M-rules for predicting a malignant tumor		B-rules for predicting a benign tumor	
M1	Irregular solid tumor	B1	Unilocular cyst
M2	Presence of ascites	B2	Presence of solid components, where the largest solid component has a diameter < 7 mm
M3	At least 4 papillary structures	B3	Presence of acoustic shadows
M4	Irregular multilocular-solid tumor with largest diameter ≥ 100 mm	B4	Smooth multilocular tumor with largest diameter < 100 mm
M5	Strong blood flow (color score 4)	B5	No blood flow

policy regarding ovarian cancer screening during pregnancy has been proposed so far [5].

Indications for surgery to remove an adnexal mass during pregnancy are suspicion of malignancy, fast growth and large size of the tumor, or emergencies related to the adnexal mass, *e.g.*, rupture or torsion [17]. If surgery is indicated, the optimal time of it to be performed is during the second trimester [18, 19].

Objectives

Taking the above information into account, we planned an observational study in which we decided to determine if the sonographic criteria for malignancy described in the literature for nonpregnant subjects are also applicable for pregnant women.

MATERIAL AND METHODS

We performed a prospective observational study that involved pregnant subjects referred to our oncology center because of ovarian masses. Data were collected between January 2015 and December 2017. The exclusion criteria were refusal to participate and nonpregnant at the time of qualification for the study. All subjects underwent combined pelvic transvaginal and transabdominal sonograms performed using Voluson E6 ultrasound systems equipped with 5–9 MHz transvaginal and 2–5 MHz transabdominal hybrid transducers (GE Healthcare, Zipf, Austria). If an ovarian mass was confirmed, then it was evaluated by gray-scale and Power Doppler mapping (with PRF at the level of 0.6 kHz). To minimalize an inter observer errors number of observers was limited to two certified by IOTA examiners.

All masses were reported using the IOTA group terminology [20]. Based on the identified findings, the Simple Rules protocol was applied [15]. As Timmerman et al., proposed, sonographic features of a tumor can be divided in two groups: predicting malignant (M-rules) and benign (B-rules) tumors (Tab. 1). If one or more M-rules and no B-rules apply, a mass is classified as malignant. Conversely, when one or more B-rules and no M-rules is present, mass is classified as benign. The result is called inconclusive when there are no B and M findings or pictures from both categories are identified [15]. On the basis of M- and B-rules it is also possible to estimate the risk of malignancy (given in percentages), which allows to classify all adnexal masses (without inconclusive results) [21].

Clinical records of all subjects were reviewed and compared based on the following parameters: age, gravidity, gestational age at the time of diagnosis, and Ca-125 serum levels. Serum Ca-125 was measured with *electrochemiluminescence immunoassay* (ECLIA) method using Cobas 8000 analyzer (Roche Diagnostics, Mannheim, Germany).

All scan reports were reviewed by the oncology team, and subjects were counseled regarding the scan findings and underwent routine evaluation according to the local policy. The examiners were not involved in decision making process regarding patients' therapies. Second ultrasound scans were performed at this level. Every patient underwent follow-up ultrasound scans every 2–4 weeks till surgery. All cases qualified by the oncology team for surgical treatment were reviewed in terms of histopathology evaluation, including cases operated on after conclusion of the pregnancy. Subjects diagnosed with malignancy were included in Group M, and those with benign masses were included in Group B. For the purpose of the study, lesions indicating borderline characteristics on histopathology were classified as malignant (Group M). The follow-up ultrasound scan was scheduled between 6 and 20 weeks postpartum. The local ethics committee approval was acquired, and a written informed consent was obtained from all patients.

Statistical analysis

Normality of the continuous variable distribution was validated with the Kolmogorov-Smirnov test. The χ^2 test was used to show differences. None of the continuous variables presented a Gaussian distribution. Nonparametric tests were conducted. Two groups of independent variables were compared in this case using the Mann-Whitney U-test.

All 10 of the sonographic features (M-rules and B-rules) were computed by logistic regression with one categorical independent variable to demonstrate their odds ratios in predicting malignancy.

The Simple Rules performance was evaluated against the histopathological results, which was the reference stand-

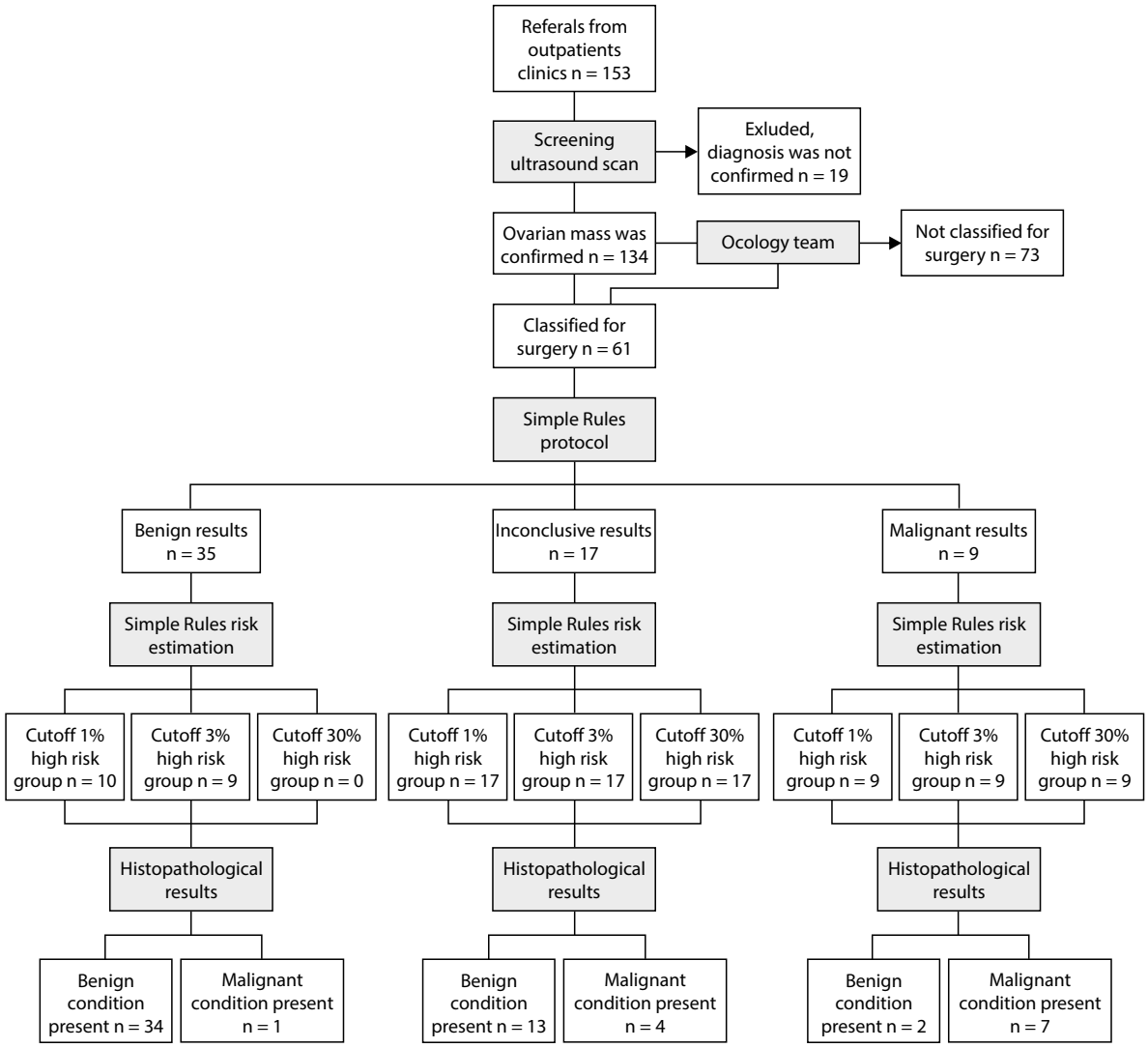


Figure 1. Study population breakdown diagram

ard in this case. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), positive likelihood ratio (LR+), negative likelihood ratio (LR-) and diagnostic accuracy were calculated for the Simple Rules for all patients who underwent surgery.

Five calculation strategies were applied. First method, by assigning masses presenting inconclusive picture (no B and M features or features from both categories) as probably malignant (Calculation 1), second, by excluding masses with inconclusive findings (Calculation 2), third, fourth and fifth, by calculating risk of malignancy with Simple Rules risk calculator at 1% (Calculation 3), 3% (Calculation 4) and 30% (Calculation 5) cutoffs [21]. Statistical analysis was carried out using the Statistica 13 system (StatSoft, Cracow, Poland). The values of $p < 0.05$ were considered as statistically significant.

RESULTS

Study population

A total of 153 subjects diagnosed with an ovarian mass associated with pregnancy were referred to our oncology center. In 19 patients, ovarian masses were excluded by sonography at the time of qualification. The remaining 134 subjects were counseled by the oncology team. The diagnosis of ovarian mass was confirmed by sonography in all of 134 patients. Additionally, 73 subjects were not qualified for surgery, and thus, the remaining 61 patients constituted the study population and underwent surgery due to ovarian masses with histopathology evaluation. The details are shown in Figure 1. The surgery was performed during pregnancy in 35 subjects (4 patients with malignant, 5 with borderline and 26 with benign tumors) and the mean time between the suspicion on sonography and the first surgery was

Table 2. The number of surgeries performed on the basis of particular indications

	Group B tumor removed:			Group M tumor removed:		
	During pregnancy n = 26	During cesarean section n = 12	After pregnancy n = 11	During pregnancy n = 10	During cesarean section n = 2	After pregnancy n = 0
Suspicious of malignancy (M features or fast growth of the tumor)	8	2	1	10	1	0
Torsion or rupture	4	1	1	0	0	0
Chronic abdominal pain	6	0	2	0	0	0
Other symptoms of lesions	8	0	0	0	0	0
Tumor as an obstacle for vaginal delivery	0	3	0	0	1	0
Obstetric indications for cesarean section	0	6	0	0	0	0
Tumor persistence after course of pregnancy	0	0	7	0	0	0

If patient has more than one surgery, only first one is included in the table

Table 3. Basic statistics of major study population parameters: maternal age, gestational age, and Ca-125

	Benign			Malignant			
	Mean	Median	SD	Mean	Median	SD	Statistical significance
Maternal age	28.94	28.00	5.48	29.83	28.50	6.09	0.68
Gestational age	16.37	15.00	7.66	16.04	17.79	4.69	0.82
Ca-125 level [U/mL]	41.37	27.56	38.11	93.49	33.40	159.12	0.90

2.5 weeks (range 0–8 weeks). In 14 subjects, surgery was performed at the time of cesarean section (one case of mucinous carcinoma, one case of seromucionous borderline tumor and 12 benign cases), and the mean time from the suspicious sonogram findings to the surgery was 22 weeks (range 8–31 weeks). In 11 subjects, surgery was performed after the course of pregnancy (only benign tumors) and the mean time from the first scan to the surgery was 23.5 weeks (range 11–36 weeks). Patient with Burkitt lymphoma was diagnosed with ovarian mass at 19 weeks of gestation, and her first surgery was performed at 26 weeks and consecutive removal of recurrences during cesarean section performed at 31 weeks.

Indications for surgeries are shown in Table 2. In our study population there were six cases of emergency surgical interventions due to torsion or rupture of the mass. In all these six subjects Simple Rules suggested benign character of the tumor, and it was confirmed in histopathology.

The median maternal age was 30 years (range: 16–44, SD 5.1 years). The median maternal age for patients in Group M was 28.5 years (range: 19–41, SD 6.09 years) and 28 years (range: 18–44, SD 5.48 years) in Group B (no statistical significance p = 0.68). Gestational age at diagnosis and Ca-125 data are shown in Table 3. There were no statistical differences between the two groups regarding maternal age, gestational age at the time of sonography or Ca-125 levels (Tab. 3).

In Group B there were 34 patients (69.4%) in their first pregnancy, 12 (24.5%) in their second, 2 (4.1%) in their third, and 1 (2%) in her fifth. In Group M there were 7 patients (58.3%) in their first, 3 (25%) in their second and 2 (16.7%) in their third pregnancy.

Histopathology

The malignancy rate was 7.84% (12/153). Among the studied subjects, a benign teratoma was the most common finding. Detailed histopathology results are presented in Table 4.

Ultrasound findings

Among the benign lesions there were 21 masses (42.9%) described as unilocular, 11 (22.4%) as multilocular, 8 (16.3%) as unilocular-solid, 6 (12.2%) as multilocular-solid and 3 (6.1%) as solid. In Group M, 2 masses (16.7%) were unilocular, 3 (25%) unilocular-solid, 3 (25%) multilocular-solid and 4 (33.3%) solid. There were no multilocular lesions in Group M. The dominant sonographic features in Group B were anechoic in 12 masses (24.5%), low level of echogenicity in 5 (10.2%), ground glass in 6 (12.2%), hemorrhagic in

Table 4. Distribution of the histopathology findings in the study population

Prevalence of specific pathologies	
Tumor type	**n (%)**
All benign	52
Benign teratoma	19 (29.69)
Endometrioma	7 (10.94)
Simple cyst	7 (10.94)
Functional cyst	3 (4.8)
Parasalpingeal cyst	2 (3.13)
Mucinous cystadenoma	8 (12.5)
Fibroma	2 (3.13)
Fibrothecoma	2 (3.13)
Cystadenofibroma	2 (3.13)
All malignant	12
Serous borderline tumor	3 (4.69)
Mucinous borderline tumor	1 (1.56)
Seromucinous borderline tumor	2 (3.13)
Yolk sac tumor	2 (3.13)
Serous carcinoma	1 (1.56)
Mucinous carcinoma	1 (1.56)
Burkitt lymphoma	1 (1.56)
Secondary metastatic cancer	1 (1.56)

There were three tumors of mixed histology: yolk sac tumor together with mucinous cystadenoma, yolk sac tumor together with benign teratoma, and endometrioma together with a simple cyst. These tumors are shown as separate diagnoses

Table 5. Odds ratios (ORs) for the M and B features based on the logistic regression model

	p	OR	95% CI for OR	
			Lower limit	**Upper limit**
M1*	0.036	7.833	1.141	53.757
M2*	0.022	16	1.49	171.59
M3*	0.002	34.286	3.476	338.16
M4*	0.068	5.111	0.886	29.486
M5*	0.999	7915826838	0	
B1*	0.03	0.095	0.011	0.791
B2*	0.999	0	0	
B3*	0.999	0	0	
B4*	0.999	0	0	
B5*	0.003	0.04	0.005	0.339

* — definition in the Table 1

4 (8.2%) and as mixed in 22 (44.9%). In Group M there was 1 mass (8.3%) described as anechoic, 1 as low level (8.3%), 1 as ground glass (8.3%), 2 as hemorrhagic (16.7%) and 7 as mixed (58.3%). Color score 1 was given for 37 (75.5%) benign tumors, color score 2 for 7 (14.3%), 3 for 5 (10.2%) and 4 for none of them. One (8.3%) malignant tumor had color a score of 1, four (33.3%) had a color score of 2, six (50%) a color score 3 and only one (8.3%) a color score of 4. Differences in type, dominant sonographic features and blood flow between benign and malignant masses were not tested for statistical significance because of the small number of tumors in each particular group.

All 10 of the sonographic features (M-rules and B-rules) were computed by logistic regression with one categorical independent variable. Odds ratios of predicting malignancy are presented in Table 5.

The results were statistically significant for rules M1 — irregular solid tumor (OR 7.83), M2 — ascites (OR 16), M3 — at least four papillary structures (OR 34.29), M4 — irregular multilocular-solid tumor with largest diameter ≥ 100 mm (OR 5.11), B1 — unilocular cyst (OR 0.1), B5 — no blood flow (OR 0.04). M5 — very strong blood flow was present only in two cases, but all of them were malignant (2/2); B2 — presence of solid components, where the largest has a diameter < 7 mm, was present in three tumors, all of them benign (3/3); B3 — presence of acoustic shadows was present in five tumors, all of them benign (5/5); and B4 — smooth multilocular tumor with a largest diameter < 100 mm was present in three tumors, all of them benign (3/3).

Key findings

Screening performance of all proposed by us Calculation models is shown in Table 6.

Follow-up

A total of 86 (63%) patients attended a postpartum follow-up scan. In the group of patients who did not undergo surgery, ultrasounds showed normal ovaries in 37 subjects and ovarian cyst in 11 subjects. All of 11 ovarian masses indicated benign character (10 endometriomas and one simple cyst). Among patients who underwent surgery normal ovaries were found in 37 subjects (2 of those patients were in consecutive pregnancy). In one subject an ovarian cyst was found. It was a dermoid cyst in a patient who underwent cystectomy due to dermoid cyst in contralateral ovary.

DISCUSSION

Simple Rules performance has been already evaluated in multicenter studies conducted by the IOTA group on a population of nonpregnant women [22]. To the best of our knowledge, our study is one of the first performed on a population of pregnant women [10]. The results of this study confirmed that Simple Rules reliably discriminated between benign and malignant adnexal masses detected in pregnant subjects.

One of the strengths of the study is the use of the same standardized lesion qualification as previously used in

Table 6. Screening performance

	Calculation model 1 (inconclusive results as probably malignant)	Calculation model 2 (exclusion of inconclusive results)	Calculation model 3 1% risk cutoff	Calculation model 4 3% risk cutoff	Calculation model 5 30% risk cutoff
Sensitivity	91.67% CI 61.52–99.79	87.5% CI 47.35–99.68	100% CI 73.54–100	91.67% CI 61.52–99.79	91.67% CI 61.52–99.79
Specificity	69.39% CI 54.58–81.75	94.44% CI 81.34–99.32	51.02% CI 36.34–65.58	53.06% CI 38.27–67.47	73.47% CI 58.92–85.05
Diagnostic accuracy	73.77% CI 60.93–84.20	93.18% CI 81.77–97.65	60.66% CI 47.31–72.93	60.66% CI 47.31–72.93	77.05% CI 47.31–72.93
PPV	42.31% CI 31.76– 53.61	77.78% CI 47.02–93.24	33.33% CI 27.31–39.95	32.35% CI 25.34–40.26	45.83% CI 34.00–58.16
NPV	97.14% 83.76–99.56	97.14% CI 84.44–99.53	100%	96.30% CI 79.63–99.43	97.3% CI 84.55–99.58
LR+	2.99 CI 1.90–4.72	15.75 CI 3.99–62.11	2.04 CI 1.53–2.72	1.95 CI 1.39–2.75	3.46 CI 2.10–5.67
LR–	0.12 CI 0.02–0.79	0.13 CI 0.02–0.83	0	0.16 CI 0.02–1.04	0.11 CI 0.02–0.75

nonpregnant subjects. The results may therefore be compared. The Simple Rules performance in nonpregnant showed a sensitivity of 95% and specificity of 78% if inconclusive results were classified as probably malignant and sensitivity of 92% and a specificity of 96% after exclusion masses with inconclusive result [22]. Simple Rules risk estimation with 1% risk cutoff showed sensitivity of 99.7% and a specificity of 33.7%, and with 30% cutoff, sensitivity of 89.0% and specificity of 84.7% [21].

These results are in line with our findings in pregnant women. Another similarity is that the same as in nonpregnant population, the presence of M-features increases the risk of malignancy, whereas the presence of B-features decreases this risk [15].

However, several observations were dissimilar. In pregnant subjects, the M3 feature (at least 4 papillary structures) was the most predictive for malignancy, contrary to the IOTA group studies on nonpregnant subjects where, the most predictive feature was M2 (ascites). Nevertheless, both studies suggested that M4 (irregular multilocular-solid tumor with a largest diameter larger than 100 mm) is the least predictive one. Moreover, the B5 feature (no vascular signals within the lesion) was the most predictive for the benign character, while B1 (unilocular cyst) was the least predictive. In the IOTA group studies the B1 feature was the most predictive of a benign character and B3 (presence of acoustic shadows) was the least predictive [21]. These differences in tumor characteristics may be probably explained by the younger age of our pregnant subjects. The median maternal age for patients in our Group M was 28.5 years (range: 19–41 years) and 28 years (range: 18–44 years) in Group B. In the IOTA studies the group of patients consisted of both pre- and postmenopausal women and their mean age was 57 years (range: 47–66 years) for patients with a malignant tumor and 42 years (range: 32–54 years) for patients with a benign condition [21]. We would also argue that the pregnancy itself likely influence sonographic appearance of the tumor by inducing hormonal dependent changes in tissues and accelerating the blood flow in pelvic vessels. Moreover, the visualization of ovaries may by difficult due to volume of pregnant uterus. These hypotheses however require detailed verification.

Among the strengths of our study are also its prospective protocol and the inclusion of IOTA certified examiners. Moreover, only patients who underwent surgery with detailed histopathology assessment were included.

Simple Rules in their original version is applicable in 72% of adnexal masses in pregnant subjects. This result is in line with the figure of 76% observed in nonpregnant women by other researchers [15]. For inconclusive results proposed approach is to qualify the lesion as potentially malignant or to use Simple Rules risk calculation [21]. However, definition of applicable cutoffs for pregnant subjects is necessary to enhance screening potential of risk of malignancy calculation models. So far, there is a general agreement that for masses that cannot be simply classified, scan performed by an expert sonologist should be offered [21, 22].

Limitations of the study are the fact that the data comes from a single center and the final database consisted of 61 subjects only. The above-mentioned facts indicate main future research direction. Larger series are necessary to confirm our findings in pregnant subjects.

CONCLUSIONS

This study suggests that majority of ovarian masses in pregnant patient are correctly categorized as benign

or malignant using Simple Rules. If there is no tool dedicated to ovarian cancer screening in pregnant patients, Simple Rules may fill this gap. There is no question that for both pregnant and nonpregnant subjects, sonography performed by an expert is the method with the highest sensitivity for discriminating between malignant and benign adnexal lesions [21, 22]. However, the Simple Rules method may help less experienced examiners to achieve reliable qualification of adnexal masses in pregnant women. The common usage of Simple Rules would probably reduce the number of patients that need to be referred for expert ultrasound scanning. The development of the optimal tool dedicated to ovarian mass assessment in pregnant patients will require further prospective multi-center studies and the involvement of larger cohorts of patients.

Acknowledgements

The work was supported by the Department of Gynecology and Oncology, University Hospital in Cracow, Poland.

Conflict of interest

The authors state that there are no conflicts of interest to disclose.

REFERENCES

1. de Haan J, Verheecke M, Amant F. Management of ovarian cysts and cancer in pregnancy. Facts Views Vis Obgyn. 2015; 7(1): 25–31, indexed in Pubmed: 25897369.
2. Fruscio R, de Haan J, Van Calsteren K, et al. Ovarian cancer in pregnancy. Best Pract Res Clin Obstet Gynaecol. 2017; 41: 108–117, doi: 10.1016/j.bpobgyn.2016.09.013, indexed in Pubmed: 28029502.
3. Leiserowitz GS. Managing ovarian masses during pregnancy. Obstet Gynecol Surv. 2006; 61(7): 463–470, doi: 10.1097/01.ogx.0000224614.51356.b7, indexed in Pubmed: 16787549.
4. Leiserowitz GS, Xing G, Cress R, et al. Adnexal masses in pregnancy: how often are they malignant? Gynecol Oncol. 2006; 101(2): 315–321, doi: 10.1016/j.ygyno.2005.10.022, indexed in Pubmed: 16310839.
5. Hakoun AM, AbouAl-Shaar I, Zaza KJ, et al. Adnexal masses in pregnancy: An updated review. Avicenna J Med. 2017; 7(4): 153–157, doi: 10.4103/ajm.AJM_22_17, indexed in Pubmed: 29119081.
6. Bernhard L, Klebba PK, Gray D, et al. Predictors of persistence of adnexal masses in pregnancy. Obstetrics & Gynecology. 1999; 93(4): 585–589, doi: 10.1016/s0029-7844(98)00490-6.
7. Mukhopadhyay A, Shinde A, Naik R. Ovarian cysts and cancer in pregnancy. Best Pract Res Clin Obstet Gynaecol. 2016; 33: 58–72, doi: 10.1016/j.bpobgyn.2015.10.015, indexed in Pubmed: 26707193.
8. Webb KE, Sakhel K, Chauhan SP, et al. Adnexal mass during pregnancy: a review. Am J Perinatol. 2015; 32(11): 1010–1016, doi: 10.1055/s-0035-1549216, indexed in Pubmed: 26007316.
9. Palmer J, Vatish M, Tidy J. Epithelial ovarian cancer in pregnancy: a review of the literature. BJOG. 2009; 116(4): 480–491, doi: 10.1111/j.1471-0528.2008.02089.x, indexed in Pubmed: 19250360.
10. Moro F, Mascilini F, Pasciuto T, et al. Ultrasound features and clinical outcome of patients with malignant ovarian masses diagnosed during pregnancy: experience of a gynecological oncology ultrasound center. Int J Gynecol Cancer. 2019; 29(7): 1182–1194, doi: 10.1136/ijgc-2019-000373, indexed in Pubmed: 31326950.
11. Van Calster B, Timmerman D, Bourne T, et al. Discrimination between benign and malignant adnexal masses by specialist ultrasound examination versus serum CA-125. J Natl Cancer Inst. 2007; 99(22): 1706–1714, doi: 10.1093/jnci/djm199, indexed in Pubmed: 18000221.
12. Valentin L, Jurkovic D, Van Calster B, et al. Adding a single CA 125 measurement to ultrasound imaging performed by an experienced examiner does not improve preoperative discrimination between benign and malignant adnexal masses. Ultrasound Obstet Gynecol. 2009; 34(3): 345–354, doi: 10.1002/uog.6415, indexed in Pubmed: 19585547.
13. Jacobs I, Oram D, Fairbanks J, et al. A risk of malignancy index incorporating CA 125, ultrasound and menopausal status for the accurate preoperative diagnosis of ovarian cancer. Br J Obstet Gynaecol. 1990; 97(10): 922–929, doi: 10.1111/j.1471-0528.1990.tb02448.x, indexed in Pubmed: 2223684.
14. Timmerman D, Testa AC, Bourne T, et al. International Ovarian Tumor Analysis Group. Logistic regression model to distinguish between the benign and malignant adnexal mass before surgery: a multicenter study by the International Ovarian Tumor Analysis Group. J Clin Oncol. 2005; 23(34): 8794–8801, doi: 10.1200/JCO.2005.01.7632, indexed in Pubmed: 16314639.
15. Timmerman D, Testa AC, Bourne T, et al. Simple ultrasound-based rules for the diagnosis of ovarian cancer. Ultrasound Obstet Gynecol. 2008; 31(6): 681–690, doi: 10.1002/uog.5365, indexed in Pubmed: 18504770.
16. Van Calster B, Van Hoorde K, Valentin L, et al. International Ovarian Tumour Analysis Group. Evaluating the risk of ovarian cancer before surgery using the ADNEX model to differentiate between benign, borderline, early and advanced stage invasive, and secondary metastatic tumours: prospective multicentre diagnostic study. BMJ. 2014; 349: g5920, doi: 10.1136/bmj.g5920, indexed in Pubmed: 25320247.
17. Zanetta G, Mariani E, Lissoni A, et al. A prospective study of the role of ultrasound in the management of adnexal masses in pregnancy. BJOG. 2003; 110(6): 578–583, doi: 10.1046/j.1471-0528.2003.02940.x, indexed in Pubmed: 12798475.
18. Whitecar P, Turner S, Higby K. Adnexal masses in pregnancy: A review of 130 cases undergoing surgical management. Am J Obstet Gynecol. 1999; 181(1): 19–24, doi: 10.1016/s0002-9378(99)70429-1, indexed in Pubmed: 10411786.
19. D'Ambrosio V, Brunelli R, Musacchio L, et al. Adnexal masses in pregnancy: an updated review on diagnosis and treatment. Tumori. 2021; 107(1): 12–16, doi: 10.1177/0300891620909144, indexed in Pubmed: 32180534.
20. Timmerman D, Valentin L, Bourne TH, et al. International Ovarian Tumor Analysis (IOTA) Group. Terms, definitions and measurements to describe the sonographic features of adnexal tumors: a consensus opinion from the International Ovarian Tumor Analysis (IOTA) Group. Ultrasound Obstet Gynecol. 2000; 16(5): 500–505, doi: 10.1046/j.1469-0705.2000.00287.x, indexed in Pubmed: 11169340.
21. Timmerman D, Van Calster B, Testa A, et al. Predicting the risk of malignancy in adnexal masses based on the Simple Rules from the International Ovarian Tumor Analysis group. Am J Obstet Gynecol. 2016; 214(4): 424–437, doi: 10.1016/j.ajog.2016.01.007, indexed in Pubmed: 26800772.
22. Timmerman D, Ameye L, Fischerova D, et al. Simple ultrasound rules to distinguish between benign and malignant adnexal masses before surgery: prospective validation by IOTA group. BMJ. 2010; 341: c6839, doi: 10.1136/bmj.c6839, indexed in Pubmed: 21156740.

VIA MEDICA

ORIGINAL PAPER / OBSTETRICS

Ginekologia Polska
2022, vol. 93, no. 8, 650–654

ISSN 0017–0011, e-ISSN 2543–6767

DOI 10.5603/GP.a2022.0040

Could laparoscopic cystectomy improve intrauterine insemination with controlled ovarian hyperstimulation outcomes in women with endometrioma?

Ebru Sahin Gulec[1], Deniz Oztekin[2], Suna Yıldırım Karaca[1]

1Department of Obstetrics and Gynecology, Izmir Tepecik Training and Research Hospital, Izmir, Turkey
2Department of Obstetrics and Gynecology, Izmir Bakircay University Faculty of Medicine, Izmir, Turkey

ABSTRACT

Objectives: To clarify the effects of laparoscopic cystectomy of endometriomas on intrauterine insemination with controlled ovarian hyperstimulation (COH + IUI) success in women with the disease.

Material and methods: We performed a retrospective study with endometrioma patients having at least one patent fallopian tube. The study group consisted of 57 infertile patients with a history of laparoscopic cystectomy who underwent 83 COH + IUI cycles. The control group consisted of 88 patients with endometrioma who underwent 161 COH + IUI cycles without surgery.

Results: The total number of antral follicles was significantly lower in the study group than in the control group (10.1 ± 5.1 vs 11.9 ± 5.0; p = 0.008). No significant difference was observed in the clinical pregnancy and live birth rates per cycle [(9.6% vs 7.6%; p=0.7175 OR: 1.195% CI: 0.6–2.1) and (7.2% vs 6.2%; p = 0.9544 OR: 1.1 95% CI: 0.5–2.1], respectively) between the operated and non-operated groups.

Conclusions: The results of the study show that the presence of an endometrioma with at least one patent fallopian tube does not require any cystectomy before COH+IUI treatment because no improvement was observed in the treatment outcomes of the patients who underwent preceding surgery. We conclude that an operation may be taken into consideration when malignancy cannot be ruled out or severe pelvic pain related to endometrioma cannot be relieved.

Key words: endometrioma; ovulation induction; insemination; laparoscopic surgery; pregnancy rate; live birth

Ginekologia Polska 2022; 93, 8: 650–654

INTRODUCTION

Endometrioma, defined as an ovarian cystic mass arising from ectopic endometrial tissue on the ovaries, also called ovarian endometriosis, is common in reproductive-aged women [1]. As a common form of endometriosis, endometrioma may be present in up to 20–40% of women with endometriosis [2]. Subfertility is a significant complication of endometrioma. One of the challenging areas in endometriosis-associated infertility is the presence of ovarian endometriomas.

Up to 10–25% of women with the disease require assisted reproductive treatment [1]. The presence of endometrioma does not alter ovarian function, but there is confusion on whether this affects fertility treatment outcomes. In addition to the publications claiming to reduce it [2], studies reporting that it does not affect it, have also been reported [3].

Ovarian cystectomy is the treatment of choice for endometriomas, given the low recurrence rate and associated high spontaneous pregnancy rate. On the other hand, surgical treatment of endometriomas is associated with the unintentional removal or destruction of ovarian follicles, which can cause a postoperative reduction in serum anti-Müllerian hormone (AMH) levels or antral follicle count (AFC) on ultrasound [4, 5].

In vitro fertilization (IVF) may be warranted in this setting as a primary intervention (where fertility is the only issue) since the documented loss of the ovarian cortex may further impair fertility. The problem arises when women do not want to have IVF.

Corresponding author:
Ebru Sahin Gulec
Department of Obstetrics and Gynecology, Izmir Tepecik Training and Research Hospital, Izmir, Turkey
e-mail: drebru9298@hotmail.com

Received: 11.10.2021 Accepted: 27.04.2022 Early publication date: 3.06.2022

Controlled ovarian stimulation + intrauterine insemination (COH + IUI) is one of the treatment choices for patients with endometrioma who do not want to undergo IVF treatment. Optionally, COH + IUI treatment can follow a preceding surgery.

This surgery must be performed in a way that will provide the best results. However, the surgical management of endometriomas before COH + IUI treatment is still controversial.

In this study, COH + IUI cycles following surgery of infertile women treated with laparoscopic cystectomy for severe pelvic pain due to endometrioma were examined. The aim of the study was to evaluate the effects of laparoscopic endometrioma excision (with at least one patent fallopian tube) on COH + IUI cycles.

MATERIAL AND METHODS

In this retrospective study, the effect of surgery on COH+IUI cycles was evaluated in infertile women who underwent laparoscopic cystectomy for endometrioma and pelvic pain. The data were obtained from the hospital records of 1972 patients who were treated in the reproductive health clinic of the university hospital between July 1, 2015, and December 31, 2019. A total of 145 infertile women with endometrioma aged 18-40 years having at least one patent fallopian tube who participated in our program of COH + IUI were included in the study. Patients with unexplained infertility, bilateral tubal obstruction, advanced male factor infertility, (total motile sperm count less than 5×10^6) abnormal ovulatory function (oligo-anovulation due to polycystic ovary syndrome, hyperprolactinemia, thyroid dysfunction) were excluded from the study. Women who had deep infiltrating endometriosis, endometrial polyps, uterine fibroid, focal or diffuse adenomyosis, hydrosalpinx, and congenital uterine anomalies, also were excluded after clinical, pelvic ultrasound scan, and surgical observations.

The study group (operated group) consisted of 57 women who had a history of laparoscopic cystectomy for pelvic pain unresponsive to medical therapy and endometrioma larger than 3 cm and underwent 83 COH + IUI cycles in the following six months. In comparison, the control group comprised 88 women with endometrioma who were treated only with 161 COH + IUI cycles during the same period.

All patients with laparoscopic cystectomy were operated on by the same surgical team in our clinic, and in addition to cystectomy, removal of endometriotic lesions and adhesiolysis was performed when necessary.

Endometrioma was diagnosed by laparoscopy in the study group and by vaginal ultrasound in the control group. Laparoscopic cystectomy was performed in the study group. The diagnosis of tubal patency was confirmed via hysterosalpingography and laparoscopic methylene blue perturbation in control and study groups, respectively. This study was conducted followed by the approval of the University Ethics Committee.

All patients had undergone COH + IUI treatment. Ovulation induction was initiated on day 3 (D3) with recombinant follicle-stimulating hormone (r-FSH, GONAL-f®, Merck Global). The gonadotropin dose was determined as 50–100 IU daily according to the patient's age, total antral follicle count, and D3 basal hormonal levels. Ovarian response was monitored by transvaginal ultrasound. On day 5 of the stimulation, a transvaginal ultrasound (TVUS) examination was carried out. If the size of the dominant follicle did not reach the required size, the administration of r-FSH was continued, with daily TVUS examination. When leading follicles with an average diameter higher or equal to 17 mm were detected and endometrial thickness was measured at more than 7 mm, ovulation was induced with 250 international units of recombinant human chorionic gonadotropin (r-hCG, OVITRELLE®, Merck Global). Intrauterine insemination was scheduled 36 hours after the injection of r-hCG.

The double gradient method was used for semen preparation. Ejaculates, obtained by masturbation after 2–5 days of abstinence, were prepared for IUI. Semen was prepared on the day of insemination by centrifugation on a density gradient, as previously described [6]. The prepared sperm was gently inserted within 1 cm of the fundal extend of the uterine cavity using a soft catheter. Women remained supine for 20 minutes after the procedure. Micronized progesterone (200 mg/day) was used until the serum hCG test after IUI.

In patients with more than three follicles ≥ 14 mm in diameter, the cycles were aborted before triggering ovulation with r-hCG due to the risk of hyperstimulation syndrome.

A serum hCG test was performed to confirm pregnancy at the time of the first expected menstrual period. Clinical pregnancy was defined as the ultrasonographic demonstration of an intrauterine gestational sac two weeks after a positive test. Pregnancies over 22 weeks resulting in a live birth were included in the live birth rate.

For the statistical analyses presented in the following section, Statistical Package for the Social Sciences (SPSS) for Windows (version 26.0; SPSS Inc., Chicago, IL, USA) was used. A two-sample t-test for parametric variables and Fisher's exact test for nonparametric variables were performed to compare the two groups. A p-value < 0.05 was considered statistically significant.

RESULTS

The average age of the patients in the study and control groups were 32.19 ± 4.51 years and 31.98 ± 5.53 years, respectively. The characteristics of the patients in the operated and non-operated groups are shown in Table 1. There were

Table 1. Characteristics of the women in the operated and non-operated groups

	Operated group (n = 57)	Non-operated group (n = 88)	p-value
Age [years]	32.1 ± 4.5	31.9 ± 5.5	0.76
Duration of infertility [months]	85.1 ± 44.1	97.4 ± 54.9	0.07
Bilaterality of endometrioma, n (%)	14 (24.5%)	23 (26.1%)	0.99
Primary infertility	41 (71.9%)	67 (76.1%)	0.70

Data are presented as the mean ± standard deviation and n (percentage) where appropriate; P < 0.05 is statistically significant

Table 2. Characteristics of the operated and non-operated group cycles

	Operated group cycles (n = 83)	Non-operated group cycles (n = 161)	p-value
Total motile sperm count [10^6]	76.3 ± 83.9	61.1 ± 72.3	0.14
D3 E2 [pg/mL]	42.9 ± 28.9	44.8 ± 28.9	0.62
D3 FSH [IU/mL]	8.3 ± 3.1	7.8 ± 2.6	0.20
Total antral follicle count	10.1 ± 5.1	11.9 ± 5.0	0.00
Total gonadotrophin doses [IU]	971.4 ± 181.2	986.3 ± 170.5	0.53
Duration of stimulation [days]	12.4 ± 3.3	11.8 ± 4.1	0.21

Data are presented as the mean ± standard deviation; D3 — Day 3; E2 — estradiol; FSH — follicle stimulating hormone; IU — International Unit; mL — milliliter; pg — picogram; p < 0.05 is statistically significant

no significant differences in age, duration of infertility, type of infertility (primary/secondary), or bilaterality of disease between the two groups.

Total motile sperm count, D3 basal hormone levels [estradiol (E2), FSH], total gonadotropin dose, and duration of stimulation between the operated and non-operated group cycles were not significantly different, whereas the total antral follicle count was significantly lower in the operated group cycles than in the non-operated control group as shown in Table 2 (10.1 ± 5.1 vs 11.9 ± 5.0; p = 0.008).

The effect of endometrioma surgery before COH + IUI treatment on clinical pregnancy rate and pregnancy outcomes is evaluated in Table 3. Clinical pregnancy and live birth rates per cycle were not significantly different between the operated and non-operated group cycles [(9.6% vs 7.6%; p = 0.7175, OR = 1.1, 95% CI: 0.6–2.1) and (7.2% vs 6.2%; p = 0.9544, OR = 1.1, 95% CI: 0.5–2.1), respectively].

The cancellation rate was similar in both study and control groups (6.0% vs 8.0%; p = 0.7651, OR = 0.8, 95% CI: 0.3–1.7). The reason for two cycle cancellations in the control group was that patients had more than three follicles with a diameter greater than 14 mm before triggering ovulation with r-hCG. All five cycle cancellations in the operated group and eleven cycle cancellations in the non-operated group occurred due to no response to stimulus despite increasing the gonadotropin dose by 50%.

Only one patient with a twin pregnancy in the study group suffered from hyperstimulation syndrome at the sixth week of gestation. She was treated conservatively with close follow-up.

DISCUSSION

Although endometrioma is one of the causes of subfertility, there is no consensus on the management of these patients. According to the American Society for Reproductive Medicine (ASRM) guidelines, endometriomas that cause pain and mass effects can be removed to relieve patient complaints [5].

The European Society for Reproductive and Embryology (ESHRE) endometrioma treatment guidelines suggest that IVF is an appropriate treatment, especially if the tubal function is compromised, severe male factor infertility is present, or other treatments have failed [7]. In the absence of these conditions and in patients who do not prefer IVF, COH + IUI treatment should be kept in mind as an option for subfertility treatment. The effect of removal of endometriomas on pregnancy outcomes varies according to the type of treatment to be applied.

According to a Cochrane review, removal of endometriomas by laparoscopic cystectomy improves spontaneous pregnancy rates while not altering pregnancy outcomes in IVF treated patients [8]. In patients who are planning to

Table 3. Treatment outcomes of controlled ovarian stimulation + intrauterine insemination in operated and non-operated group cycles

	Operated group cycles (n = 83)	Non-operated group cycles (n = 161)	p-value	OR (95% CI)
Clinical pregnancy, n [%]	8 (9.6%)	12 (7.4%)	0.717	1.1 (0.6–2.1)
Live birth, n [%]	6 (7.2%)	10 (6.2%)	0.954	1.1 (0.5–2.1)
Cancellation, n [%]	5 (6.0%)	13 (8.0%)	0.765	0.8 (0.3–1.7)
Hyperstimulation, n	1	0	—	—
Multiple pregnancy, n	1	0	—	—

Data are presented as numbers (percentages) where appropriate; $p < 0.05$ is statistically significant; CI — confidence interval; COH + IUI — controlled ovarian stimulation + intrauterine insemination; OR — odds ratio

receive COH + IUI treatment, the effect of removal of endometriomas before treatment on pregnancy outcomes has not been clarified. Leone Roberti Maggiore et al. [9] reported that an endometrioma itself does not diminish ovarian function. In their study, ovulation rates of normal and endometriotic ovaries were similar. However, an endometrioma may reduce the number of follicles recruited in the ovary by exogenous FSH stimulation, there is no evidence that the cyst affects pregnancy or live birth rates after IVF [10].

On the other hand, ovarian surgery to remove the endometrioma could be associated with reduced ovarian reserve [11, 12]. Recently, laparoscopic cystectomy to remove endometrioma has caused concerns regarding damage to ovarian reserve [13]. Damage to the ovary becomes more severe as the diameter of the endometrioma increases [14]. Furthermore, Busacca et al. reported that patients who have undergone operations for bilateral endometrioma have a 2.4% risk of premature ovarian failure after surgery [15]. However, premature ovarian failure is associated with reduced ovarian reserve with a significant decrease in serum anti-Müllerian hormone (AMH) levels but not in antral follicle counts [11, 12].

However, in our study, we observed that the number of antral follicles decreased significantly in the operated group compared to the non-operated group, which was not in agreement with this study. A limitation of our study is that we did not measure serum AMH levels to assess ovarian reserve. Therefore, we did not know whether there is a change in AMH values. Nevertheless, when interpreting the decreased serum AMH levels after surgery, it should be kept in mind that the predictive value of AMH alone for ovarian reserve is not better than the total number of antral follicles in a clinically eligible patient for IUI [16].

Benaglia et al. reported that the presence of endometrioma in women selected for IVF did not significantly affect their response to ovarian stimulation [17]. Bongioanni et al. compared women with ovarian endometriosis and tubal factor-induced infertility and found that endometriomas did not impair IVF outcomes. In addition, the authors reported that laparoscopic removal of endometriomas has no beneficial effect on IVF outcomes but may have a negative effect on ovarian response to gonadotropins [18].

A recent meta-analysis showed that resection of endometriomas before IVF treatment does not improve pregnancy outcomes [19]. Decreased ovarian reserve is a potential risk factor for surgical resection of endometriomas, especially in women with bilateral disease [20]. Since endometriomas are associated with dense adhesions in most patients, standard surgical risks such as adjacent visceral injuries should be considered when deciding on the operation [5]. Surgery is not routinely recommended for patients with asymptomatic endometrioma due to subfertility in our clinic. However, many patients with endometrioma have had surgery for pelvic pain.

Gandhi et al. [21] showed that COH+IUI treatment did not improve pregnancy rates at any stage of endometriosis compared to spontaneous cycles. They recommended that patients who have been operated on for endometrioma should also receive IVF treatment. Conversely, Kereszturi et al. [22] reported that COH + IUI treatment following surgery was more effective than surgery alone. In our clinic, we recommend COH + IUI treatment instead of spontaneous follow-up to patients who have subfertility and have undergone surgery for endometrioma but do not want IVF treatment. In our study, clinical pregnancy and live birth rates per cycle were not different in the operated and non-operated groups after COH + IUI treatment. The cycle cancellation rate was similar in both groups.

CONCLUSIONS

According to the results of the study, laparoscopic cystectomy of endometriomas before COH + IUI treatment did not significantly improve the pregnancy outcomes in treated patients. Surgical removal of endometriomas in women suffering from subfertility should be considered if they are symptomatic or have malignancy potential. However, the risks of persistent endometriomas, such as the rupture of an endometrioma, infections, and future malignancy, should not be ignored. Further randomized controlled trials are needed to clarify the effect of endometrioma surgery on

treatment outcomes in COH + IUI cycles in women experiencing subfertility.

Conflict of interest

The authors declare that there are no conflicts of interest.

Authors' statement

All authors certify that they have no affiliations with or involvement in any organization or entity with any financial or nonfinancial interests in the subject matter or materials discussed in this manuscript.

REFERENCES

1. Alborzi S, Zahiri Sorouri Z, Askari E, et al. The success of various endometrioma treatments in infertility: A systematic review and meta-analysis of prospective studies. Reprod Med Biol. 2019; 18(4): 312–322, doi: 10.1002/rmb2.12286, indexed in Pubmed: 31607791.
2. Kolanska K, Cohen J, Bendifallah S, et al. Pregnancy outcomes after controlled ovarian hyperstimulation in women with endometriosis-associated infertility: GnRH-agonist versus GnRH-antagonist. J Gynecol Obstet Hum Reprod. 2017; 46(9): 681–686, doi: 10.1016/j.jogoh.2017.09.007, indexed in Pubmed: 28970135.
3. Hamdan M, Dunselman G, Li TC, et al. The impact of endometrioma on IVF/ICSI outcomes: a systematic review and meta-analysis. Hum Reprod Update. 2015; 21(6): 809–825, doi: 10.1093/humupd/dmv035, indexed in Pubmed: 26168799.
4. Zondervan KT, Becker CM, Missmer SA. Endometriosis. N Engl J Med. 2020; 382(13): 1244–1256, doi: 10.1056/NEJMra1810764, indexed in Pubmed: 32212520.
5. Practice Committee of the American Society for Reproductive Medicine. Treatment of pelvic pain associated with endometriosis: a committee opinion. Fertil Steril. 2014; 101(4): 927–935, doi: 10.1016/j.fertnstert.2014.02.012, indexed in Pubmed: 24630080.
6. Cai He, Gordts S, Sun J, et al. Reproductive outcomes with donor sperm in couples with severe male-factor infertility after intracytoplasmic sperm injection failures. J Assist Reprod Genet. 2020; 37(8): 1883–1893, doi: 10.1007/s10815-020-01828-0, indexed in Pubmed: 32440933.
7. Schleedoorn MJ, Nelen WL, Dunselman GAJ, et al. EndoKey Group, European Society of Human Reproduction and Embryology. ESHRE guideline: management of women with endometriosis. Hum Reprod. 2014; 29(3): 400–412, doi: 10.1093/humrep/det457, indexed in Pubmed: 24435778.
8. Hart RJ, Hickey M, Maouris P, et al. Excisional surgery versus ablative surgery for ovarian endometriomata. Cochrane Database Syst Rev. 2005(3): CD004992, doi: 10.1002/14651858.CD004992.pub2, indexed in Pubmed: 16034960.
9. Maggiore UL, Scala C, Venturini PL, et al. Endometriotic ovarian cysts do not negatively affect the rate of spontaneous ovulation. Hum Reprod. 2015; 30(2): 299–307, doi: 10.1093/humrep/deu308, indexed in Pubmed: 25432923.
10. Benschop L, Farquhar C, van der Poel N, et al. Interventions for women with endometrioma prior to assisted reproductive technology. Cochrane Database Syst Rev. 2010(11): CD008571, doi: 10.1002/14651858.CD008571.pub2, indexed in Pubmed: 21069706.
11. Muzii L, Di Tucci C, Di Feliciantonio M, et al. The effect of surgery for endometrioma on ovarian reserve evaluated by antral follicle count: a systematic review and meta-analysis. Hum Reprod. 2014; 29(10): 2190–2198, doi: 10.1093/humrep/deu199, indexed in Pubmed: 25085800.
12. Younis JS, Shapso N, Ben-Sira Y, et al. Endometrioma surgery - a systematic review and meta-analysis of the effect on antral follicle count and anti-Müllerian hormone. Am J Obstet Gynecol. 2022; 226(1): 33–51.e7, doi: 10.1016/j.ajog.2021.06.102, indexed in Pubmed: 34265271.
13. Benaglia L, Somigliana E, Vighi V, et al. Rate of severe ovarian damage following surgery for endometriomas. Hum Reprod. 2010; 25(3): 678–682, doi: 10.1093/humrep/dep464, indexed in Pubmed: 20083485.
14. Tang Y, Chen SL, Chen X, et al. Ovarian damage after laparoscopic endometrioma excision might be related to the size of cyst. Fertil Steril. 2013; 100(2): 464–469, doi: 10.1016/j.fertnstert.2013.03.033, indexed in Pubmed: 23587701.
15. Busacca M, Riparini J, Somigliana E, et al. Postsurgical ovarian failure after laparoscopic excision of bilateral endometriomas. Am J Obstet Gynecol. 2006; 195(2): 421–425, doi: 10.1016/j.ajog.2006.03.064, indexed in Pubmed: 16681984.
16. Dondik Y, Virji N, Butler TS, et al. The value of anti-Müllerian hormone in predicting clinical pregnancy after intrauterine insemination. J Obstet Gynaecol Can. 2017; 39(10): 880–885, doi: 10.1016/j.jogc.2017.01.029, indexed in Pubmed: 28647445.
17. Benaglia L, Pasin R, Somigliana E, et al. Unoperated ovarian endometriomas and responsiveness to hyperstimulation. Hum Reprod. 2011; 26(6): 1356–1361, doi: 10.1093/humrep/der097, indexed in Pubmed: 21478182.
18. Bongioanni F, Revelli A, Gennarelli G, et al. Ovarian endometriomas and IVF: a retrospective case-control study. Reprod Biol Endocrinol. 2011; 9: 81, doi: 10.1186/1477-7827-9-81, indexed in Pubmed: 21679474.
19. Hamdan M, Dunselman G, Li TC, et al. The impact of endometrioma on IVF/ICSI outcomes: a systematic review and meta-analysis. Hum Reprod Update. 2015; 21(6): 809–825, doi: 10.1093/humupd/dmv035, indexed in Pubmed: 26168799.
20. Goodman LR, Goldberg JM, Flyckt RL, et al. Effect of surgery on ovarian reserve in women with endometriomas, endometriosis and controls. Am J Obstet Gynecol. 2016; 215(5): 589.e1–589.e6, doi: 10.1016/j.ajog.2016.05.029, indexed in Pubmed: 27242204.
21. Gandhi AR, Carvalho LF, Nutter B, et al. Determining the fertility benefit of controlled ovarian hyperstimulation with intrauterine insemination after operative laparoscopy in patients with endometriosis. J Minim Invasive Gynecol. 2014; 21(1): 101–108, doi: 10.1016/j.jmig.2013.07.009, indexed in Pubmed: 23911563.
22. Keresztúri A, Kozinszky Z, Daru J, et al. Pregnancy rate after controlled ovarian hyperstimulation and intrauterine insemination for the treatment of endometriosis following surgery. Biomed Res Int. 2015; 2015: 282301, doi: 10.1155/2015/282301, indexed in Pubmed: 26247014.

VIA MEDICA

ORIGINAL PAPER / OBSTETRICS

Ginekologia Polska
2022, vol. 93, no. 8, 655–661

ISSN 0017–0011, e-ISSN 2543–6767

DOI 10.5603/GP.a2022.0044

The attitude of Polish women planning pregnancy and/or having children towards vaccinations: a cross-sectional survey study

Carlo Bienkowski[1–3], Monika Kowalczyk[4, 5], Agata Golik[4, 5], Joanna Kacperczyk-Bartnik[6], Pawel Bartnik[6], Agnieszka Dobrowolska-Redo[6], Ewa Romejko-Wolniewicz[6], Maria Pokorska-Spiewak[2, 3]

[1]Doctoral School, Medical University of Warsaw, Poland
[2]Department of Children's Infectious Diseases, Medical University of Warsaw, Poland
[3]Warsaw Hospital of Infectious Diseases, Warsaw, Poland
[4]Student's Scientific Group Affiliated to the Department of Children's Infectious Diseases, Medical University of Warsaw, Poland
[5]Student's Scientific Group Affiliated to the 2nd Department of Obstetrics and Gynaecology, Medical University of Warsaw, Poland
[6]2nd Department of Obstetrics and Gynaecology, Medical University of Warsaw, Poland

ABSTRACT

Objectives: Infectious diseases in pregnant women can cause birth defects. Implementing appropriate prevention methods while planning pregnancy can help avoid some of them.

Material and methods: A cross-sectional survey study was performed. The questionnaire investigated attitudes towards vaccinations, as well as opinions on anti-vaccine movements and the so-called "chickenpox parties". The questionnaire was developed for the purpose of this study and the survey was conducted using the google form, which was posted on social media groups for women planning pregnancy, being pregnant or for mothers' groups from Poland.

Results: The study group consisted of 2402 women; their median age was 31 years (range 16–54 years). Most women were from cities > 100,000 inhabitants (49.7%, 1194/2402) and had higher education (71.9%, 1726/2402). A positive attitude towards vaccinations was more common among younger, nulliparous women from big cities ($p = 0.02$, $p = 0.04$ and $p = 0.01$, respectively). 2068/2402 (86.1%) of respondents were not vaccinated before pregnancy and 1931/2402 (80.4%) of women were not vaccinated during pregnancy. While most women (1545/2402, 64.3%) considered vaccination safe, and effective (1904/2402, 79.3%) against infectious diseases, many (n = 296/2402 12.3%) have no opinion on the so-called chickenpox party.

Conclusions: Most surveyed women had a positive attitude towards vaccinations and consider vaccines a safe and effective method of protection against infectious diseases. Since a significant proportion of women were not vaccinated before or during pregnancy and about 12% of women are undecided, the physician's role is crucial in educating and persuading the patient to be vaccinated.

Key words: anti-vaccination movement; infections; newborn diseases; pregnancy; vaccines

Ginekologia Polska 2022; 93, 8: 655–661

INTRODUCTION

Intrauterine or perinatally transmitted infections are a significant cause of fetal and neonatal mortality and an important contributor to morbidity in early and late childhood. The term TORCH complex is used to describe common mother-to-child infections, including toxoplasmosis, other: syphilis, hepatitis B and C viruses (HBV and HCV), human immunodeficiency virus (HIV), human papillomavirus (HPV), parvovirus B19, varicella and zoster virus (VZV) and enteroviruses. The acronym also includes rubella (MMR), cytomegalovirus (CMV) and herpes simplex virus (HSV). The majority in this group are infections of viral etiology [1].

Preconception care should be given to every woman of childbearing age. The main goals of antenatal care include

Corresponding author:
Carlo Bienkowski
Department of Children's Infectious Diseases, 37 Wolska St, 01-201 Warsaw, Poland
e-mail: carlo.bienkowski@gmail.com

Received: 1.03.2022 Accepted: 29.04.2022 Early publication date: 3.06.2022

identifying potential risks to the mother, fetus and pregnancy, and providing information about potential risk factors, and intervention options [2–4].

A detailed medical interview is essential for risk assessment. It is important to gather accurate information about past and present chronic diseases, including diabetes and hypertension, as well as family history of genetic and congenital diseases. Information about gynecological diseases and previous obstetric history, data on the course of previous pregnancies, way of their termination, and data on children's health are also important [2, 5]. Regular medical visits and laboratory testing reduce the risk of complications during pregnancy and delivery [2, 5, 6].

On January 1, 2019, new recommendations were introduced in Poland, outlining the scope of diagnostic tests and medical consultations that should be performed throughout the course of pregnancy. The testing scheme for vertical infections is considered correctly implemented if the first testing towards toxoplasmosis, rubella, HIV, HCV, and syphilis are performed before the tenth week of gestation. If the first tests for toxoplasmosis are negative, reassessment is recommended between the twenty-first and twenty-sixth week of gestation. Moreover, testing for HBV and HIV is recommended between the thirty-third and thirty-seventh week of gestation [4]. Many interventions before and during pregnancy can reduce the incidence of birth defects, congenital diseases, fetal impairment or pregnancy complications. Some interventions need to be performed before conception. They include glycemic control, weight loss, folic acid supplementation [7–9]. Pregnant women should give up drinking and smoking. It is also important to discontinue the administration of teratogenic drugs, and if the patient needs treatment, these drugs should be replaced with medications that are safe for the fetus. It is also important to maintain healthy body weight, as obesity increases the risk of birth defects and may cause many complications for the mother [7, 8]. During pregnancy, women should pay attention to hygiene. Hand washing, avoiding eating uncooked meat and unpasteurized food reduce the risk of developing diseases such as toxoplasmosis, and listeriosis [7, 9].

According to the recommendations of the Advisory Committee on Immunization Practices at Centers for Disease Control and Prevention and the American College of Obstetrics and Gynecology, a woman who is planning to become pregnant should be vaccinated against MMR and chickenpox at least four weeks before conception (as these vaccinations are contraindicated during pregnancy), unless she has had varicella or rubella or has been vaccinated against these diseases. From the second trimester of pregnancy, every woman should be vaccinated against influenza and hepatitis B (unless she has previous history of these diseases or has been vaccinated against them). Vaccination against pertussis (DTP) with an acellular vaccine between 27 and 34 weeks (36 weeks in Poland) of pregnancy is also recommended in order to pass the antibodies to her child (irrespective of her previous history of infection or immunization) [10].

Objectives

The aim of the study was to evaluate the attitude of Polish women who have children or are planning a pregnancy towards vaccination, infectious diseases that may cause vertical infections, their medical knowledge and the main sources of medical information.

MATERIAL AND METHODS

A cross-sectional survey study was performed anonymously, which checked the attitudes of Polish women planning pregnancy, being pregnant or already having children towards various aspects related to vaccinations and vertical infections. Moreover, attitudes towards anti-vaccine movements and chickenpox parties were also analyzed. The survey analyzed the vaccination coverage among surveyed women. The analysis included whether women were vaccinated appropriately when planning pregnancy, and whether these vaccinations were recommended by doctors. In addition, it was verified, whether women were vaccinated during pregnancy against the diseases according to recommendations. The study also checked women's willingness to vaccinate their children, and if they consider vaccination to be safe and effective against infectious diseases.

The questionnaire was developed for the purpose of this study and the survey was conducted using the google form, which was posted on social media groups for women planning pregnancy, being pregnant or for mothers' groups from Poland. Women from these groups were only once exposed to the questionnaire. Groups were chosen based on the names "Mothers", "Future mothers", "Planning pregnancy" and a combination of these titles along with the names of specific areas of Poland, namely provinces and voivodeships. Every surveyed woman, when completing the questionnaire, had to agree to complete it and had given permission to analyze and publish data collected from her survey. The design of the work conforms to standards currently applied in the Medical University of Warsaw's Bioethics Committee. Approval number: AKBE/131/2021.

Normality of continuous variables was tested using Shapiro-Wilk's test. The U-Mann Whitney test was used to compare continuous variables and the chi^2 test was used to evaluate categorical variables. A p value of < 0.05 was considered significant. Logistic regression was used to calculate adjusted odds ratios and to determine variables independently associated with the attitude towards vaccinations. Statistical analysis was performed using programme Statistica version 13.3.

RESULTS

The collected data were grouped into 4 subgroups:

- study group characteristics,
- vaccination-related data,
- infectious diseases during pregnancy,
- attitude towards anti-vaccine movements and chickenpox parties.

Study group characteristics

The study group consisted of 2402 women planning pregnancy or having children. The median age was 31 years (range: 16–54 years). The largest group consisted of women living in cities > 100,000 inhabitants (n = 1194/2402, 49.7%), with higher education (n = 1726/2402, 71.9%), married (n = 1841/2402, 76.6%) and in a relationship (n = 2329/2402, 97%). Most of the surveyed women had been once pregnant (n = 1009/2402, 42%) and gave birth once (n = 1211/2402, 50.4%). When implementing the survey, 788/2402 (32.8%) of women were pregnant. The survey also checked if women have contact with school-age children (1491/2402, 62.1%) and the source of their knowledge about vaccines, which was mostly medical staff (1848/2402, 76.9%). Baseline characteristics of the study group are presented in Table 1.

Vaccination-related data

Most women had been previously vaccinated according to their vaccination schedule [against tuberculosis, hepatitis B, DTP, MMR, polio (n = 1283/2402, 53.4% for polio to 1728/2402, 71.9% for DTP) almost a quarter of women did not remember what infectious diseases they were vaccinated against in the past (n = 566/2402, 23.6%) (Fig.1). Most women had not been vaccinated while planning pregnancy (n = 2069/2402, 86.1%) (Fig. 2). This may be because physicians often do not recommend vaccinations before the pregnancy (n = 1989/2402, 82.2%). The study shows that only about 3% (67–91/2402, 2.8–3.8%) of physicians recommended vaccination against influenza or pertussis to pregnant women. Nonetheless 1712/2402 (71.27%) of women have a positive attitude towards vaccinations. It was more common among nulliparous, younger women living in more populous cities (Tab. 2). A total of 71.3% (n = 1712/2402) of women consider vaccinations necessary for their children's health. Also, 64.3 % (n = 1544/2402) of respondents consider vaccinations safe for their children, while 79.3% (n = 1905/2402) consider them effective in preventing infectious diseases.

Infectious diseases during pregnancy

The study also checked women's knowledge of the risk associated with infectious diseases during pregnancy. Polish women were also asked about the most dangerous, in their opinion, pathogenic factors that may affect the development of the fetus (Tab. 3). Seventy three percent (n = 1752/2402) of women have never heard the acronym TORCH. Most women know that fetal birth defects can be caused by infectious agents (n = 1718/2402, 74.1%), but almost a quarter were not aware of this fact (n = 544/2402, 22.6%). Among the five most dangerous in surveyed women's opinion infectious diseases for the fetus, were: toxoplasmosis (n = 1594/2402, 66.4%), rubella (n = 1195/2402, 49.8%), CMV (n = 912/2402, 38%), HIV (n = 810/2402, 33.7%) and measles (n = 643/2402, 26.8%). According to respondents, the five most dangerous fetal defects caused by infectious agents were: nervous system defects (n = 1599/2402, 66.6%), heart defects (n = 1549/2402, 64.5%), intrauterine death (n = 1445/2402, 60.2%), extremities hypoplasia (n = 1009/2402, 42%), and body mass deficiency (n = 729/2402, 30.3%).

Attitude towards anti-vaccine movements and chickenpox parties

Our study showed 57% (n = 1350/2402) of the surveyed women fully disagree with anti-vaccine movements, 22.9% (n = 549/2402) partially agree, and 11.8% (n = 284/2402) have no opinion and 6.2% (n = 149/2402) fully agree. In case of chickenpox party, as much as 83.1% (n = 2013/2402) of women consider this phenomenon dangerous for children's health, 12.3% (n = 296/2402) have no opinion on this matter, and 3.9% (n = 93/2402) consider it a good way for children to acquire immunity. Women living in cities > 100,000 inhabitants considered chickenpox party more often as a dangerous phenomenon for children's health (51.19%, n = 989 vs 43.62%, n = 205, p = 0.04).

DISCUSSION

Our study revealed that a positive attitude towards vaccinations was more common among nulliparous, younger women living in more populous cities (Tab. 3).

Interestingly, it seems that there is no real correlation between attitudes towards vaccination and socio-economic status or level of education. Much better predictors are high levels of underground thinking, low tolerance to perceived personal freedom, aversion to needles or blood, and religious issues. But most importantly, worried parents are the consumers of misinformation [11].

A German study conducted by Betsch C et al. [12] demonstrated that accessing vaccine-critical websites for five to ten minutes increases the perception of risk of vaccination and decreases the perception of risk resulting from omitting vaccinations as well as the willingness to vaccinate. This is worrying given that as many as 76.1% (n = 1829/2402) of surveyed women use the internet as a source of knowledge about vaccination.

Anti-vaccine movement is a colloquial term for initiatives of people who negate the effectiveness and

Table 1. Baseline characteristics of the study group

		n = 2402	%
Place of residence	Village	549	22.8
	City < 10 000	167	7
	City 10 000–100 000	492	20.5
	City > 100 000	1194	49.7
Education	Medium	530	22.01
	Vocational school	97	4
	Higher	1726	71.9
	Other	492	2
Marital status	Single	440	18.03
	Married	1841	76.6
	Divorced	69	2.09
	Widowed	52	2.02
Stable relationship	Yes	2329	97
	No	73	3
Number of pregnancies	0 pregnancies	98	4.1
	1 pregnancy	1009	42
	2 pregnancies	832	34.6
	3 pregnancies	299	12.4
	> 4 pregnancies	164	6.9
Number of births	0 births	243	10.1
	1 birth	1211	50.4
	2 births	754	31
	> 4 births	203	8.5
Current pregnancy status	Not pregnant	456	19
	Pregnant	1614	67.2
	Not pregnant, planning pregnancy	332	13.8
Sources of information about medical knowledge	Medical staff	1848	76.9
	Books	837	34.7
	Press	426	17.7
	Internet	1829	76.1
	Television	298	12.4
	Family	748	31.3
	Friends	756	31.5
	Lamaze class	318	13.2
	University class	5	0.2
	Science publications	3	0.1
	Leaflets	85	3.5

expediency of vaccinating. The history of anti-vaccination movements dates back to the nineteenth century, when Edward Jenner proved that vaccinia virus infection protects against smallpox virus infection and its complications. Already then many people disapproved his actions [13]. Nowadays, the anti-vaccine movement has increased significantly, following the publication of a paper by Andrew Wakefield in 1998 in which he argued that measles, mumps, rubella (MMR) vaccination was associated with autism [14]. The greatest intensification of anti-vaccine movements in Europe took place after the publication of Wakefield's pseudo-research, the consequences of which we must face today. In the UK, the MMR vaccination rate dropped from 92% in 1996 to 84% in 2002. In 2003, the rate was as low as 61% in some parts of London, far below the rate needed to avoid an epidemic of measles [15]. Anti-vaccine movements

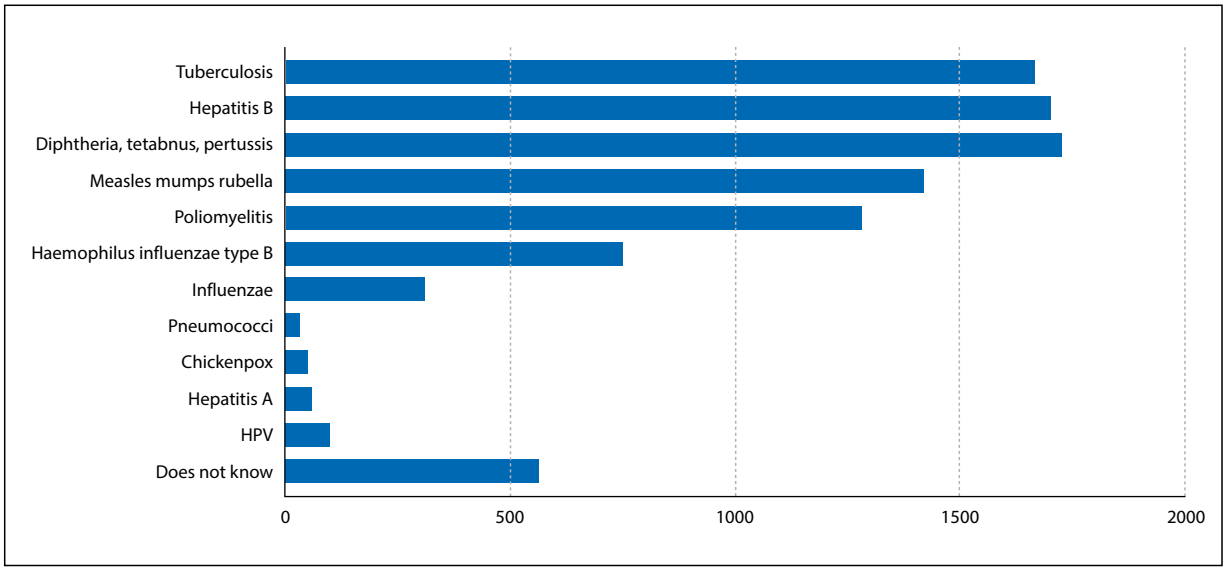


Figure 1. Data presents which pathogens the surveyed women had been vaccinated against according to their individual vaccination schedule; HPV — human papillomavirus

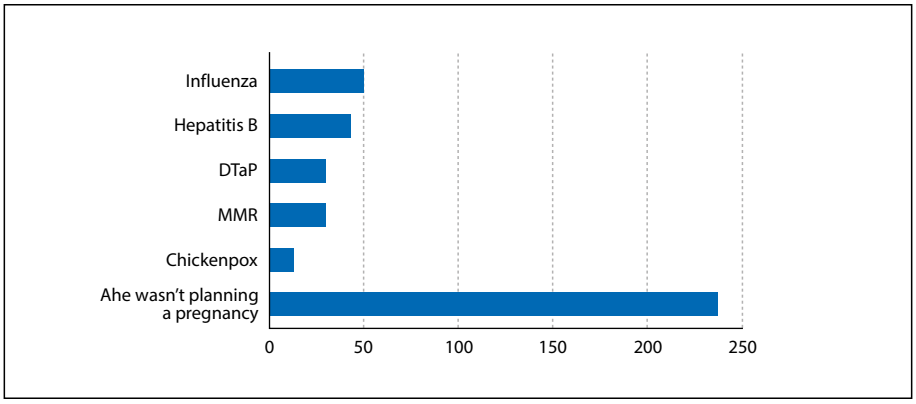


Figure 2. Data presents which pathogens the surveyed women had been vaccinated against due to planning her pregnancy; MMR — rubella; DTaP — Diphteria, tetanus, pertussis

are also gaining more and more popularity in Poland. In our country, the number of people who avoid vaccination is constantly increasing. In 2010, as a result of the parents' refusal, 3437 children were not vaccinated with compulsory vaccines, whereas in 2018 about 40,000 parents had already evaded their vaccinations [14]. In a survey conducted by Furman et al. [16] 2.3% of parents declared that they have avoided mandatory childhood vaccination at least once, 8.5% of parents would stop vaccinating their children if the vaccination obligation was abolished. The aftermath of these activities can also be seen in Poland, the level of vaccination against measles, mumps and rubella fell below 95%, ensuring a safe level for society. Our study showed that 57% (n = 1350/2402) of the surveyed women fully disagree with anti-vaccine movements. It is difficult to reduce this tendency if women planning pregnancy in Poland are not vaccinated according to recommendations (86.1%, n = 2069/2402). On the other hand, if a woman is planning her pregnancy and is under medical care, the physician should inform her about the recommended vaccinations. Analyzing the vaccination coverage of Polish women against influenza, data from the National Institute of Public Health — National Institute of Hygiene show that in 2018 only 2.5% of people have been vaccinated against influenza [14]. Our study showed that only 3% of doctors recommended pregnant women to vaccinate against influenza.

Recently popular among parents are the so-called "chickenpox party", these are deliberate organized meetings of healthy children with people infected with chickenpox virus. The purpose of the meeting is to infect healthy children so that their immune system develops natural

Table 2. Factors influencing the attitude towards vaccinations

Attitude towards vaccinations	Positive	Negative	p-value
n	1712	690	
Median age	30.76 ± 5.5 years	31.34 ± 5.2 years	0.002
Parous	70.63 %	29.37%	0.0039
Nulliparous	76.95 %	23.05 %	
City > 100 000	51.34 %	45.65 %	0.013
City < 100 000	48.66 %	54.35 %	

immunity after illness [17]. An Italian Study revealed that 2.2% of the parents believed that varicella could cause serious health problems [18]. In our study 83.1% (n = 2013/2402) of women consider the phenomenon of chickenpox party as dangerous for their children's health. This attitude was more common in women living in cities > 100,000 inhabitants (51.19%, n = 989 vs 43.62%, n = 205, p = 0.04).

Limitations of the study

Since it was a questionnaire study, women completing the survey might have not understood some questions, since it was performed via social media, we could not explain it enough for some of them. On the other hand, most of surveyed women had higher education, which may suggest that they understood the questionnaire properly. However, one cannot be sure if the answers were honest. We decided to collect a high amount of correctly completed surveys in order to minimize the risk of getting dishonest answers and having unreliable results.

Most of the surveyed women live in big cities. It might be worth considering extending the study among rural areas in order to collect more representative data, especially when most women are obtaining their knowledge about vaccines mainly from medical staff, and medical care is more limited in the countryside.

CONCLUSIONS

To sum up, most of surveyed women want to be vaccinated and to vaccinate their children, they consider vaccines safe and effective against infectious diseases. A significant proportion of women planning to become pregnant or being pregnant is not vaccinated, the role of physician convincing the patient to be vaccinated is crucial in this matter. About 12% of women are the undecided fraction, and the educational role of physicians is essential to convince them of the importance of vaccination.

Ethics approval and consent to participate

The design of the work conforms to standards currently applied in Medical University of Warsaw's Bioethics Committee. Approval number: AKBE/131/2021.

Table 3. Presents which infectious diseases are Polish women the most afraid or would have been afraid of due to their pregnancy/planning pregnancy

A) Infectious diseases that Polish women are the most afraid of due to their pregnancy	
Infectious disease	**n = 2402**
Toxoplasmosis, n (%)	1594 (66.4)
Rubella, n (%)	1195 (49.8)
CMV, n (%)	912 (38.0)
HIV, n (%)	810 (33.7)
Measles, n (%)	643 (26.8)
Chickenpox, n (%)	603 (25.1)
Herpes, n (%)	575 (23.9)
Syphilis, n (%)	515 (21.4)
Pertussis, n (%)	484 (20.1)
Hepatitis B, n (%)	483 (20.1)
Tuberculosis, n (%)	450 (18.7)
Mumps, n (%)	395 (16.4)
Influenza, n (%)	392 (16.3)
Tetanus, n (%)	271 (11.3)
Polio, n (%)	247 (10.3)
Diphtheria, n (%)	157 (6.5)
I am not afraid, n (%)	126 (5.3)
B) Congenital defects caused by infections agents according to Polish women	
Congenital defect associated with infectious agent	**n = 2402**
Defects of the nervous system, n (%)	1599 (66.6)
Congenital heart defects, n (%)	1549 (64.5)
Intrauterine death, n (%)	1445 (60.2)
Hydrocephalus, n (%)	1009 (42.0)
Hypoplasia of the limbs, n (%)	1009 (42.0)
Weight loss, n (%)	729 (30.3)
Deafness, n (%)	694 (28.9)
Does not know, n (%)	558 (23.2)
AIDS, n (%)	471 (19.6)
Congenital cataract, n (%)	237 (9.9)
There is no risk, n (%)	41 (1.7)

CMV — cytomegalovirus; HIV — human immunodeficiency virus

Funding

The Article Processing Charges were funded by the Foundation for Science Development in Warsaw Hospital of Infectious Diseases.

Ethics and consent to participate

Written informed consent to participate was obtained from all participants.

Availability of data and material

The data sets used and/or analyzed during the current study can be made available by the corresponding author on reasonable request.

Authors' contributions

CB, MK, AG, JKB conceived and designed the analysis, collected the data, wrote the paper, PB conceived and designed the analysis, performed the analysis. ADR, ERW and MPS conceived and designed the analysis, contributed to critically refining the article. All authors have read and approved the final article.

Conflict of interest

The authors declare no conflict of interest.

REFERENCES

1. Neu N, Duchon J, Zachariah P. TORCH infections. Clin Perinatol. 2015; 42(1): 77–103, viii, doi: 10.1016/j.clp.2014.11.001, indexed in Pubmed: 25677998.
2. Johnson K, Posner S, Biermann J, et al. Recommendations to Improve Preconception Health and Health Care--United States: A Report of the CDC/ATSDR Preconception Care Work Group and the Select Panel on Preconception Care. PsycEXTRA Dataset. 2006, doi: 10.1037/e506902006-001.
3. Mazza D, Chapman A, Michie S. Barriers to the implementation of preconception care guidelines as perceived by general practitioners: a qualitative study. BMC Health Serv Res. 2013; 13: 36, doi: 10.1186/1472-6963-13-36, indexed in Pubmed: 23368720.
4. Bieńkowski C, Aniszewska M, Kowalczyk M, et al. Analysis of preventable risk factors for infection in pregnant women: case-control study. J Clin Med. 2022; 11(4), doi: 10.3390/jcm11041105, indexed in Pubmed: 35207377.
5. Bernstein PS, Sanghvi T, Merkatz IR. Improving preconception care. J Reprod Med. 2000; 45(7): 546–552, indexed in Pubmed: 10948464.
6. Bieńkowski C, Aniszewska M, Pokorska-Śpiewak M. Correct implementation of screening testing toward congenital infections during pregnancy reduces the risk of abnormal fetal ultrasound. Pediatr Infect Dis J. 2022; 41(6): e271–e272, doi: 10.1097/INF.0000000000003509, indexed in Pubmed: 35389954.
7. Viswanathan M, Treiman KA, Kish-Doto J, et al. Folic acid supplementation for the prevention of neural tube defects: an updated evidence report and systematic review for the us preventive services task force. JAMA. 2017; 317(2): 190–203, doi: 10.1001/jama.2016.19193, indexed in Pubmed: 28097361.
8. Korenbrot CC, Steinberg A, Bender C, et al. Preconception care: a systematic review. Matern Child Health J. 2002; 6(2): 75–88, doi: 10.1023/a:1015460106832, indexed in Pubmed: 12092984.
9. American Diabetes Association. 2. Classification and Diagnosis of Diabetes. Diabetes Care. 2021; 44(Suppl 1): S15–S33, doi: 10.2337/dc21-S002, indexed in Pubmed: 33298413.
10. Swamy GK, Heine RP. Vaccinations for pregnant women. Obstet Gynecol. 2015; 125(1): 212–226, doi: 10.1097/AOG.0000000000000581, indexed in Pubmed: 25560127.
11. Swingle CA. How do we approach anti-vaccination attitudes? Mo Med. 2018; 115(3): 180–181, indexed in Pubmed: 30228713.
12. Betsch C, Renkewitz F, Betsch T, et al. The influence of vaccine-critical websites on perceiving vaccination risks. J Health Psychol. 2010; 15(3): 446–455, doi: 10.1177/1359105309353647, indexed in Pubmed: 20348365.
13. Dubé E, Vivion M, MacDonald NE. Vaccine hesitancy, vaccine refusal and the anti-vaccine movement: influence, impact and implications. Expert Rev Vaccines. 2015; 14(1): 99–117, doi: 10.1586/14760584.2015.964212, indexed in Pubmed: 25373435.
14. Jolley D, Douglas KM. The effects of anti-vaccine conspiracy theories on vaccination intentions. PLoS One. 2014; 9(2): e89177, doi: 10.1371/journal.pone.0089177, indexed in Pubmed: 24586574.
15. Murch S. Separating inflammation from speculation in autism. Lancet. 2003; 362(9394): 1498–1499, doi: 10.1016/S0140-6736(03)14699-5, indexed in Pubmed: 14602448.
16. Furman FM, Zgliczyński WS, Jankowski M, et al. The state of vaccine confidence in Poland: a 2019 nationwide cross-sectional survey. Int J Environ Res Public Health. 2020; 17(12), doi: 10.3390/ijerph17124565, indexed in Pubmed: 32599943.
17. Hambleton S, Arvin AM. Chickenpox party or varicella vaccine? Adv Exp Med Biol. 2005; 568: 11–24, doi: 10.1007/0-387-25342-4_2, indexed in Pubmed: 16107063.
18. Vezzosi L, Santagati G, Angelillo IF. Knowledge, attitudes, and behaviors of parents towards varicella and its vaccination. BMC Infect Dis. 2017; 17(1): 172, doi: 10.1186/s12879-017-2247-6, indexed in Pubmed: 28241788.

VIA MEDICA

ORIGINAL PAPER / OBSTETRICS

Ginekologia Polska
2022, vol. 93, no. 8, 662–664

ISSN 0017–0011, e-ISSN 2543–6767

DOI 10.5603/GP.a2021.0169

Diagnosis and management of non-communicating rudimentary horn pregnancy

Yan Jiang, Yajuan Zhong, Lan Dong, Lili Zhan, Panpan Li, Fengqin Guo, Zhixin Huang

Department of Obstetrics and Gynecology, Renmin Hospital of Wuhan University, East Lake High-Tech Development Zone, Wuhan, China

ABSTRACT

Objectives: Non-communicating rudimentary horn pregnancy is a rare condition associated with serious complications and consequences.

Material and methods: We reported a case of a 44-day non-communicating rudimentary horn pregnancy who was diagnosed by three-dimensional ultrasound (3D-US) and pelvic magnetic resonance imaging (MRI), followed by treatment via laparoscopic resection.

Results: The 3D-US and pelvic MRI scan showed a consistent result. Serious complications and consequences were avoided. Postoperative diagnosis showed that the malformation was classified as type IIc.

Conclusions: For such diagnosis as a unicornuate uterus with a rudimentary horn, if there are no symptoms, it cannot be treated. Once pregnancy is in the rudimentary horn, 3D-US or MRI should be conducted to determine the implantation location of the pregnancy capsule and the operation should be performed as soon as possible to avoid uterine rupture. Laparoscopic surgery can be chosen in the early stage.

Key words: laparoscopy; non-communicating rudimentary horn pregnancy; three-dimensional ultrasound

Ginekologia Polska 2022; 93, 8: 662–664

INTRODUCTION

Pregnancy in a non-communicating rudimentary horn is rare with the low prevalence, estimated to be 1 in 76,000––150,000 pregnancies [1, 2]. However, 80% or more of gravid rudimentary horns will cause uterine rupture, resulting in hemorrhage and a 0.5% maternal mortality rate [3]. Excision of the rudimentary horn by laparotomy is traditional approach, which is increasingly replaced with increasing expertise in laparoscopy. Recently, the three-dimensional ultrasound (3D-US) is reported to be highly accurate for uterine malformations diagnosis, which has a good consistency with magnetic resonance imaging (MRI) [4].

MATERIAL AND METHODS

A 39-year-old woman was admitted to the hospital due to postmenopausal period for 44 days and noncommunicating rudimentary uterine horn pregnancy for one day. She had no pregnancy history, and her menstrual history was: menarche at 13 years of age, menstrual period of 5 days, cycle of 30 days, and no dysmenorrhea. Gynecological examination detected a mass (3 × 3 cm in size) on the right side of the uterine body, which was not clear from the uterine boundary and had no obvious tenderness. Gynaecological 3D-US showed abnormal morphology of the uterus (left unicornuate uterus with right rudimentary uterine horn, 4.6 × 4.4 × 4.2 cm) A hypoechoic area (1.13 × 1.16 cm) was seen on the right side of the uterus, inside which an anechoic region (0.37 × 0.28 cm) was observed (considering rudimentary horn pregnancy). There was no communication between left unicornuate uterus and right rudimentary horn (Fig 1A). The consistent results were obtained by pelvic MRI (Fig. 1B).

RESULTS

On the third day of admission, the patient underwent laparoscopy combined with hysteroscopy under general anesthesia. Laparoscopic exploration showed abnormal uterine morphology. The thickness of the junction between left unicornuate uterus (4 × 4 cm) and right rudimentary horn (3 × 3 cm, blue-purple surface) was about 2 cm.

Corresponding author:
Zhixin Huang
Department of Obstetrics and Gynecology, Renmin Hospital of Wuhan University, East Lake High-Tech Development Zone, Wuhan, Hubei Province, 430000 China, 430000 Wuhan, China
e-mail: huanjiu472qiaohuai@163.com

Received: 25.10.2020 Accepted: 20.01.2021 Early publication date: 23.11.2021

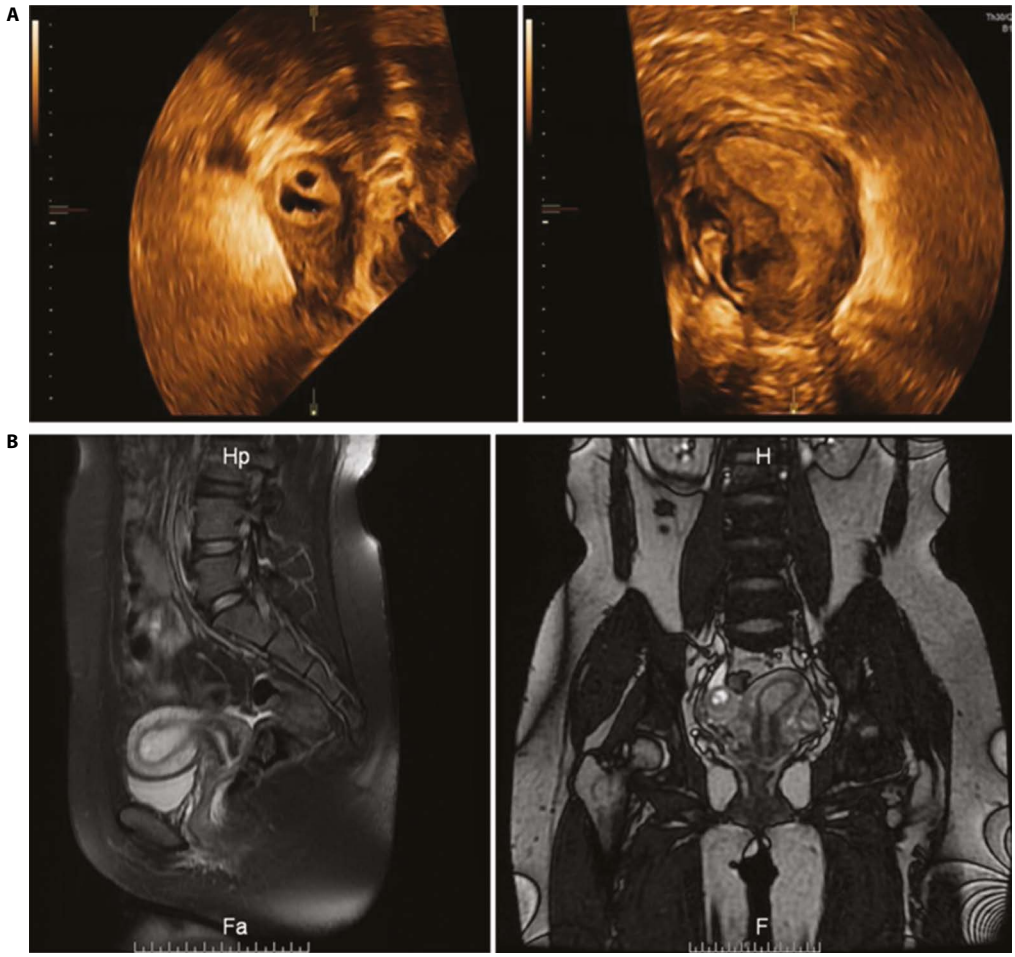


Figure 1. Three-dimensional ultrasound (**A**) and pelvic magnetic resonance imaging (**B**) showed the rudimentary horn pregnancy

Normal tubal and ovarian structures were seen on both sides. Hysteroscopy examination revealed a single cervix. The endometrium of the left single horn was thickened and only the opening of the left fallopian tube was visible. During the operation, Meilan drainage was performed. Under laparoscopy, Meilan solution was seen at the end of the left oviduct umbrella, but not the right oviduct umbrella. The right rudimentary horn with the right fallopian tube was excised. The operation time was one-hour, intraoperative bleeding was about 10 mL, and the operation was successful. She recovered well and was discharged five days after the operation. Postoperative pathological diagnosis confirmed the right rudimentary horn pregnancy, classified as type IIc.

DISCUSSION

Rudimentary horn pregnancy is a very rare form of ectopic gestation. In our case, postoperative diagnosis showed that the malformation was classified as type IIc, which was always diagnosis failure due to the absence of clinical symptoms of dysmenorrhea or misdiagnosis.

3D-US and pelvic MRI scan are shown to have high accuracy in the diagnosis of mullerian anomalies, and give comparable results [5]. In our case, both 3D-US and pelvic MRI were performed, obtaining the same conclusions. Given the advantages of 3D-US, such as non-invasive way, low price, and short examination time, we advised that 3D-US can be popularized clinically in the diagnosis of uterine malformations.

Most rudimentary horn pregnancies result in a high rate of complications, like uterine rupture. Once rupture, the consequences are disastrous, often leading to hemorrhagic shock and even death of pregnant women [6]. Because of the high risk of serious complications, it is recommended by most that, once the rudimentary horn pregnancy is diagnosed, surgery excision of the pregnant rudimentary horn and ipsilateral fallopian tube is immediately performed [7]. The common surgical methods are laparotomy and laparoscopy. Laparoscopy is an attractive option than laparotomy due to the advantage of short operation time, less intraoperative blood loss and early postoperative recovery. Based on the imaging diagnosis, laparoscopy combined with hysteroscopy was performed

in our case, which could be used for evaluation operation difficulty and risk of bleeding. Notably, the connection between the unicornuate uterus and rudimentary horn may be fibrous or fibromuscular. If thick fibromuscular tissue is present, laparoscopic resection is more technically challenging, and laparoscopic suture to close the myometrium is recommended to avoid uterus rupture during pregnancies. In our case, only a 1 cm thick fibrous band was present, so there was no need to close the muscular layer.

CONCLUSIONS

The presentation of this case shows that once pregnancy in rudimentary horn, 3D-US or MRI should be conducted to determine the implantation location of the pregnancy capsule and the operation should be performed as soon as possible to avoid uterine rupture. Laparoscopic surgery can be chosen in the early stage.

Conflict of interest

All authors declare no conflict of interest.

REFERENCES

1. Shiekh Y, Ilyas M, Khan I. Rupture of non-communicating rudimentary horn of unicornuate uterus with pregnancy. Journal of Fetal Medicine. 2018; 5(3): 201–203, doi: 10.1007/s40556-018-0172-4.
2. Parveen R. Detection and management of pregnancy in rudimentary horn of uterus. J Coll Physicians Surg Pak. 2019; 29(6): S70–S72, doi: 10.29271/jcpsp.2019.06.S70, indexed in Pubmed: 31142429.
3. Blancafort C, Graupera B, Pascual MÀ, et al. Diagnosis and laparoscopic management of a rudimentary horn pregnancy: Role of three-dimensional ultrasound. J Clin Ultrasound. 2017; 45(2): 112–115, doi: 10.1002/jcu.22393, indexed in Pubmed: 27612443.
4. Graupera B, Pascual MA, Hereter L, et al. Accuracy of three-dimensional ultrasound compared with magnetic resonance imaging in diagnosis of Müllerian duct anomalies using ESHRE-ESGE consensus on the classification of congenital anomalies of the female genital tract. Ultrasound Obstet Gynecol. 2015; 46(5): 616–622, doi: 10.1002/uog.14825, indexed in Pubmed: 25690307.
5. Yassin A, Munaza S, Mohammed A. Tale of rudimentary horn pregnancy: case reports and literature review. The Journal of Maternal-Fetal & Neonatal Medicine. 2017; 32(4): 671–676, doi: 10.1080/14767058.2017.1387533.
6. Harzallah H, Ben Khelil M, Hamdoun M. A Case of Death Resulting from the Complications of a Rudimentary Uterine Horn Pregnancy. J Obstet Gynaecol Can. 2018; 40(2): 139, doi: 10.1016/j.jogc.2017.11.029, indexed in Pubmed: 29447699.
7. Herchelroath D, Miller J, Wang K. Novel Management of Ectopic Pregnancy in a Noncommunicating Rudimentary Horn of a Unicornuate Uterus. Journal of Osteopathic Medicine. 2018; 118(9): 623–626, doi: 10.7556/jaoa.2018.137.

VIA MEDICA

REVIEW PAPER / GYNECOLOGY

Ginekologia Polska
2022, vol. 93, no. 8, 665–669

ISSN 0017–0011, e-ISSN 2543–6767

DOI 10.5603/GP.a2022.0079

Branched-chain amino acids as a novel biomarker of metabolic disturbances in women with polycystic ovary syndrome — literature review

Hanna Szmygin[1], Monika Lenart-Lipinska[1], Joanna Szydelko[1], Slawomir Wozniak[2], Beata Matyjaszek-Matuszek[1]

[1]Department of Endocrinology, Diabetology and Metabolic Disorders, Medical University of Lublin, Poland
[2]3rd Chair and Department of Gynecology, Medical University of Lublin, Poland

ABSTRACT

Polycystic ovary syndrome (PCOS) is a common, heterogeneous endocrine disorder which effects 5–10% of reproductive-age women. Recently, an association between PCOS and an increased risk of developing metabolic disturbances, such as insulin resistance, prediabetes, type 2 diabetes mellitus as well as obesity has been emphasised. Branched-chain amino acids (BCAAs), including valine (Val), leucine (Leu) and isoleucine (Ile), are a group of essential amino acids that cannot be synthesized in human body and need to be obtained from food. Several recent studies provide evidence that plasma BCAAs also serve as crucial nutrient signals and metabolic regulators. Interestingly, latest metabolomics analysis shows abnormalities in amino acid catabolism and biosynthesis in patients with PCOS, particularly in BCAAs. A growing body of evidence proves that elevated levels of BCAAs may have adverse effects on metabolic health leading to the development of insulin resistance, prediabetes, type 2 diabetes mellitus and obesity both in human and animal models. The aim of this review is to assess the current state of knowledge about the potential role of BCAAs as a novel biomarker of metabolic disturbances in women with polycystic ovary syndrome based on recent scientific literature published up to July 2021 and searches of the PubMed, Google Scholar, and Web of Science databases.

Key words: branched-chain amino acids; PCOS, metabolic syndrome; insulin resistance; type 2 diabetes; obesity

Ginekologia Polska 2022; 93, 8: 665–669

INTRODUCTION

Polycystic ovary syndrome (PCOS) is a common, heterogeneous endocrine disorder which effects 5–10% of reproductive-age women [1, 2]. According to the current 2003 Rotterdam criteria, there are four phenotypes of PCOS and the diagnosis requires the presence of two or more of the following symptoms: chronic ovulatory disorder, presence of hyperandrogenism and ultrasound evidence of polycystic ovaries [3].

Recently, an association between PCOS and an increased risk of developing metabolic disturbances, among them insulin resistance, prediabetes, type 2 diabetes mellitus as well as obesity has been emphasised [1, 2]. Alterations in several metabolic pathways including carbohydrate, lipid and amino acid metabolisms are observed among patients with PCOS [4]. However, there is limited knowledge about the exact pathogenesis of the disorder, which highlights the need to explore the metabolic dysfunction in PCOS for prevention of long-term complications [4, 5].

Interestingly, latest metabolomics analysis shows abnormalities in amino acid catabolism and biosynthesis in patients with PCOS, particularly in branched chain amino acids (BCAAs) [4, 6]. BCAAs, including valine (Val), leucine (Leu) and isoleucine (Ile), are a group of essential amino acids that cannot be synthesized in human body and need to be obtained from food [7–9]. They account for about 20% of total protein intake and make up one-third of the dietary essential amino acids [7–9]. Their main function is promoting protein synthesis and suppressing proteolysis [8]. Several recent studies provide evidence that plasma BCAAs also serve as crucial nutrient signals and metabolic regulators [8], mainly by influencing various aspects of glucose homeostasis [7, 10]. BCAAs have been reported to have positive metabolic effects improving body composition,

Corresponding author:
Hanna Szmygin
Department of Endocrinology, Diabetology and Metabolic Disorders, Medical University of Lublin, 8 Jaczewskiego St, 20-954 Lublin, Poland
phone: +48 662 596 262; e-mail: koszelh@gmail.com

Received: 18.11.2021 Accepted: 22.03.2022 Early publication date: 3.08.2022

glycaemia levels and satiety [8, 11]. However, a growing body of evidence shows that elevated levels of BCAAs may have adverse effects on development of insulin resistance, prediabetes, type 2 diabetes mellitus and obesity both in human and animal models [11–14], making BCAAs a potential biomarker to identify women with PCOS who are at risk of developing metabolic disorders, so that appropriate preventative measures can be taken.

The aim of this review is to outline the potential role of BCAAs as a novel biomarker of metabolic disturbances in patients with polycystic ovary syndrome.

DISCUSSION

BCAAs in metabolic disorders

Elevated levels of plasma BCAAs and their catabolic by-products have been linked to the pathogenesis of metabolic disorders such as insulin resistance [11, 15, 16], type 2 diabetes [11, 15, 16] and obesity [11]. One of the main theories explaining increased BCAAs concentration in metabolic disturbances implies a disruption of BCAAs catabolism due to decreased expression of BCAA catabolic enzymes in adipose and hepatic tissue, leading to BCAAs build-up in the circulation [5, 12, 14]. An alternative explanation for elevated BCAAs concentrations suggests increased proteolysis of skeletal muscle in states of insulin resistance [12]. A few studies have also demonstrated that dietary BCAAs intake could contribute to impaired glucose metabolism [14]. However, most authors claim it is unlikely that dietary protein consumption is responsible for elevated BCAA serum concentrations prior to the development of insulin resistance [13] and suggest that elevated BCAAs concentration may potentiate glucose intolerance by increasing the supply of BCAA metabolites glutamate and alanine for gluconeogenesis [5, 11]. Additionally, it has been revealed that BCAAs plasma concentrations could also be affected by gut microbiome, which may alter protein degradation [7, 14]. Nonetheless, the exact mechanism underlying the correlation between BCAAs and metabolic disorders is not yet fully understood.

BCAAs and insulin resistance

A number of recent metabolomics-based studies show that changes in metabolic pathways in insulin resistance are associated not only with disorders in carbohydrate and lipid metabolism, but also concern amino acids, including BCAAs [14–16]. It is well known that glucose and amino acid metabolism are closely interrelated [12]. On one hand amino acids can be used for gluconeogenesis and on the other non-essential amino acids can be synthesized de novo from glucose [12]. Moreover, free amino acids influence insulin and glucagon secretion, thus modulating glucose metabolism [12].

In a large population-based cohort study on young, healthy Finnish individuals the relationship between insulin resistance and fasting glucose levels and BCAAs concentrations was investigated during a 6-year follow-up [17]. The study revealed that plasma BCAAs concentrations predict insulin resistance index (HOMA-IR) in young adults, with the most pronounced associations observed for men [17, 18]. No correlation was observed for glycaemia, which indicates that altered branched-chain metabolism precedes the development of insulin resistance already in early adulthood, prior to the occurrence of impaired fasting glucose [17]. Consistent results were shown in a study by Thalacker-Mercer et al. [19], in which leucine and isoleucine were negatively correlated with glucose disposal rate in non-obese and type 2 diabetic patients using the hyperinsulinemic-euglycemic clamp technique. In line with these studies, insulin resistance was associated with increased levels of valine, leucine and isoleucine in a study on 263 non-obese Asian-Indian and Chinese men [20]. In a study by Piccolo et al. [21] a direct correlation between plasma BCAAs concentration and insulin resistance parameters in women with metabolic syndrome was revealed. BCAAs exhibited predictive associations with fasting glucose, fasting insulin and HOMA-IR [21]. Worth noticing is the fact, some authors provide evidence that BCAAs are even more strongly correlated with insulin sensitivity than lipid-related factors [22]. Interestingly, in a randomized, placebo-controlled, double-blinded study it was proved that a short-term dietary reduction of BCAAs increases whole-body insulin sensitivity, decreases postprandial insulin secretion and improves white adipose tissue metabolism as well as gut microbiome composition [7].

BCAAs and prediabetes and type 2 diabetes mellitus

Recent studies provide evidence that BCAAs catabolism is altered in various metabolic disorders, among them in prediabetes and type 2 diabetes [11, 23–26].

In a study by Tulipani et al. [23] a positive correlation between plasma concentrations of BCAA valine and insulin resistance as well as prediabetes was observed, independently from the BMI. Moreover, several recent population-based studies show a significant correlation between BCAAs and their metabolites and impaired fasting glucose (IFG) and type 2 diabetes [24, 25].

Nakamura et al. [26] examined the relationship between glucose- and insulin-related markers and plasma amino acid profile in individuals already diagnosed with type 2 diabetes. The results showed that BCAAs were significantly increased in people with hyperinsulinemia. Moreover, there was a positive correlation between BCAAs concentrations and HbA1c, c-peptide, insulin and HOMA-IR. In addition to

this, in this study, BCAAs were negatively correlated with adiponectin concentrations.

Interestingly, many studies show that plasma-free amino acid (PFAA) profile, especially the levels of BCAAs, are altered long before the onset of type two diabetes and precede the development of the disorder and thus could be used as biomarkers of type 2 diabetes development [11, 16, 22]. In the long-term cohort Framingham Heart Study, the authors examined whether metabolite profiles could predict the development of diabetes [27]. In a group of 201 people who developed diabetes, serum levels of BCAAs were increased up to 12 years prior to the onset of the disease, implying that hyper aminoacidemia is a very early sign of type 2 diabetes [27]. Moreover, the risk of developing diabetes was 4-fold higher in individuals with high plasma amino acid concentrations [27]. In another study on 429 Chinese individuals' early elevation of valine, leucine and isoleucine was associated with future development of type 2 diabetes during a 10 year follow-up, which highlights their predictive value as early markers of diabetes [28].

BCAAs and obesity

The relationship between elevated circulating BCAA levels and obesity has been thoroughly investigated throughout recent years.

A large prospective, observational, community-based study on over 2300 participants investigated metabolic signatures of obesity and found a strong positive correlation between BCAAs and BMI as well as HOMA-IR, HDL and triglycerides [29]. Similar results were obtained by Zhou et al. [30] who analysed the differences in amino acid profiles between obese and lean subjects and found that in a group of 100 non-diabetic individuals, 19 out of 42 examined amino acids differed in obese subjects, among them valine, leucine and isoleucine were significantly increased. Consistent results were shown in a study by Newgard et al. [31]. The authors observed that levels of the BCAAs valine and leucine/isoleucine were 20% and 14% higher respectively, in obese compared to lean individuals. In line with these observations, concentrations of BCAAs were positively correlated with BMI in children and adolescents aged 8–18 years [32]. Interestingly, some studies show a stronger correlation of obesity and insulin resistance with BCAAs than with lipid metabolites [5, 22].

In another study aimed to investigate the association between plasma BCAA, obesity and metabolic syndrome, Jennings et al. [33] found that overweight/obese group with metabolic syndrome had the highest levels of each BCAA, overweight/obese participants without metabolic syndrome had intermediate levels and normal weight individuals had the lowest levels of plasma BCAA. Moreover, there was a positive correlation between isoleucine levels and waist circumference as well as HOMA-IR among overweight/obese individuals irrespective of the metabolic syndrome status [33].

In a study aimed to detect the metabolic differences between metabolically healthy obese (MHO) and metabolically unhealthy obese (MUO) phenotypes significant alterations in amino acid concentrations were observed [34]. Both MHO and MUO individuals had higher serum concentrations of valine, isoleucine and leucine compared to lean healthy (LH) subjects. Of the three BCAAs isoleucine showed the most significant changes of an increase up to 40% in MUH individuals and 26% in MHO. Moreover, an association between BCAAs and insulin sensitivity was supported in this study by a positive correlation between BCAAs and HOMA-IR and HbA1c values.

BCAAs and PCOS

Since the pathogenesis of PCOS is linked to the development of metabolic disturbances, such as insulin resistance, prediabetes, type 2 diabetes and obesity, which lead to various complications and increase the morbidity and mortality among those patients, many recent studies have focused on finding novel biomarkers that could predict the development of the aforementioned disorders [35].

A review by Galazis et al. [35] aimed to identify a panel of metabolomics biomarkers that could potentially help in early detection of impaired glucose tolerance (IGT) and type 2 diabetes mellitus in women with PCOS and found 9 compounds, among them leucine, isoleucine and valine.

A recent study by Chang et al. [5] was designed to examine the differences in metabolic pathways in obese women with PCOS and obese controls with metabolic syndrome. Firstly, the study showed that insulin sensitivity was more impaired in obese patients with PCOS than in those with metabolic syndrome, which suggest that greater insulin resistance is a key factor for the metabolic disturbances in PCOS. Moreover, PCOS women had higher LDL cholesterol plasma concentrations when compared to patients with metabolic syndrome. Interestingly, metabolomics analysis showed a significant difference in 385 metabolites and metabolic pathways that distinguished patients with PCOS and those with metabolic syndrome. The strongest correlation was observed for amino acid metabolites, especially elevated concentration of BCAAs distinguished PCOS from metabolic syndrome.

Consistent results were obtained by Zhao et al. [4]. Valine and leucine were closely related to insulin resistance and obesity in PCOS patients [4]. Moreover, a decrease of BCAA to aromatic amino acid ratio, accompanied by elevated levels of valine and leucine was directly associated with the development of PCOS [4, 10].

In a 7.5-year longitudinal study on Finnish girls, a positive correlation was observed between all amino acids and

HOMA-IR, both before and after menarche [36]. The strongest association with insulin resistance during pubertal development, independent of adiposity was observed for BCAAs [36].

CONCLUSIONS

In summary, several recent studies indicate that BCAAs might be used a as potential novel risk factor for the metabolic disturbances in women with PCOS. However, further research is warranted to explore the exact role these biomarkers may play in the pathophysiology of PCOS.

Funding

This study was not supported by any funding.

Conflict of interest

The authors declare that they have no conflict of interest.

Contributions

All authors contributed significantly to the paper. HSz, MLL, BMM designed the study. HSz, BMM and SW prepared the manuscript. All authors were involved in data interpretation and analysis. All authors approved the manuscript.

REFERENCES

1. Widecka J, Ozegowska K, Banaszewska B, et al. Is copeptin a new potential biomarker of insulin resistance in polycystic ovary syndrome? Ginekol Pol. 2019; 90(3): 115–121, doi: 10.5603/GP.2019.0021, indexed in Pubmed: 30949999.
2. Beyazit F, Hiz MM, Turkon H, et al. Serum spexin, adiponectin and leptin levels in polycystic ovarian syndrome in association with FTO gene polymorphism. Ginekol Pol. 2021; 92(10): 682–688, doi: 10.5603/GP.a2020.0176, indexed in Pubmed: 33914321.
3. Bialka-Kosiec AA, Wilk K, Pytel M, et al. Body mass composition and dietary habits in adolescents with polycystic ovary syndrome. Ginekol Pol. 2019; 90(10): 589–595, doi: 10.5603/GP.2019.0103, indexed in Pubmed: 31686416.
4. Zhao Y, Fu Li, Li R, et al. Metabolic profiles characterizing different phenotypes of polycystic ovary syndrome: plasma metabolomics analysis. BMC Med. 2012; 10: 153, doi: 10.1186/1741-7015-10-153, indexed in Pubmed: 23198915.
5. Chang AY, Lalia AZ, Jenkins GD, et al. Combining a nontargeted and targeted metabolomics approach to identify metabolic pathways significantly altered in polycystic ovary syndrome. Metabolism. 2017; 71: 52–63, doi: 10.1016/j.metabol.2017.03.002, indexed in Pubmed: 28521878.
6. Ye Z, Zhang C, Zhao Y. Potential effects of adropin on systemic metabolic and hormonal abnormalities in polycystic ovary syndrome. Reprod Biomed Online. 2021; 42(5): 1007–1014, doi: 10.1016/j.rbmo.2021.01.020, indexed in Pubmed: 33612434.
7. Karusheva Y, Koessler T, Strassburger K, et al. Short-term dietary reduction of branched-chain amino acids reduces meal-induced insulin secretion and modifies microbiome composition in type 2 diabetes: a randomized controlled crossover trial. Am J Clin Nutr. 2019; 110(5): 1098–1107, doi: 10.1093/ajcn/nqz191, indexed in Pubmed: 31667519.
8. Siddik MdA, Shin AC. Recent progress on branched-chain amino acids in obesity, diabetes, and beyond. Endocrinol Metab (Seoul). 2019; 34(3): 234–246, doi: 10.3803/EnM.2019.34.3.234, indexed in Pubmed: 31565875.
9. Arany Z, Neinast M. Branched chain amino acids in metabolic disease. Curr Diab Rep. 2018; 18(10): 76, doi: 10.1007/s11892-018-1048-7, indexed in Pubmed: 30112615.
10. Hajitarkhani S, Moini A, Hafezi M, et al. Differences in gene expression of enzymes involved in branched-chain amino acid metabolism of abdominal subcutaneous adipose tissue between pregnant women with and without PCOS. Taiwan J Obstet Gynecol. 2021; 60(2): 290–294, doi: 10.1016/j.tjog.2020.12.008, indexed in Pubmed: 33678329.
11. Nie C, He T, Zhang W, et al. Branched chain amino acids: beyond nutrition metabolism. Int J Mol Sci. 2018; 19(4): 954, doi: 10.3390/ijms19040954, indexed in Pubmed: 29570613.
12. Gar C, Rottenkolber M, Prehn C, et al. Serum and plasma amino acids as markers of prediabetes, insulin resistance, and incident diabetes. Crit Rev Clin Lab Sci. 2018; 55(1): 21–32, doi: 10.1080/10408363.2017.1414143, indexed in Pubmed: 29239245.
13. Allman BR, Diaz EC, Andres A, et al. Divergent changes in serum branched-chain amino acid concentrations and estimates of insulin resistance throughout gestation in healthy women. J Nutr. 2020; 150(7): 1757–1764, doi: 10.1093/jn/nxaa096, indexed in Pubmed: 32275314.
14. Woo SL, Yang J, Hsu M, et al. Effects of branched-chain amino acids on glucose metabolism in obese, prediabetic men and women: a randomized, crossover study. Am J Clin Nutr. 2019; 109(6): 1569–1577, doi: 10.1093/ajcn/nqz024, indexed in Pubmed: 31005973.
15. Guevara-Aguirre J, Rosenbloom AL. Branched chain and aromatic amino acids are associated with insulin resistance during pubertal development in girls. J Adolesc Health. 2019; 65(3): 313–314, doi: 10.1016/j.jadohealth.2019.05.012, indexed in Pubmed: 31445663.
16. Jang C, Oh SF, Wada S, et al. A branched-chain amino acid metabolite drives vascular fatty acid transport and causes insulin resistance. Nat Med. 2016; 22(4): 421–426, doi: 10.1038/nm.4057, indexed in Pubmed: 26950361.
17. Würtz P, Soininen P, Kangas AJ, et al. Branched-chain and aromatic amino acids are predictors of insulin resistance in young adults. Diabetes Care. 2013; 36(3): 648–655, doi: 10.2337/dc12-0895, indexed in Pubmed: 23129134.
18. Gannon NP, Schnuck JK, Vaughan RA. BCAA metabolism and insulin sensitivity - dysregulated by metabolic status? Mol Nutr Food Res. 2018; 62(6): e1700756, doi: 10.1002/mnfr.201700756, indexed in Pubmed: 29377510.
19. Thalacker-Mercer AE, Ingram KH, Guo F, et al. BMI, RQ, diabetes, and sex affect the relationships between amino acids and clamp measures of insulin action in humans. Diabetes. 2014; 63(2): 791–800, doi: 10.2337/db13-0396, indexed in Pubmed: 24130332.
20. Tai ES, Tan MLS, Stevens RD, et al. Insulin resistance is associated with a metabolic profile of altered protein metabolism in Chinese and Asian-Indian men. Diabetologia. 2010; 53(4): 757–767, doi: 10.1007/s00125-009-1637-8, indexed in Pubmed: 20076942.
21. Piccolo BD, Comerford KB, Karakas SE, et al. Whey protein supplementation does not alter plasma branched-chained amino acid profiles but results in unique metabolomics patterns in obese women enrolled in an 8-week weight loss trial. J Nutr. 2015; 145(4): 691–700, doi: 10.3945/jn.114.203943, indexed in Pubmed: 25833773.
22. Newgard CB. Interplay between lipids and branched-chain amino acids in development of insulin resistance. Cell Metab. 2012; 15(5): 606–614, doi: 10.1016/j.cmet.2012.01.024, indexed in Pubmed: 22560213.
23. Tulipani S, Palau-Rodriguez M, Miñarro Alonso A, et al. Biomarkers of morbid obesity and prediabetes by metabolomic profiling of human discordant phenotypes. Clin Chim Acta. 2016; 463: 53–61, doi: 10.1016/j.cca.2016.10.005, indexed in Pubmed: 27720726.
24. Menni C, Fauman E, Erte I, et al. Biomarkers for type 2 diabetes and impaired fasting glucose using a nontargeted metabolomics approach. Diabetes. 2013; 62(12): 4270–4276, doi: 10.2337/db13-0570, indexed in Pubmed: 23884885.
25. Xu F, Tavintharan S, Sum CF, et al. Metabolic signature shift in type 2 diabetes mellitus revealed by mass spectrometry-based metabolomics. J Clin Endocrinol Metab. 2013; 98(6): E1060–E1065, doi: 10.1210/jc.2012-4132, indexed in Pubmed: 23633210.
26. Nakamura H, Jinzu H, Nagao K, et al. Plasma amino acid profiles are associated with insulin, C-peptide and adiponectin levels in type 2 diabetic patients. Nutr Diabetes. 2014; 4: e133, doi: 10.1038/nutd.2014.32, indexed in Pubmed: 25177913.
27. Wang TJ, Larson MG, Vasan RS, et al. Metabolite profiles and the risk of developing diabetes. Nat Med. 2011; 17(4): 448–453, doi: 10.1038/nm.2307, indexed in Pubmed: 21423183.
28. Chen T, Ni Y, Ma X, et al. Branched-chain and aromatic amino acid profiles and diabetes risk in Chinese populations. Sci Rep. 2016; 6: 20594, doi: 10.1038/srep20594, indexed in Pubmed: 26846565.
29. Ho JE, Larson MG, Ghorbani A, et al. Metabolomic profiles of body mass index in the framingham heart study reveal distinct cardiometabolic phenotypes. PLoS One. 2016; 11(2): e0148361, doi: 10.1371/journal.pone.0148361, indexed in Pubmed: 26863521.

30. Zhou Y, Qiu L, Xiao Q, et al. Obesity and diabetes related plasma amino acid alterations. Clin Biochem. 2013; 46(15): 1447–1452, doi: 10.1016/j.clinbiochem.2013.05.045, indexed in Pubmed: 23697717.
31. Newgard CB, An J, Bain JR, et al. A branched-chain amino acid-related metabolic signature that differentiates obese and lean humans and contributes to insulin resistance. Cell Metab. 2009; 9(4): 311–326, doi: 10.1016/j.cmet.2009.02.002, indexed in Pubmed: 19356713.
32. McCormack SE, Shaham O, McCarthy MA, et al. Circulating branched-chain amino acid concentrations are associated with obesity and future insulin resistance in children and adolescents. Pediatr Obes. 2013; 8(1): 52–61, doi: 10.1111/j.2047-6310.2012.00087.x, indexed in Pubmed: 22961720.
33. Jennings A, MacGregor A, Pallister T, et al. Associations between branched chain amino acid intake and biomarkers of adiposity and cardiometabolic health independent of genetic factors: A twin study. Int J Cardiol. 2016; 223: 992–998, doi: 10.1016/j.ijcard.2016.08.307, indexed in Pubmed: 27591698.
34. Badoud F, Lam KP, DiBattista A, et al. Serum and adipose tissue amino acid homeostasis in the metabolically healthy obese. J Proteome Res. 2014; 13(7): 3455–3466, doi: 10.1021/pr500416v, indexed in Pubmed: 24933025.
35. Galazis N, Iacovou C, Haoula Z, et al. Metabolomic biomarkers of impaired glucose tolerance and type 2 diabetes mellitus with a potential for risk stratification in women with polycystic ovary syndrome. Eur J Obstet Gynecol Reprod Biol. 2012; 160(2): 121–130, doi: 10.1016/j.ejogrb.2011.11.005, indexed in Pubmed: 22136882.
36. Guevara-Aguirre J, Rosenbloom AL. Branched chain and aromatic amino acids are associated with insulin resistance during pubertal development in girls. J Adolesc Health. 2019; 65(3): 313–314, doi: 10.1016/j.jadohealth.2019.05.012, indexed in Pubmed: 31445663.

VIA MEDICA

REVIEW PAPER / GYNECOLOGY

Ginekologia Polska
2022, vol. 93, no. 8, 670–674

ISSN 0017–0011, e-ISSN 2543–6767

DOI 10.5603/GP.a2022.0051

The role of selected molecular factors in ovarian cancer metastasis

Anna Markowska[1], Wlodzimierz Sawicki[2], Jakub Zurawski[3], Joanna Fechner[1], Janina Markowska[4]

[1]*Department of Perinatology and Women's Diseases, Poznan University of Medical Sciences, Poland*
[2]*Chair and Department of Obstetrics, Gynecology and Gynecological Oncology, Medical University of Warsaw, Poland*
[3]*Department of Immunobiology, Poznan University of Medical Sciences, Poland*
[4]*The Clinic of Oncology, Poznan University of Medical Sciences, Poznan, Poland*

ABSTRACT

The main reason for treatment failure in ovarian cancer is chemoresistance and the presence of metastasis. Ascites, which allows the physical movement of cancer cells, the lymphovascular pathway, and several molecular factors and signalling axes, are involved in metastasis.

Ascites, with the involvement of cytokines and chemokines, MAPK/STAT1 and NOTCH as well as CXCL12/CXCR4 signaling pathways and circulating anoikis induces cancer dissemination, in particular to the peritoneum and omentum.

The spread of lymphatic and bloodstream cancer cells is a multi-stage process. Tumour infiltration of the stroma and lymphovascular space (LVSI) produces biologically active cancer-associated fibroblasts and macrophages (CAFs, TAMs) that secrete numerous cytokines, chemokines and growth factors, inhibit NK function, induce epithelial-mesenchymal transition (EMT), resulting in an increase of the metastatic potential of cancer cells and the formation of cancer stem cells (CSCs).

Overexpression of some genes, and microRNAs, in LVSI-(LMGS) associated with metastasis has been identified.

The role of extracellular vesicles (EVs) transporting metastasis-associated factors has been described as has the role of cancer stem cells (CSCs) in chemotherapy resistance and metastasis. Sirtuins, enzymes involved in metastasis formation, have also been detected. Certain types of microRNAs (miR-509-3p, microRNA-506-3p) and melatonin have been shown to inhibit metastasis.

Key words: ovarian cancer; metastasis; ascites; CAFs; microRNA; molecular signature

Ginekologia Polska 2022; 93, 8: 670–674

INTRODUCTION

Ovarian cancer (OC) is the seventh most common malignancy in women worldwide. It is the leading cause of death among all gynaecological cancers. More than 70% of ovarian cancers are diagnosed in advanced clinical stages. After successful primary therapy, approximately 80% of patients are found to have recurrent ovarian cancer with a 5-year survival rate of 25–35%. In 90% of cases ovarian cancer is the cause of death [1–3].

The primary type of OC is epithelial carcinoma with five subtypes, among which high-grade serous ovarian cancer (HGSC) is the most aggressive and associated with a poor prognosis [4–7].

Chemo-resistance and metastasis, in addition to the clinical stage of cancer, are fundamental reasons for treatment failure. Metastasis is a complex process in which cancer cells migrate to different parts of the body, acquire invasive features, and cause the formation of new cancer foci.

The mechanism of metastasis is regulated by specific genes using various cytokines, chemokines, growth factors, signalling pathways and intercellular interactions. Metastasis is associated with high death rates [8–16].

A considerable number of molecular mechanisms involved in metastasis have been described, as well as pathways involved in this process. According to Kim et al. [4],

Corresponding author:
Janina Markowska
The Clinic of Oncology, Poznan University of Medical Sciences, 60–569 Poznan, Poland
e-mail: jmarkmed@poczta.onet.pl

Received: 26.04.2022 Accepted: 14.05.2022 Early publication date: 6.06.2022

the presence of ascites modulates the behaviour of cancer cells released from the tumour, contributing to tumour heterogeneity related to different responses to treatment. Ascites forms a microenvironment containing various factors: cytokines- IL-6 and IL-8, IL-10, pro-angiogenic VEGF, stromal cells — including a fraction of cancer-associated fibroblasts (CAFs) — that promote cancer cell proliferation, migration, invasion, and chemoresistance. Aggregates of cells, spheroids, with typical stem cell expression were isolated from ascites: CD 44 and CD 24 which represent the chemoresistant population and cells expressing metastasis-related genes including TGF-β and integrin [4, 17].

Ascites contains a significant number of proteins and exosomes, the extracellular vesicles (EVs) involved in transferring information between metastatic cells [4, 18].

According to Weidle et al. [17], ascites fluid, in addition to the physical condition that allows the movement of exfoliated cancer cells, promotes the interaction of cancer cells with the microenvironment and the induction of multiple pathways that promote metastasis, including MAPK/STAT1 and NOTCH.

Furthermore, metastasis is favoured by the activation of some chemokines and their receptors, including CXCL12--CXCR4 axes, as well as the overexpression of transmembrane tyrosine kinase C-MET promoting cancer dissemination [19, 20].

In the promotion of ovarian cancer dissemination, attention has been paid to the resistance of anoikis — cells detached from the tumour that have acquired metastatic features and which under non-adherent conditions can circulate as CTCs (circulating tumour cells) participating in metastasis formation [18].

The presence of ascites, as well as tumor-stromal interaction, TGF-α excreted by ovarian cancer cells and CAF--secreted TGF-α together with EGFR, AKT and ERK signalling pathways promote metastasis to the omentum [14].

Lymphatic and vascular dissemination play a key role in the formation of both intraperitoneal and distant metastases [21, 22].

The initial stage of this process is neoplastic infiltration of the stroma and the presence of cancer cells in the lymphovascular space invasion (LVSI). The tumour-infiltrated lining contains numerous biologically active cells, including the aforementioned fibroblasts — CAFs and tumour-associated macrophages (TAMs). CAFs produce cytokines and chemokines of autocrine and paracrine function as well as growth factors including CXCL1, TGF-α, VEGF1, IL-6, IL-8, COX-2, and overexpress the homeotic gene HOXA9 associated with the promotion of the cancer microenvironment [21, 23].

CAFs also enhance the expression of matrix metalloproteinases (MMPs) and induce epithelial-mesenchymal transition (EMT) associated with the increased metastatic potential of the transformed cell [24]. TAMs secrete many factors such as TGF-β, IGF, and PDGF, inhibiting NK cell function, maintaining the metastatic niche, and helping to maintain CAFs activity [25].

The described activity of CAFs and TAMs facilitates cancer invasion and metastasis. Infiltration of the lining by CAFs is associated with a positive LVSI that correlates with increased serous cancer invasion and worse overall survival ($p = 0.0205$). Results of a targeted therapy study with factors secreted by CAFs and TAMs have been described and appear promising [21].

Numerous other factors are also involved in the metastatic process of ovarian cancer: genetic factors, including microRNAs, extracellular molecules, stem cells, and many others.

METASTASIS-ASSOCIATED GENE SIGNATURE

Yue et al. [21] showed that cancer stromal activation is associated with a differentially expressed gene (DEC). They identified a lymphovascular metastasis gene signature (LMGS) with an increased expression that correlates with an increased risk of metastasis via the lymphatic and circulatory routes. These genes are POSTN, LUM, THBS2, COL3A1, COL5A2, FAP, and FBN1.

It has been shown that there is a relationship between LMGS expression and TGF-β pathway activation. Since TGF-β has been shown to be an essential factor in fibroblast activation and CAFs formation, therefore CAFs also contribute to LMGS overexpression. The cited paper describes the results of a phase I and phase II study of targeted therapies currently under development that are associated with overexpression of the genes under investigation [21].

THE ROLE OF microRNAs IN METASTASIS

MicroRNAs (miRNAs) are a family of small non-coding RNAs that regulate the expression of approximately 50% of protein-coding genes. They play a crucial role in cell cycle regulation, proliferation, differentiation, motility, and apoptosis. In addition, they participate in angiogenesis, epithelial-mesenchymal transition (EMT), and resistance of cancer cells to chemotherapy. According to several studies, they too are involved in metastasis but may also be suppressors of cancer dissemination [8, 11, 26–29].

Braga et al. [11] showed that non-coding RNAs (ncRNAs) are involved in ovarian cancer progression and metastasis by participating in EMT, in which the cell acquires characteristics typical of a stem cell.

Similarly, Ghafouri-Farad et al. [29] showed that a number of microRNAs, including miR-135a, miR-200c, miR-216a, and miR-340 regulate EMT by modulating cell invasiveness through mTOR and PI3K/AKT pathways. According to the authors above, these microRNAs may have applications as biomarkers and provide a therapeutic perspective.

Another paper reported the study of miRNA-205 contained in exosomes, which promotes metastasis by inducing angiogenesis via the PTEN-AKT pathway [28].

Loginov et al. [26] detected 20 abnormally methylated miRNA genes involved in different stages of ovarian cancer development and metastasis to various locations, including the peritoneum. They demonstrated a significant correlation between methylation levels and the presence of microRNAs in metastases. Among the genes studied, thirteen miRNAs were hypermethylated at early stages of cancer development and hypermethylation of MIR-1258, MIR203A, MIR137 and MIR375 was evident in metastatic foci. They also identified three miRNA genes (MIR148A, MIR9-1, and MIR193A) that regulated EMT and were present in macroscopic peritumoral nodules.

A review by Nguyen et al. [8] reported the diverse role of microRNAs in ovarian cancer metastasis. Some microRNAs exhibit metastasis-related activity; these microRNAs showed increased expression and were present in tumour tissues. Their presence correlated with a clinical grade, omental or lymph node metastasis, presence of ascites, or recurrence. Many anti-metastatic miRNAs with decreased expression in ovarian cancer tissues were also detected — e.g., miR-509-3p inhibiting migration, invasion, and steroid formation, positively associated with HGSC survival.

Sun et al. [27] described microRNA -506-3p that inhibits ovarian cancer metastasis by decreasing the expression of EZH2 (enhancer of zeste homolog 2), a key transcription factor in tumour development. Some miRNAs were found to be present in exosomes or circulating body fluids [8].

EXTRACELLULAR VESICLES (EVs) IN METASTASIS

Exosomes are spherical membrane nanobubbles of 30–100 nm in size, which are carriers of various biological molecules, including genetic material. They participate in the modulation of intercellular communication, the immunological activity of fibroblasts, macrophages, and angiogenesis. Proteins and microRNAs are transported in exosomes, thus participating in cancer metastases [13, 28].

In a review by Tian et al. [13], EVs were shown to play a role in drug resistance, as well as the progression and promotion of metastasis. For example, the cell adhesion molecule CD44 is translocated by EVs from cancer cells to peritoneal mesothelial cells, thereby initiating metastasis. CD147-containing vesicles released from ovarian cancer can induce angiogenesis both by expressing E-cadherin on their surface and by using PTEN-AKT and STAT3 signalling to facilitate peritoneal and omental metastasis [28, 30].

Studies show that ascites-derived EVs affect EMT in cells by translocating miR-6780b-5p to target organs, preparing the microenvironment for tumour growth [31].

The promotion of EMT by EV-containing factors is associated with the development of cancer stem cells (CSCs) responsible for carcinogenesis.

CANCER STEM CELLS IN METASTASIS

CSCs are a small subpopulation of cells, accounting for about 2% of tumour mass, but appear to play a key role in chemotherapy resistance and metastasis. They most likely arise from somatic stem cells that have transformed due to genetic and epigenetic factors. They have the ability to self-renew, residing in an inactive state as "dormant cells", and are capable of DNA repair. Ovarian cancer CSC markers have been identified: CD44, CD133, CD24, CD117, Nestin, Nanog, Oct3/4, as have functional markers: ALDHA1 and ABC (associated with cytostatic resistance). They exploit various signalling pathways: PI3K/AKT/mTOR, MAPK, NOTCH, and canonical Wnt [5, 32–35].

Some cells with the CD24 phenotype have been found to have strong renewal properties, are resistant to chemotherapy, play a role in CSCs migration, metastasis and promote interactions between CSCs and the tumour microenvironment [5, 36]. According to Kleinmans et al. [37], CD24 is overexpressed in 70% of solid tumours, including ovarian cancer. It may serve as a preclinical and clinical biomarker of OC and perhaps a future target for therapy. Other studies provided similar data. Tarhriz et al. [38] found CD24 to be an important molecule. Overexpressed in OC, CD 24 is a CSC marker and is associated with ovarian cancer development, invasion and metastasis. According to the above authors, CD24 may be an independent survival indicator for OC patients.

CSCs achieve their metastatic potential through multiple mechanisms. One such mechanism may be the inhibitory effect on the apoptosis pathway and the exploitation of the NF-kB signalling pathway. Inhibitors that reprogram chemoresistance have already been described (e.g., PFKFB3 inhibitor). This issue, however, needs further investigation [12].

Another pathway of metastatic activity of CSCs is the activation of the angiotensin II (ANG II) pathway and its receptor (AGTR1), which enhance spheroid formation and cell migration, thus promoting metastasis, especially to the peritoneum. Studies are underway to influence lipid homeostasis and suppress endoplasmic reticulum (ER) stress which would decrease the formation of spheroids and the CSCs they contain [16].

OTHER MECHANISMS INVOLVED IN METASTASIS

Sirtuin deacetylases (SIRTs) are enzymes that cleave acetyl groups from various proteins. Of the seven groups of SIRTs, SIRT3 has been described to support metastasis, it has been found in ascites and peritoneal metastases in ovarian cancer.

The mechanism that promotes metastasis is the reduction of oxidants induced by oxidative stress. This facilitates the avoidance of anoikis apoptosis, whose detachment from the primary tumour is associated with rapid oxidative stress [9].

MELATONIN

In vitro and in vivo studies have shown that chronic restraint stress (CRS) promotes OC abdominal metastasis and increases the expression of EMT-related markers — including the transcription factor SLUG [39]. Increased expression of β-catenin and norepinephrine (NE) was found to be associated with poor clinical status in ovarian cancer patients. Melatonin (MLT) effectively inhibited tumour burden by inhibiting the complex NE/AKT/β-catenin/SLUG (catecholamine, proliferative-transcriptional) axis.

The authors believe these findings suggest a novel mechanism for CRS-mediated ovarian cancer metastasis, and MLT has potential therapeutic efficacy [39].

Conflict of interest

All authors declare no conflict of interest.

REFERENCES

1. Siegel R, Miller K, Jemal A. Cancer statistics, 2020. CA Cancer J Clin. 2020; 70(1): 7–30, doi: 10.3322/caac.21590, indexed in Pubmed: 31912902.
2. Gaona-Luviano P, Medina-Gaona LA, Magaña-Pérez K. Epidemiology of ovarian cancer. Chin Clin Oncol. 2020; 9(4): 47, doi: 10.21037/cco-20-34, indexed in Pubmed: 32648448.
3. Pawar A, Chowdhury OR, Chauhan R, et al. Identification of key gene signatures for the overall survival of ovarian cancer. J Ovarian Res. 2022; 15(1): 12, doi: 10.1186/s13048-022-00942-0, indexed in Pubmed: 35057823.
4. Kim S, Kim B, Song YS. Ascites modulates cancer cell behavior, contributing to tumor heterogeneity in ovarian cancer. Cancer Sci. 2016; 107(9): 1173–1178, doi: 10.1111/cas.12987, indexed in Pubmed: 27297561.
5. Bregenzer ME, Horst EN, Mehta P, et al. The role of cancer stem cells and mechanical forces in ovarian cancer metastasis. Cancers (Basel). 2019; 11(7), doi: 10.3390/cancers11071008, indexed in Pubmed: 31323899.
6. Köbel M, Kang EY. The evolution of ovarian carcinoma subclassification. Cancers (Basel). 2022; 14(2), doi: 10.3390/cancers14020416, indexed in Pubmed: 35053578.
7. Hojnik M, Šuster NK, Smrkolj Š, et al. AKR1B1 as a Prognostic Biomarker of High-Grade Serous Ovarian Cancer. Cancers (Basel). 2022; 14(3), doi: 10.3390/cancers14030809, indexed in Pubmed: 35159076.
8. Nguyen VuH, Yue C, Du KY, et al. The role of microRNAs in epithelial ovarian cancer metastasis. Int J Mol Sci. 2020; 21(19), doi: 10.3390/ijms21197093, indexed in Pubmed: 32993038.
9. Kim YS, Gupta Vallur P, Jones VM, et al. Context-dependent activation of SIRT3 is necessary for anchorage-independent survival and metastasis of ovarian cancer cells. Oncogene. 2020; 39(8): 1619–1633, doi: 10.1038/s41388-019-1097-7, indexed in Pubmed: 31723239.
10. Sun P, Song Y, Liu D, et al. Potential role of the HOXD8 transcription factor in cisplatin resistance and tumour metastasis in advanced epithelial ovarian cancer. Sci Rep. 2018; 8(1): 13483, doi: 10.1038/s41598-018-31030-3, indexed in Pubmed: 30194340.
11. Braga EA, Fridman MV, Moscovtsev AA, et al. LncRNAs in ovarian cancer progression, metastasis, and main pathways: ceRNA and alternative mechanisms. Int J Mol Sci. 2020; 21(22), doi: 10.3390/ijms21228855, indexed in Pubmed: 33238475.
12. Jiang YX, Siu MKY, Wang JJ, et al. PFKFB3 regulates chemoresistance, metastasis and stemness IAP proteins and the nf-κb signaling pathway in ovarian cancer. Front Oncol. 2022; 12: 748403, doi: 10.3389/fonc.2022.748403, indexed in Pubmed: 35155224.
13. Tian W, Lei N, Zhou J, et al. Extracellular vesicles in ovarian cancer chemoresistance, metastasis, and immune evasion. Cell Death Dis. 2022; 13(1): 64, doi: 10.1038/s41419-022-04510-8, indexed in Pubmed: 35042862.
14. Lau TS, Chan LKY, Wong ECH, et al. A loop of cancer-stroma-cancer interaction promotes peritoneal metastasis of ovarian cancer via TNFα-TGFα-EGFR. Oncogene. 2017; 36(25): 3576–3587, doi: 10.1038/onc.2016.509, indexed in Pubmed: 28166193.
15. Yung MMH, Tang HWM, Cai PCH, et al. GRO-α and IL-8 enhance ovarian cancer metastatic potential via the CXCR2-mediated TAK1/NFκB signaling cascade. Theranostics. 2018; 8(5): 1270–1285, doi: 10.7150/thno.22536, indexed in Pubmed: 29507619.
16. Zhang Q, Yu S, Lam MM, et al. Angiotensin II promotes ovarian cancer spheroid formation and metastasis by upregulation of lipid desaturation and suppression of endoplasmic reticulum stress. J Exp Clin Cancer Res. 2019; 38(1): 116, doi: 10.1186/s13046-019-1127-x, indexed in Pubmed: 30845964.
17. Weidle UH, Birzele F, Kollmorgen G, et al. Mechanisms and targets involved in dissemination of ovarian cancer. Cancer Genomics Proteomics. 2016; 13(6): 407–423, doi: 10.21873/cgp.20004, indexed in Pubmed: 27807064.
18. Cai J, Gong L, Li G, et al. Exosomes in ovarian cancer ascites promote epithelial-mesenchymal transition of ovarian cancer cells by delivery of miR-6780b-5p. Cell Death Dis. 2021; 12(2): 210, doi: 10.1038/s41419-021-03490-5, indexed in Pubmed: 33627627.
19. Kasagi Y, Harada Y, Morodomi Y, et al. Peritoneal dissemination requires an sp1-dependent CXCR4/CXCL12 signaling axis and extracellular matrix-directed spheroid formation. Cancer Res. 2016; 76(2): 347–357, doi: 10.1158/0008-5472.CAN-15-1563, indexed in Pubmed: 26744523.
20. Hassan W, Chitcholtan K, Sykes P, et al. Ascitic fluid from advanced ovarian cancer patients compromises the activity of receptor tyrosine kinase inhibitors in 3D cell clusters of ovarian cancer cells. Cancer Lett. 2018; 420: 168–181, doi: 10.1016/j.canlet.2018.02.013, indexed in Pubmed: 29432847.
21. Yue H, Wang J, Chen R, et al. Gene signature characteristic of elevated stromal infiltration and activation is associated with increased risk of hematogenous and lymphatic metastasis in serous ovarian cancer. BMC Cancer. 2019; 19(1): 1266, doi: 10.1186/s12885-019-6470-y, indexed in Pubmed: 31888563.
22. Paik ES, Choi HJ, Kim TJ, et al. Molecular signature for lymphatic invasion associated with survival of epithelial ovarian cancer. Cancer Res Treat. 2018; 50(2): 461–473, doi: 10.4143/crt.2017.104, indexed in Pubmed: 28546526.
23. Ko SYi, Barengo N, Ladanyi A, et al. HOXA9 promotes ovarian cancer growth by stimulating cancer-associated fibroblasts. J Clin Invest. 2012; 122(10): 3603–3617, doi: 10.1172/JCI62229, indexed in Pubmed: 22945634.
24. Curtis M, Kenny HA, Ashcroft B, et al. Fibroblasts mobilize tumor cell glycogen to promote proliferation and metastasis. Cell Metab. 2019; 29(1): 141–155.e9, doi: 10.1016/j.cmet.2018.08.007, indexed in Pubmed: 30174305.
25. Nowak M, Klink M. The role of tumor-associated macrophages in the progression and chemoresistance of ovarian cancer. Cells. 2020; 9(5), doi: 10.3390/cells9051299, indexed in Pubmed: 32456078.
26. Loginov VI, Pronina IV, Filippova EA, et al. Aberrant methylation of 20 miRNA genes specifically involved in various steps of ovarian carcinoma spread: from primary tumors to peritoneal macroscopic metastases. Int J Mol Sci. 2022; 23(3), doi: 10.3390/ijms23031300, indexed in Pubmed: 35163224.
27. Sun Y, Meng C, Liu G. MicroRNA-506-3p inhibits ovarian cancer metastasis by down-regulating the expression of EZH2. J Cancer. 2022; 13(3): 943–950, doi: 10.7150/jca.66959, indexed in Pubmed: 35154460.
28. He L, Zhu W, Chen Q, et al. Ovarian cancer cell-secreted exosomal miR-205 promotes metastasis by inducing angiogenesis. Theranostics. 2019; 9(26): 8206–8220, doi: 10.7150/thno.37455, indexed in Pubmed: 31754391.
29. Ghafouri-Fard S, Shoorei H, Taheri M. miRNA profile in ovarian cancer. Exp Mol Pathol. 2020; 113: 104381, doi: 10.1016/j.yexmp.2020.104381, indexed in Pubmed: 31954715.
30. Cai J, Gong L, Li G, et al. Exosomes in ovarian cancer ascites promote epithelial-mesenchymal transition of ovarian cancer cells by delivery of miR-6780b-5p. Cell Death Dis. 2021; 12(2): 210, doi: 10.1038/s41419-021-03490-5, indexed in Pubmed: 33627627.
31. Li J, Hu K, Gong G, et al. Upregulation of MiR-205 transcriptionally suppresses SMAD4 and PTEN and contributes to human ovarian cancer

progression. Sci Rep. 2017; 7: 41330, doi: 10.1038/srep41330, indexed in Pubmed: 28145479.
32. Visvader JE, Lindeman GJ. Cancer stem cells: current status and evolving complexities. Cell Stem Cell. 2012; 10(6): 717–728, doi: 10.1016/j.stem.2012.05.007, indexed in Pubmed: 22704512.
33. Markowska A, Sajdak S, Markowska J, et al. Angiogenesis and cancer stem cells: New perspectives on therapy of ovarian cancer. Eur J Med Chem. 2017; 142: 87–94, doi: 10.1016/j.ejmech.2017.06.030, indexed in Pubmed: 28651817.
34. Muñoz-Galván S, Carnero A. Targeting cancer stem cells to overcome therapy resistance in ovarian cancer. Cells. 2020; 9(6), doi: 10.3390/cells9061402, indexed in Pubmed: 32512891.
35. Zhou N, Wu X, Yang Bo, et al. Stem cell characteristics of dormant cells and cisplatininduced effects on the stemness of epithelial ovarian cancer cells. Mol Med Rep. 2014; 10(5): 2495–2504, doi: 10.3892/mmr.2014.2483, indexed in Pubmed: 25119644.
36. Deng J, Wang Li, Chen H, et al. Targeting epithelial-mesenchymal transition and cancer stem cells for chemoresistant ovarian cancer. Oncotarget. 2016; 7(34): 55771–55788, doi: 10.18632/oncotarget.9908, indexed in Pubmed: 27304054.
37. Kleinmanns K, Fosse V, Bjørge L, et al. The Emerging Role of CD24 in Cancer Theranostics-A Novel Target for Fluorescence Image-Guided Surgery in Ovarian Cancer and Beyond. J Pers Med. 2020; 10(4), doi: 10.3390/jpm10040255, indexed in Pubmed: 33260974.
38. Tarhriz V, Bandehpour M, Dastmalchi S, et al. Overview of CD24 as a new molecular marker in ovarian cancer. J Cell Physiol. 2019; 234(3): 2134–2142, doi: 10.1002/jcp.27581, indexed in Pubmed: 30317611.
39. Bu S, Wang Q, Sun J, et al. Melatonin suppresses chronic restraint stress-mediated metastasis of epithelial ovarian cancer via NE/AKT/β-catenin/SLUG axis. Cell Death Dis. 2020; 11(8): 644, doi: 10.1038/s41419-020-02906-y, indexed in Pubmed: 32811805.

VIA MEDICA

CLINICAL VIGNETTE

Ginekologia Polska
2022, vol. 93, no. 8, 675–676

ISSN 0017–0011, e-ISSN 2543–6767

DOI 10.5603/GP.a2022.0048

The 13-year-old girl with unicornuate uterus with non-communicating uterine horn

Katarzyna Wilk, Maja Zieba-Domalik, Rafal Stojko, Agnieszka Drosdzol-Cop

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

Key words: unicornuate uterus; uterine anomalies; case presentation

Ginekologia Polska 2022; 93, 8: 675–676

INTRODUCTION

A properly formed uterine cavity is formed as a result of joining the utero-vaginal canal of both Müller's intrarenal ducts. Uterine development ends at 22 weeks of gestation [1, 2]. In the case of a unicornuate uterus, only one of the two Müller's ducts is differentiated properly. According to the literature, the frequency of the unicornuate uterus anomaly is estimated between 0.1–2% in women [3]. In the patient described below, the defect of the uterus was classified as: Class 2/ U4a by the American Society of Fertility, the European Society of Human Reproduction and Embryology and the European Society of Gynecological Endoscopy that is: unicornuate uterus with uterine horn not communicating with the present endometrial tissue [1, 2].

Cyclical growth of the active hormonal endometrium located in the non-communicating corner of the uterus leads to accumulation of the menstrual blood inside the uterine cavity and then in the fallopian tube, causing abdominal pain [1, 3]. Initially, pain may be related to the painful menstrual cycle. Delayed diagnosis may cause the symptoms of endometriosis in the future, and in the procreation period may have an effect on obstetric failures [1–3].

A unicorned uterus with a non-communicating horn increases the risk of obstetric and gynecological complications. It should undergo surgical correction to limit processes such as ectopic pregnancies, hematometry or endometriosis [1–3].

CASE PRESENTATION

A case of a 13-year-old-girl with a unicornuate uterus with non-communicating uterine horn (class U4a in the ESHRE/ESGE classification) was reported. The patient was admitted to the Department of Pediatric and Adolescent Gy-

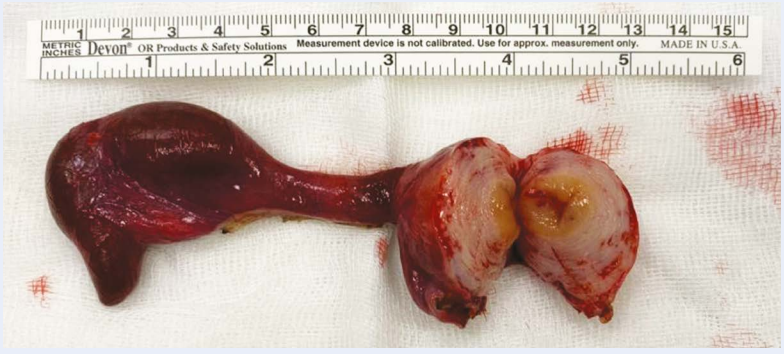


Figure 1. Non-communicating uterine horn with right fallopian tube

Corresponding author:
Katarzyna Wilk
Chair and Department of Gynecology, Obstetrics and Gynecological Oncology, Medical University of Silesia, 87 Markiefki St, 40-211 Katowice, Poland
e-mail: kkatarzynawilkk@gmail.com

Received: 21.05.2022 Accepted: 22.05.2022 Early publication date: 21.07.2022

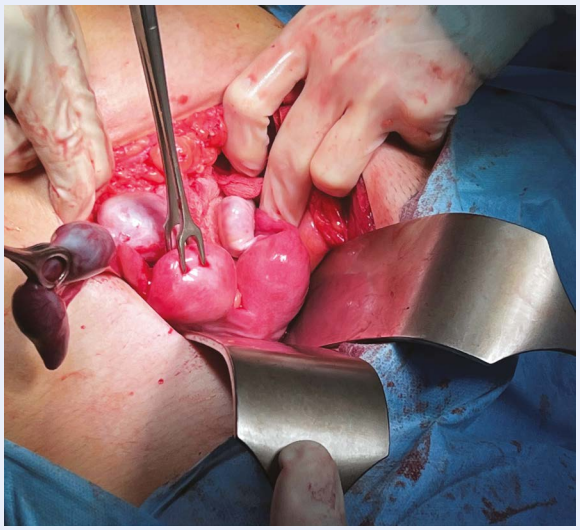


Figure 2. Laparotomy — unicornuate uterus with noncommunicating uterine horn

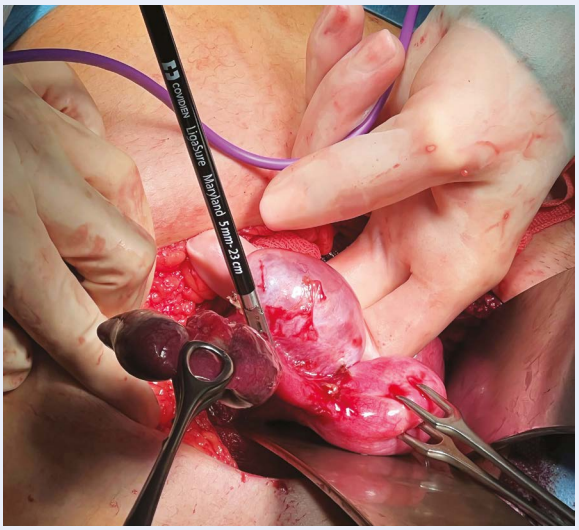


Figure 3. Laparotomy — right ovary with right fallopian tube

necology in Katowice from the Department of Pediatric Surgery due to complaints of worsening lower abdominal pain and with the suspicion of didelphys uterus. She experienced regular menstrual cycles from menarche at the age of 12.

For over 3 months, the girl had a few episodes of severe lower abdominal pain following her menses. A physical examination was unremarkable with normal secondary sexual characteristics.

During the hospitalization, transabdominal ultrasonography of the pelvis revealed a didelphys uterus, right sized at 45 x 33 mm, uterine cavity measured as 18 mm filled with blood similar to hematometra, left uterus 33 x 24 mm, endometrium measuring about 8 mm. Pelvic magnetic resonance imaging (MRI) revealed a normal uterus on the left side with a properly developed vagina, the uterine cavity on the right side was dilated measuring 18 mm, vagina on the right side was not visible. The inflammatory markers were in the normal range.

Laparotomy showed a unicornuate uterus with a normal cervix with a non-communicating uterine horn on the right side, the ampulla section of the fallopian tube was enlarged and distended with bloody fluid, the right ovary was the proper size. The girl was treated with surgical resection of the right non-communicating uterine horn and fallopian tube. The left tube and both ovaries were preserved. After the procedure, the patient was comfortable during the postoperative period.

A further follow-up of the patient was recommended.

CONCLUSIONS

In the diagnosis of Müller duct anomalies, it is important that the patient undergoes appropriate imaging diagnostics. A 2D, 3D ultrasound, MRI or hysterosalpingography should be considered [1, 3]. Patients with a unicornuate uterus after resection of the non-communicating horn of the uterus with appendages have a worse obstetric prognosis due to poorer blood supply to the reproductive organ and limited possibilities of uterine enlargement with growth of the fetus. This may result in miscarriage, prematurity, intrauterine growth restriction, ectopic pregnancies, isthmus-cervical failure or uterine rupture or intrauterine death [1, 2].

Conflict of interest

All authors declare no conflict of interest.

REFERENCES

1. Passos Id, Britto RL. Diagnosis and treatment of Müllerian malformations. Taiwan J Obstet Gynecol. 2020; 59(2): 183–188, doi: 10.1016/j.tjog.2020.01.003, indexed in Pubmed: 32127135.
2. Delić R. Pregnancy in a unicornuate uterus with non-communicating rudimentary horn: diagnostic and therapeutic challenges. Acta Med Litu. 2020; 27(2): 84–89, doi: 10.15388/Amed.2020.27.2.6, indexed in Pubmed: 34113213.
3. Ludwin A, Lindheim SR. Unicornuate uterus and the noncommunicating functional horn: continued debate on the diagnosis, classification, and treatment. Fertil Steril. 2020; 113(4): 772–773, doi: 10.1016/j.fertnstert.2020.01.006, indexed in Pubmed: 32147179.

VIA MEDICA

CLINICAL VIGNETTE

Ginekologia Polska
2022, vol. 93, no. 8, 677–678

ISSN 0017–0011, e-ISSN 2543–6767

DOI 10.5603/GP.a2022.0030

A rare case of hemimegalencephaly diagnosed prenatally

Anna Wojtowicz[1], Agnieszka Duczkowska[2], Hubert Huras[1]

[1]*Department of Obstetrics and Perinatology, Jagiellonian University Medical College, Cracow, Poland*
[2]*Department of Diagnostic Imaging Institute of Mother and Child, Warsaw, Poland*

ABSTRACT

Hemimegalencephaly (HME), or unilateral megalencephaly, is a rare congenital brain malformation defined as overgrowth of one cerebral hemisphere or part of it resulting from abnormal cortical development and neuronal migration. However, cortical developmental abnormalities are rarely diagnosed prenatally. This is the reason for our study, in which we describe and compare ultrasound and MRI findings in a fetus with HME.

Key words: fetus; hemimegalencephaly; central nervous system; ultrasound

Ginekologia Polska 2022; 93, 8: 677–678

Hemimegalencephaly (HME), or unilateral megalencephaly, is a rare congenital brain malformation defined as overgrowth of one cerebral hemisphere or part of it resulting from abnormal cortical development and neuronal migration. In addition to overgrowth, abnormal cortical development can manifest as polymicrogyria, agyria, pachygyria, lissencephaly, or grey matter heterotopia [1, 2]. The risk of chromosomal anomalies with HME is low but the risk of non-chromosomal abnormalities is relatively high. HME may be either isolated or associated with some neurocutaneous syndromes such as Proteus syndrome, epidermal nervus syndrome, tuberous sclerosis [1, 2]. Clinically, HME is associated with severe psychomotor delay and intractable epilepsy. The prognosis is poor, and the only possible treatment is a hemispherectomy to control seizures [3]. Evaluation of HME may be made by ultrasound or magnetic resonance imaging (MRI) [1–5]. However, cortical developmental abnormalities are rarely diagnosed prenatally. This is the reason for our study, in which we describe and compare ultrasound and MRI findings in a fetus with HME.

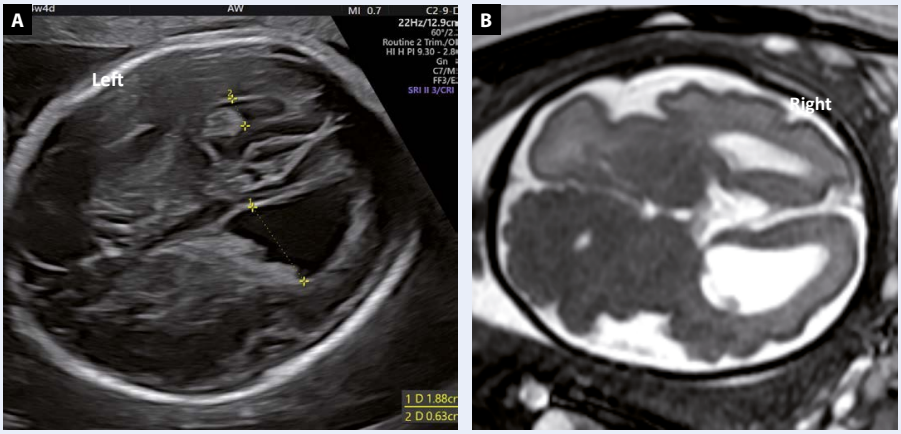


Figure 1. Hemimegalencephaly. Transventricular plane showing enlarged right cerebral hemisphere and the unilateral right side ventriculomegaly with midline shifted to the left. (**A**) 2D transabdominal ultrasound scan at 24 gestational weeks; (**B**) foetal MRI at 29 gestational weeks, FIESTA, axial plane

A 45-year-old pregnant woman at 22 weeks of pregnancy was referred to our department due to ventriculomegaly at anomaly scan. It was her fifth pregnancy, with no family history of central nervous system anomalies, and with a negative TORCH test result. A first trimester screening for aneuploidy was not performed. Ultrasound examination showed normal growth and normal anatomy except for the brain. Neuro-

Corresponding author:
Anna Wojtowicz
Department of Obstetrics and Perinatology, Kopernika 23, 31-501 Cracow, Poland
e-mail: anna.3.wojtowicz@uj.edu.pl

Received: 22.02.2022 Accepted: 1.04.2022 Early publication date: 25.05.2022

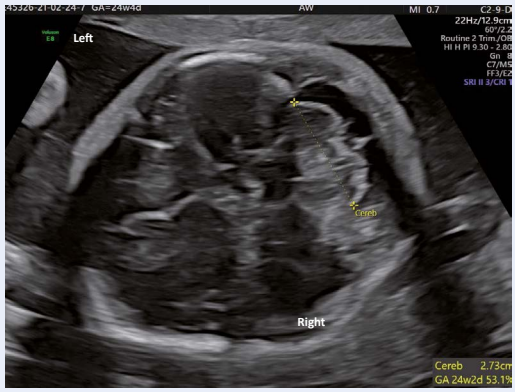


Figure 2. Hemimegalencephaly with normal anatomy of the cerebellum (2D ultrasound at 24 weeks of gestation)

sonography revealed unilateral right ventriculomegaly, the midline shifted to the left with right hemisphere overgrowth (Fig. 1A), and a head circumference in the 98th percentile. Transcerebellar section showed normal anatomy of the posterior fossa (Fig. 2). In the coronal plane, both the genu of the corpus callosum, and an abnormal and excessive gyration of the right hemisphere were visible (Fig. 3A). Hemimegalencephaly with gyral abnormality was suspected and the patient was referred for an MRI, by which, at 29 weeks of gestation our diagnosis was confirmed. Fetal MRI showed hemimegalencephaly of the right cerebral hemisphere with polymicrogyria and heterotopia (Fig. 1B and Fig. 3B). During pregnancy the head circumference and biparietal diameter remained greater than the 90th percentile. The mother underwent an elective cesarean section at 40 weeks' gestation and gave birth to a male infant weighing 3710 g, Ap 10 with birth head circumference of 38 cm (> 99th percentile). Array-based comparative genomic hybridisation (aCGH) performed after birth from peripheral blood was normal and genetic counselling did not show any other signs of neurocutaneous syndromes. Postnatally the child was provided with neurological and rehabilitation care. No seizures were observed during the neonatal period.

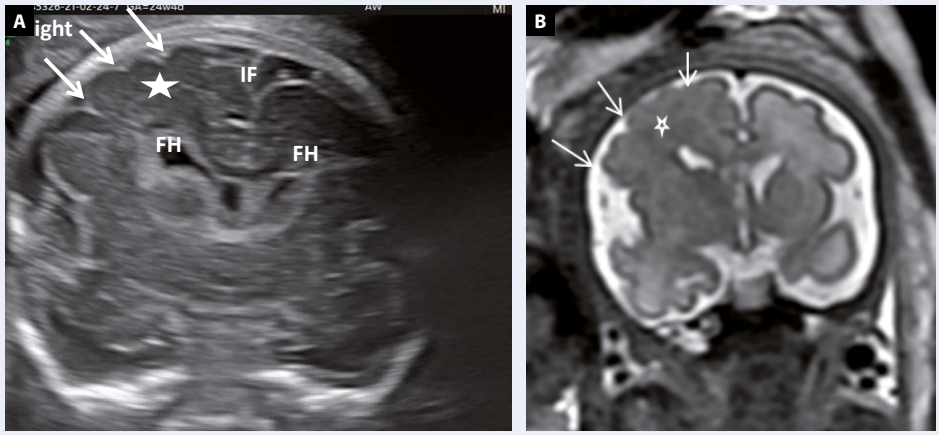


Figure 3. Hemimegalencephaly. Coronal view of the fetal brain showing an owergrowth of the right hemisphere and abnormally developed sulci and gyri (arrows): (**A**) transabdominal 2D ultrasound view at 24 weeks; (**B**) fetal MRI at 29 gestational weeks; SSFSE/T2, coronal plane, apart from abnormally developed sulci and gyri (arrows) hypointensity of the right cerebral white matter (asterisk) as a sign of migration abnormality is visible; IF — interhemispheric fissure; FH — frontal horn

In conclusion, HME is a difficult but possible diagnosis to make using antenatal ultrasound. However, fetal MRI should be considered in cases where unilateral ventriculomegaly is diagnosed at ultrasound. In utero diagnosis of HME allowed a multidisciplinary approach for providing optimal prenatal and postnatal patient counselling and treatment.

Conflict of interest

All authors declare no conflict of interest.

REFERENCES

1. Flores-Sarnat L. Hemimegalencephaly: part 1. Genetic, clinical, and imaging aspects. J Child Neurol. 2002; 17(5): 373–84; discussion 384, doi: 10.1177/088307380201700512, indexed in Pubmed: 12150586.
2. Manoranjan B, Provias JP. Hemimegalencephaly: a fetal case with neuropathological confirmation and review of the literature. Acta Neuropathol. 2010; 120(1): 117–130, doi: 10.1007/s00401-010-0663-4, indexed in Pubmed: 20237789.
3. Alvarez RM, García-Díaz L, Márquez J, et al. Hemimegalencephaly: prenatal diagnosis and outcome. Fetal Diagn Ther. 2011; 30(3): 234–238, doi: 10.1159/000329937, indexed in Pubmed: 21921574.
4. Romero XC, Molina FS, Pastor E, et al. Hemimegalencephaly: 2D, 3D Ultrasound and MRI Correlation. Fetal Diagn Ther. 2011; 29(3): 257–260, doi: 10.1159/000322012, indexed in Pubmed: 21109730.
5. Senapati G, Levine D. Prenatal-postnatal correlations of brain abnormalities: how lesions and diagnoses change over time. J Pediatr Neuroradiol. 2012; 1(3): 171–184, doi: 10.3233/PNR-2012-027, indexed in Pubmed: 24078783.

RAK PIERSI 2022

Aktualne wytyczne postępowania diagnostyczno–terapeutycznego PTOK

Przewodniczący Komitetu Naukowego:

prof. dr hab. n. med. Piotr Wysocki
prof. dr hab. n. med. Maciej Krzakowski

VIRTUAL MEETING

12.05.2022 r.

VIRTUAL MEETING

6.10.2022 r.

Szczegółowe informacje i rejestracja na stronie internetowej: **www.rakpiersiptok.viamedica.pl**

PATRONAT
Polskie Towarzystwo Onkologii Klinicznej

ORGANIZATOR
VIA MEDICA

PATRONAT MEDIALNY
tvmed

PARTNER
ikamed.pl

Virtual Meeting jest skierowany 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 2019 r. poz. 499).

21-0756.001.002

IV FORUM GINEKOLOGII I PERINATOLOGII PRAKTYCZNEJ

STANDARDY POSTĘPOWANIA W POŁOŻNICTWIE I GINEKOLOGII

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

ŁÓDŹ, 23–24 września 2022 roku

Zapraszamy serdecznie na naszego Facebooka!
www.facebook.com/FGiPP

Szczegóły oraz rejestracja na stronie internetowej:

www.forumginekologii.viamedica.pl

Kontakt w sprawie uczestnictwa:

forumginekologii@viamedica.pl

tel.: (58) 320 94 94

PATRONAT

ORGANIZATOR

PATRONAT MEDIALNY

PARTNER

22-3410.001.012

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).