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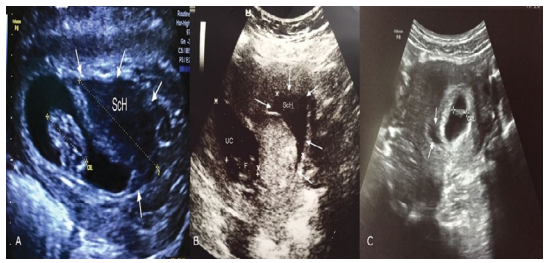

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Clinical evaluation of transvaginal myomectomy surgery: a retrospective study of 138 cases

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ABSTRACT

Objectives: The aim of this study was to evaluate the safety, feasibility, and effectiveness of transvaginal myomectomy surgery.

Material and methods: We conducted a retrospective study in Shengjing Hospital of China Medical University. In all, 138 patients underwent transvaginal myomectomy from March 2009 to March 2019. The perioperative clinical data, such as position and size of myomas, operative duration, blood loss, intraoperative and postoperative complications, and hospitalization time were retrospectively analyzed.

Results: All transvaginal myomectomies were performed without conversion to laparotomy. The mean vaginal operating time was 56.0 (± 17.2) minutes. The mean operative estimated blood loss was 89.2 (± 36.8) mL. No significant intraoperative complications occurred. The median time of intestinal function recovery after operation was 1 day (range 1–4 days). The median time of hospital stay was 4 days (range 3–10 days); 12 (8.7%) patients experienced postoperative morbidity.

Conclusions: Transvaginal myomectomy is a minimally invasive surgery that can be performed without leaving a scar on the body surface. It can be performed safely and effectively by a skilled surgeon in cases with a specific surgical indication for this approach.

Key words: uterine myomas; natural orifice surgery; vaginal myomectomy

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INTRODUCTION

Uterine fibroids are the most common benign tumors of the female reproductive organs, being found in 20–30% of women of reproductive age [1]. Leiomyoma is an important clinical condition in gynecology. It causes abnormal uterine bleeding, pelvic pressure symptoms, spontaneous abortion, and pelvic pain [2]. Most patients require surgical treatment for symptomatic fibroids. Since uterine fibroids are well-lined and non-capsulated benign tumors, myomectomy is an effective treatment option for symptomatic fibroids [3]. In recent years, with increased awareness of health care and greater requirements for quality of life, the incidence of myomectomy is increasing [4, 5]. In addition to the classical treatment strategy of laparotomy, other techniques such as laparoscopy, operative hysteroscopy and the transvaginal route have been widely used for uterine fibroids in recent decades [6]. The choice of approach for a myomectomy depends on the size, number, and location of fibroids, as well as the skill of the surgeon. In 1994, Magos et al. [7] first reported 3 cases of transvaginal myomectomy. Compared with laparoscopy, transvaginal myomectomy is considered to offer many advantages, such as leaving no external scarring, low medical cost, and quick postoperative recovery. Being that it is less invasive than laparoscopy, there is also a better psychological outcome for the patient [8, 9]. However, due to limited operating space, a restricted field of view, and other relevant complications, the application of transvaginal myomectomy is not as widespread as that of laparoscopic surgery [10]. This paper retrospectively analyzed the clinical data, complications, and outcomes of a series of patients who underwent transvaginal myomectomy performed by experienced surgeons over the past 10 years. The goals of this study are to investigate the safety, feasibility, and effectiveness of this surgical procedure.

MATERIAL AND METHODS

Subjects

This study collected 138 cases of patients with complete medical records, who underwent transvaginal myomectomy in the Department of Obstetrics and Gynecology, Shengjing

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Table 1. Demographics of 138 women who underwent vaginal myomectomy	
Characteristics of patients	
Mean age, years ± SD	39.6 ± 11.5
Nulliparous, n (%)	10 (7.2)
Parity, median (range)	1 (0–4)
Previous surgery, n (%)	
Previous cesarean section	13 (9.4)
Oophorocystectomy	5 (3.6)
Adnexectomy	2 (1.4)
Tubal ligation	2 (1.4)
Laparotomic myomectomy	1 (7.2)
Appendectomy	3 (2.2)
Symptomatic uterine fibroids, n (%)	
Menorrhagia	24 (17.4)
Menostaxis	12 (8.7)
Frequent micturition Symptoms of bladder compression	5 (3.6)
Dysmenorrhea	2 (1.4)
Rapid myoma growth	3 (2.2)

Hospital of China Medical University from March 2009 to March 2019. The characteristics of the patients are reported in Table 1. All of the patients provided informed consent. This study was approved by the Ethics Committee of our hospital.

Preoperative assessments

In addition to a complete medical history, all patients underwent careful physical and ultrasound examinations to comprehensively evaluate the uterus and fibroids (size, location, morphology, and activity). Some patients also underwent pelvic magnetic resonance imaging (MRI). Before transvaginal myomectomy, cervical cytology was routinely performed on all patients, and diagnostic curettage was performed on patients with abnormal menstruation to exclude endometrial lesions. The preoperative examinations excluded the ovarian diseases, pelvic adhesions, severe endometriosis, or pelvic inflammation.

Preoperative preparation

Sexual activity was forbidden for all patients for one week before surgery, and iodophor was used for vaginal disinfection twice per day for three days before the surgery. If vaginal inflammation was present before surgery, transvaginal myomectomy was not performed until the vaginal inflammation was cured. All patients underwent routine preoperative mechanical and chemical bowel preparation and received a single dose of prophylactic intravenous antibiotics immediately before the start of the procedure. The procedure was performed under general endotracheal anesthesia in the lithotomy position.

Surgical procedure

If uterine fibroids were located in the posterior wall of the uterus, the posterior vaginal wall was incised at the uterosacral ligament to expose the pouch of Douglas and access the retroperitoneum. If uterine fibroids were located in the anterior wall of the uterus, an incision was made along the anterior fornix bilaterally and inwardly until the anterior peritoneum was reached. If the anterior wall space was limited, it was enlarged by an inverted "T" incision; if the uterus was large, the anterior and posterior fornices were incised simultaneously to enter the abdominal cavity, which is conducive to everting the uterus. After entering the abdomen, the location, size, and number of fibroids were explored. The uterus and uterine fibroids were exposed, and the fibroids were clamped and pulled outward. Pituitrin (6–12 U) was injected into the myometrium in the vicinity of the tumor. The myometrium was bisected to the fibroid pseudocapsule, and uterine fibroids were dissected. If a fibroid was large and could not be completely removed via the vagina, it was separated while being morcellated into wedge-shaped pieces, so it could be removed via the vagina. After the removal of larger fibroids, the whole uterine body was pulled into the vagina. Careful examination was undertaken by the surgeon of the uterine body for small fibroids, which were removed if present. The fibroid pseudocapsule was trimmed using 1–0 absorbable sutures to suture the uterus with intermittent sutures of 1 to 2 layers of the myometrium and continuous suturing of the serosa layer. Subsequently, 2–0 absorbable sutures were used to suture the peritoneal reflection and the vaginal incisal margin, and a T-type tube was placed in the vaginal incision for drainage. The vagina was then filled with two pieces of iodophor-soaked gauze, a ureteral catheter was placed, and the surgery was completed.

Postoperative management and follow-up

Postoperative routine intravenous infusion of antibiotics was performed for 3 to 5 days. The patients were given a liquid diet for 6 hours after surgery and a semiliquid diet on the following day. The vaginal gauze and ureteral catheter were removed 24 hours post-surgically. Vaginal drainage generally lasted for approximately 48 to 72 hours. Routine monitoring of body temperature, hemography, and exhaust time were performed. At the 2-month, 6-month and 12-month follow-up visits to the general outpatient department, general physical examinations, gynecological examinations, and pelvic ultrasounds were performed.

Observation indicators

According to the clinical data, the following indicators were collected: the location, number, and volume of uterine fibroids; operative time; intraoperative blood loss; intra-

operative and postoperative complications; postoperative morbidity; length of postoperative hospital stay; and postoperative fever. Fever was defined as temperature increasing to greater than 38°C on two occasions at least 6 hrs apart within 24 hrs, commencing 24 hrs after surgery.

Statistical analysis

Statistical analysis was performed using SPSS software, version 16 (SPSS Inc. Chicago, IL, USA). The results are expressed as the mean ± standard deviation.

RESULTS

Characteristics of uterine fibroids

The characteristics of uterine fibroids in the 138 cases of transvaginal myomectomy are shown in Table 2. Greater than half of the cases (60.9%) had multiple fibroids. Of these cases, 8 had greater than 5 fibroids, and the greatest number of fibroids removed in one case was 13. Most cases (85.5%) had fibroids in the uterine body: 12 cases had cervical fibroids, and 8 cases had broad ligament fibroids. In two-thirds of cases (66.7%), the maximum fibroid diameter was between 5 and 10 cm, and the largest fibroid removed had a diameter of 12 cm.

Perioperative performance data

All 138 cases were successfully completed, with no adjacent organ injury or other intraoperative complications. Perioperative performance data are summarized in Table 3. No postoperative complications occurred. Postoperative analgesia was considered routine for the transvaginal myomectomy procedure. Postoperative pathological examinations revealed uterine fibroids.

Postoperative morbidity: Twelve patients had postoperative temperatures greater than 38°C, and the postoperative morbidity rate was 8.7%. All patients underwent blood culture and drug susceptibility tests, and *Escherichia coli* was detected in the cultures of two patients. The symptoms of ten patients resolved 4 to 6 days after combined treatment with antibiotics and traditional Chinese medicines that promote blood circulation and reverse blood stasis. The two other patients developed postoperative uterine and pelvic abscesses, which were treated with interventional ultrasound-guided puncture and pus aspiration. No other complications occurred after antibiotic treatment. All patients with fever were treated with early surgery. The operative time was a minimum of 1.5 hours.

Prognosis

The mean time to follow-up with patients was 9.0 ± 2.2 months (3–12 months). There were 43 patients that underwent surgery due to menometrorrhagia, menostaxis, frequent urination due to bladder compression, or lower abdominal pain. All symptoms were alleviated after surgery; no residual fibroids were found on gynecological examination or ultrasonography. Postoperative follow-up visits showed good healing of the fornix mucosa. Four patients had fertility requirements. Because contraception was required for 2 years, and the follow-up period was short, no postoperative pregnancies have been reported.

DISCUSSION

Though transvaginal myomectomy has many benefits as mentioned, it is not suitable for all patients who require myomectomy. However, there is currently no uniform standard for indications for transvaginal myomectomy [11]. Some scholars have suggested that the size of the uterus should not exceed the gravid uterus at 12, 14, or 16 weeks

Table 2. Characteristics of Myomas

Characteristics of Myomas	
Single, n (%)	54 (39.1)
Multiple, n (%)	
≤ 5	76 (55.1)
> 5, ≤ 10	6 (4.3)
> 10	2 (1.4)
Corpus myoma, n (%)	
Subserosal	47 (34.1)
Intramural	54 (39.1)
Intramural/Subserosal	17 (12.3)
submucous	0
Special position, n (%)	
Cervical myoma	11 (8.0)
Cervical/corpus	1 (0.7)
Broad ligament myoma	8 (5.8)
Broad ligament/corpus	0
Myoma size cm ± SD	6.7 ± 1.8
Diameter ≤ 5 cm, n (%)	43 (31.2)
Diameter > 5 cm ≤ 10 cm, n (%)	92 (66.7)
Diameter > 10 cm, n (%)	3 (2.2)

Table 3. Perioperative performance

Characteristic	Results
Mean operative time (min ± SD, range)	56.0 ± 17.2 (30–110)
Mean blood loss (mL ± SD, range)	89.2 ± 36.8 (40–300)
Blood transfusion rate (n, %)	1 (0.7)
Mean intestinal function recovery time, median days (range)	1 (1–4)
Postoperative fever (n, %)	12 (8.7)
Mean hospitalization after surgery, median days (range)	4 (3–10)

of gestation. Others have suggested that the diameter of fibroids should be no more than 7 cm, 10 cm or 11 cm. Still others have suggested that the number of fibroids should not exceed three, while some scholars believe that there should be no restrictions on the number of fibroids. It has also been suggested that fibroids in the anterior wall are not suitable for transvaginal myomectomy [12–15]. We believe that whether transvaginal myomectomy is a suitable treatment option depends on the patient's conditions. The decision to perform transvaginal myomectomy is determined based on a comprehensive assessment of multiple factors, including size, number, type (subserosal, intramural, etc.), and location of fibroids, vaginal conditions, the history of pelvic inflammation, proficiency of the surgeon, and the presence of an adnexal mass. Careful gynecological examination and ultrasonography are very important to determine if the patient is a candidate for this procedure. A MRI should be performed before surgery if necessary. Adequate preoperative assessment and adhering to strict indications are essential for the success of the surgery. Therefore, the incidence of intraoperative and postoperative complications can be avoided or reduced, and the likelihood of conversion to laparotomy can be minimized.

Transvaginal myomectomy has multiple advantages, which have been discussed extensively [16, 17]. These include advantages in operative time, intraoperative blood loss, degree of postoperative pain, postoperative recovery time of intestinal function, average length of postoperative hospital stay, medical expenses, and aesthetic/psychological effects without abdominal incisions [18]. The results of this study are consistent with the general conclusions of previous studies. We believe that, compared with laparoscopic surgery, the greatest advantage of transvaginal myomectomy is that the surgeon can perform every step of the operation under direct vision, which is more accurate, safe and expedient than under microscopic view. This is true especially when the fibroids are large and buried deeply in the uterus. In the case of a transvaginal approach, conventional layered sutures can be performed on deep uterine muscle wounds, which can improve the reliability of repairing large uterine defects and can compensate for the deficiency of the laparoscopic approach in this area. In addition, because transvaginal myomectomy does not require expensive and complex equipment, it is more suitable for economically underdeveloped areas.

However, transvaginal myomectomy has not been as widely practiced as laparoscopic myomectomy, mainly due to the technical difficulties of transvaginal operations, including limited operating space, restricted field of view and concerns about the injury risk of adjacent organs [17, 19]. The key to this procedure is eversion of the uterus; therefore, preoperative examination should determine the location of the major fibroids. If a fibroid protrudes from the anterior wall, it is easy to evert the uterus from the anterior fornix. Otherwise, it should be everted from the posterior fornix. When the volume of the uterus is large, or large fibroids are present, it is often necessary to gradually open the fibroid pseudocapsule while outwardly pulling the uterus. The fibroid is separated until a tenaculum can be used to grasp and remove it. Alternatively, the fibroid can be morcellated while being stripped to reduce the fibroid volume until the fibroid can be fully removed. In addition, the inherently narrow field of vaginal surgery does not have the magnification effect of laparoscopic surgery; thus, vaginal surgery is not conducive to extensive learning and training.

Postoperative fever is a common complication of vaginal myomectomy. Compared with laparoscopic surgery, vaginal myomectomy has a higher postoperative morbidity rate [11, 20]. In this group of patients, the body temperatures of 12 patients exceeded 38°C, and two patients developed postoperative uterine and pelvic abscesses, which were relieved by interventional ultrasound-guided puncture and pus aspiration, followed by 4–6 days of combined treatment using antibiotics and traditional Chinese medicines that increase blood circulation and reverse blood stasis. The reason for the high incidence of fever after transvaginal myomectomy is related to the fact that the uterus is a muscular organ with an abundant blood supply [21]. Enucleation of uterine fibroids is a process in which a large number of blood vessels are exposed, and the chance of infection is increased when the uterus, with its exposed blood vessels, remains for a long time in the bacterial environment of the vagina. In this study, all cases of postoperative fever occurred in the early study period. Since preoperative vaginal preparation was emphasized, the occurrence of postoperative fever was significantly reduced after adequate and strict vaginal disinfection. In addition, the operative time of patients with postoperative fever was close to or more than 1.5 hours in this study. With increasing surgical proficiency, the operation time was shortened, thus reducing the uterine exposure time. Therefore, the duration of uterine congestion caused by uterine eversion was minimized, and the occurrence of postoperative fever was also reduced.

In summary, transvaginal myomectomy has its own independent indications and numerous advantages, and it is a useful supplement to the transabdominal operation. As long as the surgeon is proficient in transvaginal surgical skills and is familiar with the surgical indications, it is safe to perform transvaginal myomectomy.

REFERENCES

1. De La Cruz MS, Buchanan EM. Uterine Fibroids: Diagnosis and Treatment. Am Fam Physician. 2017; 95(2): 100–107, indexed in Pubmed: 28084714.
2. Donnez J, Dolmans MM. Uterine fibroid management: from the present to the future. Hum Reprod Update. 2016; 22(6): 665–686, doi: 10.1093/humupd/dmw023, indexed in Pubmed: 27466209.
3. Glaser LM, Friedman J, Tsai S, et al. Laparoscopic myomectomy and morcellation: A review of techniques, outcomes, and practice guidelines. Best Pract Res Clin Obstet Gynaecol. 2018; 46: 99–112, doi: 10.1016/j.bpobgyn.2017.09.012, indexed in Pubmed: 29078975.
4. Dubuisson J. The current place of mini-invasive surgery in uterine leiomyoma management. J Gynecol Obstet Hum Reprod. 2019; 48(2): 77–81, doi: 10.1016/j.jogoh.2018.10.004, indexed in Pubmed: 30316905.
5. Wongpia I, Thinkhamrop J, Seejorn K, et al. Incidence of and risk factors for febrile morbidity after laparoscopic-assisted vaginal hysterectomy. Int J Womens Health. 2014; 6: 385–388, doi: 10.2147/IJWH.S57521, indexed in Pubmed: 24748819.
6. Yoong W, Zhao W, Cai H, et al. Vaginal Myomectomy Using the Dührssen (Longitudinal Median Cervical) Incision: A Case Series of 19 Patients. J Minim Invasive Gynecol. 2017; 24(5): 811–814, doi: 10.1016/j.jmig.2017.04.002, indexed in Pubmed: 28411085.
7. Magos AL, Bournas N, Sinha R, et al. Vaginal myomectomy. Br J Obstet Gynaecol. 1994; 101(12): 1092–1094, doi: 10.1111/j.1471-0528.1994.tb13593.x, indexed in Pubmed: 7826970.
8. Rakotomahenina H, Rajaonarison J, Wong L, et al. Myomectomy: technique and current indications. Minerva Ginecol. 2017; 69(4): 357–369, doi: 10.23736/S0026-4784.17.04073-4, indexed in Pubmed: 28447445.
9. Meng L, Li W. The curative effect analysis and nursing measures of the transvaginal myomectomy and transabdominal myomectomy. Pak J Pharm Sci. 2016; 29(6 Suppl): 2281–2285, indexed in Pubmed: 28167466.
10. Flyckt R, Coyne K, Falcone T. Minimally Invasive Myomectomy. Clin Obstet Gynecol. 2017; 60(2): 252–272, doi: 10.1097/GRF.0000000000000275, indexed in Pubmed: 28121646.
11. Flyckt RL. Setting the focus on patient selection for minimally invasive myomectomy: operating times and surgical morbidity in a large database study. Fertil Steril. 2019; 111(6): 1127–1128, doi: 10.1016/j.fertnstert.2019.03.031, indexed in Pubmed: 31043231.
12. Moro F, Bitonti G, Mascilini F, et al. Intraoperative transvaginal ultrasound examination during myomectomy. J Ultrasound. 2019; 22(1): 109–110, doi: 10.1007/s40477-018-0310-9, indexed in Pubmed: 30019287.
13. Chittawar PB, Kamath MS. Review of nonsurgical/minimally invasive treatments and open myomectomy for uterine fibroids. Curr Opin Obstet Gynecol. 2015; 27(6): 391–397, doi: 10.1097/GCO.0000000000000223, indexed in Pubmed: 26536205.
14. Arian SE, Munoz JL, Kim S, et al. Robot-assisted laparoscopic myomectomy: current status. Robot Surg. 2017; 4: 7–18, doi: 10.2147/RSRR.S102743, indexed in Pubmed: 30697559.
15. Lee D, Kim SKi, Kim K, et al. Advantages of Single-Port Laparoscopic Myomectomy Compared with Conventional Laparoscopic Myomectomy: A Randomized Controlled Study. J Minim Invasive Gynecol. 2018; 25(1): 124–132, doi: 10.1016/j.jmig.2017.08.651, indexed in Pubmed: 28826957.
16. Rolli R, Favilli A, Acanfora MM, et al. Vaginal myomectomy is a safe and feasible procedure: a retrospective study of 46 cases. J Obstet Gynaecol Res. 2012; 38(9): 1201–1205, doi: 10.1111/j.1447-0756.2012.01852.x, indexed in Pubmed: 22563644.
17. Faivre E, Surroca MM, Deffieux X, et al. Vaginal myomectomy: literature review. J Minim Invasive Gynecol. 2010; 17(2): 154–160, doi: 10.1016/j.jmig.2009.12.007, indexed in Pubmed: 20226401.
18. Rovio PH, Heinonen PK. Transvaginal myomectomy with screw traction by colpotomy. Arch Gynecol Obstet. 2006; 273(4): 211–215, doi: 10.1007/s00404-005-0078-y, indexed in Pubmed: 16208477.
19. Stentz NC, Cooney LG, Sammel MD, et al. Association of Patient Race With Surgical Practice and Perioperative Morbidity After Myomectomy. Obstet Gynecol. 2018; 132(2): 291–297, doi: 10.1097/AOG.0000000000002738, indexed in Pubmed: 29995738.
20. Thubert T, Foulot H, Vinchant M, et al. Surgical treatment: Myomectomy and hysterectomy; Endoscopy: A major advancement. Best Pract Res Clin Obstet Gynaecol. 2016; 34: 104–121, doi: 10.1016/j.bpobgyn.2015.11.021, indexed in Pubmed: 27400649.
21. Wen KC, Horng HC, Wang PH. Hemorrhage: A strong indicator for myomectomy-related complication. J Chin Med Assoc. 2016; 79(8): 413–414, doi: 10.1016/j.jcma.2016.02.004, indexed in Pubmed: 27080090.

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The assessment of spectral Doppler parameters in uterine arteries of patients with locally advanced squamous cell cervical cancer

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ABSTRACT

Objectives: Evaluate spectral Doppler parameters peak systolic velocity (PSV), end diastolic velocity (EDV), resistance index (RI) and pulsatility index (PI) in infiltrated and non-infiltrated uterine arteries of patients with locally advanced (stages II B, III B) squamous cell cervical cancer and their changes during treatment.

Material and methods: the study group included 36 patients aged 35–78 years old. At diagnosis, PSV, EDV, RI and PI in uterine arteries were examined and compared with MRI findings. All patients underwent transvaginal doppler ultrasonography prior to the treatment, after external beam radiation therapy and six weeks after the last application of brachytherapy.

Results: The median PSV value in the first examination was higher in infiltrated uterine arteries than compared to non-infiltrated ones ($p = 0.001$). The PSV values for all vessels decreased between the first and the third observation ($p < 0.001$). There was a significant difference in PI values between infiltrated and non-infiltrated uterine arteries between the first and the third examination ($p = 0.027$).

Conclusions: In patients with locally advanced cervical cancer of uterine arteries, assessment of PSV but not EDV, RI or PI can be helpful in differentiating infiltrated from non-infiltrated vessels. In this group of patients, radiotherapy decreases PSV, but not EDV, RI or PI values in uterine arteries. An observation conducted from the onset of radiotherapy to end of the follow-up in uterine arteries reveals that PI, but not RI, PSV or EDV, is different in infiltrated and non-infiltrated vessels.

Key words: cervical cancer; locally advanced; spectral Doppler; uterine artery; infiltration

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INTRODUCTION

In cervical cancer patients, the mode of treatment depends on staging and parametrial infiltration, which is a critical factor in determining treatment planning. When invasion of the cancer is confirmed in parametrial tissues, locally advanced disease is diagnosed with FIGO stages II B or III B [1, 2].

Clinical pelvic examination has its limitations in evaluation of the parametria. In assessment of parametrial infiltration, MRI is a method of choice with staging accuracy 75–96%, high negative predictive value (94–95%), specificity of about 94% and sensitivity of 69% [3]. CT and PET-CT are used to detect distant metastasis rather than lymph-node involvement, but are poor methods of assessing local tumor extension [3]. Some patients present contraindications to MRI, *e.g.* claustrophobia, heart pacemakers, neurostimulators and metal implants. Thus, to provide precise assessment of the parametria, other diagnostic methods are being searched [4].

Angiogenesis is a fundamental event in tumor growth, progression and metastasis [5]. The tumor vascular bed differs from the vascular system in healthy tissues. The two typical findings are arteriovenous shunts and new large capillaries or sinusoids devoid of smooth muscle in the walls [6, 7]. They demonstrate decreased resistance to flow and therefore receive greater flow volume. Thus, a growth of

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carcinomatous tissue is more rapid than the one that would occur in vessels with normal resistance. During radiotherapy, radiation most often damages capillaries, sinusoids and small arteries, whereas lesions of veins are observed less frequently [8]. All these features lead to changes in hemodynamics in both intratumoral vessels and tumor feeding vessels, that can be assessed qualitatively and quantitatively during a Doppler examination [9–14]. Infiltration of uterine arteries is not equal to parametrial involvement since the latter also consists of fatty tissue surrounding both the uterine corpus and the cervix, but it confirms inoperable stage of the cancer.

Objectives

The aim of this study was to evaluate spectral Doppler parameters, *i.e.* peak systolic velocity (PSV), end diastolic velocity (EDV), resistance index (RI) and pulsatility index (PI) in infiltrated and non-infiltrated uterine arteries of patients with locally advanced cervical cancer and their changes during treatment.

MATERIAL AND METHODS

The study group consisted of 36 patients with squamous cell cervical cancer, staged II B and III B, treated at the Department of Teleradiotherapy of the Copernicus Memorial Hospital of Lodz, in 2015–2017. Detailed clinical data of the studied population are presented in Table 1.

The treatment scheme involved application of external beam radiotherapy (EBRT) to the pelvis, uterus, both adnexa and regional lymph nodes up to a dose of 44 Gy, fractionated at 2 Gy, with weekly injections of cisplatin (P) at a dose of 40 mg/m^2. In patients with contraindications to P, only EBRT was applied. After EBRT with or without P was completed, high-dose rate brachytherapy (HDR BT) was implemented, fractionated at one application 7 Gy weekly for four weeks up to a total dose of 28 Gy, or EBRT was continued to the uterus and primary infiltrating tissues, up to a total dose of 60 Gy. Follow-up monitoring was carried out in an oncological outpatient clinic.

All patients underwent an MRI of the pelvis prior to the treatment. The infiltration of uterine arteries was assessed in the MRI, performed with Siemens Magnetom Avanto 1.5 T before the treatment. Evaluation of parametrial vessels invasion was done on T2-weighted turbo spin echo axial plane images.

All patients underwent a transvaginal Doppler ultrasonography (TVDU) prior to the treatment, after EBRT and six weeks after the last application of HDR BT. Both MRI and TVDU were consecutively performed and analyzed by the same examiner with long experience in both methods.

The TVCD examinations were performed using Philips iU22 with 10MHz endovaginal probe C10-3v. The scanning protocol was the same throughout the study period and all examinations began with the same setting of the ultrasound system. Once parametrial arteries flow signals were identified, velocity waveforms were recorded by placing the sample volume over colored vessels, prior to angle correction. After three uniform consecutive waveforms one of them was manually outlined and spectral Doppler parameters were recorded. The PSV, EDV, RI and PI were analyzed. RI was defined as the ratio of the difference between the PSV and EDV to PS. The PI was defined as the ratio of the difference between the PSV and EDV to the mean velocity. Both RI and PI were calculated automatically and are not dependent on the angle of sampling. Parametrial arteries were assessed bilaterally. Each patient's right and left uterine arteries were analyzed independently.

The group size was estimated using standard power analysis methods. We assumed that clinically-relevant differences would need to exceed 1/3 standard deviation of the analyzed spectral Doppler parameters. Therefore, in order to maintain statistical power > 80% with a predetermined type 1 error probability < 0.05 we calculated that a group of 30 patients is the required minimum. This group was

Table 1. Characteristics of the study group

Selected clinical and pathological data		n	[%]
Age [years]	≤ 50 51–65 > 65	10 16 10	27.8 44.4 27.8
Pregnancies	no yes	3 33	8.3 91.7
Deliveries	0 1–2 ≥ 3	5 18 13	13.9 50.0 36.1
Menopausal status	premenopausal postmenopausal	11 25	30.6 69.4
Other diseases	arterial hypertension diabetes ischemic heart disease	9 1 2	25.0 2.8 5.6
FIGO staging	II B III B	29 7	80.6 19.4
WHO grading	G 1 + G 2 G 3	30 6	83.3 16.7
Largest tumor diameter	< 4 cm ≥ 4 cm	17 19	47.2 52.8
Tumor volume	< 20 cm^3 20–40 cm^3 > 40 cm^3	17 12 7	47.2 33.4 19.4
Treatment	EBRT (60 Gy/2 Gy) EBRT (44 Gy/2 Gy) + HDR BT EBRT (44 Gy/2 Gy) + P + HDR BT	1 2 33	2.8 5.5 91.7
Total		36	100.0

EBRT — external beam radiotherapy; HDR BT — high-dose rate brachytherapy; P — cisplatine

increased by 20% to account for missing data, which results in 6 additional patients enrolled.

The statistical analysis was carried out using Statistica 13.1 software (Statsoft, Tulsa, OK, US). Nominal variables were expressed as percentages and analyzed using the Chi-square test with appropriate corrections (the Yates's correction for continuity or the Fisher exact test), if needed. The normality of the distribution of continuous variables was verified with the Shapiro-Wilk test. Continuous variables were presented as medians with 25% to 75% values and compared using the Mann-Whitney U test. Paired comparisons across the 3 timepoints were analyzed using the repeated-measures analysis of variance. Sphericity assumption was tested using the Mauchly's test. A multivariable analysis was performed with the application of general linear models. The p values lower than 0.05 were considered statistically significant. The study was approved by the Bioethics Commission of the Medical University of Lodz no.RNN/94/15/KE.

RESULTS

The univariate analysis revealed that the median PSV value in the first examination was higher in infiltrated uterine arteries than compared to non-infiltrated ones [30.6 cm/s (18.8–39.9 cm/s) vs 16.8 cm/s (13.1–22.3 cm/s)] ($p = 0.001$), as shown in Figure 1. This was further confirmed in the multivariate analysis, in which PSV values in infiltrated uterine arteries, detected in an MRI, differed significantly from PSV values of non-infiltrated uterine arteries ($p = 0.023$). In addition, the PSV values for all vessels decreased between the first and the third observation ($p < 0.001$). There was no significant difference in PSV values between infiltrated and non-infiltrated uterine arteries between the first and the third examination ($p = 0.360$; Fig. 2).

Both the univariate and multivariate analyses revealed that there were no differences in median EDV values between infiltrated and non-infiltrated uterine arteries, measured in the first examination [7.86 (4.97–12.40) vs 9.32 (6.77–11.70] ($p = 0.523$ and $p = 0.459$, respectively), as shown in Figure 3. Between the first and the third examinations, EDV values for all vessels did not significantly change ($p = 0.148$). There was no difference in EDV values between infiltrated and non-infiltrated uterine arteries between the first and the third examination ($p = 0.786$; Fig. 4).

Both the univariate and multivariate analyses revealed that there were no differences in median RI values in the first examination between infiltrated and non-infiltrated uterine arteries [0.73 (0.58–0.78) vs 0.66 (0.62–0.76)] ($p = 0.568$ and 0.947, respectively), as shown in Figure 5. Between the first and the third examinations, RI values for all vessels did not significantly change ($p = 0.228$). There was no difference in RI values between infiltrated and non-infiltrated uterine arteries between the first and the third examination ($p = 0.297$; Fig. 6).

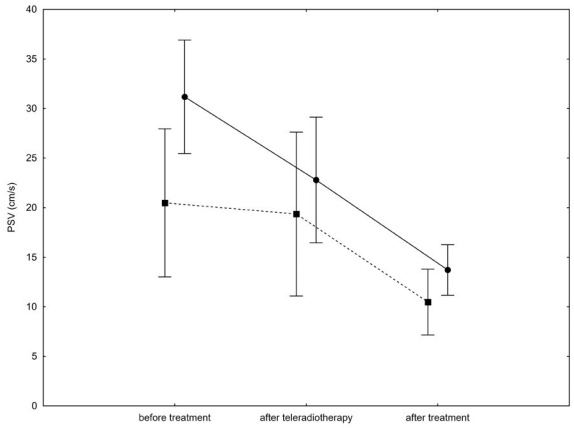

Figure 2. Changes of PSV in uterine arteries during treatment; solid line — parametrial invasion in MRI; broken line — no parametrial invasion in MRI

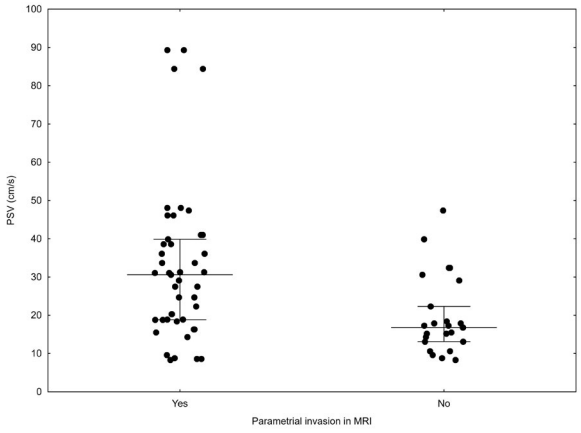

Figure 1. Comparison of PSV values in uterine arteries, depending on parametrial invasion in MRI

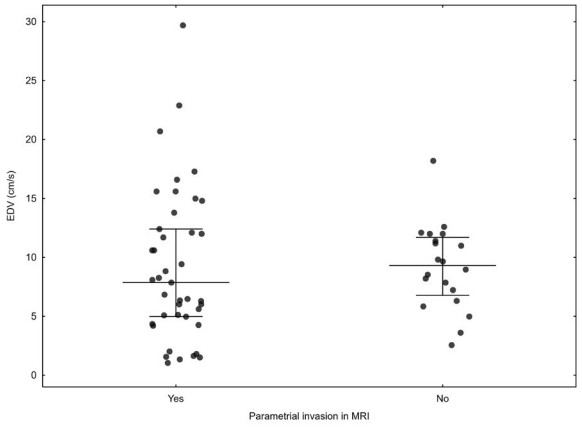

Figure 3. Comparison of EDV values in uterine arteries, depending on parametrial invasion in MRI

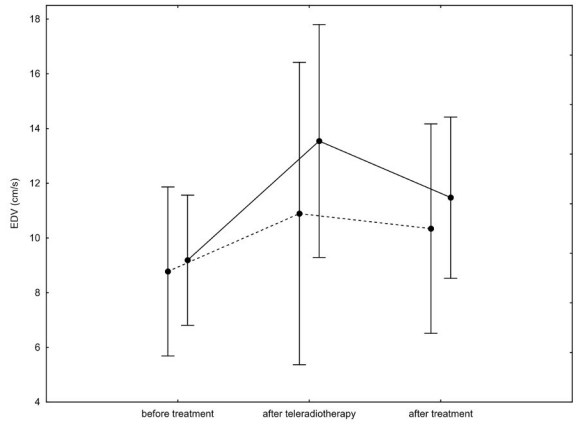

Figure 4. Changes of EDV in uterine arteries during treatment; solid line — parametrial invasion in MRI; broken line — no parametrial invasion in MRI

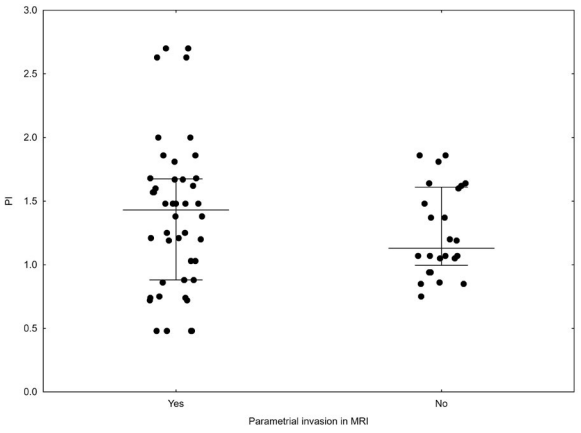

Figure 7. Comparison of PI values in uterine arteries, depending on parametrial invasion in MRI

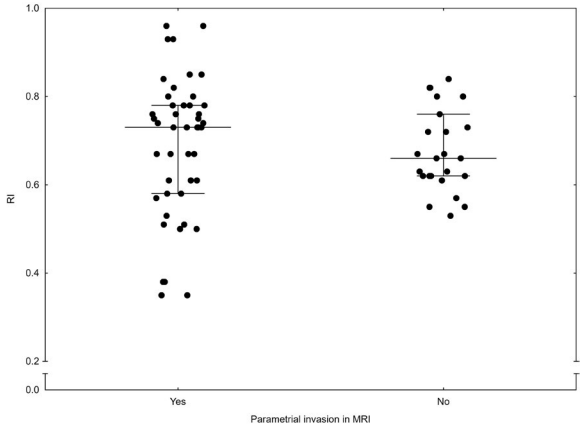

Figure 5. Comparison of RI values in uterine arteries, depending on parametrial invasion in MRI

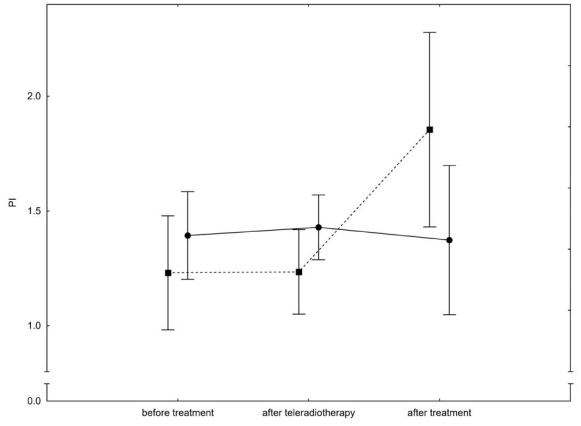

Figure 8. Changes of PI in uterine arteries during treatment; solid line — parametrial invasion in MRI; broken line — no parametrial invasion in MRI

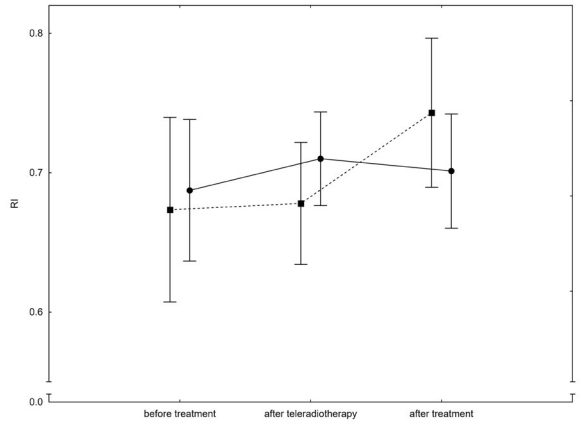

Figure 6. Changes of RI in uterine arteries during treatment; solid line — parametrial invasion in MRI; broken line — no parametrial invasion in MRI

Both the univariate and multivariate analyses revealed that there were no differences in median PI values between infiltrated and non-infiltrated uterine arteries, measured in the first examination [1.43 (0.88–1.68) vs 1.13 (1.00–1.61)] ($p = 0.460$ and $p = 0.683$, respectively), as shown in Figure 7. From the first examination to the third one, the difference in PI values for all vessels was at the limits of statistical significance ($p = 0.058$). There was a significant difference in PI values between infiltrated and non-infiltrated uterine arteries between the first and the third examination ($p = 0.027$; Fig. 8).

DISCUSSION

Transvaginal ultrasound (TVUS) and transrectal ultrasound (TRUS) are cost-efficient diagnostic tools, characterized with high specificity and moderate sensitivity in evaluating parametrial involvement in cervical cancer patients [15–19]. Fischerova et al. claimed that ultrasounds are superior to MRIs, as it enables to accurately predict parametrial infiltration in cervical cancer patients. Sensitivity

values, obtained with the application of these two imaging techniques, are 83% and 50%, respectively, whereas specificity values are 100% and 98%, respectively [15]. Results obtained by Testa et al. [16] (sensitivity 60% vs 40% and specificity 89% vs 89%) and by Epstein et al. [17] (sensitivity 77% vs 69% and specificity 98% vs 92%) were similar. Moloney et al. [20] found higher sensitivity rates (86% vs 40%) but lower specificity values (20% vs 78.8%) for TVUS in comparison with values obtained with the use of MRIs with regards to detection of parametrial infiltration. Chiappa et al. [21] described similar with MRI diagnosis of parametrial infiltration for 2D and 3D ultrasound in 76% and 79%, respectively. The usefulness of TVUS as a diagnostic but also as a prognostic tool can be improved when it is accompanied by assessment of parametrial and intertumoral blood vessels in color and power Doppler examination [13, 22, 23].

Since the early 1990s, there have been efforts to make TVDU a valuable method, that can enable identification of infiltrated parametrial vessels. Initial studies, assessing blood flow hemodynamics in cervical cancer, focused on uterine arteries and cervical branches of uterine arteries, but those reports compared cervical cancer patients with healthy volunteers [24, 25]. Enzelsberger et al. [24] found that cervical cancer patients demonstrated significantly lower median PI values, both in uterine and cervical arteries. Similar findings, which also regarded RI values, were presented by Breyer et al. [25]. Additionally, Bolla et al. [26] found a positive correlation between tumor diameter, uterine artery end-diastolic velocity and PSV, but not RI or PI. In our study, only patients with locally advanced cervical cancer were evaluated. Spectral Doppler parameters of infiltrated and not infiltrated uterine arteries before, during and after the treatment were analyzed. We did not observe any difference in EDV, PI or RI values between infiltrated and non-infiltrated vessels before the treatment, but PSV value was significantly higher in infiltrated uterine arteries. Our results correspond to those obtained by Bolla et al. [26] and cited above. In our opinion, especially when MRI cannot be used for diagnostic purposes, a high PSV value in uterine arteries can be valuable information.

Changes in spectral Doppler parameters in uterine arteries, observed during treatment of locally advanced cervical cancer, were a topic of our interest as well. We observed decreased PSV values between the first and the last examination, similarly in infiltrated and non-infiltrated vessels. When analyzing EDV, RI and PI values, some changes between infiltrated and non-infiltrated uterine arteries were observed, particularly between the second and the third examination.

Our results can be considered preliminary data only and must be confirmed in more extensive materials. The main strength of our study is its prospective design. This study describes first prospective correlation between spectral Doppler parameters in parametrial arteries and MRI images. In our paper analysis of both TVCD and MRI images by the same examiner raises the accuracy of interpretation, but we are aware that it can also be a limitation with possibility of a bias. Another limitation of our study is reproducibility of PSV and EDV measurements which are dependent on the angle of sampling and may alter due to different operators.

CONCLUSIONS

1. In patients with locally advanced cervical cancer of uterine arteries, assessment of PSV but not EDV, RI, or PI can be helpful in differentiation of infiltrated and non-infiltrated vessels.
2. In this group of patients, radiotherapy decreases PSV values in uterine arteries. Such a decrease is not observed for EDV, RI and PI values.
3. An observation conducted from the onset of radiotherapy to end of the follow-up in uterine arteries reveals that PI, but not EDV, RI or PSV, is different in infiltrated and non-infiltrated vessels.

REFERENCES

1. Bhatla N, Aoki D, Sharma DN, et al. Cancer of the cervix uteri. Int J Gynaecol Obstet. 2018; 143 Suppl 2: 22–36, doi: 10.1002/ijgo.12611, indexed in Pubmed: 30306584.
2. Kato T, Watari H, Takeda M, et al. Multivariate prognostic analysis of adenocarcinoma of the uterine cervix treated with radical hysterectomy and systematic lymphadenectomy. J Gynecol Oncol. 2013; 24(3): 222–228, doi: 10.3802/jgo.2013.24.3.222, indexed in Pubmed: 23875071.
3. Testa A, Legge ADi, Blasis IDe, et al. Imaging techniques for the evaluation of cervical cancer. Best Pract Res Clin Obstet Gynaecol. 2014; 28(5): 741–768, doi: 10.1016/j.bpobgyn.2014.04.009.
4. Sammet S. Magnetic resonance safety. Abdom Radiol (NY). 2016; 41(3): 444–451, doi: 10.1007/s00261-016-0680-4, indexed in Pubmed: 26940331.
5. Folkman J, Watson K, Ingber D, et al. Induction of angiogenesis during the transition from hyperplasia to neoplasia. Nature. 1989; 339(6219): 58–61, doi: 10.1038/339058a0, indexed in Pubmed: 2469964.
6. Gammill SL, Shipkey FH, Himmelfarb EH, et al. Roentgenology-pathology correlative study of neovascularity. AJR Am J Roentgenol. 1976; 126(2): 376–385, doi: 10.2214/ajr.126.2.376, indexed in Pubmed: 175707.
7. Taylor KJ, Ramos I, Carter D, et al. Correlation of Doppler US tumor signals with neovascular morphologic features. Radiology. 1988; 166(1 Pt 1): 57–62, doi: 10.1148/radiology.166.1.2447604, indexed in Pubmed: 2447604.
8. Fajardo LF, Berthrong M. Vascular lesions following radiation. Pathol Annu. 1988; 23 Pt 1: 297–330, indexed in Pubmed: 3387138.
9. Alcázar JL, Castillo G, Martínez-Monge R, et al. Transvaginal color Doppler sonography for predicting response to concurrent chemoradiotherapy for locally advanced cervical carcinoma. J Clin Ultrasound. 2004; 32(6): 267–272, doi: 10.1002/jcu.20033, indexed in Pubmed: 15211671.
10. Alcázar JL, Jurado M. Transvaginal color Doppler for predicting pathological response to preoperative chemoradiation in locally advanced cervical carcinoma: a preliminary study. Ultrasound Med Biol. 1999; 25(7): 1041–1045, doi: 10.1016/s0301-5629(99)00063-0, indexed in Pubmed: 10574335.
11. Kerimoğlu U, Akata D, Hazirolan T, et al. Evaluation of radiotherapy response of cervical carcinoma with gray scale and color Doppler ultrasonography: resistive index correlation with magnetic resonance findings. Diagn Interv Radiol. 2006; 12(3): 155–160, indexed in Pubmed: 16972223.
12. Testa AC, Ferrandina G, Distefano M, et al. Color Doppler velocimetry and three-dimensional color power angiography of cervical carcinoma. Ultrasound Obstet Gynecol. 2004; 24(4): 445–452, doi: 10.1002/uog.1703, indexed in Pubmed: 15343602.

13. Wu YC, Yuan CC, Hung JH, et al. Power Doppler angiographic appearance and blood flow velocity waveforms in invasive cervical carcinoma. Gynecol Oncol. 2000; 79(2): 181–186, doi: 10.1006/gyno.2000.5889, indexed in Pubmed: 11063641.
14. Pirhonen JP, Grenman SA, Bredbacka AB, et al. Effects of external radiotherapy on uterine blood flow in patients with advanced cervical carcinoma assessed by color Doppler ultrasonography. Cancer. 1995; 76(1): 67–71, doi: 10.1002/1097-0142(19950701)76:1<67::aid-cncr2820760109>3.0.co;2-0, indexed in Pubmed: 8630878.
15. Fischerova D, Cibula D, Stenhova H, et al. Transrectal ultrasound and magnetic resonance imaging in staging of early cervical cancer. Int J Gynecol Cancer. 2008; 18(4): 766–772, doi: 10.1111/j.1525-1438.2007.01072.x, indexed in Pubmed: 17892456.
16. Testa AC, Ludovisi M, Manfredi R, et al. Transvaginal ultrasonography and magnetic resonance imaging for assessment of presence, size and extent of invasive cervical cancer. Ultrasound Obstet Gynecol. 2009; 34(3): 335–344, doi: 10.1002/uog.7325, indexed in Pubmed: 19705403.
17. Epstein E, Testa A, Gaurilcikas A, et al. Early-stage cervical cancer: tumor delineation by magnetic resonance imaging and ultrasound — a European multicenter trial. Gynecol Oncol. 2013; 128(3): 449–453, doi: 10.1016/j.ygyno.2012.09.025, indexed in Pubmed: 23022593.
18. Gaurilcikas A, Vaitkiene D, Cizauskas A, et al. Early-stage cervical cancer: agreement between ultrasound and histopathological findings with regard to tumor size and extent of local disease. Ultrasound Obstet Gynecol. 2011; 38(6): 707–715, doi: 10.1002/uog.9037, indexed in Pubmed: 21538643.
19. Csutak C, Badea R, Bolboaca SD, et al. Multimodal endocavitary ultrasound versus MRI and clinical findings in pre- and post-treatment advanced cervical cancer. Preliminary report. Med Ultrason. 2016; 18(1): 75–81, doi: 10.11152/mu.2013.2066.181.csk, indexed in Pubmed: 26962558.
20. Moloney F, Ryan D, Twomey M, et al. Comparison of MRI and high-resolution transvaginal sonography for the local staging of cervical cancer. J Clin Ultrasound. 2016; 44(2): 78–84, doi: 10.1002/jcu.22288, indexed in Pubmed: 26294324.
21. Chiappa V, Di Legge A, Valentini AL, et al. Agreement of two-dimensional and three-dimensional transvaginal ultrasound with magnetic resonance imaging in assessment of parametrial infiltration in cervical cancer. Ultrasound Obstet Gynecol. 2015; 45(4): 459–469, doi: 10.1002/uog.14637, indexed in Pubmed: 25091827.
22. Alcázar JL, Castillo G, Jurado M, et al. Intratumoral blood flow in cervical cancer as assessed by transvaginal color doppler ultrasonography: Correlation with tumor characteristics. Int J Gynecol Cancer. 2003; 13(4): 510–514, doi: 10.1046/j.1525-1438.2003.13302.x, indexed in Pubmed: 12911729.
23. Hsu KF, Su JM, Huang SC, et al. Three-dimensional power Doppler imaging of early-stage cervical cancer. Ultrasound Obstet Gynecol. 2004; 24(6): 664–671, doi: 10.1002/uog.1756, indexed in Pubmed: 15517537.
24. Enzelsberger H, Skodler WD, Vavra N, et al. Ultrasonic Doppler flow studies of the uterine arteries in women with cervix cancer. Gynecol Obstet Invest. 1991; 32(2): 112–114, doi: 10.1159/000293007, indexed in Pubmed: 1748318.
25. Breyer B, Despot A, Predanic M, et al. Characteristics of blood flow in cancer of the uterine cervix. Ultrasound Obstet Gynecol. 1993; 3(4): 268–270, doi: 10.1046/j.1469-0705.1993.03040268.x, indexed in Pubmed: 12797274.
26. Bolla D, In-Albon S, Papadia A, et al. Doppler Ultrasound Flow Evaluation of the Uterine Arteries Significantly Correlates with Tumor Size in Cervical Cancer Patients. Ann Surg Oncol. 2015; 22 Suppl 3: S959–S963, doi: 10.1245/s10434-015-4655-4, indexed in Pubmed: 26036189.

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Use of electrical impedance spectroscopy as an adjunct to colposcopy in a pathway of cervical intraepithelial neoplasia diagnostics

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ABSTRACT

Objectives: Screening with cytology decreases cervical cancer burden, but new methods have emerged. We assessed the diagnostic value of electrical impedance spectroscopy (EIS) in the real-world gynecological setting. The study aimed to determine the diagnostic usefulness of EIS used as an adjunct to colposcopies in the diagnosis of high-grade squamous intraepithelial lesions in women with abnormal cytology findings.

Material and methods: A cross-sectional, single center, observational study considered 143 women. All were subjected to a colposcopy and EIS with ZedScan. ZedScan-guided or colposcopically-guided biopsies were carried out.

Results: Data from 118 women were analyzed. The average age of the included women was 38.29 ± 12.52 years (range: 22–86 years). Overall, 27 had a diagnosis of CIN2+ and above on histopathological examination, 99 had low-grade colposcopy results, 18 had high-grade colposcopy results, and 80 had positive ZedScan examination. No adverse events related to the examination with ZedScan were observed. EIS used as an adjunct to colposcopies showed sensitivity of 96.30% (95% CI: 81.03–99.91) and specificity of 39.56% (95% CI: 29.46–50.36), and accuracy of 52.54% (95% CI: 43.15–61.81). The procedure allowed to detect 11 additional cases with positive histo-pathological result in comparison to colposcopies alone.

Conclusions: Colposcopies performed with ZedScan as an adjunct were effective in detecting high-grade cervical lesions. Advantages of ZedScan include real-time result display, no additional diagnostic burden posed on the patient, and good safety profile. Studies on large patient cohorts are needed for further evaluations of this diagnostic procedure and factors which may affect its diagnostic accuracy.

Key words: electrical impedance spectroscopy; colposcopy; squamous intraepithelial lesions; sensitivity; specificity; predictive value

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INTRODUCTION

Cervical cancer is one of the most important health problems in women. This cancer ranks as the fourth most commonly diagnosed cancer and the fourth leading cause of cancer-related death in women worldwide. In 2018, the total estimated number of cases reached 570,000 while deaths 311,000 [1]. In 2016, the Polish National Cancer Registry reported 2,622 new cases of cervical cancer and 1,550 cancer-related deaths [2].

The incidence and mortality rates due to cervical cancer have been decreasing in many countries, mainly due to the elimination of risk factors and the introduction of screening. The rates are lower in well-developed countries than in developing countries [1]. Factors associated with this drop include the overall improvement in socioeconomic status and genital hygiene, reduced parity, and a decreasing incidence of sexually transmitted diseases [1, 3]. Cervical cancer screenings include cytology, high-risk human papillomavirus (hrHPV) testing, and other approaches to identification of preinvasive disease [4]. Although screening programs based on cytology contribute to decreasing cervical cancer burden, their efficiency is still insufficient. The study conducted on 687 women with histologically confirmed cervical intraepithelial neoplasia (CIN) from the Polish population revealed that cytology had a sensitivity of 58.02% and specificity of 63.28% in the diagnosis of CIN. A colposcopy, which is recommended if cervical screening gives abnormal findings, was more accurate in this group of patients with

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a sensitivity of 89.21% and % specificity of 98.87 [5]. Authors from other centers report lower diagnostic parameters of this method. The meta-analysis based on pooled data from 6,281 patients showed the weighted sensitivity and specificity of coloscopies were 85% and 69% respectively [6]. Relatively low sensitivity and specificity of those methods often associated with prolonged waiting times for the result have led to the development of new diagnostic techniques. The measurements of electrical impedance spectra are the most promising, cheap and fast method of detection of abnormal cell arrangements in cervical tissue [7].

The use of electrical impedance measurements has been evaluated in a wide range of cancers. In vivo, this method is used to help identify superficial tissues with an altered structure as a result of a neoplastic transformation. Reports from the literature show that electrical impedance spectroscopy was found to be useful in differentiation between normal and abnormal skin lesions, especially in detecting malignant melanoma [8]. In gynecology, preliminary reports on the use of electrical impedance spectroscopy (EIS) as an adjunct to colposcopies in the diagnosis of CIN showed increased accuracy [9]. An introduction of intraoperative evaluation of electrical impedance spectroscopy-on-a-needle may serve as an additional tool to diminish the risk of positive surgical margins while maximizing tissue sparing [10]. The altered electrical impedance of excised cancer tissue and metastases awaits a determination of its clinical significance [11].

Increasing interest in EIS and growing evidence showing benefits for both patients and physicians encourage further research. We attempted to assess the diagnostic value of EIS in gynecological practice. The aim of the study was to determine the diagnostic accuracy of EIS when used as an adjunct to colposcopies in the diagnosis of high grade squamous intraepithelial lesions in women with abnormal cytology findings.

MATERIAL AND METHODS

This is a cross-sectional, single center, observational study conducted in the real-world settings. All eligible women were referred to colposcopies to our institution due to abnormal cytology results, following conization, and for follow-up of previously diagnosed LSIL and inflammatory changes. On the qualification visit, women with diagnosed cancer of the cervix, vaginal bleeding or active menstruation, and those who had used vaginal contraceptives and vaginal medications up to 2 days before the visit were excluded. Included females were subjected to colposcopies, EIS and histopathology examination when needed. All diagnostic procedures were conducted by two experienced gynecologists. All biopsies were evaluated by a histopathologist with experience in assessment of cervical pathology. In total, 143 women were recruited to participate in the study, but complete data were available for 118 women. The study was conducted after obtaining the written informed consent for participation in the study and undergoing diagnostic procedures. The study was approved by the Commission of Bioethics at Wroclaw Medical University.

All women were subjected to the same diagnostic procedure. Colposcopies using Videocolposcope HD-1000 with IRIS software (Medicom, Wroclaw, Poland) was conducted according to our local procedures. Colposcopic examinations were video recorded for comparison with the results of other procedures. Video recording was done twice, first without and next after application of 3% acetic acid. Colposcopic examinations were video recorded for comparison with the results of other procedures. Next, EIS was performed with ZedScan (Zilico Limited, Manchester, UK). The device consisted of a hand-held unit with a single use sensor on the tip of the unit. Electrical impedance was measured by 4 electrodes when the tip of the device was placed on the cervical epithelium. With each patient after the application of 5% acetic acid, 12 measurements were taken from the cervical transformation zone. Measurements were displayed on the screen of the hand-held unit and recorded. Three colors were used to identify areas of the highest probability of HSIL occurrence: red (the highest probability), amber (lower probability), and green (the lowest probability) and helped select potential areas for biopsy. In cases in which red light was displayed, single point mode was used to help select areas for diagnostic biopsy. A diagnostic procedure was completed by the application of Lugol's solution (potassium iodide) to the surface of the cervix to help identify abnormalities on the cervical epithelium without staining.

For each examination, 1 of the 3 recommendations were made based on the results given by coloscopy and ZedScan:

1. ZedScan-guided biopsy in the case of low-grade lesions identified in colposcopies and red light in ZedScan,
2. Colposcopically guided biopsy in the case of a scanty high-grade lesion in colposcopies and green light in ZedScan.

Punch biopsies for histological examination were sampled from the most abnormal areas indicated by the combined assessment carried out with colposcopies and EIS.

Data were analyzed for the three groups. Each of the patients received only one ZedScan and histopathology examination result regardless of the number of impedance measurements and biopsies. In addition, the colposcopy, results were compared to those of ZedScan carried out as an adjunct to the colposcopy.

The patient was considered to be negative for High Grade Squamous Intraepithelial Lesions (HG-SIL) when the result of the colposcopies were normal without any visible lesions, and the ZedScan results were normal (green light). The cases of a negative result in colposcopies and positive

in ZedScan were considered false negative for colposcopies. The result of the histopathological examination was used as a measure of the performance of both colposcopies and colposcopies with ZedScan. Biopsy samples were considered positive for HG-SIL when presenting with the diagnosis of CIN II and above.

Statistical analysis

Data were presented as numbers and percentages. Fisher's exact test was used to compare the distribution of results between the 2 diagnostic methods: classical colposcopies or colposcopies with ZedScan as an adjunct. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) were calculated.

RESULTS

The mean age of the 118 women included was 38.29 ± 12.52 years with a range from 22 to 86 years. All women were referred to our institution with abnormal cytology results (Tab. 1).

Of the 118 women included, 27 had CIN2 and above on histopathological examination, 99 had low-grade colposcopy results, 18 had high-grade colposcopy results, and 80 had positive ZedScan examination. ZedScan-guided biopsy (LG + ZedScan red) was carried out in 62 patients. One colposcopically guided biopsy (HG + ZedScan green) was performed. None of the patients reported adverse events that could be related to the examination with ZedScan. Histological examination was available for 118 cases. The results of histopathological examination of included patients are presented in Table 2.

To perform diagnostic test evaluation results of the 3 tests used were juxtaposed. For further analysis, samples with a histology result were considered (118 cases). ZedScan guided biopsy was performed in 47 patients. In this group, positive histopathological examination was found in 11 patients. All patients had negative colposcopy results and positive ZedScan results.

Table 1. Results of cytology results at referral

	Cytology diagnosis	No of patients
1.	Atypical glandular cells (AGC)	9
2.	Atypical squamous cells cannot exclude HSIL (ASC-H)	16
3.	Atypical squamous cells of undetermined significance (ASC-US)	14
4.	High-grade squamous intraepithelial lesion (HSIL)	23
5.	AIS	1
6.	Low-grade squamous intraepithelial lesions (LSIL)	43
7.	Negative for intraepithelial lesion or malignancy (NILM)	12

The results of colposcopy and ZedScan examinations were juxtaposed with results of histopathology (Tab. 3) allowing for calculation of sensitivity, specificity, positive predictive value, negative predictive value, and accuracy (Tab. 4).

The use of adjunct ZedScan allowed detecting of 11 additional cases with positive histo-pathological result in comparison to colposcopy alone.

DISCUSSION

EIS is a novel option in diagnosing high-grade SIL of the cervix. Currently, it is used in conjunction with colposcopies. Our study revealed that ZedScan used as an adjunct to colposcopies is a sensitive diagnostic procedure. In our cohort of 118 women with abnormal cervical cytology, common use of colposcopies and EIS allowed for detecting an additional 11 cases of high-grade CIN. ZedScan used as an adjunct to colposcopies showed sensitivity of 96.30% (95% CI: 81.03– 99.91) and specificity of 39.56% (95% CI: 29.46–50.36). Accuracy of this procedure was 52.54% (95% CI: 43.15–61.81).

The strength of this study is that it is the first report from the study conducted on the Polish population and

Table 2. Results of histopathological examination of included patients

Lp.	Histological diagnosis	No of patients
1.	Carcinowa planoepitheliale akeratodes (G1)	1
2.	High-grade squamous intraepithelial lesion (HSIL)	26
4.	Low-grade squamous intraepithelial lesion (LSIL)	12
5.	Chronic inflammation	6
6.	Acute inflammation	1
7.	Normal	72

Table 3. Test calculations

Results of the test		Histopathology results	
		Positive	Negative
Colposcopy + Zed Scan	Positive	N = 26	N = 55
	Negative	N = 1	N = 36

Table 4. Results of test evaluation

	Colposcopy + ZedScan
Sensitivity	96.30% (95% CI: 81.03–99.91)
Specificity	39.56% (95% CI: 29.46–50.36)
Positive Predictive Value	32.10% (95% CI: 28.27–36.19)
Negative Predictive Value	97.30% (95% CI: 83.80–99.60)
Accuracy	52.54% (95% CI: 43.15–61.81)

CI — confidence interval

one of the first reports on this joint diagnostic procedure worldwide. Although the study includes a relatively low number of women, the experience with using EIS in the diagnosis of cervical pathologies increases. As EIS is a new procedure, colposcopists need to develop new skills to diagnose pathological lesions correctly. Tidy et al. noted that gaining sufficient experience with EIS requires the conduct of up to 20 examinations [12], yet our experience suggests that a learning curve may be longer. In our institution, ZedScan has been used since the middle of 2017, allowing colposcopists participating in the study and gaining sufficient experience with the device and study protocol.

Our study was conducted in a real-world setting which has an important consequences. Patients were undergoing normal diagnostic procedures which reflects the reality of clinical practice and showed the feasibility of diagnosing cases of high-grade CIN, which otherwise would have been missed.

ZedScan is a relatively expensive diagnostic tool so it is currently not a part of the routine diagnostic process. Due to low evidence available, it is used as adjuncts to conventional colposcopies. This combination increases the cost of the overall diagnostic procedure, but pose no additional burden on patients. The examination is painless and free from other unpleasant experiences. A cost-effectiveness analysis performed by Peron et al. aimed to compare classical colposcopies with two methods designed to increase sensitivity of colposcopies: Dynamic Spectral Imaging System (DySIS) map and ZedScan, both used as an adjunct to colposcopies [13]. Both procedures were found to increase diagnostic accuracy when compared with colposcopies alone. ZedScan proved to be more effective, but also more costly than colposcopies alone and DySIS. Peron et al. highlighted the fact that the evidence on the use of ZedScan is limited. For this reason, a comparison between ZedScan and DySIS was not feasible [13].

Clinical reports on the diagnostic accuracy of ZedScan used as adjunct to colposcopies is limited to several publications. In the first-ever work on the clinical usefulness of EIS in gynecology practice reported by Brown et al. [7], 124 women with abnormal cervical cytology were examined. They reported a clear difference in EIS results between measurements taken from normal squamous tissues and those taken from precancerous tissues. They reported a sensitivity of 92% and a specificity of 92% in differentiating patients with normal epithelium from those with cervical intraepithelial neoplasia. Muszyński et al. [14] recruited 91 women aged 33 years on average, with a range between 23 to 61 years. They found that using ZedScan as an additional diagnostic procedure with colposcopies in comparison to colposcopies alone increases sensitivity from 61.3% to 93.3% for detecting high-grade SIL but reduces specificity from 80% to 34.4%. Balasubramani et al. [9] analyzed data from 104 women with any cervical smear abnormality or a clinical indication for colposcopies. They reported 18 cases with colposcopic impression and EIS indicating high-grade disease along with an agreement with histological diagnosis of high-grade CIN which suggest a 100% sensitivity and specificity; however, the reported sample was small. Macdonald et al. [15] evaluated the impact of hrHPV infection on the accuracy of a diagnostic procedure carried out with colposcopies and EIS as an adjunct. Their study included the largest cohort of 839 women. The researchers concluded that using EIS contributed to a significant increase in detecting CIN II and above from 85.6% to 96% regardless of hrHPV genotype status ($p < 0.0001$). Tidy et al. [12] recruited 474 women in their study. The study showed that using EIS as an adjunct to colposcopies increased specificity from 83.5% to 95.4%, but significantly reduced sensitivity from 73.6% to 62.1% in detecting high-grade CIN. The most recent study conducted by Tidy et al. [16] on a cohort of 1,237 women with abnormal cervical cytology showed additional 53 (12.8%) cases of high-grade CIN detected by a diagnostic procedure based on the joint use of colposcopies and EIS. The use of acetic acid did not affect the diagnostic accuracy of ZedScan [9, 12].

ZedScan has a good safety profile. In our study, none of the patients reported any adverse events related to measurement impedance spectra. The occurrence of adverse events in relation to diagnosing cervical abnormalities was reported only Tidy et al. [12] who reported two adverse events and one serious adverse event. The first (patient felt unwell) is not linked directly to any procedure, while the other two (bleeding) are linked to biopsies. In the present study, no adverse events were observed.

It is worth noting that ZedScan offers obtaining results in the real-time, which contributes to a reduction in the emotional burden associated with diagnostic procedures. The device is easy to use for colposcopists. Currently, it is included in the diagnostics guidance on adjunctive colposcopy technologies for assessing suspected cervical abnormalities published by NICE [17]. ZedScan has been identified as a promising diagnostic modality, yet due to insufficient evidence, further research on the effects of using the technology on clinical and patient outcomes was recommended.

Currently, ZedScan is one of the options that increase accuracy of diagnosing high-grade CIN, but other techniques emerge on the market as well. Two techniques are worth mentioning. Automated visual evaluation (AVE) uses a deep learning algorithm for cervical cancer screening during colposcopies. Evaluations are made after straining with 3–5% acetic acid. The images are recorded during colposcopies and then compared to cervical images taken during a National Cancer Institute (NCI) prospective epide-

miologic study. Studies on an algorithm that can identify cervical precancer were conducted for 7 years and involved 9,406 women. The results are promising. They indicate that AVE has higher accuracy in detection of precancer lesion in comparison to traditional method of assessment of cervical images and cytology [area under the curve (AUC) = 0.91; 95% confidence interval (CI) = 0.89–0.93 for AVE in comparison to AUC = 0.69; 95% CI = 0.63–0.74 for cervigram; $p < 0.001$ and AUC = 0.71; 95% CI = 0.65–0.77 for conventional Pap smears; $p < 0.001$] [18]. Another method is carried out based on the assessment of staining with folate-receptor-mediated (FRD). Studies have shown that folate receptor subtype α are overexpressed on the surface of cells of gynecological malignant lesions. A reduced methylene blue (MB)-folic acid complex binds with folate receptor subtype α on the neoplastic epithelial cells triggering endocytosis. Next, colorless reduced MB is converted to blue oxidized MB by the intracellular reactive oxygen species and becomes detectable [19]. The study on over 14,000 women showed the sensitivity of this method in detecting CIN2 + of 85.7%, specificity of 76.4%, the positive predictive value of 61.3% and negative predictive value of 92.5% [20]. Other studies confirmed the effectiveness of FRD emphasizing the simplicity of staining and the possibility of getting immediate result [21, 22].

CONCLUSIONS

Colposcopies performed with ZedScan as an adjunct demonstrated effectiveness in the diagnosing of high-grade cervical lesions. Advantages of ZedScan include real-time result display, no additional diagnostic burden posed on the patient, and good safety profile. The high cost of the procedure may limit its widespread use. Studies on large patient cohorts are needed for further evaluations of this diagnostic procedure and factors which may affect its diagnostic accuracy.

REFERENCES

1. Bray F, Ferlay J, Soerjomataram I, et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018; 68(6): 394–424, doi: 10.3322/caac.21492, indexed in Pubmed: 30207593.
2. PNCR. Polish National Cancer Registry. www.onkologia.org.pl (17.02.2019).
3. Green J, Berrington de Gonzalez A, Sweetland S, et al. Risk factors for adenocarcinoma and squamous cell carcinoma of the cervix in women aged 20-44 years: the UK National Case-Control Study of Cervical Cancer. Br J Cancer. 2003; 89(11): 2078–2086, doi: 10.1038/sj.bjc.6601296, indexed in Pubmed: 14647141.
4. Lees BF, Erickson BK, Huh WK. Cervical cancer screening: evidence behind the guidelines. Am J Obstet Gynecol. 2016; 214(4): 438–443, doi: 10.1016/j.ajog.2015.10.147, indexed in Pubmed: 26519782.
5. Wojciech R. The diagnostic value of cytology and colposcopy in women with cervical intraepithelial neoplasia. Ginekol Pol. 2011; 82(8): 607–611, indexed in Pubmed: 21957606.
6. Mitchell MF, Schottenfeld D, Tortolero-Luna G, et al. Colposcopy for the diagnosis of squamous intraepithelial lesions: a meta-analysis. Obstet Gynecol. 1998; 91(4): 626–631, doi: 10.1016/s0029-7844(98)00006-4, indexed in Pubmed: 9540955.
7. Brown BH, Tidy JA, Boston K, et al. Relation between tissue structure and imposed electrical current flow in cervical neoplasia. Lancet. 2000; 355(9207): 892–895, doi: 10.1016/S0140-6736(99)09095-9, indexed in Pubmed: 10752706.
8. Braun RP, Mangana J, Goldinger S, et al. Electrical Impedance Spectroscopy in Skin Cancer Diagnosis. Dermatol Clin. 2017; 35(4): 489–493, doi: 10.1016/j.det.2017.06.009, indexed in Pubmed: 28886804.
9. Balasubramani L, Brown BH, Healey J, et al. The detection of cervical intraepithelial neoplasia by electrical impedance spectroscopy: the effects of acetic acid and tissue homogeneity. Gynecol Oncol. 2009; 115(2): 267–271, doi: 10.1016/j.ygyno.2009.08.010, indexed in Pubmed: 19744703.
10. Kim HW, Yun J, Lee JZ, et al. Evaluation of Electrical Impedance Spectroscopy-on-a-Needle as a Novel Tool to Determine Optimal Surgical Margin in Partial Nephrectomy. Adv Healthc Mater. 2017; 6(18), doi: 10.1002/adhm.201700356, indexed in Pubmed: 28696572.
11. Prakash S, Karnes MP, Sequin EK, et al. Ex vivo electrical impedance measurements on excised hepatic tissue from human patients with metastatic colorectal cancer. Physiol Meas. 2015; 36(2): 315–328, doi: 10.1088/0967-3334/36/2/315, indexed in Pubmed: 25597963.
12. Tidy JA, Brown BH, Healey TJ, et al. Accuracy of detection of high-grade cervical intraepithelial neoplasia using electrical impedance spectroscopy with colposcopy. BJOG. 2013; 120(4): 400–410, doi: 10.1111/1471-0528.12096, indexed in Pubmed: 23289897.
13. Peron M, Llewellyn A, Moe-Byrne T, et al. Adjunctive colposcopy technologies for assessing suspected cervical abnormalities: systematic reviews and economic evaluation. Health Technol Assess. 2018; 22(54): 1–260, doi: 10.3310/hta22540, indexed in Pubmed: 30284968.
14. Muszynski C, Dupont E, Vaysse B, et al. The impact of using electrical impedance spectroscopy (ZedScan) on the performance of colposcopy in diagnosing high grade squamous lesions of the cervix. J Gynecol Obstet Hum Reprod. 2017; 46(9): 669–673, doi: 10.1016/j.jogoh.2017.08.007, indexed in Pubmed: 28866125.
15. Macdonald MC, Brown BH, Lyon RE, et al. Influence of high risk HPV genotype on colposcopic performance: A large prospective study demonstrates improved detection of disease with ZedScan I, particularly in non-HPV 16 patients. Eur J Obstet Gynecol Reprod Biol. 2017; 211: 194–198, doi: 10.1016/j.ejogrb.2017.02.020, indexed in Pubmed: 28292693.
16. Tidy JA, Brown BH, Lyon RE, et al. Are colposcopy and electrical impedance spectroscopy complementary when used to detect high-grade cervical neoplasia? Eur J Gyn Oncol. 2018; 39(1): 70–75.
17. NICE. Diagnostics guidance [DG32]. Adjunctive colposcopy technologies for assessing suspected cervical abnormalities: the DYSIS colposcope with DYSISmap and the ZedScan I. https://www.nice.org.uk (30.05.2019).
18. Hu L, Bell D, Antani S, et al. An Observational Study of Deep Learning and Automated Evaluation of Cervical Images for Cancer Screening. J Natl Cancer Inst. 2019; 111(9): 923–932, doi: 10.1093/jnci/djy225, indexed in Pubmed: 30629194.
19. Li D, Chen L, Wang H, et al. Clinical application of a rapid cervical cancer screening method: Folate receptor-mediated staining of cervical neoplastic epithelia. Asia Pac J Clin Oncol. 2017; 13(1): 44–52, doi: 10.1111/ajco.12573, indexed in Pubmed: 27739250.
20. Li D, Chen L, Wang H, et al. Clinical application of a rapid cervical cancer screening method: Folate receptor-mediated staining of cervical neoplastic epithelia. Asia Pac J Clin Oncol. 2017; 13(1): 44–52, doi: 10.1111/ajco.12573, indexed in Pubmed: 27739250.
21. Dai Y, Wang L, Li D. Effectiveness of novel folate receptor-mediated staining solution detection (FRD) for cervical cancer screening. Medicine (Baltimore). 2018; 97(34): e11868, doi: 10.1097/MD.0000000000011868, indexed in Pubmed: 30142780.
22. Zhao Y, Li M, Li Y, et al. Evaluation of Folate Receptor-Mediated Cervical Dyeing as a Method for Detection of Cervical Lesions. J Low Genit Tract Dis. 2019; 23(2): 133–137, doi: 10.1097/LGT.0000000000000411, indexed in Pubmed: 30817686.

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Risk factors of sexual dysfunctions in postmenopausal women

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ABSTRACT

Objectives: Both somatic and psychosocial factors influence women's sexual functioning. The main objective of the conducted research was to determine the risk factors of sexual dysfunctions in women during the postmenopausal period.

Material and methods: The researcher studied 666 women between the ages of 45–65 (M = 54.96 ± 5.42), who had their last period no later than 12 months prior. Standardised questionnaires were used to study: sexual functions (FSFI), intensity of menopausal symptoms (KI), level of depression (BDI), body esteem (BES), health behaviours (HBI).

Results: Sexual dysfunctions were diagnosed in 33.03% of the studied women. The respondents with dysfunctions differed from the respondents without dysfunctions in terms of: age ($p < 0.001$), education ($p < 0.001$), material standing ($p < 0.01$), relationship status ($p < 0.001$), body weight ($p < 0.001$), BMI ($p < 0.05$), self-assessment of health state ($p < 0.001$), presence of chronic diseases ($p < 0.05$), sexual functioning ($p < 0.001$), intensity of menopausal symptoms ($p < 0.001$), level of depression ($p < 0.001$), body self-esteem ($p < 0.001$), health behaviours ($p < 0.001$). Regression analysis demonstrated ($R2 = 0.24$) that the higher the sense of sexual attractiveness, the lower the probability of sexual dysfunctions ($B = –0.13$; $p < 0.001$). In turn, the risk increases with age ($B = 0.06$; $p < 0.001$), intensity of menopausal symptoms ($B = 0.04$; $p < 0.01$) and concern about one's own body weight ($B = 0.04$; $p < 0.05$). Living without a partner (as compared with living in an informal relationship) increases the risk of occurrence of sexual dysfunctions by as much as 129%.

Conclusions: Crucial risk factors of sexual dysfunctions in women during the postmenopausal period include: age, relationship situation, intensity of menopausal symptoms, sense of sexual attractiveness and concern about body weight.

Key words: sexual dysfunctions; postmenopausal; menopausal syndrome; depression; body self-esteem; health behaviours

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INTRODUCTION

Sexual dysfunctions in women involve the following aspects: desire, arousal, orgasm and genital-pelvic comfort. Hypoactive sexual desire dysfunction means persistent or remittent lack of sexual thoughts and fantasies. Sexual arousal dysfunction consists in permanent or remittent inability to achieve or sustain sexual arousal during a sexual activity. Orgasmic dysfunction is related to the pace of reaching an orgasm, its frequency or intensity. In turn, Genital-pelvic pain dysfunction concerns the course of sexual intercourse and is related to difficulties in vaginal penetration, hyperactivity of pelvic floor muscles, pain of the vulva and vagina or pelvis, as well as fear of such pain. Diagnosis of sexual dysfunctions takes into account the duration of symptoms (at least 3 months, and in case of genital-pelvic pain at least 1 month), their frequency (at least ¾ of all sexual experiences) and their onerousness (experiencing subjective distress) [1].

A research conducted in 29 countries on a group of over 27,000 of over 40 years of age demonstrated that the average frequency of occurrence of lack of interest in sex totalled 25.5%, problems with lubrication — 20%, pain during intercourse — 13.5%, and orgasm disorders — 16% [2]. The most frequent sexual dysfunction in middle-aged women is lack of desire, whose frequency, depending on the research, reaches as much as 98% [3]. The presence of sexual dysfunctions in the menopausal period is connected with lower emotional satisfaction and life satisfaction, poor self-image as well as with higher onerousness of symptoms of the menopausal syndrome [4, 5].

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Metanalyses point to a number of factors that are incontestably conducive to the occurrence of sexual dysfunctions in women at this stage of life. These include both physical factors (age, oestrogen deficiency, menopause type, chronic medical problems, partner's sexual problems, intensity of menopausal symptoms) and psychosocial ones (smoking tobacco, drinking alcohol, quality of relationship with the partner, separation, divorce or partner's death, level of sexual knowledge, access to healthcare, attitude towards one's health, psychological problems, depression, anxiety, body image). As far as other factors are concerned, conclusions are not unequivocal, sometimes even inconsistent. It concerns, i.a.: level of androgens, use of hormonal therapy, obstetric history, physical activity, education, practised profession, socio-economic status, duration of relationship, frequency of sexual intercourses [3, 6–10].

Many factors that have potential or actual influence on the development of sexual dysfunctions in women are interrelated. For example, it is known that changes connected with ageing and increase in body weight, which is frequent in the menopausal period, have a negative influence on women's body self-image, which can, in turn, favour the development of depressive disorders. Also, there is a negative correlation between the occurrence of depression and health-promoting behaviours, such as physical activity or health prophylaxis, and a positive correlation between the occurrence of depression and increase in the intensity of symptoms of menopausal syndrome. Concurrently, increased accidental symptoms of menopause favour the development of depression [11–15]. In the Pubmed base, which covers the years 2000–2019, there have been no reports found that would analyse cumulatively the influence of the aforementioned variables on the risk of development of sexual dysfunctions. Due to the above, the first objective of the authors' own research was to evaluate the relations between the occurrence of sexual dysfunctions in women in the postmenopausal period and: intensity of menopausal symptoms, efficiency of determined sexual functions, level of depression, body self-esteem, health behaviours. The final objective of the research was to determine the risk factors of sexual dysfunctions in the studied group.

MATERIAL AND METHODS

Participants

The research involved women in the postmenopausal period, patients of Primary Healthcare Centers (PHC) in the territory of Silesia (Poland). Random selection was used. Participation in the study was offered to all PHC patients reporting to the centres between November 2018 and March 2019 and meeting the following criteria of inclusion in the research: age between 45 and 65 years, the last period at least 12 months prior to the participation in the research, agreement to participate in the research. The following constituted exclusion criteria: health state preclusive of participation in the research, withdrawal of consent to participate in the research, diagnosed: psychosis, anxiety disorders, functional and/or secondary hyperprolactinaemia (*e.g.* associated with drugs such as selected neuroleptics, antidepressants, and spironolactone or associated with improper thyroid function or pituitary adenoma), < 1 year after cardiac infarction and cerebral vascular accident, neoplastic disease, intellectual disability. The questionnaires were filled in by 688 persons, including 22 that were incomplete. Ultimately, results of 666 women were included in the research.

Methods

The diagnostic poll method was employed, with the use of the following questionnaires:

- Female Sexual Function Index (FSFI) for the study of sexual dysfunctions; it includes 19 items in 6 subscales: Desire, Arousal, Lubrication, Orgasm, Satisfaction, lack of Pain; the respondent determines the intensity or frequency of each sexual function; the answers are correspondingly awarded points and multiplied by a determined numerical index; dysfunction is recognised at the value of ≤ 3.9 point for each subscale and ≤ 26.55 points for the general score;
- Kupperman Index (KI) for the assessment of quality and level of intensity of menopausal symptoms; it includes 11 categories: Sweating and hot flashes, Paraesthesia, Insomnia, Nervousness, Melancholia, Vertigo, Weakness (fatigue), Arthralgia and myalgia, Headache, Heart palpitations, Formication; the respondent determines the intensity of symptoms on a scale; the answers are awarded points and their sum allows for a diagnosis of lack of menopausal syndrome (≤ 20 pts) or intensity thereof: light (21–25 pts), moderate (26–30 pts), severe (> 30 pts);
- Beck Depression Inventory (BDI) for the study of depressive disorders; it includes 21 items; the respondent chooses one of four answers, adequate to the intensity of the described symptoms; the sum of points allows to ascertain lack of depression (< 9 pts) or its intensity: light (10–18 pts), moderate (19–29 pts), severe (> 30 pts);
- Body Esteem Scale (BES) for body esteem; it includes 35 items that evaluate parts or functions of the human body, grouped into 3 categories: Sexual attractiveness, Weight concern, Physical condition; the respondent takes a stance on each item, marking an appropriate number on a scale from 1 (decidedly negative) to 5 (decidedly positive);
- Health Behaviour Inventory for the assessment of health behaviours; it includes 24 statements grouped into

4 categories: Eating habits, Prophylaxis, Positive attitude, Health practices; the respondent determines the frequency of each behaviour on a scale from 1 (nearly never) to 4 (nearly always); the general score is the measure of intensity of health behaviours;

— Respondent's particulars including questions concerning sociodemographic data and data connected with state of health.

Participation in the research was voluntary and anonymous. The respondents did not obtain any remuneration for it, they answered the questions included in the questionnaires individually and on their own and the time they were given for providing the answers was not limited.

Statistical analysis and Ethical Implications

Statistical analyses were carried out with the use of the IBM SPSS Statistics 25 package. Qualitative and quantitative analyses were conducted, including logistic regression analysis. The assumed significance level equalled $\alpha = 0.05$. The research obtained a positive opinion from the Bioethical Commission at the Medical University of Silesia in Katowice (KNW/0022/K/10/18).

RESULTS

The average age of respondents equalled 55.23 ± ± 6.15 years, the average age of the last period equalled 49.01 ± 3.74 years. The majority of respondents had secondary (53.39%) or higher education (32.68%), lived in the city (79.52%), lived in a relationship (85.04%), had children (89.86%). Details concerning the results obtained by the studied persons within the scope of the remaining analysed variables are presented below (Tab. 1).

The analysis demonstrated that 33.03% of the studied group meets the diagnostic criteria of sexual dysfunctions. The respondents with sexual dysfunctions, as compared to the respondents without this type of dysfunctions: were older ($U = 34714.5$; $p < 0.001$), significantly more frequently had primary and vocational education, and significantly less frequently had higher education [$\chi^2(3) = 24.74$; $p < 0.001$], significantly less frequently assessed their material standing as very good ($p = 0.004$; $V = 0.14$), significantly more frequently did not have a partner and significantly less frequently lived in either a formal or informal relationship [$\chi^2(2) = 53.97$; $p < 0.001$], had significantly higher body weight ($U = 41515$; $p = 0.032$) and BMI ($U = 40099.0$; $p < 0.05$),

Table 1. Descriptive statistics of variables analysed in the studied group

	n	M	Me	SD	Min.	Max.
Current age [years]	665	54.96	54.00	5.42	45.00	65.00
Age of last period [years]	666	49.06	49.00	3.55	39.00	60.00
Height [centimeters]	666	163.97	164.00	5.48	150.00	182.00
Weight [kilograms]	666	72.03	70.00	12.06	43.00	164.00
BMI [kg/m^2]	666	26.81	26.50	4.47	17.22	64.06
Lenght of the relationship with the partner [years]	592	26.24	28.00	11.18	0.00	55.00
FSFI — Total score	666	28.71	30.20	9.96	2.20	45.00
FSFI — Desire	666	2.97	3.00	1.19	0.60	6.00
FSFI — Arousal	666	3.34	3.60	1.59	-0.30	6.00
FSFI — Lubrication	666	3.89	4.20	1.76	0.00	6.00
FSFI — Orgasm	666	3.79	4.00	1.72	0.00	6.00
FSFI — Satisfaction	666	4.21	4.40	1.24	0.40	6.00
FSFI — lack of Pain	666	4.19	4.40	1.67	0.00	6.00
KI — Total score	666	18.41	18.00	9.47	0.00	51.00
BDI — Total score	666	11.81	10.00	8.95	0.00	63.00
BES — Sexual attractiveness	666	45.38	45.00	9.37	16.00	65.00
BES — Weight concern	666	31.56	32.00	9.01	10.00	50.00
BES — Physical condition	666	30.66	31.00	7.26	9.00	45.00
IZZ — Total score	666	78.60	79.00	15.01	29.00	120.00
IZZ — Eating habits	666	19.79	20.00	4.79	7.00	30.00
IZZ — Prophylaxis	666	20.06	20.00	4.79	6.00	31.00
IZZ — Positive attitude	666	20.16	20.00	4.23	5.00	30.00
IZZ — Health practices	666	18.59	19.00	4.20	6.00	30.00

M — average; Me — median; SD — standard deviation

significantly less frequently assessed their state of health as very good or good and significantly less frequently as average ($p < 0.001$; $V = 0.20$), significantly more frequently suffered from chronic diseases [$\chi^2(1) = 5.56$; $p = 0.018$].

It was also demonstrated that the respondents with sexual dysfunctions differed from the respondents without such dysfunctions within the scope of all the variables assessed with the use of standardised questionnaires, which was presented in Table 2.

Because the concern about one's body weight was the only variable that achieved a higher level in the respondents without sexual dysfunction, an analysis of the relations of that variable with the declared body weight of the respondents was conducted. A negative correlation was demonstrated (rho = –0.35; $p < 0.001$).

The analysis of dependence between the studied variables demonstrated that the scales of sexual functions are positively related at a level ranging from moderate to strong. Additionally, all the dimensions of sexual functions are positively related at a level ranging from weak to moderate with the dimensions of body self-esteem and health behaviours. Moderate and negative correlations appear between depressive symptoms and sexual functions, which means that the higher the level of depression, the lower the level of sexual functions. Details concerning the dependence between the studied variables are presented in the table below (Tab. 3).

In order to establish the factors determining the occurrence of sexual dysfunctions, a logistic regression analysis was conducted with the use of the progressive selection method which included the use of the likelihood ratio method. The assumed model proved to be well adjusted to the gathered data, which is demonstrated by the Hosmer-Lemeshow test [$\chi^2(8) = 9.02$; $p = 0.341$]. This model explains 24.2% of variability of sexual dysfunctions (Cox and Snell's $R^2 = 0.242$; Nagelkerke's $R^2 = 0.341$). The regression indicator for the final model was included in Table 4.

Only for the sense of attractiveness is the direction of dependence negative, which means that the higher the level of sexual attractiveness, the lower the probability of sexual dysfunctions (with each unit in the result of the BES questionnaire by 13%). The risk of occurrence of sexual dysfunctions increases by 4% with the increase in intensity of menopausal symptoms (by 1 unit in the result of the KI questionnaire) and concern about weight (by 1 unit in the result of the BES questionnaire). The risk of dysfunctions

Table 2. Comparison of respondents with sexual dysfunctions with respondents without sexual dysfunctions in terms of sexual functions, intensity of menopausal symptoms, level of depression, body self-esteem and health behaviors

	No dysfunction			Dysfunction			U	p	η^2
	M	Me	SD	M	Me	SD			
Sexual functions (FSFI)									
Desire	3.42	3.62	1.04	1.96	1.89	0.80	12850.5	< 0.001	0.35
Arousal	4.13	4.21	0.94	1.55	1.57	1.28	5100.5	< 0.001	0.51
Lubrication	4.74	4.85	0.90	1.94	2.42	1.69	5752.5	< 0.001	0.49
Orgasm	4.63	4.84	0.88	1.87	2.40	1.63	5666.0	< 0.001	0.50
Satisfaction	4.77	4.83	0.83	2.91	3.21	1.04	7805.5	< 0.001	0.45
Lack of Pain	5.35	5.60	0.79	3.61	4.00	1.69	14526.0	< 0.001	0.31
Intensity of menopausal symptoms (KI)	17.06	17.08	9.11	21.48	21.0	9.59	34760.0	< 0.001	0.04
Level of depression (BDI)	9.93	8.05	7.54	16.08	14.05	10.36	29319.5	< 0.001	0.09
Body self-esteem (BES)									
Sexual attractiveness	48.00	48.0	8.33	39.41	39.0	8.89	22221.5	< 0.001	0.18
Weight concern	33.11	34.0	8.73	28.03	29.0	8.66	31491.5	< 0.001	0.07
Physical condition	32.21	33.0	6.59	27.12	27.0	7.47	28776.5	< 0.001	0.10
Health behaviours (IZZ)									
Total score	80.33	81.0	14.00	74.66	74.0	16.45	37111.5	< 0.001	0.03
Eating habits	20.27	20.0	4.57	18.70	19.0	5.10	39101.5	0.001	0.02
Prophylaxis	20.52	21.0	4.60	19.02	19.0	5.05	38845.0	< 0.001	0.02
Positive attitude	20.73	21.0	4.01	18.84	19.0	4.43	35477.5	< 0.001	0.04
Health practices	18.81	19.0	4.05	18.09	18.0	4.49	42275.5	0.038	0.01

U — Mann–Whitney test result; p — significance level; η2 — effect size

Table 3. Spearman's rho correlations between sexual functions, intensity of menopausal symptoms, level of depression, body self-esteem and health-promoting behaviors in the examined group

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
KI — total score	1															
Desire	–0.19**	1														
Arousal	–0.24**	0.70**	1													
Lubrication	–0.26**	0.57**	0.78**	1												
Orgasm	–0,22**	0.57**	0.82**	0.81**	1											
Satisfaction	–0.21**	0.55**	0.75**	0.68**	0.80**	1										
Lack of Pain	–0.17**	0.37**	0.59**	0.68**	0.65**	0.54**	1									
Sexual attractiveness	–0.29**	0.44**	0.43**	0.43**	0.46**	0.47**	0.32**	1								
Weight concern	–0.31**	0.30**	0.30**	0.29**	0.29**	0.29**	0.19**	0.74**	1							
Physical condition	–0.34**	0.33**	0.33**	0.33**	0.34**	0.35**	0.26**	0.75**	0.73**	1						
Eating habits	–0.13**	0.22**	0.18**	0.20**	0.18**	0.16**	0.12**	0.30**	0.26**	0.25**	1					
Prophylaxis	–0.05	0.15**	0.15**	0.13**	0.16**	0.20**	0.11*	0.31**	0.23**	0.21**	0.60**	1				
Positive attitude	–0.19**	0.22**	0.23**	0.22**	0.24**	0.28**	0.14**	0.35**	0.31**	0.30**	0.53**	0.62**	1			
Health practices	–0.14**	0.12**	0.12**	0.14**	0.09*	0.13**	0.02	0.17**	0.21**	0.12**	0.52**	0.50**	0.57**	1		
IZZ — total score	–0.15**	0.21**	0.21**	0.21**	0.21**	0.24**	0.12**	0.35**	0.31**	0.27**	0.82**	0.84**	0.82**	0.77**	1	
BDI — total score	0.42**	–0.30**	–0.35**	–0.36**	–0.36**	–0.35**	–0.33**	–0.51**	–0.43**	–0.50**	–0.35**	–0.27**	–0.48**	–0.26**	–0.41**	1

*p < 0.05; **p < 0.01; KI — Intensity of menopausal symptoms; IZZ — Health behaviours; BDI — Beck Depression Inventory

Table 4. Final model of logistic regression for prediction of sexual dysfunctions

	B	SE	Z	p	Exp (B), (95% CI)
Current age	0.06	0.02	12.36	< 0.001	1.06 (1.03–1.10)
Partnership status			21.88	< 0.001	
Partnership status (1)	1.29	0.28	21.36	< 0.001	3.62 (2.10–6.24)
Partnership status (2)	0.02	0.31	0.00	0.957	1.02 (0.55–1.88)
KI -total score	0.04	0.01	10.40	0.001	1.04 (1.02–1.06)
Sexual attractiveness	–0.13	0.02	52.16	< 0.001	0.88 (0.85–0.91)
Weight concern	0.04	0.02	5.58	0.018	1.04 (1.01–1.08)
Constant	–0.59	1.16	0.26	0.610	0.55

B — standardized regression coefficient; SE — standard error; Z — Wald test result; p — significance level; EXP (B) — odds ratio; CI – confidence interval; (1) — no partner compared to the informal relationship; (2) — formal relationship compared to informal relationship

increases by 6% with age (per 1 year). Lack of partner (as compared with living in an informal relationship) increases the risk of occurrence of sexual dysfunctions by as much as 129% and, thereby, this condition is the strongest determinant of sexual dysfunctions in the assumed model.

DISCUSSION

Women's sexual functioning in the postmenopausal period can be subject to significant changes in comparison with the previous period, among other things due to the physiological processes connected with the termination of the reproductive activity and their psychological consequences. It is also a time of increased vulnerability to different kinds of disorders in sexual and emotional life. It is estimated that while in the general population sexual dysfunctions afflict between 25 and 63% of women, in the population of middle-aged and elderly women their frequency equals over 50% [16]. In the author's own research, the criteria of sexual dysfunctions were met by over 1/3 of respondents in their postmenopausal period.

The placement of the sexual sphere in one's own value hierarchy can differ depending on a given person, yet generally it is considered an important aspect of life, also among people at more advanced ages. A research conducted on a population of over 1600 women and men of over 45 years of age confirmed that for 55–60% Americans sexual activity is an important element of a satisfying relationship and quality of life of elderly persons [17]. Disorders in the sexual sphere are, in turn, unequivocally identified with a sense of discomfort.

Due to the fact that in the authors' own research all the analysed variables (connected with one's physical and psychological wellbeing as well as behaviour) proved to significantly differentiate between women with and without dysfunctions, it can be concluded that this type of problems has a significant influence on the overall quality of life. The existence of such a relationship in a group of postmenopausal women was proven by a research conducted by Nazarpour and co-researchers. Using the Female Sexual Function Index (FSFI) and the WHO Quality of Life-BREF (WHOQOL-BREF), they demonstrated a positive relationship between the overall sexual functioning and the overall quality of life as well as with all the analysed domains of quality of life: physical health, psychological, social relationships, environment [18]. In turn, Show-Riu and co-researchers, in a cross-functional research conducted on a group of over 1000 middle-aged women, confirmed the relationship between the occurrence of sexual dysfunctions and the health-related quality of life [19]. The respondents without sexual dysfunctions were characterised by lower intensity of menopausal and depressive symptoms, whereas, on the other hand, higher efficiency of sexual functions, such as Desire, Arousal, Lubrication, Orgasm, Satisfaction, lack of Pain. Moreover, they presented more health-promoting behaviours connected with nutrition, health prophylaxis and health practices (*e.g.* sleep and rest, body weight control, adherence to doctor's recommendations) as well as a positive psychological attitude. They had also better body self-esteem within the scope of sense of sexual attractiveness and physical fitness, yet they demonstrated more behaviours connected with concern about their body weight. It is insomuch interesting as this variable proved to be at the same time one of the risk factors of sexual dysfunctions.

In order to understand this seemingly inconsistent phenomenon, we can use the fact that the respondents without sexual dysfunctions, despite greater concern about their weight, did in fact weigh significantly less than the respondents with dysfunctions, had a significantly lower BMI and better health self-assessment. Dissatisfaction with one's own weight and concern about its increase are presented by a large number of women, regardless of their current body weight, and BMI has a stronger influence on their overall body self-image than in the case of men [20]. Therefore, it can be suspected that body weight is an especially delicate aspect also in the life of postmenopausal women and constitutes a factor mediating between the concern about one's weight and the occurrence of dysfunctions in sexual life. This hypothesis, however, would require confirmation in the course of more advanced analyses, whose lack can be considered one of the limitations of the present research. The other ones are connected with the non-inclusion in the research of such significant variables as the objective state of health (*e.g.* the kind and duration of chronic diseases, taken medications, past gynaecological surgeries), history of possible treatment of sexual dysfunctions or the quality of partner relationships.

Lack of partner proved to be the strongest risk factor of sexual dysfunctions. Other authors confirm that the distress connected with sexuality concerns not only women living in relationships, but also those that currently do not have a partner and are sexually inactive [21]. Having close relationships with other people, not only those of sexual nature, has a beneficial influence on physical and psychological health of every person, since it is the source of social support [22].

Among all the diagnosed risk factors of sexual dysfunctions in women in the postmenopausal period only age is a non-modifiable variable. The other ones are subject to external influences and that is why they should be taken into account while planning health policies and implementing support programmes for women at this stage of life. General gynaecological care can, for example, contribute to the alleviation of symptoms of menopause, not only by giving women access to hormone replacement therapy, but also by education concerning health-promoting lifestyle. It seems that a special place in prophylaxis and health promotion should fall to questions connected with maintaining correct body weight, which is crucial not only in the context of physical and psychological health, but also has a significant influence on the sense of women's sexual attractiveness as well as on formation and maintenance of sexual relations.

CONCLUSIONS

There is a relation between the occurrence of sexual dysfunctions and the intensity of menopausal symptoms, efficiency of determined sexual functions, level of depression, body self-esteem and health behaviours of women in the postmenopausal period. Crucial risk factors of sexual dysfunctions in this group include: age, relationship status, intensity of menopausal symptoms, sense of sexual attractiveness and concern about body weight.

REFERENCES

1. McCabe MP, Sharlip ID, Atalla E, et al. Definitions of Sexual Dysfunctions in Women and Men: A Consensus Statement From the Fourth International Consultation on Sexual Medicine 2015. J Sex Med. 2016; 13(2): 135–143, doi: 10.1016/j.jsxm.2015.12.019, indexed in Pubmed: 26953828.
2. Nicolosi A, Laumann EO, Glasser DB, et al. Global Study of Sexual Attitudes and Behaviors Investigators' Group. Sexual behavior and sexual dysfunctions after age 40: the global study of sexual attitudes and behaviors. Urology. 2004; 64(5): 991–997, doi: 10.1016/j.urology.2004.06.055, indexed in Pubmed: 15533492.
3. Eftekhar T, Dashti M, Shariat M, et al. Female Sexual Function During the Menopausal Transition in a Group of Iranian Women. J Family Reprod Health. 2016; 10(2): 52–58, indexed in Pubmed: 27648093.
4. Ornat L, Martínez-Dearth R, Muñoz A, et al. Sexual function, satisfaction with life and menopausal symptoms in middle-aged women. Maturitas. 2013; 75(3): 261–269, doi: 10.1016/j.maturitas.2013.04.007, indexed in Pubmed: 23684086.

5. Nappi RE, Wawra K, Schmitt S. Hypoactive sexual desire disorder in postmenopausal women. Gynecol Endocrinol. 2006; 22(6): 318–323, doi: 10.1080/09513590600762265, indexed in Pubmed: 16785156.
6. Przybylski M, Spaczyński M. [Hypoactive sexual desire disorder]. Ginekol Pol. 2009; 80(7): 518–522, indexed in Pubmed: 19697816.
7. Szpak R, Folwarczny W, Drozdzol A, et al. [Partner relationships in menopausal period]. Ginekol Pol. 2010; 81(2): 115–119, indexed in Pubmed: 20232709.
8. Nazarpour S, Simbar M, Tehrani FR. Factors affecting sexual function in menopause: A review article. Taiwan J Obstet Gynecol. 2016; 55(4): 480–487, doi: 10.1016/j.tjog.2016.06.001, indexed in Pubmed: 27590367.
9. Afshari P, Houshyar Z, Javadifar N, et al. The Relationship Between Body Image and Sexual Function in Middle-Aged Women. Electron Physician. 2016; 8(11): 3302–3308, doi: 10.19082/3302, indexed in Pubmed: 28070265.
10. Heidari M, Ghodusi M, Rezaei P, et al. Sexual Function and Factors Affecting Menopause: A Systematic Review. J Menopausal Med. 2019; 25(1): 15–27, doi: 10.6118/jmm.2019.25.1.15, indexed in Pubmed: 31080785.
11. Elavsky S, McAuley E. Physical activity and mental health outcomes during menopause: a randomized controlled trial. Ann Behav Med. 2007; 33(2): 132–142, doi: 10.1007/bf02879894, indexed in Pubmed: 17447865.
12. Bosworth HB, Bastian LA, Kuchibhatla MN, et al. Depressive symptoms, menopausal status, and climacteric symptoms in women at midlife. Psychosom Med. 2001; 63(4): 603–608, doi: 10.1097/00006842-200107000-00013, indexed in Pubmed: 11485114.
13. Jackson KL, Janssen I, Appelhans BM, et al. Body image satisfaction and depression in midlife women: the Study of Women's Health Across the Nation (SWAN). Arch Womens Ment Health. 2014; 17(3): 177–187, doi: 10.1007/s00737-014-0416-9, indexed in Pubmed: 24623160.
14. Kilpela LS, Becker CB, Wesley N, et al. Body Image in Adult Women: Moving Beyond the Younger Years. Adv Eat Disord. 2015; 3(2): 144–164, doi: 10.1080/21662630.2015.1012728, indexed in Pubmed: 26052476.
15. Smith RL, Gallicchio L, Flaws JA. Factors Affecting Sexual Function in Midlife Women: Results from the Midlife Women's Health Study. J Womens Health (Larchmt). 2017; 26(9): 923–932, doi: 10.1089/jwh.2016.6135, indexed in Pubmed: 28437219.
16. Portman DJ, Gass MLS. Vulvovaginal Atrophy Terminology Consensus Conference Panel. Genitourinary syndrome of menopause: new terminology for vulvovaginal atrophy from the International Society for the Study of Women's Sexual Health and the North American Menopause Society. J Sex Med. 2014; 11(12): 2865–2872, doi: 10.1111/jsm.12686, indexed in Pubmed: 25155380.
17. American Association of Retired Persons (AARP). Sexuality at midlife and beyond: 2004 Update of attitudes and behaviors. www.aarp.org (2005). http://assets.aarp.org/rgcenter/general/2004_sexuality.pdf.
18. Nazarpour S, Simbar M, Ramezani Tehrani F, et al. Quality of life and sexual function in postmenopausal women. J Women Aging. 2018; 30(4): 299–309, doi: 10.1080/08952841.2017.1395539, indexed in Pubmed: 29077541.
19. Chang SR, Yang CF, Chen KH. Relationships between body image, sexual dysfunction, and health-related quality of life among middle-aged women: A cross-sectional study. Maturitas. 2019; 126: 45–50, doi: 10.1016/j.maturitas.2019.04.218, indexed in Pubmed: 31239117.
20. Algars M, Santtila P, Varjonen M, et al. The adult body: how age, gender, and body mass index are related to body image. J Aging Health. 2009; 21(8): 1112–1132, doi: 10.1177/0898264309348023, indexed in Pubmed: 19897779.
21. Worsley R, Bell RJ, Gartoulla P, et al. Prevalence and Predictors of Low Sexual Desire, Sexually Related Personal Distress, and Hypoactive Sexual Desire Dysfunction in a Community-Based Sample of Midlife Women. J Sex Med. 2017; 14(5): 675–686, doi: 10.1016/j.jsxm.2017.03.254, indexed in Pubmed: 28499520.
22. Umberson D, Montez JK. Social relationships and health: a flashpoint for health policy. J Health Soc Behav. 2010; 51 Suppl: S54–S66, doi: 10.1177/0022146510383501, indexed in Pubmed: 20943583.

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Perioperative outcomes of bipolar energy instruments in total laparoscopic hysterectomy

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ABSTRACT

Objectives: To compare conventional and advanced bipolar energy instruments in terms of perioperative outcomes in patients who underwent total laparoscopic hysterectomy (TLH).

Material and methods: The data of 101 patients who underwent TLH between June 2017 and December 2018 for benign gynecological disorders were analyzed retrospectively. Conventional bipolar forceps (Robi forceps) were used in 37 patients and advanced bipolar instruments (LigaSure) were used in 64 patients. Data about the characteristics of the patients, operation time, estimated blood loss, length of hospital stay and other perioperative outcomes were compared.

Results: The mean ages of the patients in the conventional bipolar and LigaSure groups were 47.6 ± 6.5 and 48.1 ± 7 years, respectively ($p > 0.05$). There was no statistically significant difference between the two groups with regard to all other patient characteristics; body mass index, parity, previous pelvic operation and indications of hysterectomy ($p > 0.05$). The mean operation time (41 ± 13.2 vs 37 ± 11.5 min), estimated intraoperative blood loss (70 ± 22 vs 65 ± 21 mL) and absolute change in hemoglobin (-1.23 ± 1.12 vs -1.11 ± 1.14 g/dL) were slightly higher in the conventional bipolar group. However, there was no statistical significance with respect to these differences between the groups ($p > 0.05$).

Conclusions: Our findings indicate that a conventional bipolar system is as safe and effective as LigaSure, and it may be used as an alternative option for patients undergoing TLH in low-income hospitals.

Key words: conventional bipolar instrument; LigaSure; vessel sealing; total laparoscopic hysterectomy

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INTRODUCTION

Hysterectomy is one of the most frequently performed gynecologic surgical procedures and may be performed by abdominal, vaginal and laparoscopic approach [1]. Total laparoscopic hysterectomy (TLH) has been performed increasingly over the years due to less postoperative pain, less risk of incision infection, reduced adhesion formation, shorter recovery time and early discharge. It has now become an indispensable part of gynecology practice [2]. Although TLH is superior to abdominal hysterectomy, the vaginal approach still preserves its current value in most benign indications.

Conventional electrosurgery comprises two types of diathermy as unipolar and bipolar. In monopolar electrosurgery, high voltage is used for cutting, dissection and fulguration. In bipolar electrosurgery, low voltage is used for coagulation [3]. The basic working principle of the conventional bipolar energy system is to denature the collagen and elastin inside the vessel wall or tissue by providing electrical energy between the two jaws. Since the electrical current is present between the two jaws, a neutral electrode is not required and surgical safety is higher [4].

There have been improvements in surgical instruments as laparoscopic operations have increased over time. Advanced vascular sealing devices that work with ultrasonic and bipolar energy have been developed [5]. These novel advanced bipolar vessel-sealing devices appear to decrease the lateral thermal spread remarkably; thus they are safe and time-efficient in comparison to traditional bipolar electrosurgical devices. These beneficial features show up more evident in difficult procedures [6, 7]. LigaSure is a hemostatic device developed as an advanced bipolar energy system (Covidien-Valleylab today Medtronic-Covidien, Boulder, CO, USA) and has demonstrated efficacy in a variety of surgical

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procedures [8]. LigaSure denatures collagen and elastin in the vessel wall and sticks with high mechanical pressure. Then the vessel is cut into two parts with the help of the knife inside of LigaSure. It was proven that it can be safely used in vessels up to 7 mm [8]. LigaSure has been shown to be on a similar level in terms of efficiency in comparison to clips, sutures and ultrasonic vessel sealing methods [9].

In this study, we aimed to compare conventional and advanced bipolar energy instruments in terms of perioperative outcomes in patients who underwent total laparoscopic hysterectomy.

MATERIAL AND METHODS

In this study, the data of 101 patients who underwent TLH between June 2017 and December 2018 for benign gynecological disorders at the Isparta City Hospital were analyzed retrospectively. Conventional bipolar forceps (Robi forceps, Karl Storz, Tuttlingen, Germany) were used in 37 patientsand the LigaSure 5 mm device (Medtronic-Covidien, Boulder, CO, USA) that is an advanced bipolar instrument was used in 64 patients. Initially, there was only a conventional bipolar device in our hospital because of financial insufficiency. Nevertheless, we performed the procedure on the first 37 patients with this device. After LigaSure was supplied, we performed the procedure on the other cases with this instrument. Patient characteristics, including age, body mass index (BMI), parity, surgical indication, previous pelvic surgery history and perioperative results were obtained from the patients' medical records. The perioperative results included uterine weight, operation time, estimated blood loss, blood transfusion, length of hospital stay and intraoperative complications. The eligibility criteria included patients who required hysterectomy for benign conditions such as symptomatic uterine fibroids, abnormal bleeding or other benign diseases. The exclusion criteria were the current pregnancy status and malignant diseases of the genital tract. All patients were managed with the same protocol for preoperative and postoperative treatments. We also administered 1 g of cephalosporin antibiotic intravenously 30 minutes before the incision for prophylaxis. All surgeries were performed by the same surgeon.

Surgical Technique

All operations were performed under general anesthesia in a dorsal lithotomy and Trendelenburg position. In all patients, the stomach was decompressed with a nasogastric tube and the catheter was inserted into the bladder before the surgery. Depending on the diameter of the cervix and the size of the uterus, the appropriate vaginal manipulator was inserted into the uterine cavity. A VCare uterine manipulator (Conmed, NY, USA) was used in the operations. The surgical procedures were performed through 3 or 4 laparoscopic trocars: a 10-mm trocar for the camera from the umbilicus, one 5-mm lateral trocar at 2 cm superior of the left iliac spina and one 5-mm suprapubic trocar for the laparoscopic instruments. In some cases, a fourth 5-mm trocar was inserted from the right lower quadrant if it was needed. The surgeon was on the left side of the patient and performed the operation using the left and midLine trocars. All operations were performed with Robi forceps and Metzenbaum scissors or LigaSure for sealing, dissection and hemostasis. The vaginal cuff was closed by intracorporal suturing using a polyglactin 910 suture that is a late absorbable material (Vicryl, Ethicon, Johnson & amp; Johnson Medical Devices Companies, USA). All laparoscopic procedures were performed without conversion to laparotomy.

Operation time was defined as the time from the initial skin incision to closure of the abdominal trocar incisions. Estimated blood loss in the operation was calculated by subtracting the given amount of fluid from the total outcome in the suction unit. The position of the patients was the reversed Trendelenburg position to obtain all intra-abdominal fluid. Furthermore, quantitative blood loss was calculated by comparing the preoperative hemoglobin value to the hemoglobin value on the first day after surgery.

Patients who had spontaneous micturition, gas outflow and stable vital signs were discharged on the first or second postoperative day.

Statistical analyses

The variables are presented with frequencies and mean ± standard deviation values. Differences between two groups were analyzed using unpaired *t*-test, chi-squared (X^2) test and Fisher's exact test. $P < 0.05$ was considered statistically significant. Statistical analyses were performed in SPSS 24.0 (IBM Corporation, Armonk, NY).

RESULTS

The data of a total of 101 patients were analyzed. The mean ages of the patients in the conventional bipolar and LigaSure groups were 47.6 ± 6.5 and 48.1 ± 7 years, respectively ($p > 0.05$). There was no statistically significant difference between the two groups with regard to all other patient characteristics; body mass index, parity, previous pelvic operation and indications of hysterectomy ($p > 0.05$) (Tab. 1).

The mean operation time (41 ± 13.2 vs 37 ± 11.5 min), estimated intraoperative blood loss (70 ± 22 vs 65 ± 21 ml) and absolute change in hemoglobin (-1.23 ± 1.12 vs -1.11 ± 1.14 g/dL) were slightly higher in the conventional bipolar group. However, there was no significance with respect to these differences between the groups ($p > 0.05$) (Tab. 2).

Blood transfusion was given in one patient in each group, but the reason was not major vessel injury. One intraoperative major complication occurred in the LigaSure

Table 1. Demographic characteristics of patients

	Conventional bipolar surgery (n: 37)	LigaSure (n: 64)	p
Age (years) (range)	47.6 ± 6.5 (39–78)	48.1 ± 7.1 (40-81)	0.76
BMI (kg/m^2) (range)	29 ± 5.3 (22–47)	30 ± 6.2 (23–45)	0.64
Parity (n) (range)	1.8 ± 1.3 (0–7)	1.7 ± 1.1 (0–5)	0.84
Indication			
Uterine myoma, n (%)	19 (51.3)	34 (53.1)	0.61
Abnormal uterine bleeding, n (%)	8 (21.6)	12 (18.7	0.23
Endometriosis, n (%)	4 (10.8)	5 (7.9)	0.14
Other benign pathologies, n (%)	6 (16.3)	13 (20.3)	0.11
Previous cesarean sections, n (%)	9 (24.3)	14 (21.8)	0.44

BMI — body mass index

Table 2. Perioperative outcomes of the two groups

	Conventional bipolar surgery (n: 37)	LigaSure (n: 64)	p
Uterine weight (gr) (range)	358 ± 261 (70–820)	372 ± 284 (85–940)	0.42
Operation time (min) (range)	41 ± 13.2 (30–75)	37 ± 11.5 (25–65)	0.18
Intraoperative blood loss (ml) (range)	70 ± 22 (10–450)	65 ± 21 (10–410)	0.22
Preoperative hemoglobin (g/dL) (range)	12.53 ± 1.42 (9.2–14.3)	12.77 ± 1.59 (9.0–15.1)	0.65
Postoperative hemoglobin (g/dL) (range)	11.28 ± 1.38 (8.8–13.7)	11.47 ± 1.53 (8.7–14.2)	0.24
Absolute change in hemoglobin(g/dL) (range)	-1.23 ± 1.12 (0.3–2.1)	-1.11 ± 1.14 (0.2–2.7)	0.15
Blood transfusion, n (%)	1 (2.7)	1 (1.6)	0.75
Hospital stay (day) (range)	2.2 ± 0.8 (1–3)	2.1 ± 0.9 (1–5)	0.53
TLH + BS, n (%)	14 (37.9)	23 (35.9)	0.48
TLH + BSO/USO, n (%)	23 (62.1)	41 (64.1)	0.57
Major complication, n (%)	0 (0.0)	1 (1.6)	0.87

TLH — total laparoscopic hysterectomy; USO — unilateral salpingo-oopherectomy; BSO — bilateral salpingo-oopherectomy; BS — bilateral salpingectomy

group. No bladder, major vessel or ureteric injury occurred in the two groups.

DISCUSSION

In this study, we investigated the differences in operative time, blood loss and other perioperative outcomes for LigaSure and conventional bipolar devices during total laparoscopic hysterectomy for benign gynecological indications.

Recently, electrosurgical sources for tissue preparation and vascular sealing have been expanded to include devices that can offer both sealing and cutting. These devices do not need to be replaced during the operation; they also resist high intraluminal pressure and have optimal coagulation properties [9]. LigaSure is an advanced bipolar device that is capable of cutting and sealing. It is able to seal vessels up to 7 mm in diameter and withstands up to threefold the normal systolic blood pressure. It has a minor thermal spread that is up to 4.0 mm [10, 11]. LigaSure has been successfully used in gynecologic operations, in addition to a variety of laparoscopic procedures, urologic and abdominal surgeries [12–14].

In the literature, variable results have been found about duration of operation in gynecologic or other abdominal surgeries for conventional and advanced bipolar devices [3, 15–20]. Many studies reported that LigaSure has a shorter operative time than conventional bipolar instruments. The reason for this increase in time was changing of the instruments for sealing and cutting during the operation in conventional device groups [16–18]. Additionally, the current delivered with LigaSure takes up to 7 seconds to achieve homeostasis [21]. In contrast to the literature, there was no significant difference with respect to operating time between the two groups in our study. If both conventional bipolar devices and scissors are used with both hands at the same time effectively and correctly, no difference in operation time may be expected.

Previous studies reported that intraoperative blood loss was lower in advanced bipolar groups in comparison to conventional groups [20, 21]. According to our results, the estimated and quantitative blood loss was similar in both groups. The discrepancy between hemoglobin decrease and estimated blood loss may be thought to be due to

postoperative hemodilution. Conventional bipolar devices and scissors may not increase the amount of bleeding when used properly. Hemostasis may be successfully achieved in both devices.

There is a doubt about the thermal spread of energy-based devices. The lateral thermal spread of electrosurgery devices may be a risk factor for major complications during laparoscopic hysterectomy. Therefore, adjacent tissues should be checked, and traction should be made while sealing and cutting during the operation. The major complication rate during laparoscopic hysterectomy is reported to be in the range from 4% to 9% in the literature [22]. In our study, this rate was 1.6%, and one intraoperative complication occurred in the LigaSure group. However, the complication was not associated with the type of instruments used for sealing in the operation. This 48-y-old patient had chronic pelvic pain and history of endometriosis. Dense adhesions and an endometriotic nodule were present between the rectum and the uterus. The rectum was injured during resection of the endometriotic nodule from the rectovaginal space. We repaired this injury via laparoscopy without conversion to laparotomy. This patient recovered without complications and was discharged on the 5th postoperative day.

In studies, the length of hospital stays in patients who underwent laparoscopic hysterectomy with conventional bipolar devices was longer than those with advanced bipolar devices. Prolonged hospital stay may be caused by major complications [19, 23]. In this study, both groups had a similar length of hospital stay following the operations. No significant difference was observed in the durations of hospital stay, because the major complication rate was the same in both groups.

The limitations of our study were the small number of patients included and its retrospective nature. Although the number of patients was not equal and the excess in the LigaSure group may seem to affect the results, the findings were not influenced because the data belonged to a single surgeon experienced in both devices. In the future, more large-scale, prospective and randomized studies will be required.

In conclusion, advanced bipolar instruments have the advantages that are closing of vascular structures in addition to their cutting capabilities, so that the process can proceed without changing instruments between hemostatic and cutting devices. In the hands of experienced surgeons, both scissors and conventional devices may be used together and there is no need to change. Thus, there is no significant difference with respect to operating time and blood loss between the two instruments. LigaSure is a disposable energy source and more expensive per case than conventional reusable energy sources. Conventional bipolar energy devices are more cost-effective due to possibility of re-use. They may be used safely and effectively in low-income hospitals that cannot access advanced bipolar energy instruments such as LigaSure.

REFERENCES

1. ACOG Committee Opinion No. 444: choosing the route of hysterectomy for benign disease. Obstet Gynecol. 2009; 114(5): 1156–1158, doi: 10.1097/AOG.0b013e3181c33c72, indexed in Pubmed: 20168127.
2. Kluivers KB, Opmeer BC, Geomini PM, et al. Women's preference for laparoscopic or abdominal hysterectomy. Gynecol Surg. 2009; 6(3): 223–228, doi: 10.1007/s10397-008-0455-1, indexed in Pubmed: 20234838.
3. Wang CJ, Yuen LT, Yen CF, et al. Comparison of the efficacy of the pulsed bipolar system and conventional bipolar electrosurgery in laparoscopically assisted vaginal hysterectomy. J Laparoendosc Adv Surg Tech A. 2005; 15(4): 361–364, doi: 10.1089/lap.2005.15.361, indexed in Pubmed: 16108737.
4. Ayroza P, Abdalla E. Manual of Gynecological Laparoscopic Surgery: Use of Electricity in Laparoscopy, 2nd ed. Tuttlingen, Germany: Endo Press. ; 2010: 43.
5. Harold KL, Pollinger H, Matthews BD, et al. Comparison of ultrasonic energy, bipolar thermal energy, and vascular clips for the hemostasis of small-, medium-, and large-sized arteries. Surg Endosc. 2003; 17(8): 1228–1230, doi: 10.1007/s00464-002-8833-7, indexed in Pubmed: 12799888.
6. Alkatout I, Schollmeyer T, Hawaldar NA, et al. Principles and safety measures of electrosurgery in laparoscopy. JSLS. 2012; 16(1): 130–139, doi: 10.4293/108680812X13291597716348, indexed in Pubmed: 22906341.
7. Richter S, Kollmar O, Schilling MK, et al. Efficacy and quality of vessel sealing: comparison of a reusable with a disposable device and effects of clamp surface geometry and structure. Surg Endosc. 2006; 20(6): 890–894, doi: 10.1007/s00464-005-0380-6, indexed in Pubmed: 16738977.
8. Landman J, Kerbl K, Rehman J, et al. Evaluation of a vessel sealing system, bipolar electrosurgery, harmonic scalpel, titanium clips, endoscopic gastrointestinal anastomosis vascular staples and sutures for arterial and venous ligation in a porcine model. J Urol. 2003; 169(2): 697–700, doi: 10.1097/01.ju.0000045160.87700.32, indexed in Pubmed: 12544345.
9. Kennedy JS, Stranahan PL, Taylor KD, et al. High-burst-strength, feedback-controlled bipolar vessel sealing. Surg Endosc. 1998; 12(6): 876–878, doi: 10.1007/s004649900733, indexed in Pubmed: 9602010.
10. Goldstein SL, Harold KL, Lentzner A, et al. Comparison of thermal spread after ureteral ligation with the Laparo-Sonic ultrasonic shears and the Ligasure system. J Laparoendosc Adv Surg Tech A. 2002; 12(1): 61–63, doi: 10.1089/109264202753486957, indexed in Pubmed: 11905864.
11. Demirturk F, Aytan H, Caliskan AC. Comparison of the use of electrothermal bipolar vessel sealer with harmonic scalpel in total laparoscopic hysterectomy. J Obstet Gynaecol Res. 2007; 33(3): 341–345, doi: 10.1111/j.1447-0756.2007.00533.x, indexed in Pubmed: 17578364.
12. Hagen B, Eriksson N, Sundset M. Randomised controlled trial of LigaSure versus conventional suture ligature for abdominal hysterectomy. BJOG. 2005; 112(7): 968–970, doi: 10.1111/j.1471-0528.2005.00561.x, indexed in Pubmed: 15958001.
13. Heniford BT, Matthews BD, Sing RF, et al. Initial results with an electrothermal bipolar vessel sealer. Surg Endosc. 2001; 15(8): 799–801, doi: 10.1007/s004640080025, indexed in Pubmed: 11443443.
14. Crawford ED. Use of the LigaSure vessel sealing system in urologic cancer surgery. Grand Rounds Urology. 1999; 1: 10–17.
15. Guerrieri M, Sanctis A, Baldarelli M, et al. Electrothermal bipolar energy-based device in laparoscopic right colectomy: our experience. Minerva Chir. 2008; 63(6): 455–460, indexed in Pubmed: 19078877.
16. Janssen PF, Brölmann HAM, van Kesteren PJM, et al. Perioperative outcomes using LigaSure compared with conventional bipolar instruments in laparoscopic hysterectomy: a randomised controlled trial. BJOG. 2011; 118(13): 1568–1575, doi: 10.1111/j.1471-0528.2011.03089.x, indexed in Pubmed: 21895949.
17. Bessa SS. Ligasure vs. conventional diathermy in excisional hemorrhoidectomy: a prospective, randomized study. Dis Colon Rectum. 2008; 51(6): 940–944, doi: 10.1007/s10350-008-9214-7, indexed in Pubmed: 18273670.
18. Taşkın S, Şükür YE, Altın D, et al. Bipolar Energy Instruments in Laparoscopic Uterine Cancer Surgery: A Randomized Study. J Laparoendosc Adv Surg Tech A. 2018; 28(6): 645–649, doi: 10.1089/lap.2017.0639, indexed in Pubmed: 29323616.

19. Cho HY, Choi KJ, Lee YL, et al. Comparison of two bipolar systems in laparoscopic hysterectomy. JSLS. 2012; 16(3): 456–460, doi: 10.4293/108680812X13462882736259, indexed in Pubmed: 23318073.
20. Wang JY, Lu CY, Tsai HL, et al. Randomized controlled trial of LigaSure with submucosal dissection versus Ferguson hemorrhoidectomy for prolapsed hemorrhoids. World J Surg. 2006; 30(3): 462–466, doi: 10.1007/s00268-005-0297-1, indexed in Pubmed: 16479346.
21. Seehofer D, Mogl M, Boas-Knoop S, et al. Safety and efficacy of new integrated bipolar and ultrasonic scissors compared to conventional laparoscopic 5-mm sealing and cutting instruments. Surg Endosc. 2012; 26(9): 2541–2549, doi: 10.1007/s00464-012-2229-0, indexed in Pubmed: 22447285.
22. Garry R, Fountain J, Mason Su, et al. The eVALuate study: two parallel randomised trials, one comparing laparoscopic with abdominal hysterectomy, the other comparing laparoscopic with vaginal hysterectomy. BMJ. 2004; 328(7432): 129, doi: 10.1136/bmj.37984.623889.F6, indexed in Pubmed: 14711749.
23. Rothmund R, Kraemer B, Brucker S, et al. Laparoscopic supracervical hysterectomy using EnSeal vs standard bipolar coagulation technique: randomized controlled trial. J Minim Invasive Gynecol. 2013; 20(5): 661–666, doi: 10.1016/j.jmig.2013.04.014, indexed in Pubmed: 23791399.

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Perinatal outcome in preterm premature rupture of membranes before 37 weeks of gestation

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ABSTRACT

Objectives: The aim of this study was to assess the maternal and neonatal outcome in patients with preterm premature rupture of membranes between 22 to 37 weeks of gestation in comparison to preterm birth patients.

Material and methods: Group of PPROM patients consisted of 127 women, the control group counted 141 women who delivered prematurely. The control group was formed by matching patient with the same gestational age at delivery and neonatal birth weight to every woman from study group. In both groups speculum and ultrasound examinations were performed, microbiological swabs were taken. In unclear cases of PPROM tests detecting amniotic proteins, such as PAMG-1 or IGFBP-1, were performed. According to gestational age at delivery, neonates were divided into subgroups: extremely premature infants (< 27 weeks 6 days), moderate premature infants (from 28 weeks 0 days to 33 weeks 6 days), late premature infants (from 34 weeks 0 days to 37 weeks 0 days).

Results: In the study group, median gestational age of delivery was 34 weeks 1 day and the same in control group — 34 weeks and 5 days ($p > 0.05$). Parameters of inflammatory status were more often reported in the PPROM group than in the preterm birth group, even if they weren't statistically significant (positive culture of cervical swab, increased leukocytosis, CRP above 5).

The rate of neonate survival was similar in both groups (93.7% and 94.1%). Congenital infection was more often diagnosed in group of neonates from PPROM pregnancies than in neonates from control group; (36% and 21.2% respectively; $p = 0.009$).

Conclusions: Our research appears to be consistent with theory of inflammatory etiology of PPROM. Optimal management of infection in PPROM patients seems to be the most important in efforts to prolong pregnancy.

Key words: 1 preterm delivery; 2 preterm premature rupture of membranes; 3 neonatology autcome

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INTRODUCTION

Preterm rupture of membranes (PROM) complicates approximately 2–5% of pregnancies before term and 8% of term gestations [1]. At term it does not significantly influence pregnancy outcome. If it happens before 37 weeks, we describe it as preterm premature rupture of membranes (PPROM) and it increases the risk of preterm labor, intrauterine infection, fetal hypoxia and intrauterine death [1, 2]. Pregnancy outcome in cases of spontaneous PPROM depends on gestational age. Approximately 50% of patients deliver within a week after PPROM, latency in the other half depends on gestational age, fetal condition and presence of infection [3].

Depending on the gestational age, fetal and maternal condition, there is a possibility of conservative management, including steroids administration, antibiotics and magnesium sulfate or active labor induction after steroids administration [4]. Tocolytics are usually not recommended because uterine contractions are usually correlated to intrauterine infection and prolongation of pregnancy in these cases does not decrease the mortality and morbidity of women and children [5, 6].

Lack of amniotic fluid in the uterus, especially before the 24th week of gestation, disturbs fetal lung development. Alveoli do not form without amniotic fluid even after steroids administration. Respiratory distress in children born after PPROM, after they had spent some time in uterus without amniotic fluid, is often more severe than we expect. Neonates have also higher risk of severe inborn infection. Both factors — respiratory distress and infection — worsen prognosis for the children after PPROM [7, 8].

There are only a few trials trying to compare different approaches to ahydramnios caused by PPROM. They

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concentrate on two topics: sealing the hole in membranes (amniopatch, immunologic sealants, membranes) and supplementing amniotic fluid (amnioinfusion). As of now, there is no answer to if any type of treatment improves pregnancy outcome [9, 10].

Objectives

Authors compared pregnancy outcome in patients who delivered before term with and without PPROM.

MATERIAL AND METHODS

The study group consisted of 127 women who were admitted to the Department of Obstetrics of Medical University from October 2009 to 2014 with preterm premature rupture of membranes (between 22 and 37 weeks of gestation).The control group (141 women) was formed by matching patient with the same gestational age at delivery and neonatal birth weight to every woman from study group. According to gestational age at delivery, neonates were divided into subgroups: extremely premature infants (< 27 weeks 6 days), moderate premature infants (from 28 weeks 0 days to 33 weeks 6 days), late premature infants (from 34 weeks 6 days to 37 weeks 0 days).

To confirm PPROM, sterile speculum examinations were performed with the visualization of amniotic fluid leaking from the cervical canal. In unclear cases tests detecting amniotic proteins, such as PAMG-1 (Placental alpha microglobulin-1) or IGFBP-1 (Insulin —like growth factor binding protein 1), were performed. Ultrasound examinations were performed in every patient — fetal well-being, amniotic fluid index and signs of placental abruption were determined. The exclusion criteria included: multiple pregnancy, intrauterine fetal death, fetal congenital malformations, previous cervical surgery and uncertain diagnosis of PPROM.

According to our Department regulation, patients with PPROM before 34 weeks 0 days of gestation were managed expectantly if no maternal or fetal contraindication were present. Induction of labor wasn't offered to these patients unless intrauterine infection was diagnosed. Tocolysis wasn't ordered to pregnant patients with PPROM. A single course of corticosteroids was offered to every pregnant woman between 24 weeks 0 days and 34 weeks 6 days. Prophylactic antibiotics were given to patients in the latent phase of PPROM from 24 weeks 0 days to 33 weeks 6 days. Every week patients were examined vaginally (speculum examination) and had cervical swabs taken. If a microbiological swab was positive, antibiotics were administered. Similarly, CRP and leukocytosis were evaluated every week. Fetal status was assessed every seven days by ultrasound examination. In case of patients with PPROM after 34 weeks 0 days of gestation, who didn't have contraindication to labor, delivery was induced, mostly with Oxytocin infusion (usually after 12 hours of expectancy for spontaneous contractions). Neither tocolysis nor corticosteroids were offered in this group of patients. Maternal infusion of magnesium sulfate as fetal neuroprotection wasn't recommended for patients before 32 weeks 0 days.

Data from medical records were analyzed to compare pregnancy complications and outcome in the study group and control group. Information regarding gestational age at PPROM, laboratory symptoms of infection (CRP > 5, leukocytosis > 15000/dL, positive culture of cervical swab), steroids and antibiotics administration, gestational age at delivery, mode of delivery, indication for cesarean section, birth weight of neonate, respiratory distress syndrome (type of assisted ventilation), leukocytosis and CRP in neonate, results of microbiological tests in neonates, length of hospital stay of neonate was collected. Congenital infection was diagnosed based on a minimum of two signs of infection in clinical examination and/or increased values of inflammatory parameters in neonate. Clinical symptoms of congenital infection were defined as breathing disturbances (tachypnea, apnea), tachycardia, bradycardia, significant variability of heart rate, emesis, hypotonia, muscle tremors, convulsions, instability of body temperature, lethargy, circulation disturbances, and metabolic disturbances.

The normality of the layout of continuous variables was assessed by means of the Shapiro-Wilk test. Statistical characteristics of continuous variables were presented by means of arithmetic means, standard deviations, medians as well as minimal and maximal values. For inter-group comparisons Student's t-test for non-linked variables or U Mann-Whitney test were applied. In order to compare the layouts of discrete variables, Pearson's chi-squared test or Fisher's exact test were used. All calculations were carried out by means of Statistica10 software (StatSoft, the USA), where value $p < 0.05$ was accepted as a statistically significant.

RESULTS

Average patient age at admission to hospital was 30.2 ± 5.4 years in the study group and 29.8 ± 4.8 years in the control group ($p > 0.05$). As far as gravidity was concerned, 48% of the patients in study group and 43.3% of the patients in control group were nulliparous, while 52% and 56.7% had had at least one delivery ($p > 0.05$). In the study group of 127 women median gestational age of delivery was 34 weeks 1 day (23 weeks and 5 days to 37 weeks 0 days) and the same in the control group — 34 weeks and 5 days, from 22 weeks and 4 days to 37 weeks and 0 days ($p > 0.05$). Median gestational age of delivery in subgroups was: before 27 weeks and 6 day — 26 weeks and 0 days in PPROM group and 25 weeks 5 days in control group ($p > 0.05$), from 28 weeks and 0 days to 33 weeks and 6 days — 31 weeks and 4 days in both groups ($p > 0.05$) and from

34 weeks and 0 days to 37 weeks and 0 days — 35 weeks and 3 days in PPROM group and 35 weeks 4 days in control group ($p < 0.05$).

The median gestational age of PPROM in the study group was 33 weeks 5 days (from 21 weeks and 4 days to 36 weeks and 6 days). In details: in the group of patients who delivered before 27 weeks 6 days — 24 weeks 6 days, from 28 weeks 0 days to 33 weeks 6 days — 30 weeks 1 day, from 34 weeks 0 days to 37 weeks 0 days — 35 weeks 2 days. The median time from PPROM to delivery was 1 day (0 to 71 days); 9 days in patients, who delivered before 28 weeks of gestation; 11 days in patients who delivered from 28 weeks and 0 days to 33 weeks and 6 days and 1 day in patients who delivered after 33 weeks and 6 days. In the analyzed group 42 patients (33%) delivered on the day, when PPROM occurred, while 85 (66.9%) delivered later. Among 42 pregnant women who delivered on the day of PPROM, gestational age of 36 (85.7%) of them was greater than 33 weeks 6 days of gestation, when in 6 (14.3%) of them was between 28 weeks 0 days and 33 weeks 6 days. None of PPROM patients who delivered before 28 weeks of pregnancy delivered on the day when PPROM occurred.

Positive culture of cervical swabs were noted in 62 patients with PPROM (49%) and in 51 patients in the control group (36%) ($p > 0.05$, $p = 0.101$); in 3 patients (27%), who delivered before 28 weeks of gestation in the PPROM group and in 5 patients (50%) in the control group ($p > 0.05$); in 27 patients (56 %), who delivered from 28 weeks 0 days to 33 weeks 6 days in the PPROM group and in 16 patients (36%) in the control group ($p = 0.06$); in the group of patients who delivered from 34 weeks 0 days to 37 weeks 0 days — in 32 pregnant in the PPROM group (47%) and in 30 patients (35%) in the control group ($p < 0.05$). Increased leukocytosis was noted at least once during latent period in 65 women with PPROM (51.2%), in the control group leukocytosis greater than 15000 was found in 43 patients (30.7%) ($p < 0.001$). In details, in the study and in the control group in 6 patients (54%) versus 3 patients (33%) who delivered before 28 weeks of pregnancy, in 30 patients (62%) versus 18 patients (38%) who delivered from 28w0d to 33w6d and in 29 patients (43%) versus 22 patients (27%) who delivered later ($p > 0.05$; $p < 0.05$; $p < 0.05$; respectively) increased leukocytosis was noted. CRP above 5 was observed in 77 patients (68.7%) in the study group versus 29 patients (56.9%) in the control group ($p < 0.001$ and $p > 0.05$). CRP wasn't evaluated in 15 patients (12%) from the study group and in 90 patients (63.8%) from the control group.

During latent time prophylactic antibiotics were used in 73 patients (57.5%) in the group of PPROM patients. Additionally, antibiotics were administered if increased CRP, leukocytosis or positive microbiological swab was observed. To conclude, antibiotics were given to 99 patients in the PPROM group before delivery (78%), while in the control group 50 patients (35.5%) ($p < 0.001$).

Steroids were administered in 66 patients before 34 weeks 6 days in the study group (52%), and in 49 patients in the control group (35%) ($p < 0.05$); in a group of women who delivered before 28w0d in 10 (90%) in the PPROM group and in 7 (70%) in the preterm delivery group; in a group of patients who delivered from 28w0d to 33w6d in 41 (85%) in the study group and in 27 (56%) in the control group. Patients who delivered after 33w6d received steroids in 22% (15 pregnant) in the PPROM group and in 18% (15 pregnant) in the control group ($p > 0.05$, $p < 0.05$, $p > 0.05$; respectively).

In the study group 77 patients (61%) delivered vaginally — 73% (8 pregnant women) before 28w0d, 59% (28 pregnant) from 28w0d to 33w6d and 60% (41 pregnant women) from 34w0d to 37w0d. In the remaining 50 women (39%), cesarean sections were performed. In the control group, 38 patients delivered vaginally (27%) — 30% (3 pregnant women) before 28w0d, 29% (13 pregnant women) from 28w0d to 33w6d and 27% (22 pregnant women) from 34w0d to 37w0d. Cesarean sections were performed in 103 patients (73%). The cesarean section rate was higher in the control group ($p < 0.001$) and in the subgroups this trend was also observed ($p = 0.05$, $p < 0.05$, $p < 0.05$).

The cesarean section in the study group was performed most frequently due to fetal distress (28 women — 58.3%) or intrauterine infection (10 women — 20.8%), but also due to fetal malpresentation (9 women — 18.8%), placental abruption (2 women — 4.2%), preeclampsia (1 woman — 2.1%), threatening rupture of uterus (4 women — 8.3%) and maternal indications (8 women — 16.7%), fetal indications (1 woman — 2.1%). Indications for cesarean sections in the control group was mostly fetal distress (66 women — 64.7%). Other indications were: intrauterine infection (3 women — 2.9%), fetal malpresentation (8 women — 7.8%), placental abruption (6 women — 5.9%), preeclampsia (15 women — 14.7%), threatening rupture of uterus (4 women — 3.9%) and maternal indications (13 women — 12.7%), fetal indications (4 women — 3.9%). In three cases, indications for cesarean section were unknown. The group of extremely preterm infants consisted of 11 neonates (9%) in the PPROM group and 10 neonates (7%) in the preterm delivery group, moderate preterm infants — 48 (38%) in the PPROM group and 47 (33%) in the preterm delivery group, late preterm infants — 68 (53%) in the PPROM group and 84 (60%) in the control group ($p > 0.05$, $p > 0.05$, $p < 0.05$).

The average birth weight was similar in the study and the control group (2117.9 g and 2245.0 g respectively, $p > 0.05$). In extremely preterm infants it was 938 g and 832 g ($p > 0.05$), in moderate preterm infants 1717 g and 1766 g ($p > 0.05$) and in late preterm infants 2589 g and

2667 g (p > 0.05) in the PPROM group and the control group respectively.

The rate of neonate survival to discharge was similar in both groups (93.7% and 94.1% respectively; p > 0.05). Rates of survival increased with increasing gestational age in both groups; in the PPROM group: 73% (< 28w0d), 94% (from 28w0d to 33w6d), 99% (from 34w0d to 37w0d) and in the control group: 60%, 94%, 97% respectively (p < 0.05, p > 0.05, p > 0.05).

Incidence of neonatal respiratory distress syndrome was similar in both groups (42.5% vs 45%; p > 0.05). In extremely preterm infants in 90% (10 neonates) and in 89% (8 neonates) (p > 0.05), in moderate preterm infants in 35 (73%) and in 35 neonates (74%) (p > 0.05), in late preterm infants in 10 neonates (15%) and in 21 neonates (25%) (p > 0.05) in the PPROM group and the control group respectively.

Assisted ventilation was used in 48 neonates (38%) in the study group and in 59 children (42%) in the control group (p > 0.05); in 10 neonates (90%) and in 8 neonates (80%) in extremely preterm infants (p > 0.05), in 32 neonates (66%) and in 34 neonates (74%) in moderate preterm infants (p > 0.05), in 6 neonates (9%) and in 17 neonates (20%) in late preterm infants (p = 0.059). Congenital infection was diagnosed more often in the group of neonates from PPROM pregnancies (45 neonates) than in neonates from the control group (29 neonates); (36% and 21.2% respectively; p = 0.009). In detail, infection was present in 6 (55%) extremely preterm neonates in the PPROM group and in 3 (37%) in the control group (p > 0.05), in 25 (52%) moderate preterm neonates in the PPROM group and in 14 (31%) in the control group (p < 0.05) and in 13 (19%) late preterm neonates in study group and in 11 (13%) in preterm delivery group (p > 0.05). Differences were also noted regarding leukocytosis in neonate above 15 000/dL (61.5% and 49.2% respectively), but it was not statistically significant (p = 0.059). In detail, high leukocytosis was found in extremely preterm in 66% (6 neonates) and 37% (3 neonates) (p > 0.05), in moderate preterm infants in 56% (26 neonates) and in 40% (18 neonates) (p > 0.05) and in late preterm infants in 60% (40 neonates) and in 50% (41 neonates) (p > 0.05) in the PPROM group and the control group respectively.

Number of neonates with CRP above 5 was similar in both groups (22.3% and 24.4% respectively; p > 0.05). In extremely preterm infants CRP was above 5 in 33% (3 neonates) versus 37% (3 neonates) (p > 0.05), in moderate preterm infants 38% (17 neonates) versus 35% (15 neonates) (p > 0.05) and in late preterm infants 12% (8 neonates) versus 17% (14 neonates) (p > 0.05) in the PPROM group and the control group respectively.

Antibiotic therapy was administered in 88 (69%) of neonates from the study group versus 80 (61%) neonates from the control group (p = 0.04). In extremely preterm infants antibiotics were given to 10 neonates (90%) and in 9 neonates (90%) (p > 0.05), in moderate preterm infants in 47 neonates (98%) and in 44 neonates (94%) (p > 0.05) and in late preterm infants in 31 neonates (45%) and in 28 neonates (34%) (p > 0.05) in the PPROM group and the control group respectively.

Median hospital stay of the neonates in the study group was 11 days (0 to 79 days) and in the control group — 8 days (0 to 82 days), and the difference wasn't significant (p > 0.05). In extremely preterm infants it was 67 and 54 days (p > 0.05), in moderate preterm infants 25 and 30 days (p > 0.05) and in late preterm infants 8 and 9 days (p > 0.05) in the PPROM group and control group respectively.

DISCUSSION

According to Romero's definition preterm labor results from "pathological activation" of one or more components of "common pathway of parturition". Uterine myometrial contractility, cervical ripening and membranes rupture, if activated synchronously are said to be the most important factors leading to preterm delivery. Asynchronous activation of one of these components results in cervical insufficiency, preterm uterine contractions or preterm premature rupture of membranes [11, 12]. So far there are many dimensions identified as responsible or connected with mentioned above clinical situations [12]. Prostaglandins and matrix-degrading enzymes (mediators of infection) are considered to be crucial factors in collagen degradation and weakening of membranes, which leads to its rupture [13]. Clinical studies have confirmed infectious theory — bacteria's have the ability to cross even intact membranes and positive amniotic fluid cultures are identified in 12.8% of patients with preterm birth and 32% with preterm premature rupture of membranes according to Romero's researches [14]. Caroll S.G. et al. [15] showed that positive culture of swabs from the vagina predicts 53% of intraamniotic infections. In our study we haven't examined amniotic fluid for presence of microbial invasion, but we also observed positive culture of cervical swab significantly more frequent in group of patients with rupture of membranes than in patients with preterm birth. Similarly, increased leukocytosis and CRP were noted more often in groups of pregnant women with PPROM than in groups of patients with preterm birth. CRP isn't routinely ordered in case of patients with risk of preterm delivery, that's why increased value of this marker was observed only in 13% of patients among the patients in this group. According to literature neither CRP nor leukocytosis are considered to be highly specific in detecting intrauterine infection and are not even recommended in some countries to be assessed. The estimated sensitivity rate of leukocytosis in detecting chorioamnionitis is 29–47% [16], when specificity of CRP is 38–55% [17]. Antibiotics were applied

in groups of PPROM patients more often than in control groups. Antibiotics weren't offered routinely to everyone. Due to hospital regulation, antibiotics were offered prophylactically or in case of increased inflammatory indicators or symptoms of infection.

Nowadays, according to Polish Society of Gynecologists and Obstetricians the most optimal approach to management of PPROM patients is expectant management with antibiotics therapy to prolong latency of pregnancy. After 34 weeks of pregnancy induction of delivery with oxytocin is indicated only if intrauterine infection is suspected. Regardless of clinical management birth in 7 days following rupture of membranes occurs in 50% patients [3]. The median length of latency from PPROM to delivery in the examined group was 1 day (from 0 to 71 days). Comparing to other publications, median latency time in the PPROM group was short because in the evaluated group nearly half consisted of patients after 34 weeks of gestation, where due to hospital regulation and ACOG recommendations active management was recommended. In patients with PPROM before 28 weeks of gestation median latency time was 9 days and 11 days if delivery took place between 28 + 0 to 33 + 6, similar results were presented by A. Peaceman. In a group of 1377 patient's median latency time between 24–28 weeks was approximately 9 days, and between 30–31 weeks was 6 days [18].

The difference in the frequency of cesarean section was observed in the research. This operative procedure was more often performed in group of patients with intact membranes than in PPROM group. The main indication for cesarean section in both groups was fetal distress, while in the group of PPROM patients could have been related to active management (induction of delivery) in case of patients after 34 weeks of gestation. Threatening intrauterine infection was the second main indication for cesarean section in the PPROM group, what is consistent with published data.

Congenital infection was more often detected in all subgroups of neonates from the study group than the control group, what is consistent with fact of higher incidence of increased parameters of inflammation and positive cervical swabs in pregnant with PPROM. As a consequence of this, antibiotics were also more often administered in the study group. Comparable results were published by Moratti [19]. According to data published by Bengtson and Dale [20, 21] respiratory distress syndrome incidence in neonates from pregnancies complicated by PPROM is evaluated to be 10–40%. In general, in our study we noticed high ratio of respiratory distress, comparable in both groups of neonates (42.5% and 45%). In case of extremely and moderate preterm neonates, it was a result of early gestational age at delivery and impossibility of steroids administration. In the group of neonates delivered after 34 weeks of gestation, respiratory distress syndrome was more often observed in the control group, which is probably connected with the high percentage of cesarean section performed in this group.

Considering neonatal survival rate, we haven't found significant difference between both groups of patients. Neonatal death mostly occurred in cases of neonates born before 26 weeks of gestation with low birth weight. Glass estimates that extremely premature infants with extremely low birth weight have 30–50% risk of mortality and 20–50% risk of morbidity in survivors [22]. Probably, if patients with PPROM (especially after 28th week of pregnancy) are appropriately covered with antibiotics, which increases the latent time of pregnancy and offers the possibility of steroids and magnesium sulfate administration, the presence of PPROM doesn't influence the rate of mortality in neonates.

CONCLUSIONS

Our research appears to be consistent with theory of inflammatory etiology of PPROM. Optimal management of infection in PPROM patients seems to be the most important in efforts to prolong latency of pregnancy and decrease mortality and morbidity in neonates.

REFERENCES

1. Harger JH, Toumala RE, Gibbs RS, et al. Premature rupture of membranes. Obstet Gynecol. 2013; 122: 918–930, doi: 10.1097/01.AOG.0000435415.21944.8f.
2. Getahun D, Strickland D, Ananth CV, et al. Recurrence of preterm premature rupture of membranes in relation to interval between pregnancies. Am J Obstet Gynecol. 2010; 202(6): 570.e1–570.e6, doi: 10.1016/j.ajog.2009.12.010, indexed in Pubmed: 20132922.
3. Mercer BM. Preterm premature rupture of the membranes. Obstet Gynecol. 2003; 101(1): 178–193, doi: 10.1016/s0029-7844(02)02366-9, indexed in Pubmed: 12517665.
4. American College of Obstetricians and Gynecologists' Committee on Practice Bulletins—Obstetrics. Practice Bulletin No. 172: Premature Rupture of Membranes. Obstet Gynecol. 2016; 128(4): e165–e177, doi: 10.1097/AOG.0000000000001712, indexed in Pubmed: 27661655.
5. Jazayeri A, Jazayeri MK, Sutkin G. Tocolysis does not improve neonatal outcome in patients with preterm rupture of membranes. Am J Perinatol. 2003; 20(4): 189–193, doi: 10.1055/s-2003-40606, indexed in Pubmed: 12874729.
6. Ehsanipoor RM, Shrivastava VK, Lee RM, et al. A randomized, double-masked trial of prophylactic indomethacin tocolysis versus placebo in women with premature rupture of membranes. Am J Perinatol. 2011; 28(6): 473–478, doi: 10.1055/s-0030-1270118, indexed in Pubmed: 21170827.
7. Waters TP, Mercer BM. The management of preterm premature rupture of the membranes near the limit of fetal viability. Am J Obstet Gynecol. 2009; 201(3): 230–240, doi: 10.1016/j.ajog.2009.06.049, indexed in Pubmed: 19733274.
8. 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.
9. Sciscione AC, Manley JS, Pollock M, et al. Intracervical fibrin sealants: a potential treatment for early preterm premature rupture of the membranes. Am J Obstet Gynecol. 2001; 184(3): 368–373, doi: 10.1067/mob.2001.111796, indexed in Pubmed: 11228489.
10. Singla A, Yadav P, Vaid NB, et al. Transabdominal amnioinfusion in preterm premature rupture of membranes. Int J Gynaecol Obstet. 2010; 108(3): 199–202, doi: 10.1016/j.ijgo.2009.09.032, indexed in Pubmed: 20015490.
11. Romero R, Gomez R, Mazor M, et al. The preterm labor syndrome. In: Elder MG, Lamont RF. ed. Preterm labor. Churchill Livingstone, New York 1997: 29–49.
12. Gotsch F, Romero R, Erez O, et al. The preterm parturition syndrome and its implications for understanding the biology, risk assessment, diagnosis, treatment

and prevention of preterm birth. J Matern Fetal Neonatal Med. 2009; 22 Suppl 2: 5–23, doi: 10.1080/14767050902860690, indexed in Pubmed: 19951079.
13. Draper D, Jones W, Heine RP, et al. Trichomonas vaginalis Weakens human Amniochorion in an in vitro model of premature membrane rupture. Infect Dis Obstet Gynecol. 1995; 2(6): 267–274, doi: 10.1155/S1064744995000160, indexed in Pubmed: 18475407.
14. Romero R, Salafia CM, Athanassiadis AP, et al. The relationship between acute inflammatory lesions of the preterm placenta and amniotic fluid microbiology. Am J Obstet Gynecol. 1992; 166(5): 1382–1388, doi: 10.1016/0002-9378(92)91609-e, indexed in Pubmed: 1595794.
15. Carroll SG, Papaioannou S, Ntumazah IL, et al. Lower genital tract swabs in the prediction of intrauterine infection in preterm prelabour rupture of the membranes. Br J Obstet Gynaecol. 1996; 103(1): 54–59, doi: 10.1111/j.1471-0528.1996.tb09515.x, indexed in Pubmed: 8608099.
16. Ismail MA, Zinaman MJ, Lowensohn RI, et al. The significance of C-reactive protein levels in women with premature rupture of membranes. Am J Obstet Gynecol. 1985; 151(4): 541–544, doi: 10.1016/0002-9378(85)90285-6, indexed in Pubmed: 3976754.
17. Watts DH, Krohn MA, Hillier SL, et al. Characteristics of women in preterm labor associated with elevated C-reactive protein levels. Obstet Gynecol. 1993; 82(4 Pt 1): 509–514, indexed in Pubmed: 8377973.
18. Peaceman AM, Lai Y, Rouse DJ, et al. Eunice Kennedy Shriver National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network. Length of latency with preterm premature rupture of membranes before 32 weeks' gestation. Am J Perinatol. 2015; 32(1): 57–62, doi: 10.1055/s-0034-1373846, indexed in Pubmed: 24819145.
19. Moretti M, Sibai BM. Maternal and perinatal outcome of expectant management of premature rupture of membranes in the midtrimester. Am J Obstet Gynecol. 1988; 159(2): 390–396, doi: 10.1016/s0002-9378(88)80092-9, indexed in Pubmed: 3407697.
20. BENGTSON J, VanMARTER L, BARSS V, et al. Pregnancy Outcome After Premature Rupture of the Membranes at or Before 26 Weeks' Gestation. Am J Obstet Gynecol. 1989; 73(6): 921–927, doi: 10.1097/00006250-198906000-00002.
21. Dale PO, Tanbo T, Bendvold E, et al. Duration of the latency period in preterm premature rupture of the membranes. Maternal and neonatal consequences of expectant management. Eur J Obstet Gynecol Reprod Biol. 1989; 30(3): 257–262, doi: 10.1016/0028-2243(89)90010-5, indexed in Pubmed: 2714507.
22. Glass HC, Costarino AT, Stayer SA, et al. Outcomes for extremely premature infants. Anesth Analg. 2015; 120(6): 1337–1351, doi: 10.1213/ANE.0000000000000705, indexed in Pubmed: 25988638.

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Evaluation of catalase, myeloperoxidase and ferroxidase values in pregnant women with hyperemesis gravidarum

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ABSTRACT

Objectives: To investigate maternal serum catalase, myeloperoxidase and ferroxidase levels in pregnant women with Hyperemesis Gravidarum and to compare the results with healthy pregnancies.

Material and methods: In this study, 60 female patients admitted to the Health Sciences University, Gazi Yaşargil Training and Research Hospital, Gynecology and Obstetrics Department were evaluated. The patients were divided into two groups: Group 1 included 30 pregnant women with hyperemesis gravidarum; Group 2 included 30 healthy pregnant women. Pregnancies over 14 weeks were excluded from the study.

Results: The laboratory and laboratory characteristics of both groups are shown in Table 1. No significant differences were found between the groups in terms of the maternal age, gestational age, gravidity, parity, fasting glucose level, and BMI. The maternal blood CAT levels were significantly higher in the HG group (219.6 ± 111.3 kU/L) when compared to the control group (71.5 ± 52.5 kU/L) ($p < 0.001$). The maternal blood MPO levels were lower in the control group (121.5 ± 36.3 U/L) than in the study group (90.9 ± 56.4 U/L) ($p = 0.016$). However, the ferroxidase levels were similar between the two groups. The independent variables BMI, age, parity, gravidity and gestational week effects were adjusted according to the logistic regression method with groups. Significant differences were observed between the two groups in the levels of CAT (0.001), MPO (0.005) values.

Conclusions: This study suggests that antioxidants in response to oxidative stress gave different reactions with different mechanisms; Also, we believe that insufficient food intake suppresses the immune system and this has an important role on antioxidants.

Key words: catalase; myeloperoxidase; ferroxidase; hyperemesis gravidarum

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INTRODUCTION

Nausea and vomiting can be seen in 80% of pregnant women in the first months of pregnancy [1]. Nausea and vomiting is a severe form of hyperemesis gravidarum (HG) and occurs in 0.3–3% of all pregnancies. When severe nausea and vomiting occur more often than three times a day in a patient with ketonuria and a weight loss of more than 5%, the patient is diagnosed with HG [2–4].

The HG etiology has not yet been fully elucidated [5]; however, many oxidative stressors are known to play roles in HG [6], including an imbalance between the oxidants and antioxidants. Oxidative stress (OS) refers to an imbalance between the production of reactive oxygen species and the antioxidant defence system that buffers oxidative damage, resulting in cellular, molecular damage. It has been reported

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that antioxidant activity is significantly higher in women with healthy pregnancies when compared to women who are not pregnant [7].

The antioxidant defence system includes ferroxidase, which converts toxic ferrous iron to less toxic ferric iron, thereby reducing oxidative damage to the cellular and molecular [8, 9]. Catalase (CAT), an intracellular antioxidant, increases to compensate for redox reactions in OS [10]. Myeloperoxidase is another intracellular enzyme that acts as an antioxidant in neutrophils. A decrease in antioxidant activity or an increase in free radicals will lead to OS [11, 12].

In this study, the ferroxidase, CAT, and MPO serum levels in the blood of HG patients were determined, and the results were compared with those of healthy pregnant women.

MATERIAL AND METHODS

This prospective study included a total of 60 pregnant women admitted to the Gynecology and Obstetrics Department of the Health Science University Diyarbakır Gazi Yaşargil Training and Research Hospital in Diyarbakir, Turkey, between December 2017 and December 2018. The patients were divided into two groups: group 1 included 30 pregnant women with HG and group 2 included 30 healthy pregnant women. This research was conducted following the principles of the Helsinki Declaration, and informed consent was obtained from all of the participants.

The HG diagnosis inclusion criteria were as follows: severe and persistent nausea and vomiting more than three times per day during pregnancy, ketonuria, and greater than 5% weight loss [5]. Those patients with comorbid diseases (such as trophoblastic diseases, gestational diabetes, preeclampsia, thyroid diseases, infectious diseases, inflammatory diseases, renal diseases, hepatic diseases, and psychiatric disorders), smoking and alcohol habits, chronic medication use, and pregnancies over 14 weeks were excluded from the study. The following patient characteristics were recorded: maternal age, parity, gravidity, body mass index (BMI), and the gestational week at sampling.

Venous blood samples were centrifuged at 4,000 rpm for 10 minutes, sera were separated and stored at –80°C until the MPO, ferroxidase, and CAT levels were analysed.

Activity of CAT was evaluated by Goth's method [13]. Sample (0.2 mL) was incubated in 1.0 mL substrate (65 µmol per in 60 hydrogen peroxide (H_2O_2) mmol/L sodium-potassium phosphate buffer, pH 7.4) at 37°C for 60 seconds. The enzymatic activity was stopped with 1.0 mL of 32.4 mM ammonium molybdate, and the yellow complex of molybdate and H_2O_2 was measured at 405 nm. CAT activity was presented kU/L.

Activity of MPO was evaluated by a modification of the o-dianisidine method [14], a kinetic measurement with a yellowish orange product ratio; MPO from the oxidation of O-dianiside in the presence of hydrogen peroxide was measured at 460 nm. MPO activity was presented in units per liter serum.

The ferroxidase level was evaluated using the Erel-specified method [15]. Although this method is calorimetric and automatic, enzymatically, it depends on the oxidation of the iron ion. The results were evaluated as the units per liter of serum.

The study protocol was approved by a regional committee (216).

Statistical analysis

For the comparative between-group analyses (case vs control), a chi-squared test was used for the categorical variables, and either the Student's t-test or the Mann-Whitney U test was used for the continuous variables. Independent variables were adjusted that reduced the BMI, age, parity, gravidity and gestational week effect with the independent logistic regression method. Differences were considered significant at $p < 0.05$. All statistical analyses explained R-software v.3.5.1 (R statistics software, Institute for statistics and mathematics, Vienna, Austria).

RESULTS

Clinical and laboratory results are shown in Table 1. No significant differences were found between the groups in terms of the maternal age, gestational week, gravidity, parity, fasting glucose level, and BMI. The maternal blood CAT levels were significantly higher in the HG group (219.6 ± 111.3 kU/L) when compared to the control group (71.5 ± 52.5 kU/L) ($p < 0.001$). The maternal blood MPO levels were lower in the control group (121.5 ± 36.3 U/l) than in the study group (90.9 ± 56.4 U/L) ($p = 0.016$). However, the ferroxidase levels were similar between the two groups. The independent variables BMI, age, parity, gravidity and gestational week effects were adjusted according to the logistic regression method with groups. Significant differences were observed between the two groups in the levels of CAT (0.001), MPO (0.005) values (Fig. 1–3).

DISCUSSION

In this study, which lasted less than 14 weeks, an imbalance was found between the serum OS markers and the antioxidant defence system markers when 30 pregnant women with HG and 30 normal pregnant women were compared. Low MPO values and statistically significantly higher CAT values were found in the serum samples of the HG patients when compared to the controls.

Previous studies have shown that the risks of preeclampsia, placental anomalies, and intrauterine growth retardation are increased in pregnant women with HG [16], and many events are known to cause OS in these women [6].

Table 1. Comparison between the hyperemesis gravidarum (HG) patients and the healthy controls

Variables	HG group Mean ± SD n = 30	Control group Mean ± SD n = 30	P value	P* value
MPO (U/L)	90.9 ± 56.4	121.5 ± 36.3	0.016	0.005
Ferroxidase (U/L)	517.1 ± 99.1	524.7 ± 126.7	0.796	0.917
Catalase (kU/L)	219.6 ± 111.3	71.5 ± 52.5	< 0.001	0.001
Maternal age (years)	25.0 ± 2.6	25.6 ± 2.9	0.39	
Gestational week	8.52 ± 2.27	7.79 ± 2.02	0.2	
Gravidity	2.29 ± 1.37	2.24 ± 1.27	0.88	
Parity	1.1 ± 1.16	1.14 ± 1.18	0.89	
BMI (kg/m^2)	23.1 ± 1.5	23.6 ± 1.1	0.11	
Fasting glucose (mg/dL)	87.7 ± 17.9	83.9 ± 9.5	0.31	

SD — standard deviation, BMI — body mass index; MPO — myeloperoxidase
*The independent variables BMI, age, parity, gravidity and gestational week effects were adjusted according to the logistic regression method with groups

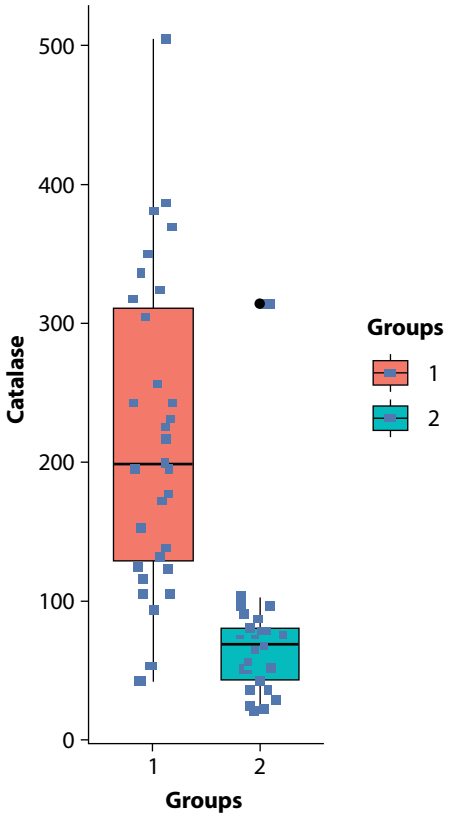

Figure 1. Compared Catalase values for the groups (Boxplot and scatter plot relationship between groups)

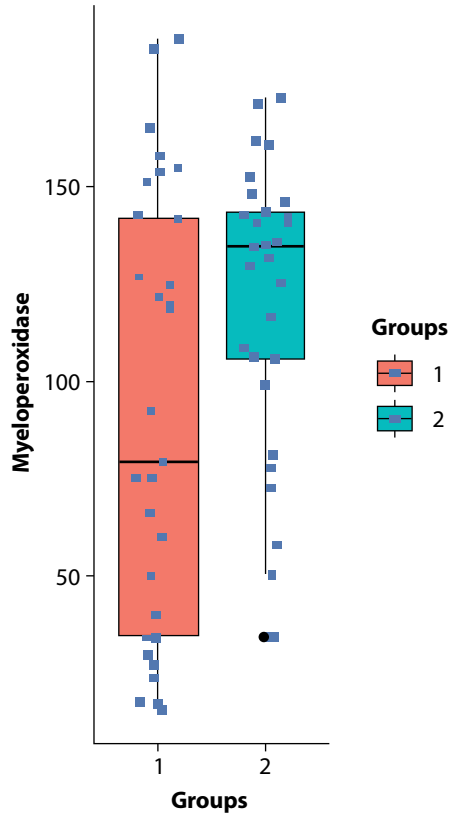

Figure 2. Compared Myeloperoxidase values for the groups (Boxplot and scatter plot relationship between groups)

The construction of reactive oxygen species in the blood is known as a normal process, and both enzymatic and non-enzymatic mechanisms are involved in counteracting the OS caused by increased reactive oxygen species levels. CAT, MPO, ferroxidase are some of the antioxidants that play this critical role [17].

HG is characterized by cell-mediated immunity [18]. MPO, which is a member of the peroxidase superfamily, is found in the azurophilic granules in neutrophils and monocytes. MPO is released by the leukocytes in inflammatory conditions, and it catalyzes the formation of various reactive species, including HOCl; therefore, it plays a role in the body's defence against microorganisms [19, 20]. Another antioxidant that responds in inflammatory conditions is adenosine deaminase (ADA), which is an enzyme necessary for the differentiation of lymphoid cells, and it contributes

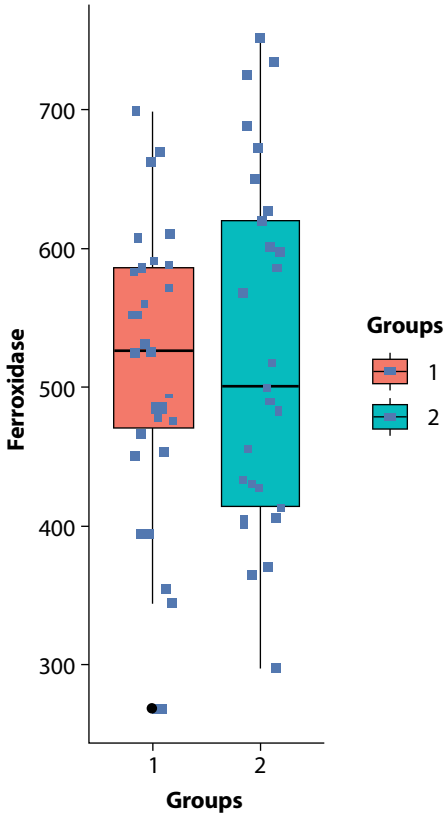

Figure 3. Compared Ferroxidase values for the groups (Boxplot and scatter plot relationship between groups)

to the production of cytokines. Although the exact mechanism is not known, lymphocytes or monocytes are thought to play an essential role in serum ADA activity [21, 22]. In the study by Biberoğlu et al. [23], although the serum ADA and CAT levels were higher in the HG group, the differences were not significant. There is no previous study of MPO in HG patients, this will be the first study. We found that the MPO levels were lower in our HG group than in the control group. We believe that the immune system is suppressed due to malnutrition, which lowers the MPO values. In addition, because HG related fasting normally leads to immune function suppression, it remains controversial whether the immune response is the cause of or a reaction to HG.

The production of CAT, which is an intracellular antioxidant enzyme, increases during OS to balance the redox reactions [10]. Güney et al. [24] found that CAT was significantly lower in HG and attributed to the deficiency of antioxidants taken with nutrients. However, Biberoğlu et al. [23] found that the CAT level was high, although this was not significant. We found that CAT levels were significantly higher in our study. In order to prevent the increase in oxidative radicals during the OS, we believe that the CAT level increases.

The copper metabolism is very complexly linked to iron metabolism. Two copper-containing enzymes ferroxidase I and ferroxidase II have the capability to oxidize ferrous (Fe2+) to ferric (Fe3+) form of iron. Ferric form is used for transport of iron. Ceruloplasmin (having ferroxidase I), is the predominant copper protein in plasma having antioxidant activity. Abnormalities in ceruloplasmin activity produce cellular iron storage that supports ferroxidase activity. The increase in copper in iron-deficient anemic mothers could be an offsetting mechanism to counteract anemia, and this is complemented by a surge in ceruloplasmin synthesis, which is having ferroxidase activity [25, 26]. Onaran et al. [27] found that the ceruloplasmin (ferroxidase 1) levels were similar between the HG group and the control group. Similarly, we did not find a significant difference between the ferroxidase levels between the groups. We believe that the levels of ferroxidase 1 do not change in patients with HG and that the nutrients and iron and copper inadequately keep each other in balance.

This study had some limitations. Initially, in the case of OS, antioxidant levels other than CAT, MPO and ferroxidase should be investigated. Many previous studies of these antioxidants have revealed different results; therefore, more work is needed. In addition, we did not analyze the antioxidant status of the patients before their pregnancies, which may have affected the OS outcome because we could not exclude the possibility of this occurring before the pregnancy. Finally, our sample size was small; therefore, future studies should include larger sample sizes.

CONCLUSIONS

In this study, the different antioxidant levels in the two groups showed that antioxidants, in response to OS, react differently with different mechanisms. Also, we believe that insufficient food intake suppresses the immune system in HG patients, and this plays an important role in the antioxidant levels.

REFERENCES

1. Niebyl JR. Clinical practice. Nausea and vomiting in pregnancy. N Engl J Med. 2010; 363(16): 1544–1550, doi: 10.1056/NEJMcp1003896, indexed in Pubmed: 20942670.
2. Goodwin TM. Hyperemesis gravidarum. Clin Obstet Gynecol. 1998; 41(3): 597–605, doi: 10.1097/00003081-199809000-00014, indexed in Pubmed: 9742356.
3. Rashid M, Rashid MH, Malik F, et al. Hyperemesis gravidarum and fetal gender: a retrospective study. J Obstet Gynaecol. 2012; 32(5): 475–478, doi: 10.3109/01443615.2012.666580, indexed in Pubmed: 22663323.
4. Einarson TR, Piwko C, Koren G. Quantifying the global rates of nausea and vomiting of pregnancy: a meta analysis. J Popul Ther Clin Pharmacol. 2013; 20(2): e171–e183, indexed in Pubmed: 23863575.
5. Verberg MFG, Gillott DJ, Al-Fardan N, et al. Hyperemesis gravidarum, a literature review. Hum Reprod Update. 2005; 11(5): 527–539, doi: 10.1093/humupd/dmi021, indexed in Pubmed: 16006438.
6. Fait V, Sela S, Ophir E, et al. Hyperemesis gravidarum is associated with oxidative stress. Am J Perinatol. 2002; 19(2): 93–98, doi: 10.1055/s-2002-23554, indexed in Pubmed: 11938483.
7. Fait V, Sela S, Ophir E, et al. Peripheral polymorphonuclear leukocyte priming contributes to oxidative stress in early pregnancy. J Soc Gynecol Investig. 2005; 12(1): 46–49, doi: 10.1016/j.jsgi.2004.08.005, indexed in Pubmed: 15629671.

8. Osaki S, Johnson DA, Frieden E. The possible significance of the ferrous oxidase activity of ceruloplasmin in normal human serum. J Biol Chem. 1966; 241(12): 2746–2751, indexed in Pubmed: 5912351.
9. Hellman NE, Gitlin JD. Ceruloplasmin metabolism and function. Annu Rev Nutr. 2002; 22: 439–458, doi: 10.1146/annurev.nutr.22.012502.114457, indexed in Pubmed: 12055353.
10. Agarwal A, Gupta S, Sekhon L, et al. Redox considerations in female reproductive function and assisted reproduction: from molecular mechanisms to health implications. Antioxid Redox Signal. 2008; 10(8): 1375–1403, doi: 10.1089/ars.2007.1964, indexed in Pubmed: 18402550.
11. Perrone S, Longini M, Bellieni CV, et al. Early oxidative stress in amniotic fluid of pregnancies with Down syndrome. Clin Biochem. 2007; 40(3-4): 177–180, doi: 10.1016/j.clinbiochem.2006.10.019, indexed in Pubmed: 17208212.
12. Uriu-Adams JY, Keen CL. Copper, oxidative stress, and human health. Mol Aspects Med. 2005; 26(4-5): 268–298, doi: 10.1016/j.mam.2005.07.015, indexed in Pubmed: 16112185.
13. Góth L. A simple method for determination of serum catalase activity and revision of reference range. Clin Chim Acta. 1991; 196(2-3): 143–151, doi: 10.1016/0009-8981(91)90067-m, indexed in Pubmed: 2029780.
14. Bradley PP, Priebat DA, Christensen RD, et al. Measurement of cutaneous inflammation: estimation of neutrophil content with an enzyme marker. J Invest Dermatol. 1982; 78(3): 206–209, doi: 10.1111/1523-1747.ep12506462, indexed in Pubmed: 6276474.
15. Erel O. Automated measurement of serum ferroxidase activity. Clin Chem. 1998; 44(11): 2313–2319, indexed in Pubmed: 9799759.
16. Roseboom TJ, Ravelli ACJ, van der Post JA, et al. Maternal characteristics largely explain poor pregnancy outcome after hyperemesis gravidarum. Eur J Obstet Gynecol Reprod Biol. 2011; 156(1): 56–59, doi: 10.1016/j.ejogrb.2011.01.010, indexed in Pubmed: 21288626.
17. Ornoy A. Embryonic oxidative stress as a mechanism of teratogenesis with special emphasis on diabetic embryopathy. Reprod Toxicol. 2007; 24(1): 31–41, doi: 10.1016/j.reprotox.2007.04.004, indexed in Pubmed: 17548185.
18. Leylek OA, Toyaksi M, Erselcan T, et al. Immunologic and biochemical factors in hyperemesis gravidarum with or without hyperthyroxinemia. Gynecol Obstet Invest. 1999; 47(4): 229–234, doi: 10.1159/000010111, indexed in Pubmed: 10352382.
19. Nicholls SJ, Hazen SL. Myeloperoxidase and cardiovascular disease. Arterioscler Thromb Vasc Biol. 2005; 25(6): 1102–1111, doi: 10.1161/01.ATV.0000163262.83456.6d, indexed in Pubmed: 15790935.
20. Klebanoff SJ. Myeloperoxidase: friend and foe. J Leukoc Biol. 2005; 77(5): 598–625, doi: 10.1189/jlb.1204697, indexed in Pubmed: 15689384.
21. Martinez-Hernandez D, Arenas-Barbero J, Navarro-Gallar F, et al. Adenosine deaminase in acquired immunodeficiency syndrome [letter]. Clinical Chemistry. 1988; 34: 1949.
22. Ungerer JP, Oosthuizen HM, Bissbort SH, et al. Serum adenosine deaminase: isoenzymes and diagnostic application. Clin Chem. 1992; 38(7): 1322–1326, indexed in Pubmed: 1623598.
23. Biberoglu EH, Kirbas A, Dirican AÖ, et al. Alterations in lipid peroxidation and T-cell function in women with hyperemesis gravidarum. J Obstet Gynaecol. 2016; 36(1): 93–96, doi: 10.3109/01443615.2015.1030604, indexed in Pubmed: 26368575.
24. Güney M, Oral B, Mungan T. Serum lipid peroxidation and antioxidant potential levels in hyperemesis gravidarum. Am J Perinatol. 2007; 24(5): 283–289, doi: 10.1055/s-2007-981429, indexed in Pubmed: 17514602.
25. Anderson GJ, Frazer DM, McKie AT, et al. The ceruloplasmin homolog hephaestin and the control of intestinal iron absorption. Blood Cells Mol Dis. 2002; 29(3): 367–375, doi: 10.1006/bcmd.2002.0576, indexed in Pubmed: 12547227.
26. Upadhyaya C, Mishra S, Ajmera P, et al. Serum iron, copper and zinc status in maternal and cord blood. Indian J Clin Biochem. 2004; 19(2): 48–52, doi: 10.1007/BF02894257, indexed in Pubmed: 23105456.
27. Onaran Y, Kafali H, Duvan Cİ, et al. Relationship between oxidant and antioxidant activity in hyperemesis gravidarum. J Matern Fetal Neonatal Med. 2014; 27(8): 825–828, doi: 10.3109/14767058.2013.842549, indexed in Pubmed: 24041031.

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The effect of vaginal bleeding and non-spesific pelvic pain on pregnancy outcomes in subchorionic hematomas cases

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ABSTRACT

Objectives: To determine the clinical differences and factors affecting early pregnancy outcome in the first and early second trimester subchorionic hematoma cases.

Material and methods: This study involved with the retrospective analysis and evaluation of 81 cases diagnosed with subchorionic hematoma. The patients were grouped according to the gestational periods, symptoms at the time of admission, ratio of surrounding hematoma to the gestational sac, and whether there was a pregnancy loss. The groups were compared according to the clinical features and pregnancy outcomes.

Results: The ratio of surrounding hematoma to the gestational sac in the group with pregnancy loss was significantly higher ($p = 0.002$). When the cut-off value was 35.5%, it could determine the possibility of a complication in pregnancy with 70% sensitivity and 75% specificity. Nonspecific pelvic pain were significantly higher in the pregnancy loss group than in the other group. Logistic regression analysis was performed to determine the effect of these two parameters on the pregnancy outcome. Although the presence of non-specific pelvic pain is more in the group with pregnancy loss; there was no effect of on pregnancy outcome ($p = 0.141$). The risk of pregnancy loss increased 4.5 fold if the ratio of ScH to gestational sac was above 35% ($p = 0.027$).

Conclusions: In the cases of subchorionic hematoma, we concluded that when the ratio of surrounding hematoma to the gestational sac increased and when it was accompanied by nonspecific pelvic pain, the hospitalization period of the patients increased and the ratio of pregnancy loss was higher.

Key words: subchorionic hematoma; vaginal bleeding; pelvic pain; first trimester; complication

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INTRODUCTION

Subchorionic hematoma (ScH) is defined as a crescent-shaped, echo-free area between the chorionic membrane and the myometrium. The incidence ranges from 1.3% to 3.1% [1]. It is a rare but serious cause of vaginal bleeding that is extremely common in the early gestational weeks. Although its etiology is not known exactly, the increase of assisted reproductive techniques and low-molecular-weight heparin and aspirin use are among the risk factors [2]. It is usually diagnosed in patients admitted due to vaginal bleeding. In addition, non-specific pelvic pain (NsPP), such as low back, groin and around of umbilicus pains may accompany vaginal bleeding. ScH can be diagnosed in routine ultrasonography examinations for asymptomatic patients [3–5]. It is generally classified as small, medium, or large according to the ratio of the diameter of the hematoma to that of the gestational sac [6]. In addition, ScH is also classified according to its surrounding ratio to the gestational sac [7]. In cases with ScH, early pregnancy complications like missed abortion and spontaneous complete or incomplete abortion and late complications of pregnancy, such as premature rupture of membranes, preterm delivery, and intrauterine growth retardation, have been reported to be more frequent [8–10].

In almost all of the previous studies, the effect of hematoma size on early and late pregnancy complications in patients with first trimester period ScH was evaluated. The study evaluating the effect of NsPP on early complications of ScH cases is not available in the literature.

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The aim of this study was to determine the parameters that affect the early pregnancy losses except hematoma size in the first and early second trimester ScH cases. In our current study, we found that pregnancy was more complicated in ScH cases with non-specific pelvic pain.

MATERIAL AND METHODS

The study was approved by the "University Local Ethics Committee" before a retrospective file search was conducted for the study. The archive files, ultrasonography reports, and image records of 684 patients hospitalized with vaginal bleeding in "University Obstetrics and Gynecology Department" between January 2015 and October 2018 were reviewed. We detected total of 106 patients who had ultrasonography reports and visual hematoma measurement records.

A total of 25 ScH cases were excluded from the study which pregnancies without a fetal heartbeat on ultrasonography reports, multiple pregnancies, and pregnancies assisted by supportive reproduction methods. Because, almost all of the pregnancies formed by assisted reproductive technique had a history of using acetylsalicylic acid, low molecular heparin or depot progesterone.

In addition, other pregnant women who developed spontaneous pregnancy but who used acetylsalicylic acid (aspirin), low-molecular-weight heparin and warfarin for another indication were excluded from the study. Demographic data like age, gravida, parity, history of surgery, and pregnancy formation method were obtained from the patients' anamnesis information. In addition, the patients' initial complaints at the time of admission were determined and recorded. In our study, we classified the ScHs according to the surrounding ratio to the gestational sac. We compared the circumference of the entire gestational sac with the gestational sac surface separated from the myometrium, and thus we obtained the inclusion ratio of hematomas in the gestational sac. We indicated the results as a percentage. The ratio of surrounding hematoma to the gestational sac was determined using the Generic Area program on the GE Voluson P8 device. The measurement of subchorionic hematomas is shown in Figure 1. The measurements were evaluated by two obstetricians who were not aware of the study parameters. The other important parameter was NsPP. While evaluating the pain of low back, groin and around of umbilicus during pregnancy, all abdominal organs and musculoskeletal pathologies should be considered [11]. There was no organic pathology to explain the pain we identified as NsPP. Patients with musculoskeletal system, gastrointestinal and urinary tract pathologies were not evaluated as NsPP [12]. In our clinic, three questions are asked in the evaluation of the pain around the groin, waist and umbilicus in the pregnancy.

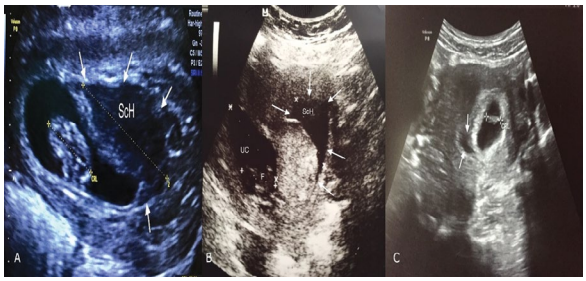

Figure 1. USG measurements of ScHs; **A.** A case of subchorionic hematoma (white arrow) surrounding approximately 50% of the gestational sac; **B.** A case of subchorionic hematoma (white arrow) that surrounds approximately 30% of the gestational sac; **C.** A case of subchorionic hematoma (white arrow) that surrounds approximately 10% of the gestational sac; ScH — subchorionic hematoma; CRL — crown rump length (Fetus); UC — uterine cavity; F — fetus

Are these pains present during pregnancy and are they new?

Do you need analgesics in case of pain?

Do you wake up from your sleep in pain?

NsPP is added to the diagnosis of patients who give a yes response to the first question and either of the other two questions.

A gestational period of 42–98 days was classified as first trimester, while 99–140 days was classified as early second trimester pregnancy. Complications like missed abortion, complete or incomplete abortion, and termination of pregnancy after amnion fluid loss during the treatment before the 20th gestational week were evaluated within the early period pregnancy complication. These pregnancies resulted in loss. Pregnant women who reached over 20 weeks were accepted as the group without early period complications.

The patients were grouped as having vaginal bleeding and having vaginal bleeding + NsPP according to the symptoms at the time of admission. The patients were compared according to the gestational age, hematoma size, early complication status, and priority admission symptoms.

Statistics

The Statistical Package for the Social Sciences, version 15 (SPSS, Chicago, IL) program was used for the statistical analysis. The data were classified as being with or without normal distribution using the Kolmogorov–Smirnov test. Normally distributed data were evaluated using the independent sample t-test, while non-normally distributed data were compared using the Mann–Whitney U test. The Chi-square test was used for categorical variables. The level of statistical significance was set as $p < 0.05$. Receiver operating characteristic (ROC) analysis was performed to determine the efficiency of the ratio of surrounding ScH to the gestational sac in foreseeing the gestational results. Logistic regression analysis was used to determine

the risk factors affecting pregnancy outcome and to calculate odds ratio.

RESULTS

The number of pregnant women who were examined in the first trimester or early second trimester weeks in the University Obstetrics and Gynaecology outpatient clinic was 5.889 during the period included in the study. A total of 106 vaginal bleeding patients were detected. The incidence of vaginal bleeding in our clinic was 11.6%. ScH was detected in 106 patients with vaginal bleeding. The incidence of ScH in patients with vaginal bleeding in our clinic was 15.4%. The patients were treated with similar abortion imminence treatments during hospitalization. In our study, pregnancy loss was detected in 17 (21%) patients. The other 64 (79%) patients did not develop early pregnancy complications, and their pregnancies reached the 20th gestational week. The ratio of surrounding ScH to the gestational sac was statistically lower in the group without pregnancy loss than it was in the group with pregnancy loss (p = 0.002). The factors affecting pregnancy loss are listed in Table 1. First trimester (49–98 days) and early second trimester (99–140 days) pregnancies were compared in terms of the symptoms, hospitalization times, and ratio of surrounding hematoma to the gestational sac. In the first trimester group, 41 (83.7%) patients had vaginal bleeding and 8 (16.3%) had primary symptoms of vaginal bleeding + NsPP. In the early second trimester group, 17 (53.1%) patients had vaginal bleeding and 15 (46.9%) had primary symptoms of vaginal bleeding + NsPP. The difference between the two groups was statistically significant (p = 0.003). The hospitalization period in the first trimester group was statistically lower than that in the early second trimester group (p < 0.001). In the first trimester group, the ratio of surrounding ScH to the gestational sac was statistically lower than it was in the early second trimester group (p = 0.005; Tab. 2). The patients were compared according to the symptoms of vaginal bleeding and vaginal bleeding + NsPP. In the vaginal bleeding + NsPP group, the ratio of surrounding hematoma to the gestational sac, duration of hospitalization, and pregnancy loss were statistically higher (p = 0.002, p < 0.001, p < 0.001, p < 0.001, p < 0.001, respectively). There was no statistically significant effect of maternal age on symptoms in the ScH cases (p = 0.623; Tab. 3). ROC analysis was performed to determine the efficiency of the ratio of surrounding hematoma to the gestational sac in foreseeing gestational results. When the cutoff value was 35.5%, it could determine the prognosis

Table 1. Clinical characteristics of patients according to pregnancy outcomes

Variables		No loss of pregnancies	Loss of Pregnancies	p
n		64	17	
Patients age [year], mean ± SD		26.6 ± 4.7	28.2 ± 4.5	0.222
Gravity n (min–max)		3 (1–5)	4 (1–7)	0.212
Live Children n (min–max)		2 (0–4)	2 (0–4)	0.323
Abortion n (min–max)		0 (0–1)	0 (0–3)	0.296
Pregnancy age [day], mean ± SD		83.5 ± 21.7	96.1 ± 28.3	0.051
Hospitalization time [day], mean ± SD		6.5 ± 3.1	7.9 ± 4.9	0.165
Symptoms N (%)	Bleeding	51 (79.7)	7 (41.2)	0.002
	Bleeding + non-specific pelvic pain	13 (20.3)	10 (58.8)	
GS Surrounded by Hematoma, % mean ± SD		26.0 ± 14.9	39.3 ± 15.5	0.002

SD — standard deviation; GS — gestational sac

Table 2. Clinical outcomes of the patients according to the duration of pregnancy

Variables		First trimester	Early second trimester	p
n		49	32	
Symptom N (%)	Bleeding	41 (83.7)	17 (53.1)	0.003
	Bleeding & non-specific pelvic pain	8 (16.3)	15 (46.9)	
Outcome of pregnancy N (%)	No loss of pregnancy	41 (83.7)	23 (71.9)	0.202
	Loss of pregnancy	8 (16.3)	9 (28.1)	
Hospitalization time (day), mean ± SD		5.2 ± 2.6	9.3 ± 3.4	< 0.001
GS Surrounded by Hematoma, % (mean ± SD)		24.915.4	34.8 ± 4.9	0.005

SD — standard deviation; GS — gestational sac

Table 3. Clinical features of the patients according to the symptoms

Variables	Bleeding	Bleeding + non-specific pelvic pain	p
n	58	23	
GS Surrounded by Hematoma, % (mean ± SD)	22.9 ± 13.1	43.8 ± 11.9	**< 0.001**
Pregnancy Age (day), (mean ± SD)	78.7 ± 21.4	105.0 ± 17.9	**< 0.001**
Patient Age (year) (mean ± SD)	26.8 ± 5.1	27.3 ± 3.8	0.623
Hospitalization time (day), (mean ± SD)	5.8 ± 2.7	9.4 ± 4.1	**< 0.001**

SD — standard deviation; GS — gestational sac

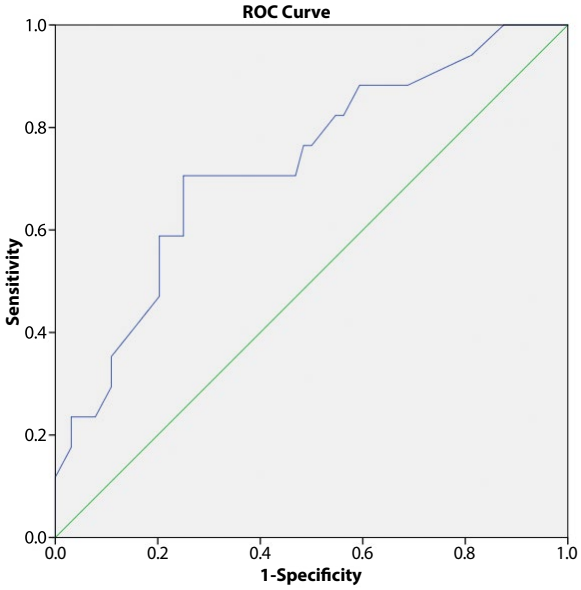

Figure 2. Receiver operating characteristic (ROC) analysis of percentage of subchorionic hematoma surrounding GS in predicting pregnancy outcome. The cut-off value for subchorionic hematoma surrounding GS was 35.5% while the sensitivity and specificity values were 70 and 75%, respectively. Area under the ROC curve (AUC): 0.727, sensitivity: 70%, specificity: 75%, 95% CI: 0.590–0.864, p = 0.004; GS — gestational sac

of negative pregnancy with 70% sensitivity and 75% specificity [Area Under the ROC Curve (AUC): 0.727, sensitivity: 70%, specificity: 75%, 95% CI: 0.590–0.864, p = 0.004; Fig. 2]. In the logistic regression analysis to predict the outcome of pregnancy, the effect of NsPP was statistically insignificant. However, if the percentage of ScH was greater than 35%, the risk of pregnancy loss increased by 4.5 times (Wald: 4.881, Odss ratio: 4.527, 95% CI: 1.186–17.281, p = 0.027).

DISCUSSION

The hematoma diameter is one of the important parameters affecting the clinical outcome in ScH cases [1]. However, we believe that other parameters other than hematoma diameter have important effects on clinical status. In this study, we aimed to evaluate the effects of NsPP on early complications of pregnancy in patients with abortus imminence and subchorionic hematoma. In our current study, we found that pregnancy was more complicated in ScH cases with NsPP. We think that ScHs are often small in the first trimester of pregnancy and complicate pregnancy less, and they appear to occur less frequently in early second trimester pregnancies, but they complicate these pregnancies more. In addition, we think that the hematoma diameter may be larger and pregnancy loss may be higher in pregnant women with NsPP accompanied by vaginal bleeding.

The incidence of vaginal bleeding in our clinic was 11.6%. This result was similar to the literature. In their study, Hasan et al. [13], found that the incidence of vaginal bleeding was 7–25%. In another study with a larger series of cases, Weiss et al. [14], reported the incidence of vaginal bleeding as 14.2%. In our study the incidence of SCH in patients presenting with vaginal bleeding was 15.4%. There is a wide range of data for the incidence of SCH in patients with vaginal bleeding in the literature. In the review of Pearlstone, this rate is stated in a very wide range as 4–22% [15]. This rate suggests that patients presenting with vaginal bleeding should be examined more carefully for ScH. We believe that our article will be the most accurate information providing data to the literature on this subject.

In our study, we found that the higher the ratio of surrounding hematoma to the gestational sac was, the greater the possibility of pregnancy loss became [1, 7, 8, 16]. In their study, Bennett et al. [7], used a subjective evaluation including large, medium, and small values for the ratio of surrounding hematoma to the gestational sac. They reported that the risk of pregnancy loss was three times higher in the group with a greater percentage of hematoma than it was in the other two groups. Bennett et al used a small, medium and large subjective criterion for the diameter of the hematoma. In our study, we reported the size of the hematoma in terms of percentages according to the gestational sac containment.

This numerical value (35.5%) obtained for the ratio of surrounding hematoma to the gestational sac would be more helpful to obstetricians in predicting the outcome of the treatment and complications that may occur in patients with ScH. In the literature, we have found that many studies on ScH were mostly evaluated in the first trimester of pregnancy. In these studies, many similar results have been obtained in first trimester ScH cases related to symptoms, findings, and early and late pregnancy complications [17–19]. However, we could not find any study evaluating the cases of early second trimester ScH. In our clinical experi-

ence, we have seen a significant number of ScHs in the early second trimester of pregnancy. In addition, we observed that the symptoms, clinical findings, and complications were different in these cases after the first trimester. In our study, vaginal bleeding was the most common symptom in first trimester ScH cases. There were no other symptom frequently associated with vaginal bleeding. However, in the early second trimester ScH cases, we found that NsPP was frequently accompanied by vaginal bleeding. In early second trimester ScH cases, with a percentage of hematoma, the duration of hospitalization was longer. In the group with vaginal bleeding and NsPP, pregnancy loss was statistically higher, but in the logistic regression analysis to predict the outcome of pregnancy, the effect of NsPP was statistically insignificant. Although the effect of NsPP on early pregnancy loss is meaningless in logistic regression analysis; we think that clinicians who are evaluating ScHs cases should consider this symptom. The ratio of surrounding hematoma to the gestational sac was found to be significantly higher in early second trimester ScH cases. As this ratio increases, it causes greater separation of the gestational sac from the uterine wall. As a result, inflammatory cell infiltration and inflammatory mediators will occur more around the gestational sac [20, 21]. These inflammatory mediators result in the formation of smooth muscle-tightening molecules, such as prostaglandin I2 and thromboxane A2 [22, 23]. We think that prostaglandin and thromboxane A2 cause NsPP [24]. In addition, the uterus will be larger than normal for the gestational week in cases where the ScH is larger [25, 26]. We think that the stretched visceral peritoneum of the uterus and the inflammatory mediators occurred due to hematoma contribute to the formation of NsPP.

CONCLUSIONS

ScH was more common in first trimester pregnancies, which was found to have a smaller diameter and cause fewer complications in pregnancy. Although ScH was less common in the early second trimester group, it was found to have a larger diameter, so it caused more complications in pregnancy. In addition, in cases of ScH, it should be kept in mind that the hematoma diameter may be larger and pregnancy may be more complicated in cases in which vaginal bleeding is accompanied by NsPP. Furthermore, NsPP cannot be explained for another reason in ScH, should be a stimulant for pregnancy complication. In order to better understand the effect of NsPP on early pregnancy losses, studies with larger case numbers are needed.

REFERENCES

1. Nagy S, Bush M, Stone J, et al. Clinical significance of subchorionic and retroplacental hematomas detected in the first trimester of pregnancy. Obstet Gynecol. 2003; 102(1): 94–100, doi: 10.1016/s0029-7844(03)00403-4, indexed in Pubmed: 12850613.
2. Truong A, Sayago MM, Kutteh WH, et al. Subchorionic hematomas are increased in early pregnancy in women taking low-dose aspirin. Fertil Steril. 2016; 105(5): 1241–1246, doi: 10.1016/j.fertnstert.2016.01.009, indexed in Pubmed: 26820772.
3. Abu-Yousef MM, Bleicher JJ, Williamson RA, et al. Subchorionic hemorrhage: sonographic diagnosis and clinical significance. AJR Am J Roentgenol. 1987; 149(4): 737–740, doi: 10.2214/ajr.149.4.737, indexed in Pubmed: 3307354.
4. Mandruzzato GP, D'Ottavio G, Rustico MA, et al. The intrauterine hematoma: diagnostic and clinical aspects. J Clin Ultrasound. 1989; 17(7): 503–510, doi: 10.1002/jcu.1870170708, indexed in Pubmed: 2506245.
5. Pedersen JF, Mantoni M. Prevalence and significance of subchorionic hemorrhage in threatened abortion: a sonographic study. AJR Am J Roentgenol. 1990; 154(3): 535–537, doi: 10.2214/ajr.154.3.2106217, indexed in Pubmed: 2106217.
6. Benson CB, Doubilet PM, Cooney MJ, et al. Early singleton pregnancy outcome: effects of maternal age and mode of conception. Radiology. 1997; 203(2): 399–403, doi: 10.1148/radiology.203.2.9114094, indexed in Pubmed: 9114094.
7. Bennett GL, Bromley B, Lieberman E, et al. Subchorionic hemorrhage in first-trimester pregnancies: prediction of pregnancy outcome with sonography. Radiology. 1996; 200(3): 803–806, doi: 10.1148/radiology.200.3.8756935, indexed in Pubmed: 8756935.
8. Heller HT, Asch EA, Durfee SM, et al. Subchorionic Hematoma: Correlation of Grading Techniques With First-Trimester Pregnancy Outcome. J Ultrasound Med. 2018; 37(7): 1725–1732, doi: 10.1002/jum.14524, indexed in Pubmed: 29341210.
9. Tuuli MG, Norman SM, Odibo AO, et al. Perinatal outcomes in women with subchorionic hematoma: a systematic review and meta-analysis. Obstet Gynecol. 2011; 117(5): 1205–1212, doi: 10.1097/AOG.0b013e31821568de, indexed in Pubmed: 21508763.
10. Biesiada L, Krekora M, Krasomski G. [Subchorionic hematoma as a risk factor of pregnancy and delivery in women with threatening abortion]. Ginekol Pol. 2010; 81(12): 902–906, indexed in Pubmed: 21395080.
11. Amundsen PA, Evans DW, Rajendran D, et al. Inclusion and exclusion criteria used in non-specific low back pain trials: a review of randomised controlled trials published between 2006 and 2012. BMC Musculoskelet Disord. 2018; 19(1): 113, doi: 10.1186/s12891-018-2034-6, indexed in Pubmed: 29650015.
12. Vas J, Cintado MC, Aranda-Regules JM, et al. Effect of ear acupuncture on pregnancy-related pain in the lower back and posterior pelvic girdle: A multicenter randomized clinical trial. Acta Obstet Gynecol Scand. 2019; 98(10): 1307–1317, doi: 10.1111/aogs.13635, indexed in Pubmed: 31034580.
13. Hasan R, Baird DD, Herring AH, et al. Patterns and predictors of vaginal bleeding in the first trimester of pregnancy. Ann Epidemiol. 2010; 20(7): 524–531, doi: 10.1016/j.annepidem.2010.02.006, indexed in Pubmed: 20538195.
14. Weiss JL, Malone FD, Vidaver J, et al. FASTER Consortium. Threatened abortion: A risk factor for poor pregnancy outcome, a population-based screening study. Am J Obstet Gynecol. 2004; 190(3): 745–750, doi: 10.1016/j.ajog.2003.09.023, indexed in Pubmed: 15042008.
15. PEARLSTONE M, BAXI L. Subchorionic Hematoma. Obstetrical & Gynecological Survey. 1993; 48(2): 55–68, doi: 10.1097/00006254-199302000-00001.
16. AYDIN O, BOSTAN PA, ÖZGÜR E. Spatial Distribution and Modelling of the Total Fertility Rate in Turkey Using Spatial Data Analysis Techniques. Journal of Geography. 2018: 27–45, doi: 10.26650/jgeog434650.
17. Kurjak A, Schulman H, Zudenigo D, et al. Subchorionic hematomas in early pregnancy: clinical outcome and blood flow patterns. J Matern Fetal Med. 1996; 5(1): 41–44, doi: 10.1002/(SICI)1520-6661(199601/02)5:1<41::AID-MFM10>3.0.CO;2-Q, indexed in Pubmed: 8796766.
18. Maso G, D'Ottavio G, De Seta F, et al. First-trimester intrauterine hematoma and outcome of pregnancy. Obstet Gynecol. 2005; 105(2): 339–344, doi: 10.1097/01.AOG.0000152000.71369.bd, indexed in Pubmed: 15684162.
19. Johns J, Hyett J, Jauniaux E. Obstetric outcome after threatened miscarriage with and without a hematoma on ultrasound. Obstet Gynecol. 2003; 102(3): 483–487, doi: 10.1016/s0029-7844(03)00580-5, indexed in Pubmed: 12962928.
20. Christiansen OB, Nielsen HS, Kolte AM. Inflammation and miscarriage. Semin Fetal Neonatal Med. 2006; 11(5): 302–308, doi: 10.1016/j.siny.2006.03.001, indexed in Pubmed: 16682265.

21. Kwak-Kim J, Yang KM, Gilman-Sachs A. Recurrent pregnancy loss: a disease of inflammation and coagulation. J Obstet Gynaecol Res. 2009; 35(4): 609–622, doi: 10.1111/j.1447-0756.2009.01079.x, indexed in Pubmed: 19751318.
22. Ricciotti E, FitzGerald GA. Prostaglandins and inflammation. Arterioscler Thromb Vasc Biol. 2011; 31(5): 986–1000, doi: 10.1161/ATVBAHA.110.207449, indexed in Pubmed: 21508345.
23. Jabbour HN, Sales KJ, Smith OP, et al. Prostaglandin receptors are mediators of vascular function in endometrial pathologies. Mol Cell Endocrinol. 2006; 252(1-2): 191–200, doi: 10.1016/j.mce.2006.03.025, indexed in Pubmed: 16701939.
24. Wang C, Wang Z, Yang Y, et al. Pirt contributes to uterine contraction-induced pain in mice. Mol Pain. 2015; 11: 57, doi: 10.1186/s12990-015-0054-x, indexed in Pubmed: 26376721.
25. Ganer Herman H, Miremberg H, Dekalo A, et al. Preterm uterine contractions ultimately delivered at term: safe but not out of danger. Eur J Obstet Gynecol Reprod Biol. 2016; 199: 1–4, doi: 10.1016/j.ejogrb.2016.01.019, indexed in Pubmed: 26874238.
26. Mei Y, Lin Y. Clinical significance of primary symptoms in women with placental abruption. J Matern Fetal Neonatal Med. 2018; 31(18): 2446–2449, doi: 10.1080/14767058.2017.1344830, indexed in Pubmed: 28629246.

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Application of auxological methods, including dental age estimation, in the assessment of delayed puberty in girls in gynecological practice

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ABSTRACT

Developmental gynecology uses methods practiced in auxology — the science of human ontogenetic development. An important and jointly used concept in gynecology and auxology is the concept of developmental age, which, unlike calendar age, is a measure of the biological maturity of the organism, indicating the stage of advancement in the development of certain features or body systems. Developmental age assessment methods include: a) morphological (somatic) age — body height and weight, b) secondary sex characteristics — breast in girls, genitalia (penis and testes) in boys, and pubic hair in both sexes, c) bone age — hand and wrist x-ray, and d) dental age. An important marker of developmental age is also age at menarche, treated as a late indicator of puberty in girls. All of these methods are useful in the context of assessing regularity and disorders of puberty, such as delayed puberty. The paper discusses developmental age assessment methods that can be used to diagnose delayed puberty as well as the causes of delayed puberty in girls. It should be emphasized that in assessing the process of physical development of a given individual, the cooperation of specialists in the field of developmental gynecology, pediatrics, auxology, dentistry, endocrinology, and dietetics would be the most desirable.

Key words: developmental age; delayed puberty; girls

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INTRODUCTION

Puberty is a period of dynamic human development leading to sexual maturity. It is a transition period between childhood and adulthood, which takes place in several sequential stages controlled by neuroendocrine factors. It is characterized by the development of secondary and tertiary sexual characteristics and acceleration of linear growth, referred to as adolescent growth spurt [1]. The first external symptom of puberty in girls is breasts development (between 9–13 years of age). A relatively late event during puberty is menarche, which usually occurs about 1.2 to 1.3 years after reaching a maximum rate of linear growth (peak height velocity, PHV) [2]. In recent years the mean age at menarche in Poland ranged from 12.5 to 13 years [3, 4].

METHODS FOR ASSESSING DEVELOPMENTAL AGE

In both auxology and developmental gynecology, an important concept is developmental (biological) age, understood as progress toward a mature state, or, in other words, as the degree of physiological development of the organism. Significant interindividual variance exists for the level (magnitude of change), timing (onset of change), and tempo (rate of change) of biological maturation.

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An individual's developmental age may proceed at a different pace than the calendar age. It depends, to a large extent, on the genetic background, sex, environmental factors, body type, or ethnicity [5]. One of the most important reasons for assessing developmental age is to see how far it varies from chronological age. Estimation of differences between these two traits helps to identify signs of abnormal development, which may be precocious or delayed puberty [6]. Developmental age can be measured in several ways, including physical (morphological) maturity, stage of advancement in the development of secondary sex characteristics, skeletal maturity, and dental maturity. The physical maturity is assessed on the basis of height and weight. However, a more precise method of assessing physical maturity is the estimation of height velocity [7]. An informative marker of physical maturity during adolescence is both the age of onset of adolescent growth spurt (Age at Take Off, ATO), i.e. the moment when velocity of body height growth is the smallest, and the age when velocity of body height growth is the highest (Age at Peak Height Velocity, APHV) [2]. The take-off of the growth spurt (TO) in girls appears on average around 8–9 years, about 2 years earlier than in boys. Peak height velocity (PHV) occurs in girls aged 11.5 years, and in boys aged 13.5 [2, 3]. In the assessment of developmental age during puberty, the markers of secondary sexual characteristics appear to be one of the most important. They are classified with the use of Tanner stages: breast stage in girls, genital stage in boys and pubic hair stage in both sexes [1]. Tanner stages (scores) describe the visible signs of sexual maturation. Stage one describes the absence of any symptoms of puberty, while stage five presents a fully developed form of assessed traits [5]. In girls, onset of puberty is defined as the first sign of breast development (B2 on the Tanner scale) and not pubic hair, because the latter does not necessarily herald activation of the gonads, and may be due to increasing secretion of adrenal androgens (adrenarche). Furthermore, in both gynecological practice and auxology, the age of the first menstruation, i.e. menarche, is an invaluable marker of the tempo of development. Skeletal age is usually estimated using hand-wrist radiograph, based on the appearance of individual bones or the degree of fusion of epiphyseal plate [8]. Another marker available for developmental age estimation is the dental age, based on tooth eruption or tooth mineralization assessed from dental radiographs. In each of the methods described, the child's status is compared with age-related norms. It is then assumed that the developmental age is the mean chronological age corresponding to her or his developmental status [7].

CAUSES OF DELAYED PUBERTY IN GIRLS

Delayed puberty in girls is defined as a lack of evidence of breast development by the age of 13 years and amenorrhea 5 years after the start of the puberty with no full secondary sex features development [9]. It is also defined as the lack of signs of puberty at two standard deviations above the mean age for the general population [10]. Delayed puberty occurs in 3% of the population, more often in boys than girls. It may result from constitutional delay of puberty, hypogonadotropic or hypergonadotropic states, existing chronic diseases (as a secondary symptom), or intense physical exercise [11].

Delayed puberty is most often due to a functional defect in the production of gonadotropin-releasing hormone (GnRH). Among the reasons for the abnormal secretion of GnRH from the hypothalamus is the constitutional delay of growth and puberty (CDGP), undernutrition or chronic illness. The result of GnRH deficiency is inadequate ovarian steroid secretion. Other causes of delayed puberty include a variety of hypothalamic, pituitary, and gonadal disorders [12].

In most cases, delayed puberty is caused by the constitutional delay of growth and puberty (CDGP) and is considered a temporary form of hypogonadotropic hypogonadism [10, 13]. CDGD refers to a slower developmental tempo in children with no physical abnormalities causing the delay. These children start puberty late and are most often of short stature [5]. CDPG is 10 times more common in boys than girls and does not require advanced medical evaluation and treatment.

Many authors are emphasizing the influence of nutritional status and diet on estradiol concentration and puberty course. A common diagnosis for very slim girls with delayed puberty is functional gonadotropin deficiency. It is worth mentioning that this unusual thinness can result from either eating disorders, such as anorexia nervosa, or intense physical activity without enough caloric intake to maintain normal weight. Girls practicing: competitive swimming, ballet dancing, and gymnastics show the high risk of delayed menarche [6]. Intensive physical activity is connected with delayed puberty because of negative energetic balance, special diet, and corticotropic axis stimulation in increased stress leading to gonadoliberin excretion disturbances [13]. The relationship between the percentage of fat tissue and the dynamics of the puberty process has been demonstrated in girls [3, 14]. Leptin secreted by adipose tissue is a key factor affecting the age of puberty onset since it has been shown to have a direct effect on the secretion of gonadotropins and gonadotropin releasing hormone (GnRH) [15]. Leptin receptors are identified in the hypothalamus, anterior pituitary gonadotropic cells and ovarian follicular cells. Abnormal leptin level in underweight girls with a low percentage of body fat generally result in amenorrhea and delayed puberty [16]. The same explanation is likely for girls who are very thin due to chronic illness. In gen-

eral, the negative energy balance can disturb the pattern of pulsatile gonadotropin secretion leptin/neuropeptide Y or using other neurotransmitters. Quantitative and qualitative nutritional status, BMI, fat tissue mass, and leptin blood level are important features in intense systemic and chronic disease state. A lot of chronic diseases are connected to delayed or arrest in the puberty stage which depends on the point at which the disease occurred. Malnourishment, or low BMI resulting from negative energy balance can cause the disturbance of pulsatile gonadoliberin secretion, as well as: a) gastrointestinal diseases: celiac disease should be considered when unexplained delayed of puberty and growth is observed, positive diagnosis should be confirmed by detection of transglutaminase antibodies and atrophic villi in jejunal biopsy; b) inflammatory bowel disease might be connected with delayed puberty in case of steroid therapy and weight loss; c) chronic lung diseases like cystic fibrosis can cause the same deficiencies which are caused mostly by malnourishment; d) chronic renal failure prior to transplantation or nephrotic syndrome sensitive to steroids; e) thalassemia major or sickle cell anemia can inhibit puberty by the deposition of iron in pituitary gland [9, 13].

Delayed puberty can also be caused by hypergonadotropic hypogonadism (primary ovarian failure), which may result from either karyotype abnormality (Turner syndrome) or autoimmune destruction of the ovaries, associated with conditions such as type 1 diabetes mellitus, hypothyroidism, Addison disease or hypoparathyroidism. The risk group of primary ovarian failure also includes girls undergoing total body irradiation or chemotherapy during the treatment of various forms of malignancies [9]. Hypogonadotropic hypogonadism is defined as lack of ability of proper production of gonadotropins — FSH and LH. This deficiency can be caused by isolated pituitary gonadotropic cells abnormality or coexistent with other pituitary cells changes concerning infundibulum or hypothalamus with a change in pulsatile secretion of gonadoliberin. Isolated idiopathic hypogonadotropic hypogonadism (IHH) is often mistaken by CDGP because in both cases there is a low level of steroid hormones and gonadotropins. In CDGP, the response to gonadotropin agonists plays an important role in the differential diagnosis. Some girls with delayed puberty, usually with coexisting delayed growth and short stature (-2 SD on average height according to age) do not suffer from CDGP, but just a variation of development time. In this case, spontaneous beginning of puberty and acceleration of linear growth are observed. Hence, it is hard to differentiate between CDGP and IHH, even if some symptoms can help with proper treatment choice. The main aim of the clinical, radiological and biological examination is to eliminate the somatic disease. It is important to differentiate the typical growth hormone deficiency. In the case of CDGP, short stature and slow tempo of linear growth are well correlated with bone age, which is connected with delayed puberty but not chronological age. The growth hormone secretion might be low at a basal level whereas stimulation tests give positive results at a suboptimal level, which in fact corresponds to prepubertal period. The hormone level differences do not occur, which is confirmed by the tests of pituitary function. In this case systematic radiological examinations e. g. MRI do not show the signs of neoplastic process or infiltration to other organs [13]. Other causes of inappropriate gonadotropin secretion include, inter alia: organic direct gonadotropin deficiency, neoplastic origin of idiopathic hypogonadotropic hypogonadism (IHH), congenital gonadotropins deficiency (is connected with low FSH and LH level, compatible bone age and normal stature and normal karyotype; several genes connected with this condition have been identified), primary GnRH deficiency (after confirmation of GnRH deficiency, treatment with recombinant growth hormone will trigger puberty, which implies the need of IGF-1 treatment. IGF-1 is proved to enhance LH and FSH ovarian stimulation), Prader-Willi Syndrome, Laurence-Moon-Bardet-Biedl syndrome, Kallmann syndrome (uncommon in females, probably because the most common form, due to a defective KAL1 gene, is X-linked [9]. Delayed puberty may also be observed in patients with FSH or LH receptor coding gene mutation. Deactivating mutation of FSH receptor is connected with premature ovarian failure or primary amenorrhea. The size of ovaries is at a normal level and pathological examination shows multiple growing ovarian follicles. Several cases were observed in homozygotic XX females with primary amenorrhea, who developed sex features and elevated LH but normal FSH levels and ovarian vesicles with no corpus luteum. In case of absence of response on gonadoliberin stimulation test and pulsatile gonadoliberin application, we can consider gonadoliberin receptor gene mutation on chromosome 4. There are reports about few autosomal recessive forms of isolated IHH with that kind of mutations. However, this phenotype occurs in various forms — from partial to full [9, 13]. Only a few mutations inactivating FSH β subunit was identified. The gene is situated in Xp21u in a female. One mutation presents with only partially developed secondary sexual characteristics and two with primary amenorrhea. DAX1 gene mutation (gene causing congenital adrenal dysplasia in case of X-linked inheritance). DAX1 is transcription factor from "orphan nuclear receptors" family, which take part in differentiation process of adrenal glands, hypothalamus, pituitary and gonads. Mutation of this gene connected with the X chromosome in men leads to congenital hypoplasia with insufficiency in the neonatal period and delayed IHH that is manifesting during adolescence. There are reports about isolated IHH in women that might corre-

spond to mild male HH connected with congenital adrenal hypoplasia [13].

The analysis of delayed puberty with hypogonadotropic hypogonadism of various etiologies reveals how important the molecular tests are in the process of diagnosis [17–20].

The hypergonadotropic hypogonadism with characteristic elevated FSH and/or LH level caused by ovarian failure requires rule out of female phenotype, uterine and ovarian functional tissue ultrasonographical verification, and karyotype assay [9, 13]. The examples of such conditions are gonadal dysgenesis with a chromosomal aberration. The most frequent cause of primary ovarian failure is Turner syndrome in classic monosomy 45, XO form with female phenotype (poor growth, sexual infantilism, etc.). Swyer syndrome with 46, XY karyotype is characterized by the female phenotype, female internal genital genitalia (Mullerian duct derivatives), normal or bigger height, gonadal dysgenesis, sexual infantilism, and primary amenorrhea. Ovarian dysgenesis with normal 46, XX karyotype is characterized by diminished ovarian size and female phenotype. An interesting example of hypogonadotropic hypogonadism is Perrault syndrome as autosomal recessive ovarian dysgenesis coexisting with deafness. The diagnostic evaluation must include a detailed physical examination, height and bone maturation, measurements of general hematological and biochemical parameters, gonadotropins, sex steroids, prolactin, thyroid hormones, growth hormone and growth factors, and personal and familial antecedents [11].

It is important to conduct diagnosis per exclusionem - diagnosis by exclusion - clinical examination with assessing the features of puberty, regular checkups, puberty progression) and biochemical examination including estradiol/testosterone, prolactin, GnRH antagonist, hCG level (hCG/hMG), hands X-ray, ultrasonography of uterine and ovaries, head CT or MRI if necessary.

THE ROLE OF DEVELOPMENTAL AGE ASSESSMENT IN GIRLS WITH DELAYED PUBERTY

The age at puberty depends on the interaction between genetic and environmental factors, which is the reason for the large phenotypic variance of its start and course. Thus, in the diagnosis of delayed puberty, the calendar age is not a sufficient measure of the level of advancement in biological development. The status of development of a child is usually assessed in relation to events that take place during the progress of growth. Hence, in the assessment of the biological age, various parameters are taken into account, such as bone age, age at menarche, body height, body mass, but also dental age [21]. While such markers of biological age as body height or weight, age at menarche or the level of development of secondary sexual characteristics assessed using the Tanner scale are known in gynecological practice, dental age is still used to a small extent. Many studies have demonstrated that sex hormones have an important role in osteogenic differentiation and hard tissue metabolism [22, 23]. They have an effect on facial and cranial base growth and are odontogenic [24]. However, their effects on dental development have not been clearly described in the literature. More than half a century ago, Garn et al. reported that children more advanced somatically or sexually were more advanced dentally, while children with retarded development showed delayed dental maturation but to a lesser degree than skeletal maturation [25]. The results were based on the systematic exploration of tooth formation in a variety of endocrine and non-endocrine developmental retardations and precocities. Two decades later, Demirjian et al. stated that the mechanisms controlling dental development do not depend on somatic and/or sexual maturity [26]. In their study, the age at which French-Canadian girls attained 90% of the dental development showed no significant relationships with the other maturity indicators.

In idiopathic precocious puberty, Roberts et al. found that dental ages were delayed in relation to their chronological age in children [27]. Conversely, the recent study by Lee et al. revealed early maturation of the mandibular teeth in girls with central precocious puberty [28]. As far as delayed puberty is concerned, Gaethofs et al. observed significant retardation of dental maturation in boys with CDGP. However, it should be emphasized that, the examined group was small and consisted of only 8 subjects [29].

As reminded by Różyło-Kalinowska et al., the assessment of dental maturity can be a valuable method for initial assessment of the level of skeletal maturity of a child [30]. However, it cannot be used as the only measure of development, especially in atypically developing patients, such as those with endocrine disorders, congenital diseases, or other signs and symptoms. Dental age is most commonly assessed with the use of the Demirjian method [31]. However, this method has some concerns. As mentioned above, the reference group was French-Canadian, and the possible effect of ethnicity was not taken into account. Another problem associated with the Demirjian method is that it does not include third permanent molars, therefore it cannot be used in young adults. According to Fudalej et al., the Demirjian method overestimates the dental age of Polish children of about 12 months [32]. Wites et al. stated that the dental age slightly proceeds the chronological age during puberty [33]. Zatylna et al. proved that the dental age assessed by Demirjian's method differs from the chronological age, more significantly in girls [34]. Dental maturation has been shown to be mildly but consistently delayed in patients with delayed development [35]. Therefore, in order to assess the abnormalities of the puberty process in a comprehensive way, apart from specialists in developmental

gynecology, pediatrics, auxology or endocrinology, it would be worth including dentists who would add another marker of developmental age, which is dental age.

SUMMARY

Evaluation of developmental age during puberty using as many methods as possible (morphological age, secondary sexual characteristics, menarche age, bone age, dental age) allows the most comprehensive indication of signs of abnormal development, such as delayed puberty. Relationship between sexual maturation, skeletal age, dental age, general health, and a lifestyle support the need for collaboration between pediatricians, endocrinologists, pediatric gynecologists, dieticians and dentists in the management of irregularities of age at puberty.

REFERENCES

1. Marshall WA, Tanner JM. Variations in pattern of pubertal changes in girls. Arch Dis Child. 1969; 44(235): 291–303, doi: 10.1136/adc.44.235.291, indexed in Pubmed: 5785179.
2. Kaczmarek M. Adolescent growth and its relation to menarche, dental and somatic maturation. Anthropol Rev. 2002; 65: 27–42.
3. Durda-Masny M, Hanć T, Czapla Z, et al. BMI at menarche and timing of growth spurt and puberty in Polish girls - longitudinal study. Anthropol Anz. 2019; 76(1): 37–47, doi: 10.1127/anthranz/2019/0920, indexed in Pubmed: 30648186.
4. Gomula A, Koziel S. Secular trend and social variation in age at menarche among Polish schoolgirls before and after the political transformation. American Journal of Human Biology. 2017; 30(1): e23048, doi: 10.1002/ajhb.23048.
5. Hermanussen M. Auxology. Studying human growth and development. Germany Schweizerbart. ; 2013.
6. Malina Eb. Young Athletes Biological Psychological Educational Perspectives. Medicine & Science in Sports & Exercise. 1991; 23(9): 1116, doi: 10.1249/00005768-199109000-00022.
7. Cole TJ. The evidential value of developmental age imaging for assessing age of majority. Ann Hum Biol. 2015; 42(4): 379–388, doi: 10.3109/03014460.2015.1031826, indexed in Pubmed: 26133364.
8. Greulich W, Pyle S. Radiographic atlas of skeletal development of the hand and wrist. The American Journal Of The Medical Sciences. 1959; 238(3): 393, doi: 10.1097/00000441-195909000-00030.
9. Kaplowitz PB. Delayed puberty. Pediatr Rev. 2010; 31(5): 189–195, doi: 10.1542/pir.31-5-189, indexed in Pubmed: 20435710.
10. Vaaralahti K, Wehkalampi K, Tommiska J, et al. The role of gene defects underlying isolated hypogonadotropic hypogonadism in patients with constitutional delay of growth and puberty. Fertil Steril. 2011; 95(8): 2756–2758, doi: 10.1016/j.fertnstert.2010.12.059, indexed in Pubmed: 21292259.
11. Argente J. Diagnosis of late puberty. Horm Res. 1999; 51 Suppl 3: 95–100, doi: 10.1159/000053168, indexed in Pubmed: 10592450.
12. Crowley WF, Pitteloud N. Approach to the patient with delayed puberty. https://www.uptodate.com/contents/approach-to-the-patient-with-delayed-puberty.
13. Jarząbek-Bielecka G, Pisarska-Krawczyk M. Opóźnione dojrzewanie płciowe jako problem w ginekologii dziecięcej. In: Pisarska-Krawczyk M, Jarząbek-Bielecka G. ed. Zagadnienia interdyscyplinarne w ginekologii praktycznej. Kalisz Wydawnictwo PWSZ 2014: 69–93.
14. Frisch RE, Revelle R. Height and weight at menarche and a hypothesis of menarche. Arch Dis Child. 1971; 46(249): 695–701, doi: 10.1136/adc.46.249.695, indexed in Pubmed: 5118059.
15. Kaplowitz PB. Link between body fat and the timing of puberty. Pediatrics. 2008; 121 Suppl 3: S208–S217, doi: 10.1542/peds.2007-1813F, indexed in Pubmed: 18245513.
16. Shalitin S, Phillip M. Role of obesity and leptin in the pubertal process and pubertal growth--a review. Int J Obes Relat Metab Disord. 2003; 27(8): 869–874, doi: 10.1038/sj.ijo.0802328, indexed in Pubmed: 12861226.
17. Entrala-Bernal C, Montes-Castillo C, Alvarez-Cubero MJ, et al. Genetic diagnosis of idiopathic hypogonadotrophic hypogonadism: a new point mutation in the KAL2 gene. Hormones (Athens). 2014; 13(2): 280–285, doi: 10.1007/BF03401342, indexed in Pubmed: 24776628.
18. Jarząbek-Bielecka G, Sowińska-Przepiera E, Szafińska-Dolata A, et al. Girls delayed puberty. Pediatric Endocrinology. 2014; 13(3): 65–70, doi: 10.18544/ep-01.13.03.1496.
19. Jarząbek-Bielecka G, Sowińska-Przepiera E, Szafińska-Dolata A, et al. Hipogonadyzm hipogonadotropowy jako przyczyna opóźnionego pokwitania dziewcząt. Endokr Pediat. 2014; 13(4): 41–45.
20. Jarząbek-Bielecka G, Drosdzol-Cop A, et al. The hypogonadism and delayed puberty in childhood and adolescent gynecology. Archives of Perinatal Medicine. 2017; 23(4): 229–235.
21. McKenna CJ, James H, Taylor JA, et al. Tooth development standards for South Australia. Aust Dent J. 2002; 47(3): 223–227, doi: 10.1111/j.1834-7819.2002.tb00333.x, indexed in Pubmed: 12405462.
22. Bland R. Steroid hormone receptor expression and action in bone. Clin Sci (Lond). 2000; 98(2): 217–240, indexed in Pubmed: 10657279.
23. Riggs BL, Khosla S, Melton LJ. Sex steroids and the construction and conservation of the adult skeleton. Endocr Rev. 2002; 23(3): 279–302, doi: 10.1210/edrv.23.3.0465, indexed in Pubmed: 12050121.
24. Kim SM, Lee BN, Koh JT, et al. The effect of chlormadinone acetate on odontogenic differentiation of human dental pulp cells: in vitro study. BMC Oral Health. 2017; 17(1): 89, doi: 10.1186/s12903-017-0379-0, indexed in Pubmed: 28549486.
25. Garn SM, Lewis AB, Blizzard RM. Endocrine factors in dental development. J Dent Res. 1965; 44: SUPPL:243–SUPPL:258, doi: 10.1177/00220345650440012001, indexed in Pubmed: 14242328.
26. Demirjian A, Buschang PH, Tanguay R, et al. Interrelationships among measures of somatic, skeletal, dental, and sexual maturity. Am J Orthod. 1985; 88(5): 433–438, doi: 10.1016/0002-9416(85)90070-3, indexed in Pubmed: 3864376.
27. Roberts MW, Li SH, Cutler GB, et al. Dental development in precocious puberty. J Dent Res. 1985; 64(8): 1084–1086, doi: 10.1177/00220345850640081301, indexed in Pubmed: 3860542.
28. Lee HK, Choi SH, Fan D, et al. Evaluation of characteristics of the craniofacial complex and dental maturity in girls with central precocious puberty. Angle Orthod. 2018; 88(5): 582–589, doi: 10.2319/112317-809.1, indexed in Pubmed: 29708396.
29. Gaethofs M, Verdonck A, Carels C, et al. Delayed dental age in boys with constitutionally delayed puberty. Eur J Orthod. 1999; 21(6): 711–715, doi: 10.1093/ejo/21.6.711, indexed in Pubmed: 10665201.
30. Różyło-Kalinowska I, Kolasa--Rączka A, Kalinowski P. Relationship between dental age according to Demirjian and cervical vertebrae maturity in Polish children. Eur J Orthod. 2011; 33(1): 75–83, doi: 10.1093/ejo/cjq031, indexed in Pubmed: 20558591.
31. Demirjian A, Goldstein H, Tanner JM. A new system of dental age assessment. Hum Biol. 1973; 45: 221–227.
32. Fudalej P, Chrostowska E, Maciejewska A. Validity of nolla's and Demirjian's method of dental age assessment in children with a normal craniofacial structure. Czas Stomatol. 2007; 11: 744–751.
33. Wites M, Kalukin J, Niżankowska-Jędrzejczyk A, et al. Prediction of the growth spurt based on panoramic radiograhps. J Stomatol. 2011; 64: 875–886.
34. Zatylna N, Rogowska K, Kozanecka A. Comparison of 6–12 year old girls' and boys' dental age using Demirjian's method. Dent Med Probl. 2013; 50(1): 64–70.
35. Pirinen S. Endocrine regulation of craniofacial growth. Acta Odontol Scand. 1995; 53(3): 179–185, doi: 10.3109/00016359509005969, indexed in Pubmed: 7572094.

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Successful *in vitro* fertilization, twin pregnancy and labor in a woman with inherited propionic acidemia

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Propionic acidemia (PA) is an inherited metabolic disorder, in which a defective form of the enzyme propionyl-coenzyme A carboxylase causes propionic acid accumulation. There are a few reports of singleton pregnancies that ended with successful births from mothers with PA. This is the first report of a twin pregnancy from in vitro fertilization (IVF) ending with successful delivery.

The presented 35-year old British Caucasian women had late-onset PA, was asymptomatic, and only on dietary treatment (protein approximately 0.8 g/kg body mass/day, L-carnitine 1 g/day). After several unsuccessful induction of ovulation cycles and an artificial insemination, in vitro fertilization (IVF) was recommended. The patient was informed about the risk of metabolic decompensation. Two weeks after IVF, she developed a bacterial vaginal infection confirmed microbiologically. Nausea accompanying early onset of pregnancy resulted in reduced food intake, which induced symptoms of metabolic decompensation within a few days including: decreased concentration, disturbance in logical thinking, logorrhea, dizziness, tachypnea, tachycardia, and anxiety. Ultrasonography revealed ovarian hyperstimulation syndrome and monochorionic diamniotic twins. Laboratory tests found partial-compensated metabolic acidosis and electrolyte imbalance. Equalization of the metabolic disturbances in the patient was achieved according to current recommendations (i.e., 10% glucose, intravenous supplemental fluids and electrolytes, L-carnitine, ammonia scavengers, and a protein-free diet for 48 hours), in parallel with the application of cefuroxime. To provide the right amount of protein for ensuring proper development of a twin pregnancy, the patient received oral medical protein supplement XMTVI Maxamum (Nutricia). The pregnancy was also complicated by hypothyroidism and gestational diabetes mellitus controlled by intensive insulin treatment. Fetuses were monitored by serial ultrasound scans demonstrated 13% discrepancy of size between the fetuses (Fig. 1) and normal amniotic fluid volumes. At week 31, an upper respiratory tract infection occurred, followed by progressive symptoms of preterm delivery. The babies were delivered by cesarean section: the first twin weighed 1550 g (Apgar scores: 5/6/7), the second weighed 1340 g (Apgar scores: 7/8/9).

On the second day after delivery, the patient started vomiting and heart failure symptoms occurred as a result of exacerbation of PA. Laboratory tests showed anemia, electrolyte and metabolic disturbances. Normalization of patient's results was achieved with 2 units of red blood cells transfusion, continuous intravenous infusion of glucose with insulin controlled supplementation, fluids and electrolytes, as well as a high-sodium, high-carbohydrate, and protein-poor diet with supplementation of L-carnitine and low molecular weight heparin therapy. The control electrocardiography showed long QT syndrome, which was normalized by intravenous supplementation of potassium and magnesium salt.

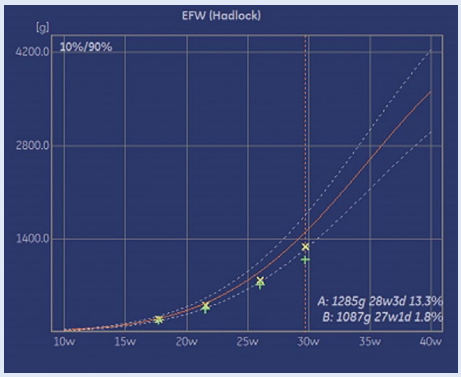

Figure 1. Fetal growth chart

Due to raised inflammatory parameters, the presence of *Klebsiella pneumoniae* in urine was revealed, which was treated with amoxiclav according to the antibiogram. Four weeks after delivery, all above regimens with dietary supplementation resulted in normalization of protein levels, with normal ammonia, lactate, and electrolytes levels.

This case report draws attention to the risk and the possibility of metabolic decompensation in PA patients during pregnancy. It is difficult to clearly indicate whether metabolic decompensation of PA patient was caused by IVF itself, or rather a twin gestation. In our opinion the IVF procedure, hormonal stimulation, induced decompensation in the initial period of pregnancy, while the metabolic decompensation just before the delivery was rather caused by the metabolic load of the body by twin pregnancy.

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