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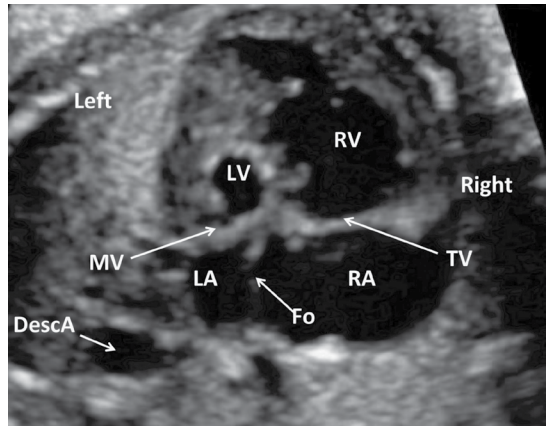

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PALM-COEIN classification system of FIGO vs the classic terminology in patients with abnormal uterine bleeding

Bekir Kahveci[1], Mehmet Sukru Budak[2], Serhat Ege[3], Mehmet Obut[3], Ihsan Bagli[3], Süleyman Cemil Oğlak[3], Mehmet Ali Vardar[1]

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ABSTRACT

Objectives: To evaluate the FIGO's novel classification system versus the classic terminology in patients with abnormal uterine bleeding.

Material and methods: A retrospective study was carried out between August 2015 and September 2019 in the Health Sciences University Gazi Yaşargil Training and Research Hospital. The pathology reports of the patients were classified according to the PALM-COEIN method and were compared with classical terminology. The operated patients with fibroids reported in the pathology results were classified as subgroups of fibroids.

Results: Evaluation was made of a total of 515 women with abnormal uterine bleeding. According to the classical terminology, 137 (26.6%) patients were defined with hypermenorrhea, 74 (14.4%) with menorrhagia, 57 (11.1%) with metrorrhagia, and 246 (47.8%) with menometrorrhagia. In the PALM-COEIN classification system, polyps were determined in 84 (16.3%) cases, adenomyosis in 228 [diffuse adenomyosis:196 (38.1%), local adenomyosis:32 (6.2%)], leiomyoma in 386 [submucous:161 (31.1%), other types: 225 (43.9%)], and malignancy and hyperplasia in 47 (9.1%).

Conclusions: The classical terminology for abnormal uterine bleeding is insufficient in terms of etiological pathologies in non-pregnant women of reproductive age. The widespread use of this novel system for the abnormal uterine bleeding classification will provide a more useful communication between physicians and researchers.

Key words: abnormal uterine bleeding; menstrual disorders; PALM-COEIN classification; classic terminology

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INTRODUCTION

Abnormal uterine bleeding (AUB) is one of the most widespread gynecological symptoms as uterine hemorrhage which is different from normal menstruation in non-pregnant women of reproductive age [1]. The prevalence of AUB has been reported to be 11–15% in non-pregnant women of reproductive age [2].

A large number of terms are used to define the symptoms, signs and causes of AUB, like menorrhagia, metrorrhagia, hypermenorrhea, menometrorrhagia, polymenorrhea and dysfunctional uterine bleeding. However, there has been an update to standardize descriptive terms, and menorrhagia, metrorrhagia, and oligomenorrhea have been replaced with the terminology of heavy menstrual bleeding (HMB), intermenstrual bleeding, and unscheduled bleeding or breakthrough bleeding with the use of hormone medication [3]. HMB is defined as an increase in the amount of menstrual bleeding that may affect physical, emotional and social quality of life. It can be objectively described by a drop in hemoglobin and the number of menstrual products used, such as tampons or pads per day [4].

This heterogeneity in the definitions of terminology, etiology and AUB causes confusion when comparing clinical treatment outcomes. Therefore, there has been seen to be a need for a standard, structured and consistent classification for the underlying etiology of AUB. The development of a useful and universally accepted classification system for AUB has been remarkable for a long time, because the classical terminology defining AUB contains terms that are not related to a particular pathological process [5].

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As a result of these concerns, the International Federation of Gynecology and Obstetrics (FIGO) improved a novel classification system in 2011 to standardize AUB terminology, management and diagnosis [6]. There are nine considerable categories, which are adjusted according to the acronym: Polyp Adenomyosis Leiomyoma Malignancy and hyperplasia-Coagulopathy Ovulatory dysfunction Endometrial Iatrogenic Not yet classified. The "PALM" group includes structural pathologies that can be measured visually using imaging techniques or histopathology, while the "COEIN" group refers to non-structural pathologies that cannot be identified by imaging or histopathology.

The American College of Obstetricians and Gynecologists has proposed classifying AUB according to this novel system [1]. This system is a practical, consistent classification system designed for understanding and increasing knowledge of AUB, and facilitating agreement between clinicians [7, 8]. A previous study identified several etiological factors responsible for AUB according to the PALM-COEIN classification among women undergoing hysterectomy, and concluded that this new classification is useful for comparative and epidemiological studies [9].

Even though some societies have established their own guidelines for the diagnosis and management of AUB according to the novel this classification system, it is hard to classify AUB for patients with leiomyoma as outpatients in many low-income countries [10]. There has also been shown to be no clear terminology and consensus classification for adenomyosis, which is among the causes of AUB [11].

The aim of this study was to evaluate whether the FIGO PALM-COEIN classification system is more effective than classical terminology in patients with AUB.

MATERIAL AND METHODS

This cross-sectional study was conducted between August 2015 and September 2019 at the Health Sciences University Gazi Yaşargil Training and Research Hospital. A retrospective evaluation was made of the files of patients who underwent surgeries such as hysterectomy, myomectomy and polypectomy due to AUB. Approval for the study was obtained from the Institutional Ethics Committee (Number: 2019/348). Informed consent was not obtained from the patients due to the retrospective nature of the study.

A normal menstrual cycle was described as a period of 24–38 days, lasting 4–8 days, with an average amount of bleeding of 35 mL and no significant changes from cycle to cycle as per FIGO guidelines. AUB was described as bleeding from the uterine corpus that occurred with abnormal regularity, volume, frequency or duration when there is no pregnancy [12].

Patient with pregnancy-related bleeding, popstmenopausal bleeding, cervix or lower genital system bleeding, suspected or diagnosed cervical carcinoma were excluded. Each patient was examined with physical examination and pelvic ultrasonography. Data were collected on patient age, parity, body mass index (BMI), and causes of AUB according to classic terminology. In addition, analysis was performed to obtain reports of surgery and pathology results for structural pathologies that were then classified according to the PALM group. Adenomyosis was divided into local and diffuse subgroups. The size, number and location of fibroids obtained from the pathology results of the operated patients were recorded and classified as a subgroup.

Statistical analysis

All statistical analyses were performed using IBM SPSS 20 software (IBM Corp. Released 2011. IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY, USA). Descriptive statistics were stated as mean ± standard deviation (SD), minimum and maximum values, number (n) and percentage (%).

RESULTS

In this study period, 620 hysterectomies, 34 myomectomies, and 36 polypectomies were performed for AUB. Of these, 515 women [465 (90.3%) hysterectomy, 24 (4.7%) myomectomy and 26 (5.0%) polypectomy] with appropriate data were determined and included. The distribution of all the patients diagnosed with AUB during the study period is summarized in Figure 1.

The mean age of the patients was 46.3 ± 6.3 years, mean parity was 4.2 ± 1.6 and mean BMI was 29.4 ± 4.2. According to the classical terminology, 137 (26.6%) patients were diagnosed with hypermenorrhea, 74 (14.4%) with menorrhagia, 57 (11.1%) with metrorrhagia, 246 (47.8%) with menometrorrhagia. According to the PALM-COEIN classification system, polyps were determined in 84 (16.3%) cases, adenomyosis in 228 (44.3%) [diffuse adenomyosis (A_D) and local adenomyosis (A_L)], leiomyoma in 386 (75%) [submucous leiomyoma (L_{SM}) and others leiomyoma (L_{OT})], and malignancy and hyperplasia in 47 (9.1%).

Of the 137 patients with hypermenorrhea, a significant part of these are leiomyoma, of the 74 patients with menorrhagia and of the 57 patients with metrorrhagia, a majority of these are leiomyoma, of the 247 patients with menometrorrhagia, a large part of these are leiomyoma and then adenomyosis according to the PALM-COEIN system (Tab. 1).

Overall, 386 patients underwent surgery for leimyoma, and according to the sub-classification, 65 (16.8%) of these had submucous myoma, and the remaining 321(83.2%) patients had other types of myoma (Tab. 2).

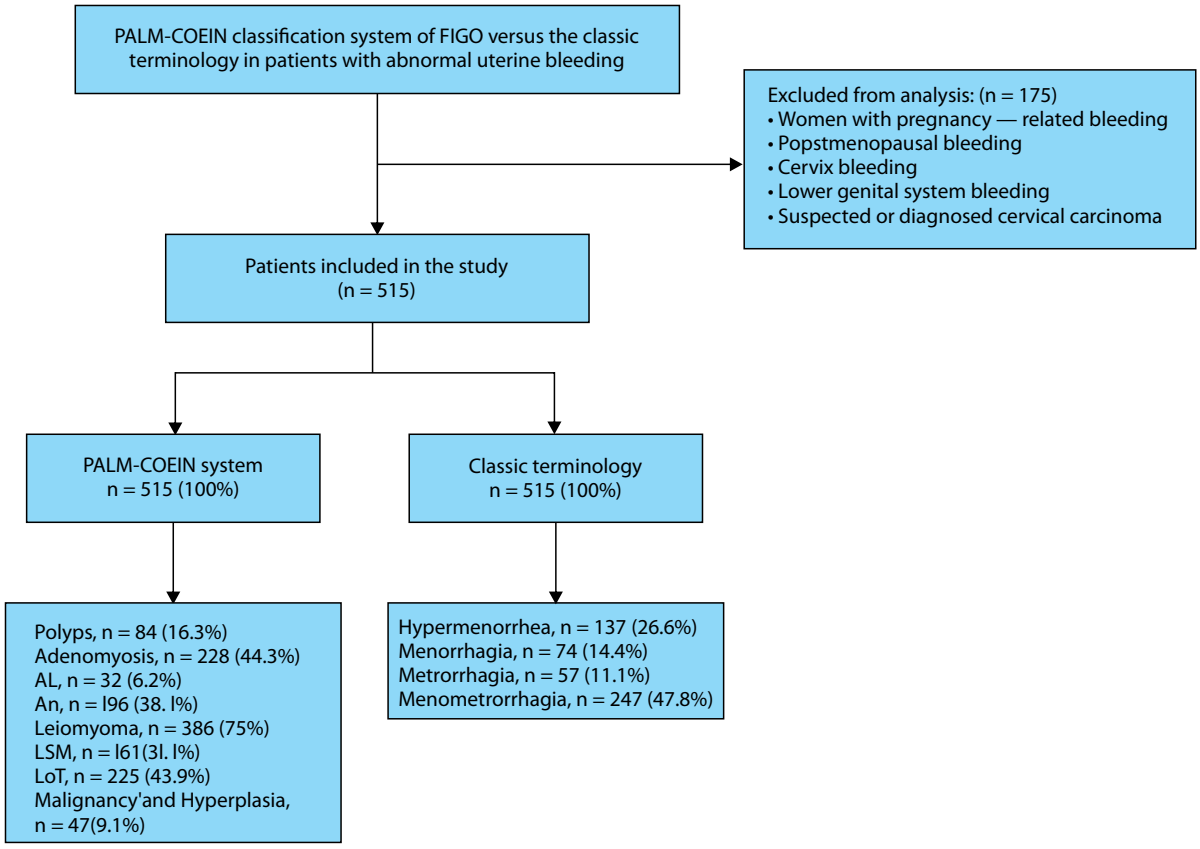

Figure 1. Study flowchart; AUB — abnormal uterine bleeding; PALM-COEIN — Polyp Adenomyosis Leiomyoma Malignancy and hyperplasia-Coagulopathy Ovulatory dysfunction Endometrial Iatrogenic Not yet classified; AL — local adenomyosis; AD — diffuse adenomyosis; LOT — others leiomyoma; LSM — submucous leiomyoma

Table 1. Comparison of cases according to classic terminology and the PALM-COEIN system[a]

PALM-COEIN system	Hypermenorrhea (n = 137)	Menorrhagia (n = 74)	Metrorrhagia (n = 57)	Menometrorrhagia (n = 247)
Polyp (n = 84)	23 (16.8)	12 (16.2)	10 (17.5)	39 (15.8)
Adenomyosis A_L (n = 32) A_D (n = 196)	 2 (1.5) 62 (45.3)	 21 (28.4) 4 (5.4)	 2 (3.5) 17 (29.8)	 7 (2.8) 112 (45.3)
Leiomyoma L_{SM} (n = 161) L_{OT} (n = 225)	 30 (21.9) 74 (54.0)	 45 (60.8) 7 (9.5)	 20 (35.1) 20 (35.1)	 66 (26.7) 124 (50.2)
Malignancy and Hyperplasia (n = 47)	15 (10.9)	9 (12.2)	7 (12.3)	17 (6.9)

PALM-COEIN — Polyp Adenomyosis Leiomyoma Malignancy and hyperplasia-Coagulopathy Ovulatory dysfunction Endometrial Iatrogenic Not yet classified; A_L — local adenomyosis; A_D — diffuseadenomyosis; L_{OT} — others leiomyoma; L_{SM} — submucous leiomyoma; [a]Values are given as number (percentage)

DISCUSSION

This study was conducted to identify the reasons of AUB based on the PALM-COEIN classification and to compare the clinical and histopathological features to determine the definitive etiology for proper management of the AUB. As the clinical classification of AUB may result in inadequate treatment, there is a need for classification of the etiology. In this study, the histopathological result of the hysterectomy specimen was accepted as the gold standard to evaluate the accuracy of the preoperative diagnosis of AUB causes. "Dysfunctional uterine bleeding (DUB)" is now a useless term as women classified in this category in the past in fact fall into the FIGO categories of a varying combination of coagulopathy, disorder of ovulation, or endometrial

Table 2. Subclassification of leiomyomas by location

Leiomyoma subclassification, n (%)	n = 386 (100)
Submucosal	
0	2 (0.5)
1	5 (1.3)
2	58 (15.5)
Other	
3	24 (5.9)
4	191 (50.4)
5	54 (13.9)
6	10 (2.4)
7	13 (2.9)
8	5 (1.1)
Hybrid leiomyomas[a]	
2–5	24 (6.1)

[a]Included in both the endometrium and serosa

pathologies considered as "unrelated to uterine structural abnormalities" [13].

Obesity has been proven to be one of the leading causes for AUB. Life-long exposure to estrogen by peripheral aromatization of adrenal androgens rises the incidence of polyps, leiomyomas and endometrial carcinomas in obese women (relative risk 3–10%) [14]. In the present study, the mean BMI of the patients was found to be in the overweight category. Therefore, care should be taken in terms of AUB in obese women.

Endometrial polyps are one of the most common etiologies of AUB in both premenopausal and postmenopausal women. Although they may also be asymptomatic, the part of polyps to AUB varies between 3.7% and 65 % [15]. Intermenstrual bleeding is the most frequent symptom in premenopausal women with endometrial polyps [16]. In the present study, 16.3% of women with AUB were found to have polyps and most had menometrorrhagia.

Uterine adenomyosis is a histological diagnosis based on the pathology evaluation of the uterus after hysterectomy. Preoperatively, the diagnosis is suggested by characteristic clinical manifestations (HMB and dysmenorrhea with a uniformly enlarged uterus), and a clinical diagnosis can be made with transvaginal ultrasound or magnetic resonance imaging findings. In some studies, the rate of adenomyosis as the cause of AUB has been reported as 14.5%–15.4% [13, 17]. In the present study, 44.3% of the women with AUB were found to have adenomyosis and most had menometrorrhagia. The higher rate of adenomyosis compared to literature was attributed to the high parity of the current study patients.

Uterine leiomyomas (fibroids or myomas) are common benign tumors. The most common presenting symptoms of uterine fibroids are heavy or prolonged menstrual bleeding. It was the most common cause of AUB followed by adenomyosis [13]. Myomas are clinically apparent in approximately 12–25% of reproductive-age women and are noted on pathological examination of approximately 80% of surgically excised uteri [18]. In a recent study of patients with AUB, 26.7% of fibroids were found to be submucosal [17]. The factor most contributing to bleeding in the PALM group is fibroids. In the present study, 75% of the patients had fibroids according to the pathology results and 16.8% were submucous myoma. It was observed that submucosal type caused more AUB compared to intramural and subserous types [19]. It has been thought that submucous fibroids distort the cavity and are more likely to cause HMB [20]. In the current study, fibroids were classified into subgroups according to the PALM-COEIN classification.

The endometrium may develop endometrial hyperplasia, which includes non-neoplastic entities characterized by a proliferation of endometrial glands of irregular size and shape, and precancerous neoplasms characterized by neoplastic features but without invasion. Endometrial hyperplasia and malignancies typically present with AUB. Therefore, endometrial sampling is still the primary diagnostic method for AUB. In the present study, endometrial hyperplasia was seen in 9.1% of cases, similar to the findings of the Mishra and Sultan study [21].

Treatment of acute AUB depends on many conditions, such as clinical stability, pain, suspected bleeding etiology, future fertility desire, and underlying medical issues. There are two basic purposes of managing acute AUB, firstly to control the current heavy bleeding attack and then to decrease blood loss during menstrual cycles. The preferred initial treatment is medical treatment, and hormonal management is the first application to be considered. There are treatment options such as IV conjugated estrogen, oral progestins and combined oral contraceptives. However, some conditions may require immediate surgical treatment. If we look at the surgical options for example dilatation and curettage, endometrial ablation, uterine artery embolization and hysterectomy can be considered [22].

CONCLUSIONS

AUB is a complex condition because there are differences between individuals, so many pathologies accompany it. It can be considered that the use of the PALM-COEIN system will help eliminate confusion about the etiology of AUB and this diagnostic will enable more effective communication with other healthcare professionals, thereby resulting in better management of treatment.

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Conflict of interests

The authors declare that they have no conflict of interests.

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A crosscut survey on reproductive health in Lithuanian childhood cancer survivors

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ABSTRACT

Objectives: Sexual dysfunction was reported to compromise the quality of life in childhood cancer survivors. The aim of our study was to evaluate the reproductive health in long-term pediatric cancer survivors by conducting a crosscut survey.

Material and methods: Childhood cancer survivors over 18 years of age, who were in remission for more than 5 years, were invited to complete a gender-specific questionnaire surveying on their reproductive health. Demographic and treatment data were retrieved from their medical records. Treatment modalities were reviewed for its potential gonadotoxicity.

Results: 34 (17 males and 17 females, respectively) from 346 addressed survivors (9.8%) completed the questionnaire. Median age and follow-up after diagnosis was 27 (18–35) and 14 (3–25) years, respectively. Some respondents reported sexual concerns: 11.8% males experienced problems with penetration, two males (11.8%) who underwent semen analysis were found to be azoospermic. Similarly, 11.8% females reported delayed puberty, the average age of menarche was 14 (12–17) years, 29.4% females reported irregular menstrual cycles. Cyclophosphamide equivalent dose (CED) differed significantly between the patients treated for leukemia, lymphoma and solid tumors (3000 vs 4352 vs 6660 mg/m^2, respectively, $p = 0.014$).

Conclusions: Low prevalence of sexual dysfunction, fertility related disorders or delayed puberty in childhood cancer survivors was found. However, the results should be interpreted with caution taking into account a low response rate.

Key words: late effects; long-term survivors; pediatric cancer; reproductive health; sexual dysfunction

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INTRODUCTION

Over the last few decades, a long-term survival rate after pediatric cancer has improved dramatically and nowadays exceeds 80% in most European countries [1]. High cure rates imply a constantly growing population of childhood cancer survivors. As a consequence, research activities are focused not only on overcoming resistant malignancies but also on the well-being of the cured persons who are at the risk for frailty, and suboptimal quality of life [2].

A healthy reproductive system is a cornerstone of the quality of life in young adult survivors. Sexual dysfunction was reported to be one of the most important side effects of pediatric cancer treatment [3]. Treatment intensity depends on cancer type, localization, spread of the disease (metastases) and other risk factors. Most patients are exposed to combined treatment including chemotherapy, surgery, radiotherapy, less frequently high-dose chemotherapy prior to hematopoietic stem cell transplantation and the immune therapy. All the approaches, used separately or in combination, could potentially have an adverse long-term effect on fertility [4, 5]. It is crucial to inform every patient (parents or guardians in pediatric setting) about the potential adverse effect of cancer treatment on the reproductive health and options for fertility preservation. The majority of childhood cancer survivors perceive they had not been provided sufficient information about reproductive health and had never underwent fertility testing [6, 7].

Studies have shown that in females chemotherapy regimens containing high-dose alkylating agents and abdominal/pelvic radiotherapy affected the gonadal function,

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and were associated with delayed puberty, premature ovarian insufficiency and follicular atresia, premature menopause and infertility [8]. In males, infertility was reported to be related to the use of alkylating agents, testicular radiation, or cranial irradiation [4]. Certain concomitant chemotherapy agents such as cisplatin, carboplatin, increase the risk of infertility in childhood cancer survivors [9–11].

Cumulative exposure to alkylating agents can be quantified using the cyclophosphamide equivalent dose (CED), as described by Green et al. [12] that compares the drugs based on the hematological toxicity. The adoption of the CED allows evaluation of the relationship between hematological toxicity and alkylating agent related late outcomes, such as infertility. The advantage of the CED is its derivation from actual drug doses rather than dependence on a drug dose distribution specific to a single population [12]. CED ≥ 4000 mg/m^2 is associated with a risk of infertility, while CED ≥ 8000 mg/m^2 is most likely to cause infertility leading to premature ovarian insufficiency in females [13] and increased chance of oligospermia and azoospermia in males [14].

The purpose of our study was to evaluate reproductive health in pediatric cancer survivors who were in a long-term remission and were in reproductive age. The research aimed at elucidating personal perception of the study participants with regard to their reproductive health, thus a surveying approach was adopted. Additionally, the exposure to gonadotoxic therapies reviewed was retrospectively.

MATERIAL AND METHODS

A single-center cross-sectional study was carried out from December 2016 to January 2018. All subjects gave their informed consent for inclusion before they participated in the study. The study was conducted in accordance with the Declaration of Helsinki. The study population included childhood cancer survivors treated at the Center for Pediatric Oncology and Hematology, Vilnius University Hospital Santaros Klinikos. The inclusion criteria were defined as 1) age 18+ years as of December 2016; 2) childhood cancer (ICD-O-10 C00-C96) diagnosed in 1982-2011; 3) In remission 5+ years since diagnosis in December 2016. The study was approved by the Vilnius Regional Committee of Biomedical Research (Approval No.158200-16-873-385).

Survivors who met the inclusion criteria were identified at the institutional database. The identified cohort was contacted by regular certificated mail to the postal address available in the medical records: an invitation to participate in the study, an informed consent form, and a questionnaire were sent to each consignee. The respondents who signed the informed consent, completed the questionnaire, and returned it to the study center were included into the final analysis.

Two gender-specific questionnaires were elaborated by a multidisciplinary team of pediatric oncologist, obstetrician-gynecologist, urologist and clinical embryologist. The participants were invited to answer 17–18 questions regarding sexual health, ability to conceive, marital status/partnership (Supp. 1 available on https://journals.viamedica.pl/ginekologia_polska/issue). As a complementary service a consultation of a gender-appropriate reproductive health specialist was offered to all contacted survivors. Additionally, a summary of the study results was offered to be shared upon request.

The answers were collected from the completed questionnaires and analyzed anonymously. Baseline characteristics and treatment-related data (diagnosis, type of chemotherapy drugs used and dosages, information on radiotherapy and surgical treatment) were retrieved from the patients' paper or electronic medical records.

The exposure to alkylating agents was assessed by CED calculation using the equation described by Green et al. [12]: CED (mg/m^2) = 1.0 (cumulative cyclophosphamide dose, mg/m^2) + 0.244 (cumulative ifosfamide dose, mg/m^2) + 0.857 (cumulative procarbazine dose, mg/m^2) + 14.286 (cumulative chlorambucil dose, mg/m^2) + 15.0 (cumulative BCNU dose, mg/m^2) + 16.0 (cumulative CCNU dose, mg/m^2) + 40 (cumulative melphalan dose, mg/m^2) + 50 (cumulative thioteps dose, mg/m^2) + 100 (cumulative nitrogen mustard dose, mg/m^2) + 8.823 (cumulative busulfan dose, mg/m^2). Cumulative treosulfan dose was not included in the original computation. The dacarbazine cumulative dose was calculated as a single drug — being quite different from other classical alkylating agents, it is not included in CED calculation. In addition, a cumulative dose of platinum compounds (carboplatin and cisplatin) was evaluated. Data on the surgery and radiotherapy for potential involvement of gonadal areas were revised. The data evaluation time-point was January 2018.

Demographic and treatment-related characteristics were assessed using descriptive statistics. The median-test was used to compare the medians of cumulative CED between different types of childhood cancer. SPSS ver. 17 (IBM Corp., Armonk, NY) was used for all quantitative analyses, p-value less than 0.05 was considered to be significant.

RESULTS

In total 346 childhood cancer survivors [195 (56.4%) males and 151 (43.6%) females] matched the inclusion criteria (Supp. 2 available on https://journals.viamedica.pl/ginekologia_polska/issue). In contrast to the expectations, the response rate was very low – only 34 (9.8%) survivors answered the questions. One hundred twenty (34.7%) consignees appeared to be unavailable: in 99 (28.6%) cases the letters were not reclaimed at the post office, in 19 (5.5%)

Table 1. Baseline characteristic of the study participants

Variables	Study participants		
	Males (n = 17)	Females (n = 17)	All (n = 34)
Current age (years) Median (min-max)	27 (18–35)	25 (18–31)	27 (18–35)
Age at cancer diagnosis (years) Median (min-max)	14 (2–17)	14 (12–18)	14 (2–18)
Follow-up time (years) Median (min-max)	13.5 (3–24)	15 (5–24)	14 (3–24)
Cancer type* Leukemia, myeloproliferative disorders, myelodysplasia n, (%) Lymphomas and reticuloendothelial neoplasms n, (%) Tumors in the Central Nervous System n, (%) Neuroblastoma and other peripheral nerve sheath tumors n, (%) Osteosarcoma and other bone malignancies n, (%) Other epithelial tumors and melanoma n, (%)	 6 (35.3) 7 (41.2) 1 (2.8) 0 2 (11.8) 1 (5.9)	 7 (36.8) 8 (47) 0 2 (10.5) 0 0	 13 (36.1) 15 (44.1) 1 (2.8) 2 (5.6) 2 (5.6) 1 (2.8)

*according to ICCC-3 (International classification of childhood cancer)

cases the postal address was no longer valid, 2 (0.6%) patients had died. However, the majority of the invited survivors 190 (54.9%) received the invitation but refrained from sharing their answers. None of them wished to take the opportunity to see a specialist in reproductive health.

Thirty-four (9.8%) respondents (17 males and 17 females) were included into the final analysis. The median age at the time of evaluation was 27 (18–35) years, meanwhile the one at cancer diagnosis — 13 (2–18) years. The age did not differ between males and females (Tab. 1). Leukemia and lymphoma were the most common types of malignancies among the respondents [13 (36.1%) and 15 (44.1%), respectively] whereas only 6 (17.6%) were affected by solid tumors. All patients were diagnosed with only one type of cancer, there were no cases of a second malignant neoplasm. The distribution of cancer types across survivors who met the inclusion criteria and were invited to participate in the study showed a slight predominance of leukemia as compared to the study cohort: among 346 survivors, 165 (47.7%) were diagnosed with leukemia, 122 (35.3%) with lymphoma, and only 59 (17.1%) with solid tumors (Supp. 2 available on https://journals.viamedica.pl/ginekologia_polska/issue).

Most of the survivors were treated with chemotherapy (n = 33, 97%), radiotherapy was delivered to 18 patients (54.5%), six (17%) patients were operated on, and two patients received an allogeneic hematopoietic stem cell transplantation (HSCT) (Tab. 2). Treatment protocols varied according to the time period of the diagnosis and type of malignancy. The majority of leukemia patients were treated according to Berlin-Frankfurt-Münster (BFM) based protocols while one respondent was cured after being treated according to the Nordic Society of Pediatric Hematology and Oncology (NOPHO) A*cute Lymphoblastic* Leukemia (ALL) 2008 guidelines. The treatment protocols are indicated in the Table 2 and are outlined in details in the Supplement 3 (available on https://journals.viamedica.pl/ginekologia_polska/issue). None of the survivors were irradiated on abdominal field, however nine respondents received cranial irradiation.

Review of the exposure to gonadotoxic drugs revealed significantly higher median cumulative CED in patients treated for solid tumors as compared to those treated for lymphoma and leukemia (6660 vs 4352 vs 3000 mg/m^2, respectively, p = 0.014). According to the expectation in leukemia cohort CED was much higher in the recipients of allogeneic HSCT as compared to non-transplanted patients. Additionally, females affected by Hodgkin lymphomas were treated with dacarbazine (median cumulative dose was 2250 mg/m^2) whereas platinum compounds were frequently added in solid tumors (the respective median cumulative dose for carboplatin and cisplatin was 1500 and 50 mg/m^2, Tab. 2).

Perception of the reproductive health in males

The answers to the questions provided by the male survivors are summarized in Table 3. All 17 respondents were able to get an erection and ejaculate, two survivors (11.8%) reported problems with penetration (both were single at the time of evaluation). Ten young men (58.8%) were married or had a partner, the remaining seven (41.2%) were single at the time of assessment. The average sexual activity was three times per week (ranged from 0 to 10). The majority of males (94.1%) felt normal sexual desire, on a ten-point scale the average libido score was nine (ranged from 3 to 10). Thirteen survivors (76.5%) used contraception, preferably the barrier one. Notwithstanding, 14 out of 17 (82.4%) did

Table 2. Details on exposure to cytotoxic drugs and other gonadotoxic treatment

Cancer type n (%)	Treatment modality			Cumulative dose of gonadotoxic drugs Median* (min-max), mg/m^2			
	Chemotherapy (n)	Radiotherapy (n)	Irradiated area	CED	Dacarbazine	Carboplatin	Cisplatin
Leukemias 13 (38.2)				**3000** (1000–8817)**	n.a.	n.a.	n.a.
ALL 9 (26.5)	#BFM-ALL-90/95/2000 (8) #NOPHO-ALL-2008 (1)	8	Cranial	3000 2000	n.a.	n.a.	n.a.
AML 2 (3.8)	#BFM-AML-98 (2)	0	n.a.	1000	n.a.	n.a.	n.a.
Cx + HSCT 2 (3.8)	#BFM-ALL-2000 + BuCyEto (1) #BFM-AML-98 + CyTreo (1)	0	n.a.	8817 5700***	n.a.	n.a.	n.a.
Lymphomas 15 (44.1)				**4352** (0–5157)**	**2250 (1500–3000)**	**1200**	n.a.
Hodgkin lymphoma 9 (26.5)	2 x OEPA 2 x ABVD (1) #HD-95 (2) #GPOHD-2001 (5) Other**** (1)	5	Chest	4000 (0–5157) 0 4571 2000 (0–4000) 5157	2250 (1500–3000) 1500 n.a. 3000 1500	n.a. n.a. n.a. n.a. 1200	n.a. n.a. n.a. n.a. n.a.
Non-Hodgkin lymphoma 6 (17.6)	#BFM-NHL-95 (6)	1	Chest	0	n.a.	n.a.	n.a.
Solid tumors 6 (17.6)				**6660** (0–35964)**	**4000**	**1500 (0–2100)**	**50 (0–640)**
CNS tumor 1 (2.9)	CPT-SIOP-2009	1	Cranial	6000	n.a.	2100	n.a.
Neuroblastoma 2 (3.8)	#NB-90	1	Chest	9720 (7320–12120)	4000	1500	640
Ewing sarcoma 1 (2.9)	IE plus VAdriaC	1	Femur	35964	n.a.	n.a.	n.a.
Osteosarcoma 1 (2.9)	COSS96+4 x BCD	n.a.	Fibula	1200	n.a.	750	100
Adenocarcinoma 1 (2.9)	No chemotherapy	n.a.	None	n.a.	n.a.	n.a.	n.a.

#for the protocol details refer to supplemental material; n.a. – not administered; *numbers corresponding to one patient indicated without range; **p = 0.007 (Median Test); ***treosulfan was not included in CED computation; ****2 x OEPA 1 x COPP 2 x ABVD 2 x JEB

Abbreviations: ABVD — doxorubicin 25 mg/m^2 on days 1 and 15, bleomycin 10,000 units/m^2 on days 1 and 15, vinblastine 6 mg/m^2 on days 1 and 15, dacarbazine 375 mg/m^2 on days 1 and 15; BCD — bleomycin 15 mg/m^2 daily, cyclophosphamide 600 mg/m^2 daily, dactinomycin 600 ug/m^2 daily for two days; BuCyEto — preparative regimen (cumulative dose) busulfan 16 mg/m^2, cyclophosphamide 120 mg/kg, etoposide 40 mg/kg; CED — cyclophosphamide equivalent dose; COPP — cyclophosphamide 650 mg/m^2 on days 1 and 8, vincristine 1.4 mg/m^2 on days 1 and 8, procarbazine 100 mg/m^2 on days 1–14, prednisone 40 mg/m^2 on days 1–14; CPT-SIOP-2009 — Intercontinental Multidisciplinary Registry and Treatment Optimization Study for Patients With Choroid Plexus Tumors – carboplatin 350 mg/m^2 on cycles 2, 4 and 6: on days 2 and 3, cyclophosphamide 1000 mg/m^2 on cycles 1, 3 and 5: on days 2 and 3, etoposide 100 mg/m^2 on cycles 1, 2, 4, 5and 6: on days 1–5, vincristine 1.5 mg/m^2 on cycles 1–6: on day 5; CyTreo — preparative regimen (cumulative dose) cyclophosphamide 120 mg/kg, treosulfan 36000 mg/m^2; Cx — chemotherapy; IE plus VAdriaC for Ewing's Sarcoma — vincristine 2mg/m^2 on day 1 only, doxorubicin 45 mg/m^2/day x 2 days, doxorubicin 35 mg/m^2/day x 2 days, cyclophosphamide 900 mg/m^2/day x 5 days, etoposide 100 mg/m^2/day x 5 days, ifosfamide 1800 mg/m^2/day x 5 days, total dose of doxorubicin 550 mg/m^2; JEB — carboplatin 600 mg/m^2 on day 1, etoposide 120 mg/m^2 on days 1–3, bleomycin 15 mg/m^2 on days 2, 9 and 12; OEPA — prednisone 60 mg/m^2 on days 1–15, vincristine 1.5 mg/m^2 on days 1, 8 and 15, doxorubicin 40 mg/m^2 on days 1 and 15, etoposide 125 mg/m^2 on days 1–5

Table 3. Responses provided by the male survivors (n = 17)

Variable	n (%)
Feel sexual desire Feel low sexual desire	16 (94.1) 1 (5.9)
Able to get an erection Unable to get an erection	17 (100) 0 (0)
Able to ejaculate Unable to ejaculate	17 (100) 0 (0)
Able to insert penis into vagina Unable to insert penis into vagina	15 (88.2) 2 (11.8)
Have a partner No partner	10 (58.8) 7 (41.2)
Sexual activities per week, median (min-max)	3 (0–10)
Libido*, median (min-max)	9 (3–10)
Do not use contraception Use contraception Barrier contraceptives *Coitus interruptus* Contraception used by partner	4 (23.5) 13 (76.5) 10 (76.9) 1 (7.7) 2 (15.4)
Trying to conceive at the moment, Not trying to conceive at the moment	3 (17.7) 14 (82.4)
Time trying to conceive (months), median (min-max)	1 (1–12)
Have biological children Do not have biological children	4 (23.5) 13 (76.5)
Time to conceiving (months), median (min-max)	2 (1–16)
Partner has children Did not know if the partner has children Partner does not have children	1 (5.9) 6 (35.3) 10 (58.8)
Azoospermic in semen analysis Did not undergo semen analysis	2 (11.8) 15 (88.2)
Received chemotherapy during adulthood Received radiotherapy during adulthood Take medication constantly	2 (11.8) 1 (5.9) 2 (11.8)
Close** relatives had fertility problems Close** relatives did not have fertility problems	1 (5.9) 16 (94.1)

*scored from 1 to 10; **defined as grandfather, father, brother, cousin

Table 4. Responses provided by the female survivors (n = 17)

Variables	n (%)
Normal puberty Delayed puberty	15 (88.2) 2 (11.8)
Age of menarche, median (min-max)	14 (12–17)
Regular menstrual cycle Irregular menstrual cycle	12 (70.6) 5 (29.4)
Have a partner Divorced No partner	10 (58.8) 2 (11.8) 5 (29.4)
Sexual activities per week, median (min-max)	1 (0–9)
Libido*, median (min-max)	5 (0–10)
Do not use contraception Use contraception Barrier contraceptives Hormonal contraceptives *Coitus interruptus* All types of contraceptives No answer	8 (47.1) 7 (41.2) 3 (42.9) 2 (28.6) 1 (14.3) 1 (14.3) 2 (11.8)
Have biological children Do not have biological children	7 (41.2) 10 (58.8)
Time to conceive (months), median (min-max)	3 (1–8)
Partner has children Partner does not have children The partner has never had another partner Has never have sexual relation	2 (11.8) 10 (58.8) 3 (17.6) 2 (11.8)
Experienced some fertility concerns No fertility problems	2 (11.8) 15 (88.3)
Had gynecological problems Did not have gynecological problems	3 (17.6) 14 (82.4)
Have been treated for infertility Treated with hormonal replacement therapy Close** relatives had fertility problems	0 0 0
Received chemotherapy during adulthood Received radiotherapy during adulthood Take medication constantly	2 (11.8) 1 (5.9) 4 (23.6)

*scored from 1 to 10; **defined as sister, mother, grandmother

not intend to conceive and did not have biological children (67.5%) at the time of the evaluation. The median time of conception after cessation of contraceptives in four males (23.5%) who had offspring was two months (range 1–16). Three males had one child each, one survivor had two healthy children. Two respondents (11.8%) underwent semen analysis, both were found to be azoospermic. Both were married or had a partner, one survivor was trying to conceive. One of the azoospermic males was treated for Ewing's sarcoma, diagnosed at 15 years of age (CED 35964 mg/m^2), another one – for Hodgkin's lymphoma, diagnosed at 12 years of age (CED 4571 mg/m^2). Another patient reported concerns potentially affecting reproductive health was chemo- and radiotherapy received beyond 18 years of age, one suffered from parotitis during childhood and one male reported impaired fertility as a family problem.

Perception of the reproductive health in females

The responses of female survivors are summarized in Table 4. Two (11.8%) out of 17 females reported delayed puberty. Median age of menarche was 14 (12–17) years — slightly delayed as compare to healthy Lithuanian population (13.5 years) [15]. Twelve (70.6%) participants had regular menstrual cycles, whereas 5 (29.4%) reported irregular bleeding. More than half of respondents (58.8%) were married or had a partner. Females reported median 1 (0–9) sexual activity per week, and 5 (0–10) points of libido on average. Seven (41.2%) survivors succeeded to conceive with a median time of conception was three [1–8] months after cessation of contraception. Eight (47.1%) females did not use any methods to avoid conception while the other half used different contraceptives (Tab. 4). The pregnancies terminated in seven full term pregnancies and three

miscarriages. Only two (11.8%) females reported fertility problems. However, gynecological concerns such as pelvic adhesion, polycystic ovarian syndrome, uterine leiomyomas /fybroids were more frequent. One participant suffered/ from a sexually transmitted disease, another one underwent surgeries of the uterus or ovaries. None of the participants were treated for infertility or sought for assisted reproduction, hormonal replacement therapy (HRT) or had family history of infertility. Two (11.8%) females reported having received chemotherapy or radiotherapy beyond the age of 18. Four respondents took daily medicines: Two (11.8%) were taking L-Thyroxine (both of them had children), one — *beta blockers*, the fourth one was on immunoglobulin replacement therapy due to a secondary immune deficiency following HSCT.

DISCUSSION

The current study is the first attempt to address the quality of reproductive health in Lithuanian childhood cancer survivors. The crosscut survey aimed at capturing impairments of reproductive health in a specific cohort of childhood cancer survivors known to have long-term late effects related to cancer treatment.

The most relevant limitation of our study is a low number of survivors who reported their experiences. The obtained results derived only from 34 out of 346 (9.8%) addressed survivors who fulfilled the questionnaires. More than half of the consignees (190, 54.9%) received the questionnaire but did not wish to participate in the survey. This fact raises a concern of feasibility to address such a delicate issue as reproductive and sexual health in childhood cancer survivors many years after treatment — the median follow-up of the respondents was 14 years. One could speculate that those who did have sexual or fertility worries were reluctant to disclose them or opted for the 'right to be forgotten' [16]. The stigma of cancer is still prevalent and many survivors prefer to avoid sharing their disease- or treatment-related experiences and its consequences. Some parents of very young children protected them from knowing that they were treated for cancer (personal experience), and presumably did not inform them about the mailed invitation. Other studies reported a variable response rate to the questionnaires regarding the reproductive function in childhood cancer survivors – the percentage of responders varied from 29.3% to 78.6% [13, 17–21]. A low response rate may suggest a response bias and limited ability to generalize the results. On the other hand, many survivors pointed out insufficient information on the impact of cancer treatment on fertility and its preservation options [6, 21–23]. Raising awareness of potential fertility harm after completion of therapy would facilitate the assessment of reproductive health in the future.

Of note, one third (34.7%) of our survivors did not receive the mail due to demographic changes in the country – the emigration rate in Lithuania was the third highest in the European Union in 2017 [24], young emigrants (20–34 years) comprising the largest group [25]. A high number of citizens who left their home country reflected a global trend of extreme mobility of young people. Thus, a pan-European system of surveillance of pediatric cancer survivors such as Survivorship Passport [26] would enable to provide an appropriate and timely care to this vulnerable population across Europe. The implementation of this digital tool translated to several European languages would facilitate access to the information on treatment and recommendations of care independently of the living place, at least in Europe.

The second limitation of the study was a retrospective way to retrieve data on treatment. In contrast to the cancer type distribution in all survivors eligible for the study (n = 346) who were treated mostly for leukemia [n = 165 (47.7%), Supp. 2] in the responders' cohort lymphoma was the predominant diagnosis [n = 15 (44.1%), Table 1]. The documentation analysis was limited to the study participants' records. As a consequence, the treatment applied was quite heterogenous, especially in the solid tumor group. Thus, only a descriptive data review could be carried out. Nevertheless, even in such a small and heterogenous group we could demonstrate much higher exposure to gonadotoxic drugs expressed as a significantly higher median CED in solid tumors as compared to leukemia and lymphoma ($p = 0.014$) as well as more complex treatment. Although there is no data comparing median CEDs across different types of childhood cancer, some studies have shown that solid tumors, particularly sarcomas, are treated with a high-dose alkylating agent therapy, which is related to males' infertility in the adulthood as well as treatment for Hodgkin lymphoma can cause infertility in males [17].

In our survey, the perception of sexual dysfunction among childhood cancer survivors was similar to that observed among healthy population: in males the rate of low sexual desire or difficulties in penetration did not exceed 11.2% that is comparable to the rate observed in young healthy Lithuanian males [27]. The results differ from data reported by other groups showing high prevalence of sexual dysfunction in childhood cancer survivors [28, 29]. The inconsistency is most probably attributable to a non-response bias as discussed above. There are no data on exact prevalence of infertility among healthy Lithuanian population. Datta et al., reported an infertility rate of 12.5% among healthy women and 10.1% among men in Britain [30]. According to World Health Organization, global infertility prevalence rates are difficult to determine, however, approximately one in every four couples in developing countries had been found to be affected by

infertility [31]. Specifically, adult cancer survivors encounter reproductive health worries as well – womens' pregnancy rates are quite low [32]. It seems that the adverse effect of systemic treatment was strongly related with a patient's age [33], therefore childhood cancer survivors are exposed at increased risk of infertility. Males are in a higher risk for hypogonadism and sexual dysfunction [34]. Both male and female survivors lacked knowledge about infertility and underestimated the risk of infertility [35]. In our study only few males had biological children and attempted to conceive probably due to the young age of the respondents (median current age was 25 years). However, in this small cohort study, two males were azoospermic, both were treated with high cumulative doses of gonadotoxic drugs, CED ≥ 4000 mg/m^2, which is known to be related to impaired spermatogenesis [17].

The percentage of men having low semen quality in male childhood cancer survivors (11.8%) are in parallel with semen quality of young men from the general population in Baltic countries (11–15% of them have low semen quality) [36]. Our study replicated the data published by other study groups who found that infertility was most prevalent among male survivors treated for sarcomas and Hodgkin lymphoma. In addition, the risk of permanent sterility was especially high when the cumulative dose of cyclophosphamide was greater than 7.5 g/m^2 [17, 37]. This finding raises a concern that the number of azoospermic survivors could be higher if semen analysis was offered as a routine follow-up investigation and points out on the relatively easy preservation of fertility in male adolescents.

Only a few of female participants reported delayed puberty, fertility-related or gynecological problems. None of the respondents was treated for infertility or used HRT, with 29.4% reported an irregular menstrual cycle. Few studies investigated the age of menarche of childhood cancer survivors. Some findings suggested that childhood cancer treatment including cranial radiation in girls resulted in a significantly earlier menarche [38]. Other stated that cranial irradiation appeared to have a minimal impact on the onset of puberty [39]. However, survivors of the central nervous system tumors appeared to be at significant risk of both early and late menarche associated with radiotherapy [40]. Our study did not include a comparison group, it would be insightful to compare reproductive health of survivors with their healthy siblings as it was done in some other studies [14, 41]. Data from other studies showed that female survivors are at a future risk of premature menopause (before 40 years) [42–44], they also had an increased risk of clinical infertility (> 1 year of attempts at conception without success) compared to siblings [41]. Our current study did not include a hormonal analysis that could have given a better estimation of the prevalence of sexual dysfunction. Other similar studies found that cancer survivors had significantly lower anti-Müllerian hormone and higher follicle-stimulating hormone levels [19, 45–48].

In addition, psychosexual and social problems of childhood cancer survivors could be taken into account as they were reported in other studies, such as lower rates of marriage and parenthood, delayed sexual intercourse, and concerns regarding the reproductive function [49, 50]. As the study included the survivors treated more than a decade ago, none of them was appropriately informed about the impact of the treatment on reproductive health. The availability of fertility preservation techniques was quite limited at that time. Due to the dramatic changes occurred in current practice, prospective counseling on fertility preservation must be offered to all patients and their families.

CONCLUSIONS

To summarize, we found a low prevalence of sexual dysfunction, fertility related or puberty disorders in childhood cancer survivors, however, considering a low response rate, the results should be interpreted with caution. Potential azoospermia after high CED in male patients should imply mandatory fertility preservation before treatment whenever possible. This study is the first attempt to address the quality of reproductive health in Lithuanian childhood cancer survivors that unraveled important concerns to be improved in clinical practice. Implementation and equal access to fertility preservation techniques (e. g. cryopreservation of semen and ovarian tissue) should be prioritized to minimize adverse effect of infertility after cancer therapy. An appropriate counseling of all cancer patients and families on potential adverse effect of the treatment on reproductive health would facilitate a highly warranted prospective research in a larger scale in the future.

Acknowledgments

Not applicable.

Conflicts of interest

The authors declare no conflict of interest.

Author contributions

ESR wrote the manuscript, ZB and ZG designed female questionnaire, RA and GV designed male questionnaire, ESR, MJ and RV collected and retrieved the data, ESR, KZ and JR analyzed the data, JR conceptualized and supervised the study. All authors contributed to the study conception, bioethical approval, critically revised the manuscript, agreed and approved the final version for submission.

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Perioperative lung ultrasound pattern changes in patients undergoing gynecological procedures — a prospective observational study

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ABSTRACT

Objectives: General anesthesia and positive pressure ventilation are associated with perioperative pulmonary complications. Lung ultrasound (LUS) is a method used to evaluate lung parenchyma. The purpose of this study was to evaluate LUS patterns in a cohort of women undergoing gynecological surgery with uncomplicated general anesthesia.

Material and methods: Patients were assessed according to the 8-zone LUS assessment protocol used to detect lung sliding, A-lines, B-lines, interstitial syndrome and lung consolidation. Each patient was screened at specific time intervals: before induction of anesthesia, at induction, 30 and 60 minutes after induction and within two hours after recovery.

Results: A total of 99 patients undergoing gynecological surgery with uneventful anesthesia from November 2017 to November 2018 were included in this study. A total of 426 LUS records were retained for further analysis. Overall, no significant changes to patients' A-line appearance were detected, regardless of the time of assessment. There was, however, an increase in the number of B-lines at the screening times of 30 and 60 minutes after induction, as compared to initial assessments ($p = 0.011$ and $p < 0.001$ respectively), and an increase in the number of positive regions (≥ 3 B-lines) at 30 and 60 minutes after induction and after recovery, as compared to initial assessment ($p < 0.001$; $p < 0.001$ and $p = 0.001$ respectively).

Conclusions: An uneventful anesthesia may predispose to abnormal LUS findings and should be considered while interpreting of LUS results in cases with perioperative pulmonary complications.

Key words: lung ultrasound; perioperative care; B-lines; interstitial syndrome

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INTRODUCTION

Lung ultrasound (LUS) is a well-recognized diagnostic tool. One benefit of this quick, easily repeated bedside assessment is to help diagnose possible reasons for patient deterioration, including alveolar consolidation, pulmonary edema, pneumothorax and pleural effusion [1–3]. There is a short learning curve when learning to use LUS technique, and high intra- and inter-observer reproducibility confirmed in rapid training for gynecologists and obstetricians [4].

There is growing evidence that LUS is a very useful tool for gynecologists and obstetricians. Published evidence concern COVID-19 obstetric patients, pre-eclamptic patients or pregnant patients during the last gestational weeks and labor where lung ultrasound is often performed by gynecologists and obstetricians [5–10]. Perioperative setting may also involve need of LUS assessment in case of respiratory complications.

The incidence of postoperative pulmonary complications (PPC) may be even up to 59% depending on the surgical patient population [11, 12]. Recently published reviews indicated a need for deeper exploration of perioperative ultrasound including scanning protocols, time intervals when scanning should occur and patient benefits [13].

Objectives

The goal of this study was to assess the LUS pattern and its changes in patients undergoing general anesthesia with positive pressure ventilation. The hypothesis behind the study was that even uneventful general anesthesia with positive pressure ventilation may cause visible changes in the LUS pattern.

MATERIAL AND METHODS

After receiving approval from the Ethics Committee of Jagiellonian University, Cracow, Poland (approval number:

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122.6120.142.2016; 23 June 2016), this prospective observational study was conducted in a single university hospital. All study participants gave written, informed consent to participate in the study before enrolment.

Patient participation was voluntary. The study population was composed of female patients scheduled for elective, gynecological procedures using general anesthesia and positive pressure ventilation. Patients chosen for this study were required to be 18 years of age or older and able to provide informed, written consent. Patients were excluded from this study if receiving pregnancy-related surgery, if the research personnel was unable to obtain all LUS assessments (i.e., the initial assessment before induction of anesthesia or any of the following within the study protocol time frames) or if patients were experiencing any respiratory or circulatory complications at the time of the study. Parameters of interest were assessed using standard perioperative monitoring devices (the Datex Ohmeda S/5 Aespire Patient Monitor, GE Healthcare Helsinki, Finland).

Data collection

Baseline patient characteristics were collected including age, weight, height, body mass index (BMI), ideal body weight (IBW) according to the Lorenz formula [14], American Society of Anesthesiologists Physical Status (ASA) [15], positive end expiratory pressure (PEEP), peak inspiratory pressure (PIP), perioperative fluids management, fraction of inspired oxygen (FiO_2) during induction and recovery from anesthesia, intra-abdominal carbon dioxide pressure during laparoscopy, type of surgery (laparoscopy, laparotomy, hysteroscopy), airway management (tracheal intubation versus supraglottic airway), patient's use of muscle relaxants, intravenous fluid volume, and duration of anesthesia. The LUS and parameters of interest were recorded before induction of anesthesia, at induction of anesthesia and 30 and 60 minutes after induction according to duration of surgery. The last LUS assessment was conducted in the recovery room within two hours after surgery.

Anesthesia

Since it was an observational study no changes were done to the anesthesia and intraoperative ventilator protocols and management used in the institution. Thirty minutes before induction of anesthesia, patients received 2mg of midazolam intravenously. General anesthesia was induced with propofol 2–3 mg kg^{-1}, fentanyl 1–2 µg kg^{-1} and, in cases of muscle relaxation, rocuronium 0.6 mg kg^{-1}. Maintenance of anesthesia was performed with oxygen/air mixture (FiO_2 0.4) and sevoflurane (0.8–1.2 of age adjusted expiratory minimal alveolar concentration), fresh gas flow 3 l min^{-1}. Ventilation rate (volume-controlled ventilation, I:E ratio of 1:2) was adjusted to maintain normocapnia with a tidal volume of 6–8 ml kg^{-1} IBW and PEEP of 2-5 cm H_2O. An infusion of intravenous crystalloid fluid therapy was initiated on each patient before induction of anesthesia. Patients received 0.5–1 mg of atropine and 2 mg of neostigmine intravenously to reverse the neuromuscular block.

Ultrasound protocol

There are various LUS assessment protocols that allow qualitative and quantitative assessment of dynamically changing LUS artefacts [16–18]. However, not all protocols are relevant to surgery in the supine position. For this reason, the 8-zone protocol, as defined in the "International evidence-based recommendations for point of care lung ultrasound" [19], was chosen for this study. All patients' lungs were assessed for the presence of lung sliding, A-lines, B-lines, interstitial syndrome [two or more bilateral positive regions (presence of three or more B-lines)], lung consolidation and pleural effusion using the 8-zone protocol [19]. For the initial and last LUS assessment, the patients were in a semi-recumbent position. During anesthesia, the patients were positioned in the Trendelenburg position according to their specific surgical needs.

All ultrasound assessments were conducted independently by two certified physicians (PK and AJ) experienced in the administration of LUS assessments. All ultrasound assessments were performed using the SignosRT instrument (Signostic Limited, Clovely Park SA, Australia) with a sector probe with lung pre-set and 10 cm of depth (3.0–5.0 MHz; Signostic Limited, Clovely Park SA, Australia).

Statistical analysis

A power analysis was conducted using data from preliminary study. A sample of 56 patients showed an overall 80% power for detecting the differences with a two tailed alpha of 0.05, as represented by the presence of three or more B-lines, 30 minutes after the "before induction" time point. In cases of normally distributed data, continuous data are presented as a mean value with standard deviation. Non-normally distributed data are presented as a median value with interquartile range. Normality was assessed using the Shapiro-Wilk test. Discrete data are presented as frequency and percentage.

The changes in the number of fields for A-lines, B-lines and ≥ 3 B-lines were assessed by pairing Wilcoxon tests with Bonferroni corrections over multiple comparisons. Comparisons of two repeated measures of dichotomic variables were made using the McNemar test. Analyses were conducted using R software (ver. 3.5.1; R Development Core Team, Austria, Vienna) [20]. Results with a p value < 0.05 were considered significant.

Table 1. Basic patient characteristics (n = 99)

Variables	Value	
Age [years] median (IQR)	39 (16)	
Weight [kg] median (IQR)	63 (19)	
Height [cm] mean ± SD	165.21 ± 6.51	
BMI [kg/m^2] median (IQR)	24.01 (7.04)	
IBW [kg] mean ± SD	57.61 ± 3.25	
Fluids administrated i.v. [mL] median (IQR)	850 (250)	
Intraabdominal laparoscopic CO_2 pressure [cm H_2O] median (IQR)	14 (1)	
PIP [cm H_2O] median (IQR)	17 (8)	
TV [mL] median (IQR)	425 (50)	
TV/IBW [mL/kg] mean ± SD	7.35 ± 0.74	
ASA (n)	ASA 1–2	93 (93%)
	ASA 3	6 (6%)
Type of surgery (n)	Laparoscopy	71 (71%)
	Laparotomy	14 (14%)
	Hysteroscopy	13 (13%)
	Missing data	1 (1%)
Muscle relaxants use	No	13 (13%)
	Yes	86 (86%)
Duration of surgery	≤ 1 h	55 (55%)
	> 1 h	44 (44%)
FiO_2 during induction and recovery from anesthesia	0.8	20 (20%)
	1.0	76 (76%)
PEEP (cmH_2O)	PEEP > 3	50 (50%)
	PEEP ≤ 3	49 (49%)

BMI — body mass index; IBW — ideal body weight; CO_2 — carbon dioxide; PIP — peak inspiratory pressure; TV — tidal volume; ASA — American Society of Anesthesiologists Physical Status; FiO_2 — fraction of inspired oxygen; PEEP — positive end expiratory pressure; IQR — interquartile range; SD — standard deviation

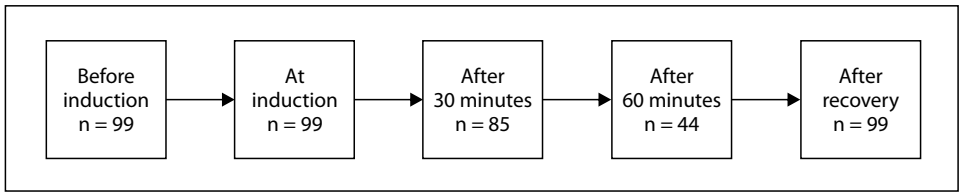

Figure 1. The study flowchart

RESULTS

One hundred patients were included in the study on a voluntary basis, from November 2017 to November 2018. One patient was excluded from the initial study group due to major bleeding and cardiovascular instability during surgery.

The following surgical procedures were performed: laparoscopic removal of non-malignant ovarian tumor – 35, laparoscopic supracervical hysterectomy – 23, diagnostic hysteroscopy – 13, laparoscopic diagnosis of infertility – 10, myomectomy – 8, gynecological oncology – 6, removal of tumor in a cesarean scar – 1, laparoscopic diagnosis of pelvic pain syndrome – 1, oncofertility – 1, sacrofixation in pelvic organ prolapse – 1.

Table 1 presents the patient characteristics. Figure 1 (study flowchart) presents the number of LUS assessments performed at specified time intervals. Four hundred and twenty-six records were collected for further analysis. All patients' vital signs were stable within normal ranges during surgery, and none demonstrated short-term PPC. Lung

Table 2. Frequency (percentage) of A-line, B-line, positive regions and consolidations detection according to the probe location during the 8-zone lung ultrasound assessment [19]

Variables	RUA	RLA	RBL	RUL	LUA	LLA	LBL	LUL
A-lines								
Before induction	80 (80.81%)	79 (79.8%)	65 (65.66%)	82 (82.83%)	68 (68.69%)	49 (49.49%)	73 (73.74%)	68 (68.69%)
After induction	72 (72.73%)	62 (62.63%)	72 (72.73%)	75 (75.76%)	80 (80.81%)	54 (54.55%)	68 (68.69%)	69 (69.7%)
30 minutes	46 (54.12%)	54 (63.53%)	55 (64.71%)	57 (67.06%)	52 (61.18%)	44 (51.76%)	60 (70.59%)	55 (64.71%)
60 minutes	30 (68.18%)	25 (56.82%)	25 (56.82%)	25 (56.82%)	23 (52.27%)	24 (54.55%)	29 (65.91%)	29 (65.91%)
2 hours after recovery	60 (60.61%)	56 (56.57%)	66 (66.67%)	63 (63.64%)	55 (55.56%)	47 (47.47%)	59 (59.6%)	67 (67.68%)
B-lines								
Before induction	21 (21.21%)	25 (25.25%)	26 (26.26%)	23 (23.23%)	22 (22.22%)	16 (16.16%)	32 (32.32%)	23 (23.23%)
After induction	24 (24.24%)	26 (26.26%)	25 (25.25%)	45 (45.45%)	29 (29.29%)	29 (29.29%)	37 (37.37%)	30 (30.3%)
30 minutes	37 (43.53%)	23 (27.06%)	20 (23.53%)	41 (48.24%)	31 (36.47%)	25 (29.41%)	39 (45.88%)	39 (45.88%)
60 minutes	25 (56.82%)	13 (29.55%)	13 (29.55%)	24 (54.55%)	16 (36.36%)	13 (29.55%)	31 (70.45%)	21 (47.73%)
2 hours after recovery	27 (27.27%)	33 (33.33%)	40 (40.4%)	29 (29.29%)	21 (21.21%)	24 (24.24%)	45 (45.45%)	41 (41.41%)
Positive regions (≥ 3 B-lines)								
Before induction	4 (4.04%)	4 (4.04%)	2 (2.02%)	6 (6.06%)	3 (3.03%)	1 (1.01%)	0 (0%)	1 (1.01%)
After induction	3 (3.03%)	2 (2.02%)	2 (2.02%)	9 (9.09%)	5 (5.05%)	0 (0%)	4 (4.04%)	7 (7.07%)
30 minutes	12 (14.12%)	5 (5.88%)	2 (2.35%)	14 (16.47%)	12 (14.12%)	0 (0%)	10 (11.76%)	16 (18.82%)
60 minutes	15 (34.09%)	5 (11.36%)	2 (4.55%)	13 (29.55%)	5 (11.36%)	0 (0%)	3 (6.82%)	8 (18.18%)
2 hours after recovery	10 (10.1%)	12 (12.12%)	12 (12.12%)	12 (12.12%)	5 (5.05%)	7 (7.07%)	0 (0%)	10 (10.1%)
Consolidation								
Before induction	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (1.01%)	21 (21.21%)	0 (0%)
After induction	0 (0%)	0 (0%)	1 (1.01%)	0 (0%)	0 (0%)	17 (17.17%)	0 (0%)	0 (0%)
30 minutes	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	12 (14.12%)	0 (0%)	1 (1.18%)
60 minutes	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	6 (13.64%)	0 (0%)	1 (2.27%)
2 hours after recovery	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (1.01%)	1 (1.01%)	23 (23.23%)	2 (2.02%)

Probe locations during the LUS assessment: RUA — right upper anterior; RLA — right lower anterior; RUL — right upper lateral; RBL — right basal lateral; LUA — left upper anterior; LLA — left lower anterior; LUL — left upper lateral; LBL — left basal lateral. Data are presented as frequencies (percentages)

sliding was present on all ultrasound areas of assessment. Records showed neither pleural effusion nor subcutaneous emphysema. Table 2 and Table 3 show the frequency (percentage) of ultrasound artefact detected during anesthesia and any changes to artefact over time.

Overall, no significant changes were detected in patients' A-line appearance, regardless of time of assessment. There was a general increase in the number of B-lines present at 30 and 60 minutes after induction, as compared to the initial assessment ($p = 0.011$ and $p < 0.001$ respectively), and an increase in the number of positive regions (≥ 3 B-lines) at 30 and 60 minutes after induction and after recovery, as compared to the initial assessment ($p < 0.001$ and $p < 0.001$ and $p = 0.001$ respectively). There was also an increase in the number of positive regions (≥ 3 B-lines) 30 minutes after induction, as compared to the number of positive regions recorded at induction ($p = 0.001$). The presence of at least one positive region was common and present in 26 (26%) patients at induction, 56 (66%) patients 30 minutes after induction, 37 (84%) patients 60 minutes after induction and 44 (44%) patients after recovery. At the time of 30 and 60 minutes after induction and after recovery there were more positive regions in upper than lower lung areas.

Lung consolidation was detected in single LUS assessment area in 21 pre-medicated patients before induction of anesthesia. After recovery twenty-three patients were found with consolidations in LUS. Their frequency of appearance did not reach statistical significance in the specific time frames.

Interstitial syndrome criteria [19] were met in six patients at different time frames: one before induction of anesthesia, one at induction, one at 30 minutes after induction. Three patients had interstitial syndrome after 60 minutes and within two hours after recovery. All six patients were offered FiO_2 1.0 during induction and recovery from anesthesia. Basic characteristics of these patients are present in Table 4. Due to small sample size logistic regression was not performed in those cases.

Table 3. Mean number of fields in 8-zone protocol with present artefacts in different time points

Mean number of fields in 8-zone protocol	A-lines	B-lines	≥ 3 B-lines
Before induction	5.7	1.9	0.21
After induction	5.58	2.47	0.32
30 minutes	4.98	3	0.84
60 minutes	4.77	3.55	1.16
2 h after recovery	4.78	2.63	0.69
Comparison			
Before vs after induction (n = 99)	p = 1	p = 1	p = 0.886
Before vs after 30 min (n = 85)	p = 0.58	p = 0.011	p < 0.001
Before vs after 60 min (n = 44)	p = 0.321	p < 0.001	p < 0.001
Before induction vs 2h after recovery (n = 99)	p = 0.241	p = 0.583	p = 0.001
After induction vs after 30 min (n = 85)	p = 1	p = 1	p = 0.001
After 30 min vs after 60 min (n = 44)	p = 1	p = 1	p = 1
After induction vs 2 h after recovery (n = 99)	p = 0.609	p = 1	p = 0.414

Table 4. Basic characteristics of the patient with interstitial syndrome detected in perioperative lung ultrasound

Patient	Age (years)	ASA	Interstitial syndrome presence	Duration of anesthesia (minutes)	BMI (kg/m^2)
1	35	1	After 30 minutes After recovery	85	18.3
2	38	1	After recovery	45	30.0
3	71	2	Before anesthesia At induction After recovery	25	25.4
4	33	1	After 60 minutes	80	19.5
5	41	2	After 60 minutes	150	23.0
6	72	2	After 60 minutes	180	22.6

ASA — American Society of Anesthesiologists Physical Status; BMI — body mass index

DISCUSSION

In the current study, we were able to identify frequent LUS pattern changes in a cohort of 99 women undergoing uneventful general anesthesia with positive pressure ventilation. There was a general increase in B-lines and positive region numbers (≥ 3 B-lines) related to anesthesia in the majority of patients. Interstitial syndrome was detected in six patients in different study time frames.

LUS assessment has previously been described in several critical care studies. In these studies, researchers used ultrasound to compare lung isolation techniques, assist with endotracheal intubation or during cricothyroidotomy. However, there is lack of data describing LUS patterns and their perioperative changes during anesthesia [13].

Ventilator induced lung injury include biotrauma, atelectrauma, barotrauma and volutrauma [21]. Lung injury is associated with mechanical power and relates to tidal volume, driving pressure, respiratory rate and positive end expiratory pressure [22].

Our study indicates that even short time intraoperative lung ventilation in group of patients with low risk of PPC [23] may induce development of abnormal LUS findings.

Results of this study show dynamic changes in LUS patterns when the LUS is performed at different intervals during general anesthesia. Several factors may contribute to B-lines during anesthesia including gravity, blood accumulation and increased lung water [18]. The increase in the appearance of B-lines and in the number of positive regions may be related to lung de-aeration during anesthesia [16, 18]. In our study we observed B-lines detected more often during anesthesia in upper areas of 8 zone protocol when patients were positioned in Trendelenburg position. This may suggest different cephalocaudal distribution of ventilation during anesthesia in Trendelenburg position.

Not all changes resolved within two hours after recovery from anesthesia; however, none of the patients presented any sings of short term PPC. The interstitial syndrome criteria [19] were met in six patients at different time frames, however the subgroup of patients was very heterogeneous. Abnormal LUS findings may affect interpretation of the LUS results in cases when patients develop PPC.

Lung consolidation found in LUS may be related to atelectasis developing through either compression of lung parenchyma or resorption of alveolar gas. Their localization would be mainly in dependent lung areas not accessible in 8 zone protocol [24], however in our study we were able to detect them which may result either from their major extent in perioperative period or their specific location in pericardiac area. In a similar group of patients undergoing laparoscopic surgery in the Trendelenburg position absorption atelectasis occurred more frequently with higher FiO_2 used during recruitment maneuvers [25]. Consolidations found before induction of anesthesia may result from hypoventilation secondary to premedication with benzodiazepines. Signs of atelectasis and pleural effusion in ASA1-2 patients were identified intraoperatively by Chun et al. when assessed with electrical impedance lung tomography [26]. The LUS pattern changes may be related to low PEEP levels observed in the study. However, optimal level of PEEP during intraoperative ventilation remains unknown [26–28].

This is a pilot study and has several limitations. First, was the inability to perform LUS assessment of posterior regions of the lungs, due to the ongoing surgical procedure. Further evaluation of the lung-dependent regions may reveal additional pattern changes to those revealed using only the 8-zone protocol. Secondly, LUS assessments were only conducted over short time intervals, which resulted from duration of surgery, instead of monitoring the patients for longer times during and post anesthesia. The number of pulmonary complications as well as additional LUS changes may increase in group of patients with risk factors, the study population was composed of patients without respiratory abnormalities [23]. Our study due to sample size was not designed to identify factors contributing to the LUS pattern changes. Thirdly, this study did not test patients' hemodynamic status, a status that may also play a role in LUS changes [29, 30]. Finally, different LUS settings and equipment than that used in this study may reveal other pattern differences [31].

CONCLUSIONS

In conclusion, abnormal LUS findings may occur during uneventful anesthesia in a healthy cohort of patients. This may significantly influence the interpretation of LUS results in cases of perioperative pulmonary complications.

Conflicts of interest

The authors declare no conflict of interest.

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Clinicopathologic characteristics and prognosis comparison of the uterine high grade endometrial carcinomas

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ABSTRACT

Objectives: Grade 3 endometrioid adenocarcinomas (G3 EAC), type two endometrial carcinomas (Type 2 EC), and also uterine carcinosarcomas (UCS) are considered as high-grade endometrial adenocarcinomas. The aim of this study was to compare the clinicopathologic features and survival of patients with UCS, G3 EAC, Type2 EC.

Material and methods: We included two hundred and thirty-five patients in this study. Patients were divided into three groups according to the type of tumor as uterine G3 EAC (group 1, n = 62), Type 2 EC (serous, clear and mixed types; group 2, n = 93), and UCS (group 3, n = 80). We compared the groups according to age, initial symptom, surgical approach, stage, myometrial invasion (MI), lymph node invasion (LNI), lymphovascular space invasion (LVSI), adjuvant therapy, and survival. When comparing the survival outcomes the Kaplan-Meier analysis was performed.

Results: The groups were similar according to age, menopausal status, nulliparity, initial symptoms, stage, LVSI, and LNI. Positive cytology was determined significantly more in group 3. There was a significant difference between the groups in terms of myometrial invasion degree. Optimal cytoreduction was similar among the groups. The primary adjuvant treatment was chemotherapy for UCS and Type2 EAC whereas radiotherapy was the main adjuvant treatment for G3 EAC. There were no significant differences among the groups according to overall survival (OS) (p = 0.290).

Conclusions: Although the survival difference among the groups can not be revealed, these patients have different clinical and pathological features and they should be considered as different groups.

Key words: endometrial cancer; high-grade endometrioid adenocarcinoma; overall survival; uterine carcinosarcoma; type 2 endometrial cancer

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INTRODUCTION

Endometrial cancer is the most common gynecological cancer according in developed countries [1]. Today, the diagnosis and classification of endometrial cancer is mainly based on morphological features and, when necessary, evaluation by immunohistochemical methods. The management of patients is decided based on the risk groups evaluated according to their clinical and pathological features [2]. Although surgical treatment is the basis of the treatment, adjuvant therapy (radiotherapy, chemotherapy and sometimes together) is recommended for patients at high risk [3]. There may be some problems, particularly in the management of patients with high-grade endometrial cancer (HGEAC). Grade 3 endometrioid adenocarcinomas (G3 EAC), type 2 adenocarcinomas (Type 2 EC), and also uterine carcinosarcomas (UCS) are considered as high-grade endometrial adenocarcinomas. Soslow et al [4]. recommends moving toward a binary scheme to grade endometrial endometrioid carcinomas by considering International Federation of Gynecology and Obstetrics defined grades 1 and 2 tumors as "low grade" and grade 3 tumors as "high grade." One thing is for sure that patients with high-grade carcinomas are at risk for recurrence and death [5]. Endometrial cancer is divided into two groups , type 1 and 2, according to their etiopathogenesis, clinical and pathological features by Bockman [6]. While endometrioid tumors constitute the type 1 group, non-endometrioid tumors (serous, clear cell and mixed) are accepted in type 2. Although advances in

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the classification and management of endometrial cancer according to its molecular characteristics are very current [7–9], Bockman's classification is still widely used due to its practical meaning [2, 3]. Approximately 15% of all cases are described in the high-risk group and mainly consisted of G3 EAC and type 2 non-endometrioid tumors [10]. Above 50% solid growth of endometrial neoplasm was defined as G3 EAC. UCS (malignant mixed mullerian tumors) are biphasic tumors (both carcinoma and sarcomatous) tumors with poor prognosis should be considered as an HGEAC [11].

Endometrial cancer is a heterogeneous group of cancer, not only in histopathological types but also in subgroups [12]. While there are many studies comparing type 1 and 2 endometrial cancer at molecular and histopathological levels [13–17], there are few studies comparing HGEAC in itself according to clinical features and prognosis [18–22]. The studies in the literature generally involve comparing the two groups, such as UCS vs G3 EAC. Therefore, we aimed to compare the clinicopathologic features and survival of patients with G3 EAC, Type2 EAC, and UCS.

MATERIAL AND METHODS

This study was performed by examining the data of 235 patients who were operated on in our clinic and had their follow-up between January 1996 and December 2016. Patients whose pathological examination was not performed in our faculty and who were not followed-up on in our clinic were excluded. There were 62 patients were in the G3 EAC group, 93 patients were in the type 2 EC and 80 patients were in the UCS group. Type 2 EC group consisted of 24 patients with serous EC, 16 patients with clear cell EC, and 53 patients with mixed type. The patients were evaluated in terms of age, main symptom (presenting symptom) menopause status, medical history (the previous cancer history and co-morbidity), surgical history (laporoscopy or laparotomy, in terms of omentectomy, bowel resection, and lymph node dissection), whether they achieved optimal cytoreduction and whether they performed secondary cytoreductive surgery due to recurrences. Stage, the degree of MI (It was separated as less than 50% and more), LNI, LVSI, the presence of positive cytology, the type of adjuvant treatment (radiotherapy, chemotherapy or both), and survival outcomes [disease free-survival (DFS) and overall survival (OS)] were evaluated and compared among the groups. The staging was performed according to the FIGO 2009. The primary surgical procedures were laparotomic or laparoscopic total hysterectomy and bilateral salpingo-oophorectomy (TH + BSO) and pelvic/para-aortic lymphadenectomy with or without omentectomy. A maximum residual tumor of < 1cm was the optimal cytoreduction. For high-risk patients, chemotherapy and radiotherapy was administered for systemic and locoregional control, respectively. Follow-up was performed in three months intervals within the first year, and then six months intervals up to five years. The time (months) between the surgery/ /diagnosis and death or last follow-up was defined as OS. The time (months) from surgery to disease progression or last follow-up was defined as DFS.

Data were analyzed using the SPSS software version 20.0 (IBM, Armonk, NY, USA). Comparisons the three groups were performed using the one-way ANOVA test. Bonferroni correction was used. A Chi-Square test was used for categorical data analysis. Results were demonstrated as mean ± SD and median (min-max), and n (%). All recorded p-values are two-tailed. With the Kaplan–Meier method, the effects of clinical variables and histopathologic subtypes on survival data were analysed. The differences of the survival curves were evaluated using the log-rank test.

RESULTS

Two hundred thirty-five patients were eligible for the study, 62 of them were in the G3 EAC (group 1) , 93 were in the type 2 EC (group 2), and 80 were in the UCS (group 3). There were no significant differences between the groups in terms of age. In groups, abnormal uterine bleeding was the main symptom, while abdominal distension was high in the group 2. We did not find a statistically significant difference between the groups regarding the menopausal status and medical history. But there were seven patients with history of another cancer, four of them had breast cancer and two of them had colon cancer and one of them had skin cancer in the group 3. Laparoscopic surgery was performed more in groups 1 and 2 than in group 3 (p = 0.002). Omentectomy rates were also significantly different between the groups (p = 0.001). Lymph node dissection rates were similar (p = 0.080). Rates of bowel resection, reaching optimal surgery, and secondary cytoreductive surgery were similar among the groups. In total, 26 patients underwent bowel resection. Secondary cytoreductive surgery was performed in 30 patients due to recurrence. The comparison of the groups in terms of demographic features and surgical approach is summarized in Table 1.

The groups were similar in terms of stage, LVSI and nodal involvement (p = 0.340, 0.071, 0.139; respectively). In the group 2, endometrium-limited polypoid tumors without myometrial invasion are more than the others (p = 0.001). Positive cytology is higher in the group 2 and 3 than the group 1 (p = 0.024). Adjuvant treatment options were significantly different between groups. While chemotherapy was the first adjuvant option in groups 2 and 3, patients in group 1 received radiotherapy as the first adjuvant option.

Mean OS was 50 months for group 1, 45 months in group 2, and 35 months in group 3. The difference between the groups in terms of OS did not reach a signifi-

Table 1. The comparison of the groups in terms of demographic features and surgical approach

	Studied groups (Mean ± SD, n%)			
	Group 1 HGEAC (n = 62)	**Group 2 Type 2 EAC (n = 93)**	**Group 3 UCS (n = 80)**	**p***
Age [years]	59.3 ± 10.2	61.7 ± 9.0	62.2 ± 10.4	0.194
Presenting symptom				0.010
Bleeding	45 (73%)	57 (61%)	66 (82%)	
Abdominal distention	5 (8%)	17 (18%)	4 (5%)	
Pain	5 (8%)	2 (2%)	5 (6%)	
Others	7 (11%)	17 (18%)	5 (6%)	
Postmenopausal status (+)	52 (83%)	49 (53%)	68 (85%)	0.583
Medical history				0.071
Previous cancer diagnosis	2 (3%)	0	7 (9%)	
Co-morbidity	30 (48%)	43 (46%)	30 (38%)	
Nodal dissection				0.080
None	16 (26%)	20 (22%)	7 (9%)	
PLN	7 (11%)	15 (16%)	5 (6%)	
PPALND	39 (63%)	55 (59%)	68 (85%)	
Omentectomy (infracolic or total))	26 (42%)	63 (68%)	42 (53%)	0.001
Colon resection	4 (6%)	8 (9%)	14 (18%)	0.169
Optimal cytoreduction	46 (74%)	73 (78%)	74 (93%)	0.214
Secondary cytoreduction surgery	8 (13%)	15 (16%)	7 (9%)	0.115

HGEAC — high grade endometrioid adenocarcinoma; Type 2 EC — type 2 endometrial cancer; UCS — utrerine carcinosarcoma; PLN — pelvic lymph node dissection; PPALND — pelvic-paraaotic node dissection; p* — the p values obtained by comparing all 3 groups using the one-way Anova test

cant level (p = 0.290). DS was significantly different among the groups (p = 0.019). The mean DFS was found to be 45 months in group 1, 29 months in group 2 and 19 months in group 3 (Tab. 2.). Figure 1 shows the prognosis of the groups in terms of OS. Figure 2 shows the prognosis of the groups for DFS.

DISCUSSION

In our study, we showed that all three groups were similar according to OS, whereas there was a difference between the groups in terms of DFS. The G3 EAC group had the best DFS, while the worst group was the UCS group. The number of studies comparing these groups is also limited. Because the frequency of this group of tumors is low, and the results of the current studies' results are limited and contradictory due to few cases numbers, difficulties in pathological evaluation and identification, inclusion criteria, and variety of adjuvant treatments.

When we look at studies comparing G3 EAC and type 2EAC, there are different results in terms of prognosis. Ayeni et al. compared 119 G3 EAC cases with 211 serous and 40 clear cell EAC [23]. They didn't show any differences with the prognosis in the groups. Myometrial invasion degree was found higher in the G3 EACs group like our results, but stage 4 disease was found higher in serous EC. Hamilton et al. [24] perform the widest comparison (serous n = 1453, clear cell n = 391, and G3 EAC n = 2316) using Surveillance, Epidemiology, and End Results Program (SEER data). This study showed that serous and clear cell type predict for lower survival rate. In another study comparing 52 patients with G3 EAC with 87 patients with serous EC, the prognosis in serous EC was reported to be worse than G3 EAC [25]. Similarly Crisano et al. showed that even in the early stage, type 2 ECs (serous n = 53, clear cell n = 18) have a higher recurrence rate and worse prognosis than other ECs (n = 509), including G3 EACs (n = 90) in accordance with the result of our study [26]. McGunigal et al. [27] also demostrated that G3 EAC had better prognsosis. Unlike the results of this study, there is also a study showing that serous and clear cell EC have better prognostic features similar to G3EAC for only stage 1 [27]. Soslow et al. [28] performed a comparison analysis among the G3 EAC (n = 89), serous EC (n = 61), and clear cell EC (n = 37) cases and they reported that there was no significant difference in the prognosis between these groups.

If we look at the studies comparing UCS with other HGEAC, our study showed a poorer prognosis in UCS. The groups were similar in terms of OS, however, in accordance with the literature, DFS was significantly shorter in UCS than the others groups. Previous studies compared the prognosis of UCS with G3 EAC [19–21, 29] and high-risk

Table 2. The comparison of the clinic/pathologic characterizations and survival

	Group 1 HGEAC (n = 62)	Group 2 Type 2 EAC (n = 93)	Group 3 UCS (n = 80)	p*
Stage				
1	32 (52%)	39 (42%)	44 (55%)	0.340
2	5 (8%)	14 (15%)	5 (6%)	
3	22 (35%)	35 (27%)	29 (36%)	
4	3 (5%)	5 (6%)	2 (3%)	
Myometrial invasion				
0	2 (3%)	18 (19%)	5 (6%)	0.001
< 50%	18 (%29)	34 (37%)	30 (40%)	
≥ 50%	42 (68%)	41 (44%)	45 (56%)	
LVSI				
–	14 (23%)	30 (32%)	29 (36%)	0.071
+	48 (77%)	63 (68%)	51 (64%)	
Nodal involvement	(n = 46)	(n = 70)	(n = 73)	
0	28 (60%)	49 (70%)	38 (52%)	
Pelvic	9 (20%)	8 (11%)	16 (22%)	0.139
Pelvic + PA	9 (20%)	13 (19%)	22 (30%)	
Cytology	n = 48	n = 65	n = 76	
negative	47%	54%	62%	0.024
positive	1 (2%)	11(17%)	14 (18%)	
Adjuvant therapy				
Chemotherapy	27 (44%)	65 (70%)	55 (69%)	0.002
Radiotherapy	48 (77%)	41 (44%)	37 (33%)	0.001
OS [month] median ± SD	50.0 ± 6.2	45.0 ± 7.3	35.0 ± 7.5	0.290
DS [month]	45.0 ± 6.7	29.0 ± 5.6	19 ± 3.7	0.019

HGEAC — high grade endometrioid adenocarcinoma; Type 2 EC — type 2 endometrial cancer; UCS — utrerine carcinosarcoma; LVSI — lymphovascular space invasion; OS — overall survival; DFS — disease free survival; p*— The p values obtained by comparing all 3 groups using the one-way Anova test

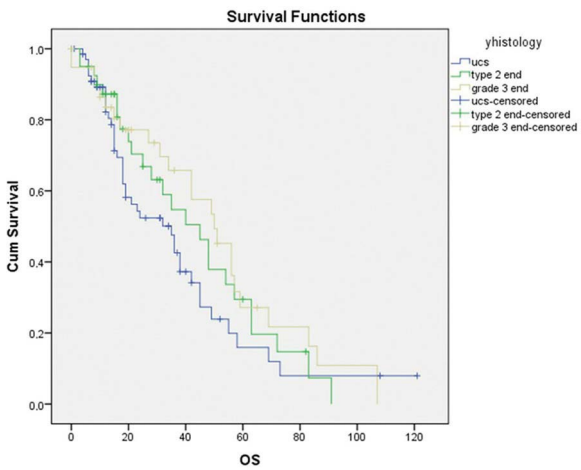

Figure 1. The comparison analysis of overall survival (OS) of the studied groups (ucs: uterine carcinosarcoma; Type 2 and: Type 2 endometrial cancer; Grade 3 and: Grade 3 endometrioid adenocarcinomas)

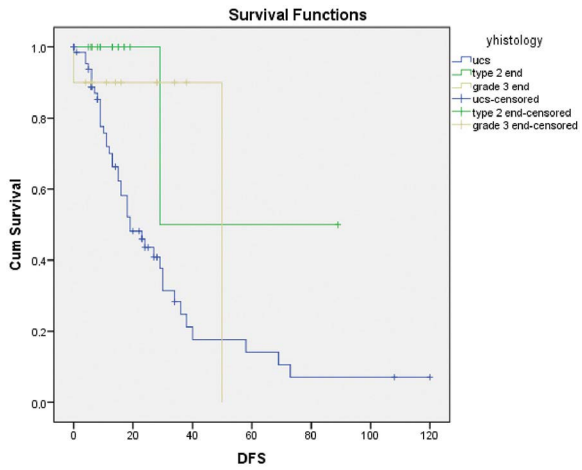

Figure 2. The comparison analysis of disease-free survival (DFS) of the studied groups (ucs: uterine carcinosarcoma; Type 2 and: Type 2 endometrial cancer; Grade 3 and: Grade 3 endometrioid adenocarcinomas)

endometrial cancer type including serous, clear, HGEAC [22, 30–32]. In a large scale study, a poorer five-year survival rate was found for all stages of UCS [19]. However, in another study similar results were reported for UCS with others [22].

There are four studies in the literature comparing the G3 EAC, type 2 EC, and UCS [22, 30, 34, 35]. Felix et al. compared the 81 UCS, 254 G3 EAC, 73 clear cell EC, and 147 serous EC cases. They showed similar results for the OS and recur-

rence free survival among the groups by the stratified stages [22]. The other study was performed by Amant et al. [30]. They evaluated 50 cases with G3 EAC, 54 cases with serous or clear cell EC, and 33 cases with UCS. The worst prognosis in this study was found in the UCS group, consistent with the results of other studies [34, 35]. However, in our study, this difference did not reach a statistically significant level. Amant et al. reported that the LNI was found higher in the UCS group than the others. There is also a significant difference among the groups in terms of LNI in the Felix et al. study [26]. LNI was not found different among the groups in our study. We found the positive cytology rate higher in the type 2 EC (20%) and UCS (18%) group compared to the G3 EAC (2%) group ($p = 0.024$). This rates were reported as 30% for UCS, 18.6% for type 2 EC, and 11.6% for G3 EAC group in the Amant et al.'s study ($p = 0.14$) [30]. While there was no difference in our study in terms of stage, the other two studies found a significant difference for the stages among the groups [22, 30]. In our study, there was a significant difference between groups in terms of adjuvant treatment options. While chemotherapy was the main adjuvant option in the type 2 EC group and the UCS group, radiotherapy was the main adjuvant treatment option in the G3 EAC group. Similar results were reported in the Felix et al study. But Amant et al. did not evaluated the adjuvant therapy option [30].

Although we had a relatively good number of cases (for only one center), more cases are needed to reveal differences in prognosis. Our evaluation was meant to reveal clinicopathological differences not only in terms of prognosis. It would not be appropriate to discuss the results of adjuvant therapy in these patient numbers. It is not easy to reach a conclusion for the studies on relatively rare group tumors. As a matter of fact, heterogeneity is high at the molecular level even in a single group [13, 14–17]. Increasing molecular studies show that these groups are very different tumors and therefore exhibit different clinical and prognosis.

CONCLUSIONS

As a conclusion, We did not show a significant difference among the groups in terms of prognosis, but there were differences among the groups in terms of prognostic clinical-pathological features. A better understanding of these tumors at the molecular level will allow them to be better managed.

Conflicts of interest

The authors declare no conflict of interest.

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An examination by year of cases applied with caesarean hysterectomy because of placenta percreta in a tertiary centre: a retrospective cohort study

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ABSTRACT

Objectives: To examine cases applied with caesarean hysterectomy because of placenta percreta by comparing changes in treatment strategies and complications according to year.

Material and methods: A retrospective examination was made of 93 patients applied with caesarean hysterectomy with a diagnosis of placenta percreta in 5-year periods of 2005–2009, 2010–2014, and 2015–2019. Demographic characteristics were recorded, and previous caesareans, history of myomectomy and curettage, gestational weeks, and infant birthweight. Intraoperative and postoperative findings were recorded as operating time, length of stay in hospital and Intensive Care Unit (ICU), transfusion requirement, the amount of erythrocyte suspension (ES) and fresh frozen plasma (FFP) transfused, and requirement for massive transfusion. Anaesthesia type, complications, and the preferred skin-uterus incision were also recorded.

Results: The 93 patients comprised 8 cases in the period 2005–2009, 23 in 2010–2014, and 62 in 2015–2019. The number of previous caesarean procedures was observed to increase in parallel with these case numbers. A significant increase was observed in the gestational week of birth, and infant birthweight, and a decrease in operating times. In later years there was seen to be a lower amount of ES and FFP transfused and fewer patients with massive transfusion. Preoperative diagnosis of placenta percreta, the highest preference for general anaesthesia, selection of midline vertical skin incision and uterine fundal incision were greatest in the period 2015–2019.

Conclusions: In cases with placenta percreta, of which there is an increasing incidence, maternal and infant outcomes can be optimised with prenatal diagnosis and planned caesarean hysterectomy by a multidisciplinary team with optimal prenatal preparation.

Key words: placenta percreta; cesarean hysterectomy; prenatal diagnosis; perinatal outcome

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INTRODUCTION

Placenta accreta spectrum (PAS) describes a disease spectrum in which there is abnormal adherence of trophoblasts to the placenta. In 79% of cases the most mild form of placenta accreta is seen, in 14%, placenta increta, and in 7%, placenta percreta is formed with the most morbidity and mortality. While there is superficial myometrial invasion in placenta accreta, there is deep myometrial invasion in placenta increta, and in cases of placenta percreta, the myometrial invasion reaching the uterus serosa reaches as far as surrounding tissue and organs. The greatest clinical problem is massive bleeding when attempting to remove the placenta from the uterus after delivery of the fetus [1, 2]. Even if the procedure is switched to hysterectomy, this intense bleeding can lead to multi-organ failure disseminated intrvascular coagulation and even death. Surviving cases, especially those with complications related to urinary system damage, require ICU admittance and transfusion-related complications may be seen [2, 3].

PAS occurs due to placental trophoblasts not attaching to scarred myometrium in the absence of a decidua basalis in a normal structure to which they would adhere secondary to endometrium damage [4]. The most common reasons for this endometrium damage are uterine surgery such as primarily caesarean procedures and myomectomy, and endometrial ablation applied by the cervical route, curettage and uterine artery embolisation [5].

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As more caesarean deliveries are performed, there has been a rapid increase over the years in the incidence of PAS. The incidence was first reported in 1937 by Irving and Hertig as 1 in 30,000 births, and this rate has now risen to 1 in 533 births [6, 7].

Significant changes have occurred in the 50-year process of the diagnosis and management of PAS cases. A fundamental change came in diagnosis of the disease with the use of ultrasonography in the preoperative period in the 1980s [8–10]. Just as preoperative diagnosis allows the referral of patients to specialised centres and the opportunity to be operated on under elective conditions, it is also useful in respect of obtaining the opinions of assistive branches such as interventional radiology, general surgery and urology. Moreover, identification of the disease in the preoperative period allows several surgical modifications to be made, ranging from modifications to the skin and uterus incisions to uterus-sparing procedures [1, 9, 10].

Objectives

The aim of this study was to examine cases applied with caesarean hysterectomy because of placenta percreta in our tertiary level clinic in the last 15 years by comparing changes in treatment strategies and complications according to year, and discussing these in the light of the relevant literature.

MATHERIAL AND METHODS

A retrospective examination was made of 125 patients applied with peripartum hysterectomy because of PAS in our university clinic between January 2005 and December 2019. From these cases, the study included 93 patients who were > 24 gestational weeks with the diagnosis of placenta percreta confirmed histopathologically, and with all data available. This study conforms with the principles of the 2008 Declaration of Helsinki and was approved by the Local Ethics Committee of our university.

A record was made for each case of demographic characteristics, previous caesareans, history of myomectomy and curettage, gestational weeks, and infant birthweight. Intraoperative and postoperative findings were recorded as operating time, rates and length of stay in the Intensive Care Unit (ICU), total length of stay in hospital, the need for transfusion, the amount of erythrocyte suspension (ES) and fresh frozen plasma (FFP) transfused, and rates of the requirement for massive transfusion. The type of anesthesia, complications of damage to adjacent organs, and the preferred skin-uterus incision were also recorded. To investigate the change in approaches and outcomes of the patients, all the cases were separated into 5-year periods of 2005–2009, 2010–2014, and 2015–2019.

Statistical Analysis

Data obtained in the study were analysed statistically using the Statistical Package for the Social Sciences vn. 21.0 software (SPSS, Armonk, New York, IL, USA). Conformity of continuous data to normal distribution was assessed with the Kolmogorov-Smirnov test. Quantitative variables were stated as mean±standard deviation (SD) and median range (minimum-maximum) values. Multiple group comparisons were made with ANOVA and the Tukey HSD test. Categorical data were stated as number (n) and percentage (%). A value of $p < 0.05$ was accepted as statistically significant.

RESULTS

The 93 patients comprised 8 cases in the period 2005–2009, 23 cases in 2010–2014, and 62 cases in 2015–2019. The increase in the number of cases was determined to be statistically significant ($p < 0.004$) (Fig. 1).

No statistically significant difference was determined between the groups in respect of patient age, BMI, gravida, parity, and history of myomectomy and curettage ($p > 0.05$ for all) (Tab. 1). The number of previous caesarean procedures was mean 1.74 ± 1.00 for the period of 2005–2009, 2.15 ± 0.95 for 2010–2014, and 2.79 ± 1.03 for 2015–2019, and the increase was determined to be statistically significant ($p = 0.012$).

In the examination of the intra-operative and postoperative findings, there was observed to be a statistically significant increase in the gestational week at which patients gave birth and a parallel increase in infant birthweight ($p = 0.026$, $p = 0.035$). When the operating times were compared, there was seen to be a statistically significant decrease in the times over the years ($p = 0.004$). No statistically significant difference was observed between the groups in respect of the rates of adult ICU admittance and the length of stay in ICU ($p = 0.157$, $p = 0.519$). The total length of hospital stay was found to be statistically significantly shorter in the period 2015–2019 compared to the earlier years ($p = 0.026$). No statistically significant difference was seen according to the years in respect of patients requiring transfusion and hypogastric artery ligation ($p = 0.215$, $p = 0.349$, respectively). As the years progressed there was determined to

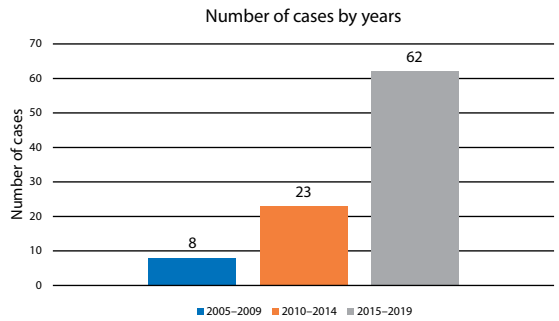

Figure 1. Number of cases by years

Table 1. Demographic characteristics of the cases

	2005–2009 (n = 8)	2010–2014 (n = 23)	2015–2019 (n = 62)	p value
Age [years]	33.20 ± 4.54	32.69 ± 3.62	34.24 ± 4.31	0.303
BMI [kg/m^2]	25.87 ± 2.30	26.34 ± 2.72	26.47 ± 3.29	0.468
Gravida	4.33 ± 1.86	4.40 ± 1.81	4.64 ± 0.99	0.756
Parity	3.40 ± 0.89	2.50 ± 1.29	2.85 ± 0.78	0.245
Number of previous caesarean procedures History of myomectomy History of curettage	1.74 ± 1.00 0/8 (0%) 2/8 (25%)	2.15 ± 0.95 1/23 (0.043%) 7/23 (30.4%)	2.79 ± 1.03 3/62 (0.048%) 15/62 (24.1%)	***0.012*** 0.521 0.622

Data are stated as mean ± standard deviation or number (n) and percentage (%). Significant p values are shown in bold and italics; BMI — body mass ındex

Table 2. Intra-operative and postoperative findings of the cases

	2005–2009 (n = 8)	2010–2014 (n = 23)	2015–2019 (n = 62)	p value
Gestational week Infant birthweight [g]	30.20 ± 6.61 2247.50 ± 376.29	34.21 ± 4.03 2508.75 ± 826.24	35.34 ± 4.80 2794.14 ± 944.24	0.026 0.035
Operating time [mins]	128.05 ± 36.48	110.54 ± 32.41	89.66 ± 27.23	0.004
Length of stay in adult ICU [days]	2.38 ± 2.14	2.50 ± 1.54	2.72 ± 2.02	0.519
Total length of hospital stay [days]	6.53 ± 3.12	5.02 ± 2.56	4.54 ± 1.43	0.026
Transfusion requirement (n/%)	7 (87.5%)	20 (86.9%)	50 (80.6%)	0.215
Transfused ES [units]	6.52 ± 2.94	5.94 ± 1.82	4.31 ± 1.91	0.039
Transfused FFP [units]	3.36 ± 2.12	2.00 ± 1.30	2.09 ± 0.83	0.041
Massive transfusion requirement (n/%)	6 (87.5%)	17 (73.9%)	19 (30.6%)	0.016
Hypogastric artery ligation (n/%)	2 (25%)	5 (21.7%)	12 (19.6%)	0.349

Data are stated as mean ± standard deviation or number (n) and percentage (%). Significant p values are shown in bold and italics; ICU — intensive care unit; ES — erythrocyte suspension; FFP — fresh frozen plasma

be a statistically significantly lower amount of ES and FFP transfused and fewer patients applied with massive transfusion (p = 0.039, p = 0.041, p = 0.016, respectively) (Tab. 2).

When all the cases were examined, the rate of preoperative diagnosis of placenta percreta was determined to be statistically significantly highest in the period 2015–2019 (p = 0.001).

The preference for general anaesthesia was determined to be statistically significantly higher in 2015-2019 compared to the other periods (p = 0.021). No difference was seen between the 5-year periods in respect of perioperative complications (p = 0.458). In the comparison of the change in skin and uterus incisions over the years, the preference of skin incision was observed to change from Pfannenstiel to midline vertical, and in parallel with this, there was a significant change in uterine incision from Kerr incision to fundal incision (p = 0.001) (Tab. 3).

DISCUSSION

For patients with a diagnosis of placenta percreta, caesarean hysterectomy is the current standard treatment, in which the infant is delivered far from the placenta (usually from the fundus) under elective conditions at an appropriate gestational week before the onset of labour and bleeding, and the uterine incision is closed without touching the placenta [11]. Cases with a confirmed preoperative diagnosis of placenta percreta in our clinic are applied with caesarean hysterectomy as standard.

In recent years, there has been an increasing trend in cases applied with caesarean hysterectomy because of placenta percreta in our clinic, and throughout the world [12]. The most common risk factor for placenta accreta is a history of caesarean delivery. A systematic review showed that this rate reached 50–67% in patients with placenta previa and a history of at least 3 caesarean deliveries [13]. In the current series, there was a noticeable increase in the history of caesarean deliveries according to the years. The increasing rate of caesareans throughout the world in the last few decades is the primary reason for the increase in the incidence of placenta percreta [1].

An interesting finding in the current series was that as the years progressed, there was an increase in the gestational week at which the infant was delivered and in parallel, an increase in infant birthweight. It was noteworthy that in the last 10 years, the cases were operated on at 34–35 weeks. When determining the optimal time of de-

Table 3. The rates of prenatal diagnosis, type of anaesthesia, incisions and complications of all the cases

	2005–2009 (n = 8)	2010–2014 (n = 23)	2015–2019 (n = 62)	p value
Prenatal Diagnosis of Placenta percreta				***0.001***
Yes	1	8	55	
No	7	15	7	
Type of Anaesthesia				***0.021***
General	4	13	59	
Regional	4	10	3	
Perioperative surgical complications				0.458
Bladder damage	2	4	15	
Ureter damage	0	1	1	
Intestine damage	0	0	0	
Skin incision				***0.013***
Pfannenstiel	8	10	10	
Midline vertical	0	13	52	
Uterine incision				***0.001***
Kerr	7	10	0	
Low vertical	1	0	10	
High vertical	0	3	2	
Fundal	0	10	50	

Data are stated as mean ±standard deviation or number (n) and percentage (%). Significant p values are shown in bold and italics

livery for these elective cases, both maternal and infant well-being must be taken into consideration, but there is no consensus as yet on this subject. The infrastucture of the neonatal ICU (NICU) and experience with pre-term infants at the hospital where the birth is to take place must also be considered. The success rates of most NICUs with newborns born after 34 gestational weeks are high. There is known to be an increased risk of maternal bleeding after the 36th gestational week [14]. Therefore, the optimal birthweek is recommended by the American College of Obstetricians and Gynecologists (ACOG) as 34^{+0}–$35^{6/7}$ [15] and by the Royal College of Obstetricians and Gynaecologists (RCOG) as 35^{+0}–36^{+6} [16].

Another interesting point of the current study was that lower amounts of blood products were transfused to patients in more recent years. In parallel, there was observed to be an increase in the rate of patients operated on with a preoperative diagnosis and shorter operating times. As the total amount of blood loss may be less in surgery under elective conditions compared to patients who start vaginal bleeding in the antenatal period and are operated on after losing blood from the vaginal route, there could therefore be less requirement for transfusion. However, another reason for shorter operating times and less bleeding could be that the operations of these types of cases under elective conditions are performed by more experienced surgeons. Therefore, a prenatal diagnosis is very important for these cases, so that surgery can be applied under elective conditions, and patients can be referred to centres where there are more experienced surgeons and a multidisciplinary approach is possible (obstetric surgeons, anaesthesiologists, neonatologists, interventional radiologists, blood bank and nursing personnel experienced in this subject) [17].

The preference of anaesthesia type for these cases was seen to have shifted over the years from regional anaesthesia towards general anaesthesia. This can be considered to be due to the increasing rate of diagnosis, because in caesarean cases where an unpredicted hysterectomy is made using a Pfannenstiel incision with no abnormal bleeding risk, the first choice is regional anaesthesia for reasons such as better postoperative pain relief, fewer adverse effects and more rapid recovery. However, in placenta percreta cases with a complex procedure applied with a large midline incision, where there is a greater possibility of more bleeding, hypovolemia and hemodynamic instabiity, the preferred anaesthesia method is general anaesthesia with a controlled airway [18]. In cases with suspected placenta percreta where a definitive diagnosis is needed intraoperatively, epidural anaesthesia can be applied as it can be later converted to general anaesthesia to be able to perform a hysterectomy.

The incision preferences were seen to have changed in recent years to a midline vertical abdominal incision and a fundal uterus incision. This is because in these patients diagnosed preoperatively with placenta percreta, the deci-

sion to perform hysterectomy has been made definitely before the operation. Although there are case series showing good results obtained with transverse incisions such as Pfannenstiel, Maylard and Cherney [19], when performing a hysterectomy in a large pregnant patient, it can be considered necessary to use a midline vertical incision to provide sufficient visualisation and to easily reach the uterus and the retroperitoneal large vessels. Another advantage of midline vertical incision is that it provides easy access to the uterine fundus when the infant has to be delivered far from the part of the uterus where the placenta has settled and in most cases this region is the uterus fundal section [11].

No significant difference was observed between the cases in this series in respect of complication rates. The majority of intraoperative complications are urinary system complications, most of which are bladder perforations at an incidence of up to 17% [20]. When there is placental invasion of the bladder and in the presence of very dense bladder adhesions, bladder complications are inevitable. Prenatal diagnosis and differences in incision type and the surgeon's experience can be considered not to have changed the rates of bladder complications.

There were some limitations to this study, primarily that when analysing the cases they were examined in 3 groups of 5-year periods. However, in the early years there were very few cases, and in more recent years there were many more cases. Therefore, to be able to statistically analyse the cases it was necessary to group them in this way. Another limitation could be considered to be that there were no follow-up data of the newborn infants of the cases.

CONCLUSIONS

There is an increasing incidence of placenta accreta, for which the primary risk factors are a history of caesarean delivery and placenta previa. A prenatal diagnosis can reduce morbidity and mortality. Ultrasound is the best imaging modality in prenatal diagnosis. The timing of the birth should be planned on an individual basis but is generally at 34–36 weeks. The standard treatment for placenta accreta is planned caesarean and hysterectomy. Maternal and infant outcomes can be optimised with a multidisciplinary team and optimal prenatal preparation.

Conflict of interest

The authors have no potential conflict of interests to declare.

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Hypoplastic left heart syndrome: from the prenatal to the postnatal period

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ABSTRACT

Objectives: To analyse a population of foetuses with prenatally diagnosed hypoplastic left heart syndrome (HLHS).

Material and methods: Retrospective study of foetuses diagnosed with HLHS between 2013 and 2017 in a referral centre.

Results: HLHS was found in 9.7% (65/665) of foetuses with cardiovascular abnormalities (CVA). As an isolated anomaly, HLHS was present in 40% of cases; in 24.5% other CVA were detected; in 14%, CVA and extracardiac anomalies; and in 21.5% only extracardiac malformations. Genetic disorders were present in 18.4% (12/65) of foetuses. 42% of cardiovascular and 25% of extracardiac anomalies were diagnosed postnatally. There were 10 (15.4%) elective terminations, 1 (1.5%) spontaneous foetal demise. Two newborns died after birth before surgery. Of the 52 children who underwent Norwood surgery, 13 (25%) died (9 with additional anomalies, and 4 with isolated HLHS). Of the 38 children who underwent stage II surgery, 2 (5.2%) with isolated HLHS died, and 1 (2.6%) with CVA.

Conclusions: A diagnosis of HLHS is an indication for a detailed examination of cardiac and noncardiac structures. It is advisable to consider genetic testing, together with the microarray assessment. The prognosis depends on underlying cardiac and extracardiac anomalies and coexisting genetic defects.

Key words: foetus; hypoplastic left heart syndrome; outcome; prenatal; postnatal

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INTRODUCTION

The term hypoplastic left heart syndrome (HLHS) refers to a group of abnormalities characterized by severe underdevelopment of the left heart structures such as hypoplasia of the left ventricle (Fig.1) with mitral atresia or stenosis, aortic atresia or stenosis, and hypoplasia of the ascending aorta (Fig.2) [1].

HLHS is proportionately one of the most common congenital cardiac defects diagnosed prenatally [2]. A prenatal diagnosis of HLHS affords the opportunity for counselling and perinatal planning. To provide parents with the most accurate counselling, the advice should be based on current experience. There are some discrepancies about accompanying anomalies and survival. In several clinical and autopsy studies considering HLHS, extracardiac anomalies and/or genetic disorders that could affect the survival of infants were noted in up to 37% of the infants [3–5]. Before the era of surgical treatment, HLHS was responsible for approximately 30% of deaths in the first week of life for reasons related to the cardiovascular system and was the most frequent cause of death for neonates with heart defects [6, 7]. Since the 1980s, when new surgical techniques were introduced, the prognosis for these patients has improved [8, 9], but the survival rates were lower in studies that included foetuses than in paediatric series [4, 10, 11]. However, most studies were conducted many years ago, and therefore, they may not reflect recent advances in the optimal management of infants with HLHS.

Therefore, the aim of this study was to present our experience with prenatally diagnosed HLHS to comprehensive analyse a population with HLHS, as well as the associated anomalies, neonatal outcomes and mortality rate in the first year of life.

MATERIAL AND METHODS

We retrospectively analysed cases of HLHS diagnosed during pregnancy between 2013 and 2017 in one Polish tertiary care referral centre for the prenatal diagnosis and management of foetal and neonatal pathology. We searched our computerized database for prenatally diagnosed HLHS,

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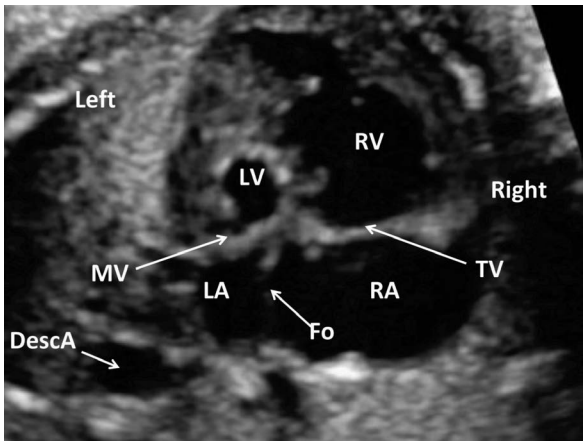

Figure 1. Four chamber view. Hypoplastic left ventricle with atretic mitral valve; DescA — descending aorta; Fo — foramen ovale; LA — left atrium; LV — left ventricle; MV — mitral valve; RA — right atrium; RV — right ventricle; TV — tricuspid valve

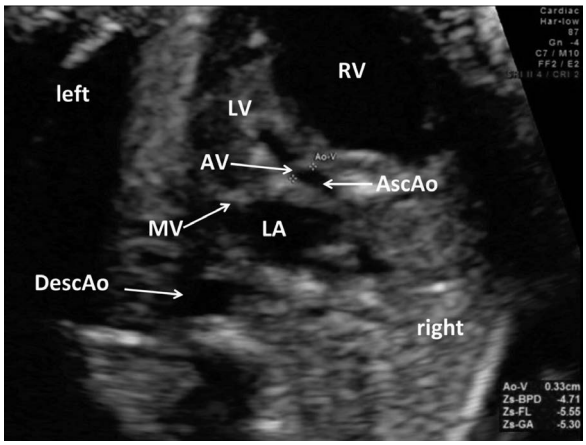

Figure 2. Left ventricle outflow tract with atretic aortic valve; AsAo — ascending aorta; AV — aortic valve; DescA — descending aorta; LA — left atrium; LV — left ventricle; MV — mitral valve; RV — right ventricle

defined as hypoplasia of the left ventricle with aortic atresia or stenosis and with mitral atresia or stenosis between January 2013 and December 2017. In these cases, cardiac topology was normal with concordant atrioventricular and ventriculoarterial relationships. Patients with minor variants of hypoplastic left heart suitable for biventricular repair, as well as with borderline hypoplastic left ventricle, were excluded. We did not include cases with critical aortic stenosis who underwent foetal aortic balloon valvuloplasty in the study.

During this period, 3654 foetal screening examinations were performed in pregnant women at an increased risk of having a child with a cardiac defect. Ultrasound examinations were carried out using a Voluson E6 (GE Healthcare Medical Systems, Milwaukee, WI, USA) system and included a detailed assessment of cardiac and noncardiac structures according to the national guidelines [12–14] and the International Society of Ultrasound in Obstetrics and Gynaecology [15]. Foetal heart examinations were performed using conventional 2-dimensional ultrasound, as well as colour and pulsed-wave Doppler ultrasound, by cardiologists and physicians specialized in prenatal diagnoses and foetal echocardiography. Detected cases were recorded at the National Registry for Foetal Cardiac Pathology (www.orpkp.pl) and reviewed by supervisors from foetal cardiac centres [14].

The parents were counselled by a paediatric cardiologist and/or cardiac surgeon and received detailed information regarding the defect and available options. Cardiac transplantation was mentioned during post diagnosis counselling as a therapeutic option, but it was not offered as an option at our institution or in Poland. The option of compassionate care was also discussed, but none of the parents selected this option.

The diagnoses of HLHS were confirmed by postnatal echocardiography, performed by experienced paediatric cardiologists, for live-born infants during their neonatal stay or based on autopsies for cases of stillbirth or termination. All patients were advised to undergo foetal karyotyping, including the exclusion of a 22q11.2 deletion and, since 2015, the use of array comparative genomic hybridization (aCGH). Foetal invasive testing was recommended whenever extracardiac anomalies or high-risk clinical factors coexisted with HLHS. Isolated HLHS cases were defined if they were not accompanied by any other intracardiac or extracardiac anomalies reported prenatally or postnatally. We also assessed foramen ovale (FO) to be restrictive in utero when the maximum diameter measured in a four-chamber view was ≤ 3 mm, with continuous high-velocity flow > 60 cm/s [16, 17] and reverse flow in pulmonary veins [18]. Data collected from the electronic medical records included gestational age at diagnosis, sonographic findings, karyotype testing results, and pregnancy outcome. In addition, we analysed the indications for referral for examination and the results of first-trimester screening for aneuploidy. First-trimester screening was performed following the Foetal Medicine Foundation, UK recommendations (www.fetalmedicine.org) [19, 20]. A nuchal translucency (NT) above the 95th percentile was considered abnormal. The long-term outcomes of the infants and children were determined. Postnatal follow-up for at least 12 months was available for 54 surviving patients (there was 1 loss to follow-up before stage II of surgery).

Data are described as the means and standard deviations or medians and ranges as appropriate. Categorical data are described as frequencies. Intergroup comparisons were made using the $\chi 2$ test, and $p < 0.05$ was considered significant.

RESULTS

Incidence and characteristics of foetuses with a prenatal diagnosis of HLHS

In a group of 665 foetuses with cardiovascular abnormalities diagnosed during the 5-year time period of the current study, HLHS was found in 65 (9.7%) cases and was more common in a male than in female foetuses (64.6% vs 35.4%). This corresponded to 1.8% (65/3654) of all foetal cardiac examinations performed during this period. All cases were diagnosed prenatally. During this time period, there was no case of HLHS that was diagnosed after birth at our institution. The average age of gravida was 29 years (Tab. 1), and in most cases, the pregnancy was low risk. Seven women were over 35 years old. For 32 women, the pregnancy was their first, and for 18 women, the pregnancy was high risk. Pregnancy loss was reported in 10 women, diabetes mellitus was reported in 2 women, and twin dichorionic pregnancies resulting from assisted reproductive technology were reported in 2 women. There was also 1 case of toxoplasmosis. For 54 (83%) cases, the reason for echocardiography was an abnormal four-chamber view.

The mean gestational age at diagnosis was 19 weeks. A total of 22 (33.8%) cases were detected in the first trimester, and 47 (72%) cases were detected at ≤ 22 weeks. First-trimester screening was performed for 51/65 (78.4%) cases, and a NT above the 95th percentile was noted in 14 foetuses (27.4%). Tricuspid regurgitation was found in 7 (14%) foetuses, a reverse a wave in the ductus venosus was found in 4 (8%) foetuses, and all these foetuses had an abnormal karyotype. Additionally, in 2 (4%) cases, there was ductus venosus agenesis.

Taking into account the anatomical type, the most common was aortic atresia with mitral valve stenosis or hypoplasia, making up 55% of cases (Tab. 1). Significant tricuspid regurgitation was found in 7 (10.7%) cases. Restriction of the foramen ovale, which required balloon atrial septostomy after birth (performed on average on the 4th day of life), was found in 4 (7.4%) cases at a mean gestational age of 36 weeks, and all children survived until hospital discharge. An intact atrial septum was detected and confirmed postnatally in one (1.8%) case at 16 weeks of gestation. In this case, balloon atrial septostomy was performed during the first five hours of life, but the infant died at 23 days of life after stage I surgery.

Foetal karyotyping was performed prenatally in 55 cases. In four cases, karyotyping was performed postnatally and was normal, and in three cases, karyotyping was performed post mortem because of dysmorphic features but showed a normal female karyotype. In three cases, the parents refused genetic testing, but detailed paediatric examinations after birth excluded the presence of any additional abnormalities. Chromosomal anomalies were detected in 12 (18.4%) cases. Five foetuses had monosomy 45X0, two cases had a 22q11.2 microdeletion, 2 cases had trisomy 13, two cases had trisomy 18, and one case had a 9p23deletion.

Among the 65 cases of HLHS, 26 (40%) had isolated HLHS, and 39 (60%) had associated anomalies.

Termination of pregnancy was chosen by 10 (15.4%) families: chromosomal anomalies were present in 7 cases, and HLHS was isolated in 3 cases. The rest of the families at the time of prenatal counselling as well as after delivery stated that they preferred aggressive neonatal interventional care. There was 1 case of intrauterine foetal demise at 18 weeks of gestation. Among the 65 cases, 54 (83%) live births were observed. The mean gestational age at delivery was 39 weeks, and preterm birth occurred in 2 cases. In 63% of cases were delivered vaginally. Caesarean section was performed in 22 women; 8 cases had caesarean sections due to suspected intrauterine foetal asphyxia, and 14 cases had elective caesarean sections, including one case of intact atrial septum.

The average birth weight was 3346 g. Four (7.4%) foetuses were diagnosed with intrauterine growth restriction (IUGR), and another two (3.7%) were small for gestational age (SGA).

On average, the neonates had an Apgar score of 9 at 1 minute, an oxygen saturation of 87.5% and a pH of 7.334. Of the 54 live-born foetuses, two (3.7%) died before treatment and were considered deaths for cardiac reasons. Thus, in our initial cohort of 65 foetuses, 52 (80%) were admitted to the cardiac surgical centre with intention to treat on average on the 3rd day of life and underwent first-stage Norwood surgery on average on the 11th day of life. Of these, 39 survived, and 13 died, leading to a Norwood operative survival rate of 75%. There was 1 loss to follow-up. Of the 38 children who underwent stage II surgery, 3 (7.9%) children died.

Foetuses with isolated HLHS

In 26 (40%) cases, HLHS was the only abnormality diagnosed prenatally and confirmed postnatally. In this group, neither the prenatal karyotype analysis nor the postnatal assessment showed any chromosomal abnormalities.

On average, the diagnosis was made at 21 weeks of pregnancy. First-trimester screening was performed in 19/26 (73.0%) cases, a NT above the 95th percentile was noted in 4 foetuses (21.0%), and tricuspid regurgitation was noted in 1 case. The diagnosis of HLHS was made during the first trimester in 7 cases (36.8%), of which aortic stenosis with mitral stenosis was present in 3 cases, aortic atresia with mitral atresia was present in 2 cases and aortic atresia with mitral stenosis was present in 2 cases.

An isolated form of HLHS was assessed as a type with aortic atresia with mitral stenosis in 69.2% of cases, while both aortic atresia with mitral atresia and aortic stenosis with

Table 1. Characteristics and outcomes of 65 foetuses with a prenatal diagnosis of hypoplastic left heart syndrome (HLHS)

Characteristics	Total n = 65	Normal intracardiac and extracardiac anatomy, n = 26 (40%)	Cardiovascular and extracardiac anomalies, n = 39 (60%)
Maternal age, years ± SD (range)	29.0 ± 4.7 (19–41)	28.3 ± 4.2 (20–36)	29.4 ± 5.0 (19–41)
Gestational age at diagnosis, weeks ± SD (range)	19.4 ± 6.4 (12–34)	21.4 ± 7.3 (12–34)	17.8 ± 5.0 (12–28)*
Diagnosis ≤ 22 weeks, n (%)	47 (72.3)	17 (65.4)	30 (77.0)
First trimester screening, n (%)	51 (78.4)	19 (73.0)	32 (82.0)
Diagnosis in the first trimester, n (%)	22 (43.1)	7 (36.8)	16 (50.0)
Male, n (%)	44 (67.7)	20 (76.9)	22 (56.4)
Abnormal karyotype, n (%): – trisomy 13, n – trisomy 18, n – monosomy 45,X0, n – 22q11.2 microdeletion, n – 9p23 deletion, n	12 (18.4) 2 2 5 2 1	0 (0.0) 0 0 0 0 0	12 (30.7) 2 2 5 2 1
Follow-up – TOP, n (%) – IUFD, n (%) – Live birth, n (%) – Death before surgery, n (%) – Death after stage I surgery, n (%) – Death after stage II surgery, n (%) – Lost to follow-up during the first year of life, n (%)	 10 (15.4) 1 (1.5) 54 (83.0) 2 (3.7) 13 (25.0) 3 (7.7) 1 (1.8)	 3 (11.5) 0 (0.0) 23 (88.4) 1 (4.3) 4 (18.2) 2 (11.1) 1 (3.8)	 7 (17.9) 1 (3.1) 31 (79.4) 1 (3.2) 9 (30.0) 1 (4.7) 0 (0.0)
Gestational age at birth, weeks ± SD (range)	39 ± 1.0 (36–42)	39.3 ± 1.0 (38–41)	39.0 ± 1.3 (36–42)
Preterm birth, n (%)	2 (3.7)	0 (0.0%)	2 (5.2)
Birth weight, grams ± SD (range)	3346 ± 545 (2000–4350)	3373 ± 496 (2300–4150)	3327 ± 594 (2000–4350)
Mode of delivery: – Caesarean section, n (%) – Vaginal delivery, n (%)	 22 (40.0) 32 (60.0)	 9 (40.0) 14 (60.0)	 13 (42.0) 18 (58.0)
SGA, n (%) IUGR, n (%)	2 (3.7) 4 (7.4)	1 (4.3) 1 (4.3)	1 (3.2) 3 (9.6)
Apgar score 1 min, median (range) 3 min, median (range) 5 min, median (range)	 9 (5–10) 10 (6–10) 10 (4–10)	 9 (5–10) 9.5 (6–10) 9 (8–10)	 9 (8–10) 10 (7–10) 10 (4–10)
Saturation, n (%)	87.5 ± 5.5	88.4 ± 3.2	86.8 ± 6.7
pH, n (%)	7.334 ± 0.056	7.322 ± 0.067	7.344 ± 0.045
Anatomical type MA/AA, n (%) MS/AS, n (%) MS/AA, n (%)	 15 (23.0) 14 (22.0) 36 (55.0)	 4 (15.4) 4 (15.4) 18 (69.2)	 11 (28.4) 10 (25.6) 18 (46.0)

*$p < 0.05$; HLHS — hypoplastic left heart syndrome; SD — standard deviation; TOP — termination of pregnancy; IUFD — intrauterine foetal demise; IUGR — intrauterine growth restriction; SGA — small for gestational age; MA — mitral atresia; MS — mitral stenosis; AA — aortic atresia; AS — aortic stenosis

mitral stenosis occurred with the same frequency of 15.4%. In this group, significant tricuspid regurgitation was noted in 2 cases, which was confirmed postnatally.

Termination of pregnancy was selected in 3 (11.5%) cases and performed at ≤ 22 weeks of pregnancy (the upper limit for termination in Poland). Among the 26 cases of isolated HLHS, 23 (88.5%) were live births. Restriction of the foramen ovale, which required balloon atrial septostomy after birth, was found in 3 (13.0%) foetuses. The mean gestational age at delivery was 39 weeks, and all pregnancies were at term. In 60% of cases, there was vaginal delivery. Caesarean section was performed in 9 women: 1 case had a caesarean section due to suspected intrauterine foetal asphyxia, and 8 cases had elective caesarean sections.

The average birth weight was 3373 g. One (4.3%) foetus was diagnosed with IUGR, and one (4.3%) was SGA. On average, the neonates had an Apgar score of 9 at 1 minute, an oxygen saturation of 88.4% and a pH of 7.322.

One neonate with isolated HLHS died due to a heart block on the second day of life before surgery. Of the 22 chil-

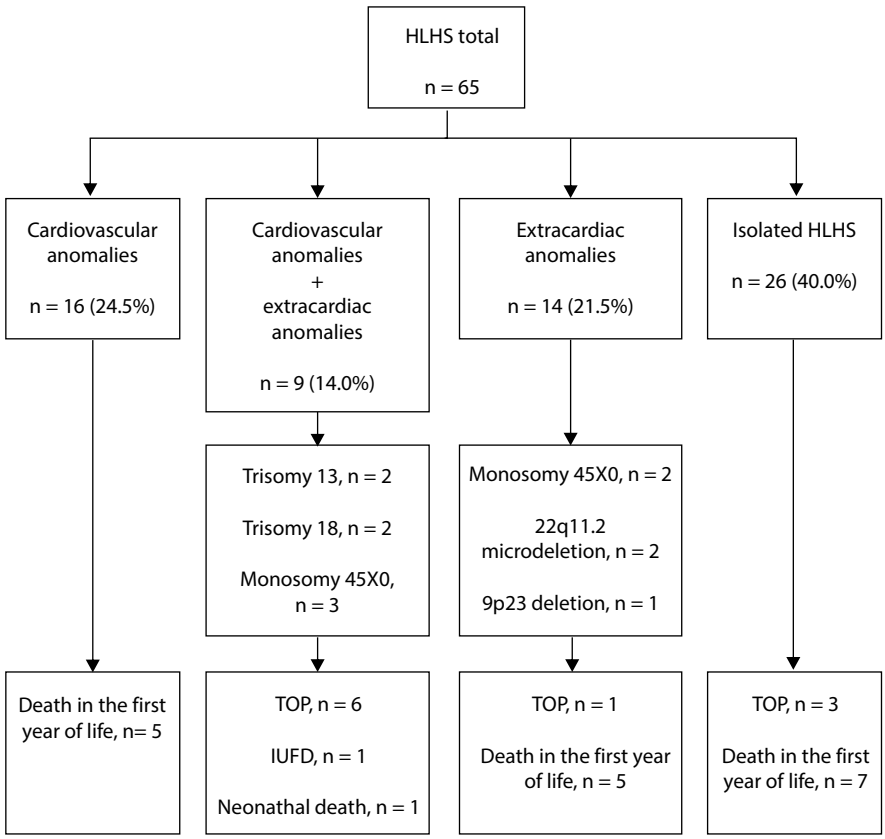

Figure 3. Hypoplastic left heart syndrome, associated conditions and outcomes of 65 foetuses; HLHS — hypoplastic left heart syndrome; IUFD — intrauterine foetal demise; TOP — termination of pregnancy

dren who underwent Norwood surgery, 4 (18%) children died. There was 1 loss to follow-up, and among 17 children who underwent stage II surgery, 2 (11.7%) died.

Foetuses with cardiovascular and extracardiac anomalies

In 39 cases of HLHS, additional anomalies were noted: 16 (41.0%) had cardiovascular anomalies, 9 (23.0%) had cardiovascular and extracardiac anomalies, and 14 (36.0%) had only extracardiac anomalies (Fig. 1). Chromosomal anomalies were detected in 12 (30.7%) cases, all of which had additional anomalies (Fig. 3). The most common heart defects were ventricular septal defects (VSDs), detected in 10 cases (40%). In the other 2 cases, postnatal echocardiography revealed atrial septal defects (ASDs). One foetus had a right aortic arch and one partial abnormal venous return. The most common vascular anomaly was a single umbilical artery, which was present in 24% of cases. A persistent left superior vena cava was found in 4 foetuses, and during first-trimester screening, agenesis of ductus venosus was detected in 2 foetuses, which was confirmed in subsequent scans.

The most common extracardiac abnormalities were foetal hydrops, which was found in 6 cases, accompanied by chromosomal abnormalities (Turner syndrome in 5 cases and trisomy 18 in 1 case). Additionally, in 6 cases, craniofacial anomalies were present, and in 6 cases, central nervous system anomalies were present. Gastrointestinal defects and genitourinary defects were also found (Tab. 2). Three cases of facial dysmorphia as well as squinting, blindness, deafness, tubular disorder and cryptorchidism were detected postnatally, accounting for 25% of extracardiac anomalies. Furthermore, 42% of cardiovascular anomalies were diagnosed postnatally (8 cases of VSD, 2 cases of ASD and 1 case of partial anomalous pulmonary venous return) (Fig. 4).

HLHS in the group of foetuses with anomalies was detected earlier than in the group with isolated HLHS ($p = 0.03$) (Tab. 1).

First-trimester screening was performed in 32/39 (82.0%) cases, and a NT above the 95th percentile was noted in 10 foetuses (31.2%). Among the foetuses with increased NT, 8 had chromosomal abnormalities, and in 2 cases a normal karyotype; however, tubulopathy with blindness was detected postnatally in 1 case, and dysmorphic features were detected in 1 case. Tricuspid regurgitation was found in 6 (18.7%) foetuses. A reverse wave in the ductus venosus was found in 4 (8%) foetuses, and all these foetuses had an abnormal karyotype. Additionally, in 2 (4%) cases, there was ductus venosus agenesis (Tab.3).

Table 2. Types of abnormalities found in association with hypoplastic left heart syndrome (HLHS)

Diagnosis	n
Type of cardiovascular anomalies associated with HLHS, n = 26	
VSD	10
ASD	2
RAA	1
PAPVR	1
Persistent LVCS	4
SUA	6
Agenesis of DV	2
Total	26
Extracardiac anomalies, n = 32	
Thymus hypoplasia/aplasia	2
Craniofacial defects, n = 6	
– Dysmorphic features/facial dysmorphia	3
– Cleft lip and palate	1
– Micrognathia	2
Skeletal defects, n = 3	
– Clubfoot	1
– Polydactyly	2
Polyhydramnios	1
Hydrops	6
Squint	1
CNS defects, n = 6	
– Mega cisterna magna	2
– Blindness	1
– Deafness	1
– CCA	1
– Ventriculomegaly	1
Gastrointestinal defects, n = 4	
– Situs inversus	2
– Omphalocele	1
– Hepatomegaly with echogenic foci	1
Genitourinary defects, n = 3	
– Hydronephrosis	1
– Tubular disorders	1
– Cryptorchidism	1
Total	32

ASD — atrial septal defect; CCA — corpus callosum agenesis; CNS — central nervous system; DV — ductus venosus; HLHS — hypoplastic left heart syndrome; LVCS — left vena cava superior; RAA — right aortic arch; SUA — single umbilical artery; VSD — ventricular septal defect; PAPVR — partial anomalous venous return

In the group of foetuses that underwent first-trimester screening for aneuploidy, the diagnosis of HLHS was made in 16 (50.0%) cases.

Termination of pregnancy was selected in 7 (22.5%) of the diagnosed 31 cases and performed at ≤ 22 weeks of pregnancy, and all of these cases had an abnormal karyotype (trisomy 13 in 2 cases, trisomy 18 in 2 cases, and Turner syndrome in 3 cases). There was 1 intrauterine foetal demise at 18 weeks of gestation (a case with Turner syndrome and hydrops in one twin of a dichorionic pregnancy).

In the group of HLHS with additional anomalies, the type was assessed as aortic atresia with mitral hypoplasia in 46% of cases, aortic atresia with mitral atresia in 28.4% of cases and aortic stenosis with mitral hypoplasia in 25.6% of cases. In this group, significant tricuspid regurgitation was noted in 5 cases, which was confirmed postnatally. Restriction of the foramen ovale, which required balloon atrial septostomy after birth, was found in 2 foetuses. In one case, an intact atrial septum was detected and confirmed postnatally, and a persistent left vena cava superior was described. In this case, after elective caesarean section, balloon atrial septostomy was performed during the first five hours of life, but the infant died at 23 days of life after stage I surgery.

Among the 39 cases of HLHS with additional anomalies, 31 (79.5%) were live born. The mean gestational age at delivery was 39 weeks. Two patients from the group with accompanying anomalies had a preterm birth at 36 weeks of gestation; one died at 12 days of life, and the second died at 64 days of life. In 58% of cases, there was vaginal delivery. Caesarean section was performed in 13 women; 7 cases had caesarean sections due to suspected intrauterine foetal asphyxia, and 6 cases, had elective caesarean sections.

The average birth weight was 3327 g. Three (9.6%) foetuses were diagnosed with IUGR, and the other foetus (3.2%) was SGA. On average, the neonates had an Apgar score of 9 at 1 minute, an oxygen saturation of 86.8% and a pH of 7.344. One neonate died on the second day of life before surgery because of sudden cardiac arrest, and during prenatal scans, an enlarged liver with hyperechogenic foci was observed. Of the 30 children who underwent Norwood surgery, 9 (30%) died, and among the 21 children who underwent stage II surgery, 1 (5.0%) died (Fig. 5).

DISCUSSION

Our data show that HLHS is successfully diagnosed during the first half of pregnancy, especially in cases where additional anomalies are present.

Moreover, the prevalence of underlying genetic causes as well as cardiovascular and extracardiac anomalies associated with HLHS is substantial. It reinforces the already known, but often overlooked, fact that patients with HLHS frequently have other noncardiac and/or chromosomal abnormalities that likely affect the outcome. In this study of children with prenatal diagnoses, we also show a better survival rate after the first two stages of surgical treatment than previously reported.

In approximately 72% of cases, the diagnosis was made before the 22nd week of pregnancy, which is consistent with the observations of other authors [4]. The diagnosis of HLHS was made early, around the 17th week, when associated anomalies were present, in contrast to cases of isolated

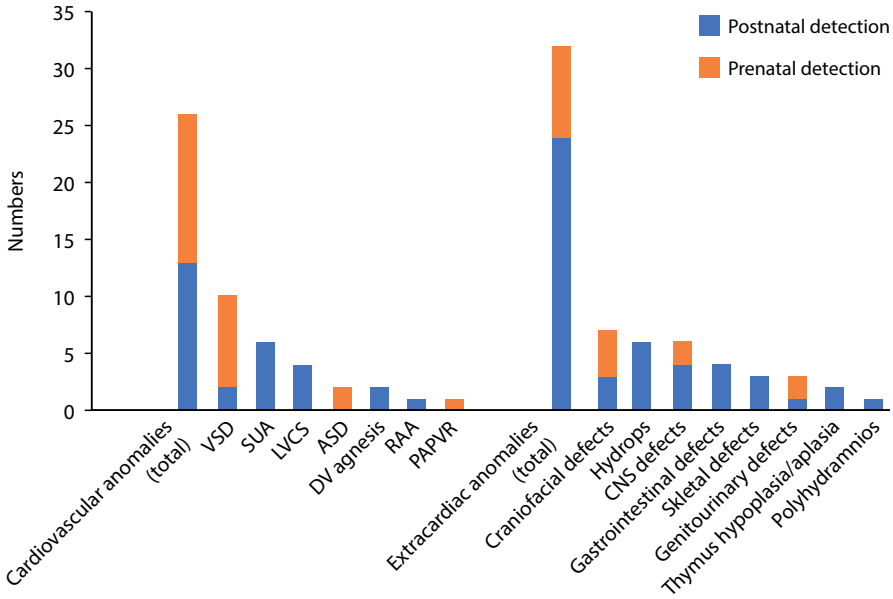

Figure 4. Hypoplastic left heart syndrome and associated anomalies detected prenatally and postnatally; ASD — atrial septal defect; CCA — corpus callosum agenesis; CNS — central nervous system; DV — ductus venosus; HLHS — hypoplastic left heart syndrome; LVCS — left vena cava superior; PAPVR — partial anomalous venous return; RAA — right aortic arch; SUA — single umbilical artery; VSD — ventricular septal defect

HLHS, where the diagnosis was made around 21 weeks of pregnancy. Interestingly, more than one-third of cases were diagnosed in the first trimester of pregnancy, and in the group with accompanying anomalies, as many as half of the cases that had undergone first-trimester screening were diagnosed with HLHS. Among the foetuses that were screened in the first trimester, the NT values in 27.4% of cases were above the 95th percentile. An NT measurement above the 95th percentile for the crown–rump length is thought to be predictive of congenital heart disease, including conditions on the HLHS spectrum [20, 21].

Early prenatal diagnosis has some important functions. First, it enables parents to be counselled in a timely and informed manner and to present information on prognosis and possible outcomes, including the option of elective termination of pregnancy. In our group, 15% of parents chose the termination option; this frequency is similar to that observed in the Rychik et al. study [22], where 11.7% of parents chose this option, but much lower than that reported in Europe (range 27–63%) [4, 23–25]. This allows us an opportunity to analyse outcomes in a cohort for which there is a high rate of "intention-to-treat" patients.

A prenatal diagnosis of HLHS has been shown to result in improved preoperative haemodynamics [26–28], reduced comorbidity [29] and a better surgical outcome [22]. However, some studies have suggested a worse prognosis for antenatally diagnosed HLHS, with a survival rate of only 38% in one study [30] and an improved rate of 64.5% in a later cohort [31], while in the studies reported by paediatricians, the survival rate after surgical treatment was up to 90% [10, 32]. In our study, the survival rate after the stage I stage Norwood operation was 75%, which is lower than that in the study by Rychik et al. [22], where the survival rate was 83.8%, but higher than that reported by other researchers [33]. Notably, the study by Rychik et al.[22] included variants of HLHS, namely, borderline hypoplastic left heart and atrioventricular septal defect.

The reasons for the worse prognosis are not clear, and this finding might indicate that the more severe spectrum of the disease is detected antenatally and that these babies would not have survived transfer to a specialist unit. Infants with an in utero diagnosis had a high frequency of complex risk factors, including prematurity, low birth weight, chromosomal anomalies, other extracardiac anomalies, additional intracardiac lesions, anatomical variants, and obstructed pulmonary venous return [34]. What is interesting, in our group FO restriction did not corresponded with higher mortality, what can be explained by the fact that it was not detected until 36 week of gestation. The study of Jadczak et al. [35] showed that earlier development and longer presence of FO restriction is associated with higher short-term mortality.

In our study, preterm delivery occurred in 2 cases, and these children died after stage I surgery. Growth disorders occurred in 6 (11%) cases, and additional cardiovascular and extracardiac abnormalities were found in approximately 60% of cases. Notably, approximately 25% of extracardiac defects and 42% of cardiovascular defects were detected only after birth. The incidence of extracardiac abnormalities reported in the literature varies between 3% and 62% [3, 34, 36].

Table 3. Characteristics of 39 foetuses with a prenatal diagnosis of hypoplastic left heart syndrome (HLHS) and associated anomalies

Case	GA at diagnosis (weeks)	NT	Associated anomalies	Karyotype	Perinatal outcome
1.	23	1.9 mm	DV agenesis, VSD	46,XY	Live birth
2.	19	1.2 mm	VSD	46,XX	Live birth
3.	20	2 mm	RAA	46,XY	Live birth
4.	13	1.7 mm	VSD	46,XX	Live birth
5.	13	2.4 mm	hypoplastic nasal bone, VSD	46,XY	Live birth
6.	25	1.4 mm	LVCS	46,XX	Live birth
7.	21	2.1 mm	LVCS	46,XY	Live birth
8.	21	1.9 mm	VSD, PAPVR	46,XY	Live birth
9.	13	1.5 mm	LVCS	46,XY	Live birth, death after stage I surgery
10.	23	2.0 mm	VSD	46,XY	Live birth
11.	21	1.8 mm	ASD, unroofed coronary sinus	46,XX	Live birth
12.	12	2.2 mm	SUA	46,XY	Live birth, death after stage I surgery
13.	26	2 mm	LVCS, RVCS agenesis, IUGR	46,XY	Live birth, death after stage I surgery
14.	21	1.6 mm	VSD	46,XY	Live birth, death after stage I surgery
15.	23	1.3 mm	VSD	46,XX	Live birth, death after stage II surgery
16.	19	1.8 mm; TR	ASD, TR	46,XY	Live birth
17.	12	3.3 mm;	SUA, reverse a wave in DV, polydactyly	47,XY,+13	TOP
18.	13	9.6 mm	One twin in dichorionic diamniotic pregnancy, hydrops	45X0	IUFD (18 weeks)
19.	13	2.8 mm	SUA, TR, micrognathia	47,XY,+18	TOP
20.	19	2.3 mm	VSD, deafness	46,XX	Live birth
21.	12	7.2 mm	Hydrops, omphalocele, hyperechogenic bowels, SUA	47,XX,+18	TOP
22.	12	12 mm	Hydrops, SUA	45X0	TOP
23.	13	2.9 mm	SUA	47,XY,+13	TOP
24.	12	11.2 mm	Hydrops in first trimester, SUA	45X0	TOP
25.	28	not done	VSD, CCA, facial dysmorphia	46,XX,dysmorphy	Live birth, death after stage I surgery
26.	21	2.1 mm	Cryptorchidism	46,XY	Live birth
27.	27	not done	Thymus aplasia, squint	46,XY,22q11.2 microdeletion	Live birth
28.	12	3.2 mm	Mega cisterna magna, facial dysmorphia, shortening of long bones, SGA	46,XX	Live birth, death after stage I surgery
29.	12	2 mm	TR, hydronephrosis	46,XY	Live birth
30.	13	4.5 mm	Hydrops	45X0	TOP
31.	25	not done	Situs inversus	46,XX	Live birth
32.	19	not done	Club foot	46,XY	Live birth, death after stage I surgery
33.	21	1.7 mm	Facial dysmorphia, IUGR	46,XX dysmorphia	Live birth, death after stage I surgery
34.	18	not done	Polyhydramnios, facial dysmorphia, thymic aplasia	46,XX, 22q11.2 microdeletion	Live birth
35.	20	not done	Enlarged liver with hyperechogenic foci	46,XY	Live birth, death on day 2
36.	12	6 mm	Hydrops 1tr	45X0	Live birth
37	20	not done	IUGR, mega cisterna magna, ventriculomegaly	46,XX, deletion in the region 9p23	Live birth, death after stage I surgery
38.	12	3.5 mm	Tubular disorder, blindness	46,XY	Live birth
39.	18	1.8 mm	Situs inversus	46,XY	Live birth

ASD — atrial septal defect; CCA — corpus callosum agenesis; DV — ductus venosus; GA — gestational age; HLHS — hypoplastic left heart syndrome; IUFD — intrauterine foetal demise (stillbirth); IUGR — intrauterine growth restriction; LVCS — left vena cava superior; NT — nuchal translucency; PAPVR — partial anomalous pulmonary venous return; RAA — right aortic arch; RVCS — right vena cava superior; SGA — small for gestational age; SUA — single umbilical artery; TR — tricuspid regurgitation; TOP — termination of pregnancy; VSD — ventricular septal defect

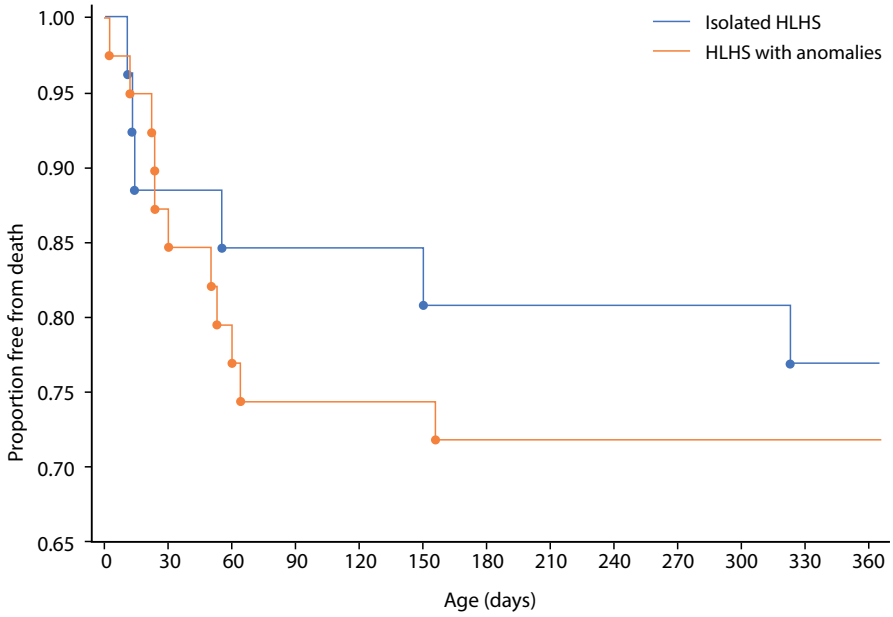

Figure 5. Kaplan Meier curve of survival to 360 days since birth after prenatal diagnosis of isolated hypoplastic left heart syndrome and hypoplastic left heart syndrome with associated anomalies

Such a wide variation in the frequency of additional defects may result from differences in the adapted definition of left hypoplasia syndrome as well as differences between the studied populations.

In a multicentre study, Song et al. [5] reported that isolated HLHS occurred in 62.8% of cases. However, in the study by Tennstedt et al. [37], only 38% of foetuses examined by autopsy were found to have isolated HLHS, which is consistent with our observations, where isolated HLHS occurred in 40% of cases.

The improvement in survival may reflect the fact that more anomalies associated with HLHS are now being noticed. Previous studies were based largely on findings by autopsy, in the context of which it was certainly difficult to detect the hearing and eye defects that were detected after birth in the patients included in our study.

Additionally, in the present study, genetic disorders were noted in 18% of cases, which is consistent with previous studies [3, 30, 34, 38]. Moreover Jansen et al. [39] showed that in left-sided congenital heart defects that appear isolated, with normal chromosome analysis and 22q11.2 FISH analysis, array analysis detected clinically significant copy number variants. All the abnormal karyotypes in our study were associated with additional cardiovascular and extracardiac structural anomalies. This is similar to observation by other studies that showed that in foetuses with isolated heart lesions, the rate of abnormal chromosomes with no anomalies on sonography was much lower than that when other anomalies were present [37].

Therefore, we suggest that all patients with HLHS should be thoroughly evaluated and undergo cytogenetic testing. Parents should also be informed that some defects can be detected only after birth.

There are several limitations to our retrospective study. First, we conducted an institutional, rather than a population-based, study that encompassed a small number of foetuses with HLHS. Our hospital provides excellent health care, including a neonatal oximetry screening programme. Conversely, as a tertiary care referral centre, our rate of associated anomalies may be overestimated because we care for higher-risk patients.

CONCLUSIONS

In summary, HLHS is currently diagnosed during the first half of pregnancy, giving parents the opportunity to decide the future of the pregnancy. A diagnosis of HLHS is also an indication for a detailed assessment of foetal anatomy, as the percentage of accompanying cardiovascular and noncardiac defects is significant. It is advisable to consider genetic testing, together with a microarray assessment, especially in cases of accompanying defects. It should also be noted that some of the anomalies can be detected only after birth. The survival rate of the foetal group after prenatal diagnosis after the first two stages of surgery is similar to those reported in paediatric analyses, but in the case of accompanying anomalies, the prognosis is poor.

Acknowledgments

None

Statement of Ethics

The institutional review board considered ethical approval for this analysis to be unnecessary since the sonographic evaluations were performed as an integral part of routine clinical visits to the ultrasound departments, for which informed consent had been obtained from the women. The scans were anonymized.

Conflict of interest

The authors have no conflicts of interest to declare.

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Maternal near-miss patients and maternal mortality cases in a Turkish tertiary referral hospital

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ABSTRACT

Objectives: This study aimed to estimate the incidence of maternal near-miss (MNM) morbidity in a tertiary hospital setting in Turkey.

Material and methods: In this retrospective study, we concluded 125 MNM patients who delivered between January 2017 and December 2017 and fulfilled the WHO management-based criteria and severe pre-eclamptic and HELLP patients which is the top three highest mortality rates due to pregnancy. Two maternal death cases were also included. The indicators to monitor the quality of obstetric care using MNM patients and maternal deaths were calculated. Demographic characteristics of the patients, the primary diagnoses causing MNM and maternal deaths, clinical and surgical interventions in MNM patients, shock index (SI) value of the patients with obstetric hemorrhage and maternal death cases were evaluated.

Results: The MNM ratio was 5.06 patients per 1000 live births. Maternal mortality (MM) ratio was 8.1 maternal deaths per 100 000 live births. SMOR was 5.14 per 1000 live births. The MI was 1.57%, and the MNM/maternal death ratio was 62.4:1. The SI of MNM patients with obstetric hemorrhage was 1.36 ± 0.43, and the SI of the patient who died due to PPH was 1.74.

Conclusions: The MNM rates and MM rates in our hospital were higher than high-income countries but were lower than in low- and middle-income countries. Hypertensive disorders and obstetric hemorrhage were the leading conditions related to MNM and MM. However, the MIs for these causes were low, reflecting the good quality of maternal care and well-resourced units. Adopting the MNM concept into the health system and use as an indicator for evaluating maternal health facilities is crucial to prevent MM.

Key words: maternal near-miss; maternal mortality; mortality index

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INTRODUCTION

Maternal mortality (MM) is still unacceptably high and remains a public health problem worldwide. It was reported that approximately 830 women die every day due to preventable causes related to pregnancy and childbirth-related complications, and the majority of these deaths occur in low- and middle-income countries [1]. Following the United Nations Millenium Development Goals signed in 2005, the goal of 'improving maternal health', which aims to reduce MM by 75% between 1990 and 2015, has been determined [2]. The number of maternal deaths, which was 390 000 in 1990, was 275 000 in 2015 with a decrease of 30% [3]. Although this target could not be met, it was stated that the reduction in maternal mortality has accelerated in many countries of the world after 2005. In Turkey, the maternal mortality rate was reported as 38.3 per 100 000 live births in 2005 and 14.7 per 100 000 live births in 2015 [4]. This remarkable improvement has been associated with several factors, such as increased birth rates in healthcare facilities, more available access to antibiotics and blood products, increased education and socioeconomic prosperity of women, and improvements in the provision of health care.

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The Sustainable Development Goals (SDGs), which adopted by all United Nations Member States in 2015, has the purpose of ending preventable maternal death by reducing the MM ratio by two-thirds by 2030 [5]. Since maternal deaths are rare even in facilites with comparatively high MM, the number of deaths is frequently insufficient to assess interventions aiming to improve maternal outcomes [6]. Also, maternal deaths are considered the 'tip of an iceberg' of severe maternal morbidity, in that for every women who dies many more women will survive serious pregnancy complications [7]. Therefore, maternal morbidity is a component of continuity that may reach from good maternal health to MM. In 2009, the WHO recommended the concept of maternal near-miss (MNM) for assessing the quality of maternal care for life-threatening pregnancy complications [8]. MNM patients have similar demographic characteristics and pathological processes as maternal deaths, with the advantages of giving a more significant number of cases for analysis, higher acceptability of individuals and facilities since death did not occur, and the opportunity of questioning the patient herself [9].

The WHO defined an MNM patient as a woman who nearly died but survived a complication that occurred during pregnancy, childbirth or within 42 days of termination of pregnancy [10]. Also, the WHO developed a tool to identify MNM patients. However, routine implementation and broader utilisation of the MNM concept as a standard tool for developing maternal care has been limited due to the lack of a standard description and unique case-identification criteria. There are three distinct approaches to identifying MNM: clinical criteria related to a specific disease entity, intervention-based criteria, and organ system dysfunction based criteria (Tab. 1) [10]. Depending on the region and the specific criteria used, the prevalence of MNM ranges from 0.5% to more than 40% of all live delivery hospitalizations [11]. However, there is currently no central database for MNM patients in Turkey.

This study aimed to estimate the incidence of MNM morbidity in a tertiary hospital setting in Turkey.

MATERIAL AND METHODS

We concluded 125 MNM patients who delivered at Department of Obstetrics and Gynecology of Diyarbakır Gazi Yaşargil Training and Research Hospital between January 2017 and December 2017 and fulfilled the WHO management-based criteria and severe pre-eclamptic and HELLP patients which is the top three highest mortality rates due to pregnancy [12, 13]. Two maternal death cases were also included. Our hospital is a tertiary center and about 25,000 deliveries per year occurred. The local ethical committee approved this retrospective study. Data were collected from our clinical database.

All patients were followed up in the intensive care unit (ICU) of the hospital. Patients who fulfilled the WHO management-based based criteria for MNM, severe pre-eclamptic patients and patients with HELLP syndrome were enrolled. In the WHO clinical criteria, pre-eclamptic patients with jaundice were classified [12]. Otherwise, we included severe pre-eclamptic patients because severe pre-eclampsia could be complicated. It should be a critical factor for MNM cases in obstetric practice, and it is a potentially life-threatening condition. Mild pre-eclampsia, mild hemorrhage, and other patients who did not meet the WHO criteria were excluded.

Patient characteristics including age, parity, the gestational week at birth, previous cesarean section history, mode of delivery, the primary diagnoses causing MNM and

Table 1. The WHO MNM criteria

Clinical criteria	Laboratory-based criteria	Management-based criteria
Shock	pH < 7.1 (severe acidosis)	Cardio-pulmonary resuscitation (CPR)
Gasping	PaO_2/FiO_2 < 200 mmHg	Continuous use of vasoactive drugs
Acute cyanosis	Lactate > 5	Dialysis for acute renal failure
Clotting failure	Oxygen saturation < 90% for ≥ 60 minutes	Transfusion of ≥ 5 units of red blood cells
Respiratory rate > 40/min (severe tachypnea) or < 6/min (severe bradypnea)	Loss of consciousness and the presence of ketoacids in urine	Intubation and ventilation for ≥ 60 minutes not related to anaesthesia
Oliguria non-responsive to fluids or diuretics	Creatinine ≥ 300 µmol/L or ≥ 3.5mg/dL	Hysterectomy due to infection or hemorrhage
Loss of consciousness lasting ≥ 12 hours	Bilirubin >100 µmol/L or > 6.0 mg/dL	
Loss of consciousness and absence of heart beat	Acute thrombocytopenia (< 50×10^3/µL)	
Stroke		
Uncontrollable fit/status epilepticus		
Jaundice in the presence of preeclampsia		

WHO — World Health Organization

maternal death, requiring clinical and surgical interventions, length of ICU stay, and length of hospital stay were recorded. The indicators to monitor the quality of obstetric care using MNM patients and maternal deaths were calculated.

Women with life-threatening conditions (WLTC) refer to all women who either qualified as having MNM or who died (WLTC = MNM + MD). MNM incidence ratio refers to the number of MNM cases per 1,000 live births (MNM IR = MNM/LB). MM ratio refers to the number of maternal death cases per 100 000 live births. Severe Maternal Outcome Ratio (SMOR) refers to the number of women with life-threatening conditions per 1,000 live births [SMOR = (MNM + MD)/LB]. Mortality index refers to the number of maternal deaths divided by the number of patients with life-threatening conditions [MI = MD/(MNM + MD)]. Shock index (SI) defined as the ratio of pulse to systolic blood pressure [14].

Statistical analyses

IBM SPSS 21.0 for Windows (SPSS Inc., Chicago, IL, USA) statistical package program was used for statistical evaluation of our research data. A descriptive analysis of the records was performed following completion of the audit. Continuous variables were presented as mean±standard deviation. Categorical variables were presented as frequencies and percentage.

RESULTS

During the study period, there were 25 088 deliveries and 24 693 live births in our hospital. A total of 125 MNM patients and two maternal deaths in the intensive care unit were identified. Therefore, there were 127 women with life-threatening conditions. The indicators to monitor the quality of obstetric care using MNM patients and maternal deaths are summarized in Table 2. The MNM ratio was 5.06 patients per 1000 live births. MM ratio was 8.1 maternal deaths per 100 000 live births. SMOR was 5.14 per 1000 live births. The MI was 1.57%, and the MNM/maternal death ratio was 62.4:1.

Demographic characteristics of the MNM patients and maternal death cases are summarized in Table 3. The maternal age of 70.4% of MNM patients ranged from 19–34 years, and 78.4% of MNM patients had parity between 1–4. Deliveries of 65.6% of the MNM patients were performed by cesarean section.

The primary diagnoses causing MNM and maternal deaths are summarized in Table 4. Severe pre-eclampsia, obstetric hemorrhage and HELLP were the most common primary diagnoses causing MNM, valuing for 54 (43.2%), 58 (46.4%), and 9 (7.2%), respectively. Less frequent diagnoses causing MNM were eclampsia and status epilepticus, valuing for 3 (2.4%), and 1 (0.8%), respectively. The diagnoses of maternal death cases were obstetric hemorrhage (one patient) and severe pre-eclampsia (one patient). Obstetric hemorrhage and hypertensive disorders had very low MI of 1.8% and 1.4%, respectively.

The mean SI value of MNM patients due to severe obstetric bleeding was 1.36 ± 0.43.

Table 5 presents that 125 patients with MNM underwent clinical and surgical interventions. Some MNM patients experienced more than one intervention. All MNM patients were hospitalized in the ICU and followed-up at the ICU until their clinical findings improved. Fifty-four patients underwent ≥five units of red blood cell transfusion, four patients

Table 2. The indicators to monitor the quality of obstetric care using maternal near-miss patients and maternal deaths

Indicators	
Total deliveries, n	25 088
Live births, n	24 693
MNM patients, n	125
Maternal deaths, n	2
MNM ratio, per 1000 live births	5.06
MM ratio, per 100 000 live births	8.1
SMOR, per 1000 live births	5.14
MI, %	1.57
MNM/maternal death ratio	62.4:1

SMOR — severe maternal outcome ratio; MI — mortality index; MNM — maternal near-miss

Table 3. Demographic characteristics of the patients

	MNM patients (n = 125)	Maternal deaths (n = 2)
Maternal age, n (%)		
≤ 18 years	1 (0.8%)	
19–34 years	88 (70.4%)	
≥ 35 years	36 (28.8%)	2 (100%)
Parity, n (%)		
0	19 (15.2%)	
1–4	98 (78.4%)	
≥ 5	8 (6.4%)	2 (100%)
Gestational week, n (%)		
≥ 34 w	72 (57.6%)	
< 34 w	53 (42.4%)	2 (100%)
Previous cesarean, n (%)		
No	79 (63.2%)	2 (100%)
Yes	46 (36.8%)	
Mode of delivery, n (%)		
Vaginal	43 (34.4%)	1 (50%)
Cesarean	82 (65.6%)	1 (50%)

MNM — maternal near-miss

Table 4. The primary diagnoses causing maternal near-miss and maternal deaths

Causes	MNM patients (n = 125)	Maternal deaths (n = 2)	Mortality index
Obstetric hemorrhages, n (%)	54 (43.2%)	1 (50.0%)	1.8%
Shock index, mean ± std	1.36 ± 0.43	1.74	
Hypertensive disorders, n (%)	70 (56.0%)	1 (50%)	1.4%
Severe pre-eclampsia, n (%)	58 (46.4%)	1	1.7%
HELLP, n (%)	9 (7.2%)	–	–
Eclampsia, n (%)	3 (2.4%)	–	–
Status epilepticus, n (%)	1 (0.8%)	–	–

MNM — maternal near-miss

Table 5. Clinical and surgical interventions in maternal near-miss patients (n = 125)

Intervention	n (%)
ICU admission	125 (100%)
≥ 5 units of red blood cell	54 (43.2%)
Hysterectomy following hemorrhage	4 (3.2%)
Continuous use of vasoactive drugs	2 (1.6%)
Intubation and ventilation	1 (0.8%)
Dialyses for acute renal failure	1 (0.8%)

ICU — intensive care unit

underwent a peripartum hysterectomy, two patients experienced continuous use of vasoactive drugs, one patient underwent intubation and ventilation, and one patient experienced dialysis for acute renal failure. Also, eight patients with severe postpartum bleeding experienced intrauterine balloon tamponade, and two of the patients who underwent peripartum hysterectomy had simultaneously undergone bilateral internal iliac artery ligation.

The mean duration of ICU stay in MNM patients was 2.6 ± 0.4 days, and the mean length of hospital stay was 5.8 ± 0.6 days.

When we examined maternal death cases, one was a severe postpartum hemorrhage patient due to postpartum atony. The SI of this patient was 1.74 and died to hypovolemic shock despite massive blood transfusion. The other maternal death case had acute respiratory distress syndrome due to severe pre-eclampsia.

DISCUSSION

The present study utilised the WHO MNM standard audit tool for describing and examining MNM patients, as well as calculating proposed indicators. The WHO management-based criteria were strictly followed to classify patients as MNM. However, we modified the WHO list of MNM to include the added categories of severe pre-eclampsia and eclampsia. Since MNM patients are related predominantly to organ system dysfunction, and pre-eclampsia/eclampsia are spread across multiple organ systems, the WHO audit tool cannot define the exact rate of MNM patients.

The MNM ratio may vary due to the wide variation in the identification of MNM patients. Also, the MNM ratio is higher in low- and middle-income countries [15]. This study revealed the incidence of MNM to be 5.03/1000 live births, which is comparable to studies in Australia and the Netherlands, with rates of 7.0, and 7.1, respectively [16, 17]. In a study conducted by Nelissen et al. [18], the MNM ratio in Tanzania was much higher when compared to our study, which reported 23.6/1000 live births. However, our MNM ratio was higher than in various high-income countries, including Scotland, the UK and Canada, where the MNM ratio was 1.34, 1.2, and 0.7, respectively [19]. This result could be explained firstly by the fact that we have a less-developed health system; secondly, we used a more comprehensive description of MNM, which involved severe pre-eclampsia and eclampsia patients.

This study found that hypertensive disorders and obstetric hemorrhages were frequent contributors to MNM, consistent with the literature [20]. Also, these leading underlying causes are similar to the top causes of MM. This similarity proves that the concept of MNM can be a placeholder for MM. The MM ratio in our study was 8.1 per 100 000 live births, which is lower than the national level of 14.7 per 100 000 live births, and lower from worldwide [4]. The ratio of MNM patients to MM was 62.4 to 1. This ratio was 49 to 1 in Scotland, 53 to 1 in the Netherlands, and 117 to 1 in the UK [17, 19]. Therefore, for studies attempting to confirm a notable improvement in outcomes by intervention, the number of subjects required to show a notable difference with MNM as an outcome would be much less than if MM only was the outcome [6]. Also, the higher ratio of MNM events to MM indicates better quality of care. This ratio was observed to be lower in poor resource settings in Asia and Africa when compared to high-income countries [19]. In an Indian study conducted by Abha et al. [21], this ratio was 2 to 1.

The overall MI was 1.57%, which is comparable to the studies from developed countries [19]. The MI was 1.8% for obstetric hemorrhages, and 1.4% for hypertensive disorders. The lower MIs for MNM patients in our hospital indicates the quality of maternal care and a functional health system. The WHO reported that obstetric hemorrhage was the leading cause, with postpartum hemorrhage (PPH) accounting for 2/3 of all maternal deaths. Severe PPH may cause to multiorgan dysfunction and requires multidisciplinary strategies in well-resourced units. The availability of uterotonics, blood and blood products, and interventions to end hemorrhage are crucial to improving standards of maternal health care [22]. Tahaoğlu et al. reported that the incidence of emergency peripartum hysterectomy was 0.77 per l000 live births in the same population in 2013 [23]. In this study, the incidence was 3.2% in MNM patients. Also, previous researches have reported a higher case mortality rate of hypertensive disorders, and was stated to be due to insufficient management of these cases [8]. In our clinical protocol, all MNM patients with hypertensive disorders received Magnesium sulphate treatment in ICU. The ICU follow-up rate among MNM patients is low, and most deaths occurred without being accepted into ICU [8]. Otherwise, in this study, there were no patients with puerperal sepsis, which has been responsible as many as 30% of maternal deaths in low and middle-income countries [20].

The hemodynamic changes of gestation may mask the impending hypovolemic shock, causes conventional vital signs to be less helpful, and signs taken in isolation may neglect impending deterioration [14]. Lee et al. [24] reported that a shock index higher than 0.9 had high sensitivity and specificity for prediction of massive transfusion and invasive procedures. El Ayadi et al. [14] recommended a shock index threshold of ≥ 1.4 indicating an urgent need for intervention, and ≥ 1.7 indicating a high risk of adverse outcome. In this study, the SI of MNM patients with obstetric hemorrhage was 1.36 ± 0.43, and the SI of the patient who died due to PPH was 1.74.

There are some limitations to this study. This study has been designed retrospectively and has the potential to contain limitations of such studies. Because of the dependence on information reported in the patient record, we could not identify risk factors for all MNM patients. The study was conducted for a one-year duration, so the number of patients were not adequate to conclude the less frequent causes of MNM. Our hospital is a tertiary referral center, and the hospital-based data might have cause to overestimating MNM and MM ratios due to the concentration of referral MNM events. Nevertheless, we can say that this bias may affect the MI to a lesser extent considering that most women with MNM are treated in hospitals.

CONCLUSION

The MNM rates and MM rates in our hospital were higher than high-income countries but were lower than in low- and middle-income countries. Hypertensive disorders and obstetric hemorrhage were the leading conditions related to MNM and MM. However, the MIs for these causes were low, reflecting the good quality of maternal care and well-resourced units. Adopting the MNM concept into the health system and use as an indicator for evaluating maternal health facilities is crucial to prevent MM.

Conflict of interest

The authors declared no conflict of interest.

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Comparison of maternal-neonatal results of vaginal birth after cesarean and elective repeat cesarean delivery

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ABSTRACT

Objective: To evaluate maternal-neonatal results in women who underwent vaginal birth after cesarean (VBAC) and elective repeat cesarean delivery (ERCD).

Material and methods: In a two-year retrospective cohort analysis, 423 patients with a history of prior cesarean section, singleton pregnancy with cephalic presentation and gestational age of 37–41 weeks were investigated. The maternal and perinatal outcomes of 195 patients desiring VBAC and undergoing a trial of labor after cesarean (TOLAC) attempt and 228 patients undergoing an ERCD were compared.

Results: While the TOLAC attempt was successful in 141 patients (72.3%), it was unsuccessful in 54 patients. No statistically significant difference was determined between VBAC and ERCD patients regarding uterine rupture, dehiscence, post-partum hemorrhage, the need for a blood transfusion and wound site infection ($p > 0.05$). When the post-partum neonatal outcomes were compared, there was no statistically significant difference between VBAC and ERCD groups regarding the prevalence of admission to the neonatal intensive care unit (NICU), respiratory distress, sepsis and birth injury ($p > 0.05$).

Conclusion: The maternal and perinatal outcomes of our study may be encouraging in favor of VBAC particularly in countries with higher cesarean rates. We think that the option of VBAC should be offered more frequently for selected appropriate patients in created safe environments.

Key words: vaginal birth after cesarean; trial of labor after cesarean; maternal morbidity; maternal mortality; neonatal morbidity; neonatal mortality

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INTRODUCTION

Although the cesarean delivery rates show wide variability by different countries and as a matter of fact in the same country according to the different institutions, it is associated with a substantial increase in recent years. Many reasons such as the widespread use of electronic fetal heart rate monitoring, reduction in operative vaginal deliveries and breech vaginal deliveries contributed to this increase [1]. Also, elective repeat cesarean sections performed due to a previous history of cesarean section increase the cesarean delivery rates dramatically. Thus, the cesarean delivery with a prior cesarean delivery was reported to be the most common indication for cesarean in 30-50% of all deliveries in the United States [2].

Flamm and Geiger developed a scoring system to predict the likelihood of vaginal birth for women who were desiring VBAC using the present factors at the time of hospital admission in 1997 [3]. Subsequently, Grobman et al. developed a model based on the present factors at the first visit for the prediction of a successful TOLAC attempt [4]. Although VBAC was considered a solution against increased cesarean rates for a long time, a reduction occurred in the trend of VBAC trials in the past two decades. While the reason for this is not known exactly, it is thought that many factors such as the patient's preference, institutional protocols, national guidelines, and the fear of litigation cause this condition [5].

American College of Obstetricians and Gynecologists (ACOG) published VBAC guidelines in 2019 and reported that the nomogram of Grobman et al. [6] reflected the real possibility for many populations and provided more specific information about the chance of VBAC, but none of

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the estimation models resulted in improvement in patient outcomes.

Objectives

The meticulous selection of the patient population in which TOLAC attempt can be successful is of vital importance. The uterine rupture, which is a worrying complication of the TOLAC attempt, is the most effective factor for moving away from the TOLAC option. The aim of this study was to compare neonatal and maternal outcomes in women going for TOLAC/VBAC versus those with an elective repeat cesarean section. The fact that VBAC gives results comparable to ERCD for mother and newborn will lead to further support of VBAC in the future, which will contribute to the reduction of placental invasion anomalies rates.

MATERIAL AND METHODS

Our study was performed in patients with a gestational age of 37–41 weeks and a history of a prior cesarean section who presented to the emergency room and admitted to the delivery room of the University of Health Sciences, Zeynep Kamil Women's and Children's Disease Training and Research Hospital. Last menstrual period and first-trimester ultrasound records were evaluated together for the determination of being term pregnancy. The birth registries of patients between November 2015 and May 2017 were retrospectively evaluated. TOLAC and ERCD were performed in 195 and 228 patients, respectively. Our study was approved by the local Research Ethics Committee. All patients were informed, and written consent was obtained from all of them before any study-related procedures were performed.

During routine pregnancy follow-ups, all patients were first admitted to the maternity follow-up outpatient clinics. VBAC and ERCD options were offered to patients who had a previous cesarean birth history and have no contraindications for normal delivery. Patients who wanted to get information about VBAC were directed to our spesific VBAC clinic, which played an important role in patients' VBAC/ /TOLAC preferences. When patients had a thorough counseling including advantages and risks of both forms of delivery in an adequate time, their preferences shifted from ERCD to VBAC/TOLAC. The data of the patients who underwent TOLAC procedure were obtained from VBAC clinical records

Suitability for vaginal delivery in our VBAC patients was determined according to ACOG guidelines [7]. Accordingly, the TOLAC attempt was performed in our patients with a history of delivery using a lower uterine segment transverse incision, with adequate pelvic dimensions, without a history of another uterine scar or rupture under normal delivery room conditions of our hospital. Concerning patients undergoing a TOLAC attempt, the women with a period of more than at least 24 months after previous cesarean delivery were included in the study. The patients with a previous classical or inverted T-shaped incision on the uterus, a history of extensive transfundal uterine surgery, a history of previous uterine rupture, medical or obstetrical complications which were barriers to vaginal delivery, nonvertex presentation, fetal anomaly, multiple pregnancies, placenta previa, vasa previa and decollement placenta were excluded from the study. The patients without complaints of pain at the presentation, no cervical opening at the vaginal examination, no uterine contraction at non-stress test assessments were included in the ERCD group.

Spontaneous onset of active-phase labor was accepted as the case with a cervical dilatation of more than 4 cm at the time of admission in the hospital. Again, it has been understood from the file registries that induction was achieved with an obstetric indication using prostaglandin E2 vaginal ovule or a low-dose oxytocin protocol in some of the patients in the TOLAC group.. Among maternal morbidities, while major complications were defined as uterine rupture and dehiscence, post-partum hemorrhage, peripartum hysterectomy, bladder or bowel injury; minor complications were defined as the need for a blood transfusion, wound site infection and puerperal fever. While the uterine rupture was defined as a full-thickness separation of both the myometrium and visceral peritoneum, dehiscence was defined as the presence of an intact serosa despite a complete separation of the myometrium. Post-partum hemorrhages were determined as hemorrhages requiring additional medical or surgical intervention other than standard procedures during the follow-up after delivery. Puerperal fever was considered as body temperature exceeding 37.5°C and concomitant wound site infection, endometritis, pulmonary infection, and urinary infections. Post-partum mobilization period, post-partum hospital discharge period, prepartum and post-partum hematocrit values were compared between groups. While the incidence of anesthesia complications was evaluated in the ERCD group and the incidences of operative delivery and perineal laceration were evaluated in the VBAC group.

The admission to the NICU, birth injury, sepsis, and respiratory distress were compared between groups as neonatal morbidity. Additionally, the fifth minute Apgar scores of the neonate were also investigated in both groups.

Statistical analysis

The data were analyzed with SPSS for Windows 23. 0 version. Average, standard deviation in descriptive statistics of continuous variables; categorical variables were expressed in numbers and percentages. The significance of the difference between the groups for categorical variables was evaluated with the Chi-Square test. Student's T test was used in the analysis of data with normal distribution in

binary group comparisons, and Mann Whitney-U test was used in data without normal distribution. The significance of the difference between repeating measurements was calculated with Paired Samples T test. The independent effect of each factor on the data that may be affected by more than one factor was evaluated by logistic regression analysis. Odds Ratio (OR) was calculated for risk analysis of risk factors. $P < 0.05$ value was considered statistically significant.

RESULTS

The demographic characteristics of the patients were shown in Table 1. The mean age was found to be similar in both groups. The gestational week was greater in the VBAC group ($p < 0.001$). Body mass index was found to be statistically significantly greater in favor of ERCD ($p = 0.035$). Comparisons of the groups according to the number of their previous vaginal deliveries and abortions were shown in Table 2.

While the spontaneous onset of active-phase labor was present in 75 patients (38.5%) of the VBAC group; it was understood that 120 patients (61.5%) were admitted to the delivery room without the onset of active-phase labor. It was determined that induction of labor was performed with low-dose oxytocin, prostaglandin E2-dinoprostone vaginal ovule in 63 (32.3%) and 7 patients (3.6%), respectively and no induction agent was administered in 132 patients (64.1%) in the VBAC group. While uterine rupture was detected in 1 patient who underwent low-dose labor induction with oxytocin, uterine rupture was not observed in any of the other patients. Operative delivery was performed using ®Kiwi OmniCup Vacuum Delivery System, vacuum extraction and forceps in 11 (5.6%), 10 (5.1%) and 4 patients (2.1%), respectively in the VBAC group. Third degree perineal laceration occurred in 5 (2.6%) patients; only two of them were observed after operative delivery. There were no deaths in either group.

A comparison of post-partum maternal outcomes between VBAC and ERCD groups was shown in Table 3. While post-partum hematocrit values were found to be significantly lower in both groups compared to prepartum hematocrit values ($p < 0.001$); the reduction rate was determined to be similar in both groups ($p = 0.433$).

A comparison of maternal morbidity outcomes between groups was shown in Table 4. There was no significant difference between groups regarding uterine rupture, dehiscence, post-partum hemorrhage, the need for a blood transfusion and wound site infection ($p > 0.05$). Peripartum hysterectomy, bowel and bladder injury were observed in none of the patients in both groups. Anesthesia complication was observed in three patients of the ERCD group. While difficult intubation and correspondingly transient desatura-

Table 1. Comparison of demographic characteristics of TOLAC and ERCD groups

	TOLAC (n: 195)	ERCD (n: 228)	P value
Age (year)	29.7 ± 5.2	29.3 ± 5.2	0.422*
Gestational week	39.6 ± 1.14	39.1 ± 0.6	**< 0.001****
BMI	29 ± 3.9	29.9 ± 4.5	**0.035***

BMI — Body mass index
*Student's t test; **Mann Whitney U test

Table 2. Comparison of demographic characteristics of TOLAC and ERCD groups

	TOLAC (n: 195)	ERCD (n: 228)	p
Number of previous NVD (n)			0.272*
0	152 (43.9%)	194 (56.1%)	
1	28 (57.1%)	21 (42.9%)	
2	9 (64.3%)	5 (35.7%)	
3	4 (40%)	4 (40%)	
4	1 (100%)	0	
5	0	1 (100%)	
6	1 (50%)	1 (50%)	
Abortion number (n)			**0.027***
0	161 (49.5%)	164(50.5%)	
1	25 (35.7%)	45 (64.3%)	
2	5 (27.8%)	13 (72.2%)	
3	3 (37.5%)	5 (62.5%)	
4	1 (50%)	1 (50%)	

*Ki-kare test; $p < 0.05$ is statistically significant; NVD — Normal vaginal delivery

Table 3. Comparison of maternal results between TOLAC and ERCD groups

	TOLAC (n: 195)	ERCD (n: 228)	P value
Postpartum fever (°C)	36.6 ± 0.3	36.5 ± 0.3	**0.030**
Mobilization time (hours)	3.7 ± 1.8	5.7 ± 2.3	**< 0.001**
Postpartum discharge time (hours)	35.5 ± 16.7	45 ± 15	**< 0.001**

*Student's t test

Table 4. Comparison of maternal morbidity results between TOLAC and ERCD groups

	TOLAC (n: 195)	ERCD (n: 228)	P value
Uterine rupture	1 (0.5%)	0	0.233
Uterine dehiscence	3 (1.5%)	2 (0.9%)	
Need for transfusion	6 (3.1%)	1 (0.4%)	0.052
Postpartum hemorrhage	9 (4.6%)	5 (2.2%)	0.132
Wound infection	3 (1.5%)	5 (2.2%)	0.731

*Ki-kare test

tion were observed in one of them, transient desaturation immediately after intubation due to pulmonary secretions was seen in one patient. Laryngeal edema and dyspnea developed after extubating in the last case determined to have a polyp at the base of the tongue during inspection before intubation. This last patient was re-intubated urgently during the post-operative period and admitted to the adult intensive care unit.

No significant difference was determined between the VBAC and ERCD groups regarding admission to the NICU, respiratory distress, sepsis and birth injury ($p > 0.05$). Respiratory distress was observed in the neonate of one patient developing uterine rupture. In the VBAC group, while clavicle fracture secondary to shoulder dystocia occurred in one neonate, a cephalic hematoma developed due to vacuum extraction in one newborn. Neonatal death occurred in none of these groups.

In the VBAC group, while the TOLAC attempt was successful in 141 patients, it was unsuccessful in 54 patients. The gestational week was determined to be significantly greater in women with unsuccessful TOLAC attempts ($p > 0.001$). Indications for repeated cesarean section in patients with unsuccessful TOLAC attempts were as following: Cephalopelvic disproportion (CPD) in 5 patients (9.2%), fetal distress in 10 patients (18.5%), unreliable nonstress test (NST) in 9 patients (16.6%), prolonged labor in 12 patients (22.2%), cord prolapsus in 1 patient (1.8%), patient's request in 13 patients (refusing TOLAC attempt) (24%), suspicion for the uterine rupture in 3 patients (5.5%), prolonged premature rupture of membranes in 1 patient (1.8%). The uterine rupture in 1 patient and dehiscence in 1 patient were determined in patients undergoing cesarean section with an indication of suspicion of rupture of membranes. The factors affecting the success of the TOLAC attempt were shown in Table 5.

DISCUSSION

With dramatically increasing rates in the actual course of the disease, cesarean deliveries are encountered as one of the most current problems in obstetrics. In 1980, Bottoms et al. [8] emphasized that elective cesarean sections performed due to a previous history of cesarean delivery provided a significant contribution to increasing cesarean rate. Therefore, deciding on a trial of labor in a subsequent pregnancy after cesarean delivery will affect future pregnancies. It has been shown that maternal morbidity increased progressively with an increasing number of cesarean deliveries and there was a dose-response relationship between placenta accreta and the number of previous cesarean deliveries particularly in the presence of placenta previa [9]. For this reason, decisions related to the TOLAC attempt will affect the outcomes of future pregnancies.

The VBAC clinic was opened in our hospital in 2015 to reduce the increased cesarean rates in our country. In our study, TOLAC preference was found to be very high (90.2%) in patients who applied to the VBAC clinic. We believe the most effective factor in this preference is giving a thorough counseling about the advantages and risks of both forms of delivery to patients with a previous cesarean delivery history in adequate time. In our study, the TOLAC success rate was determined to be 72.3%. This rate was comparable to the rates of 73% in the meta-analysis of Rossi and D'Addario and 74% in NIH statement [10, 11]. Hence, the TOLAC success rate was reported to be between 68% and 83% also in the studies of other authors [12–14].

Our uterine rupture rate was 0.5% and it was comparable to the rate of 0.3% obtained from the systematic review of Guise et al. and reported by McMahon et al. [15]. In the study performed by Shipp et al. [16], the rate of uterine rupture was reported to be 2.3% when the inter delivery interval was less than 18 months and 1% when it was more than 18 months. Soni et al. [17] reported that the low rate of uterine rupture (0.4%) in their study was due to intrapartum intensive monitoring with appropriate patient selection and early recognition of dehiscence or rupture.

Again, in our study, peripartum hysterectomy, bowel, and bladder injury among major complications were observed in none of the patients. In a recent study performed

Table 5. Factors affecting TOLAC success

Pregnancy features	Successful TOLAC (n: 141)	Failed TOLAC (n: 54)	OR
	n (%)	n (%)	95% CI
Maternal age			
≤ 19	2 (1.4%)	2 (3.7%)	0.53 (0.06–4.69)
20–24	21 (14.9%)	4 (7.4%)	2.18 (0.63–7.56)
25–29	51 (36.2%)	24 (44.4%)	1*
30–34	42 (29.8%)	13 (24.1%)	1.55 (0.66–3.61)
≥3 5	25 (17.7%)	11 (20.4%)	0.72 (0.26–1.95)
Number of previous NVD			
0	105(74.5%)	47(87%)	1*
1	24 (17%)	45 (%64.3)	3.33 (0.97–11.36)
≥ 2	12 (8.5%)	3 (5.6%)	2.07 (0.44–9.62)
Birth weight			
< 2500 g	3 (2.1%)	—	—
2500–2999 g	32 (22.7%)	5 (9.3%)	1.88 (0.62–5.65)
3000–3499 g	65 (46.1%)	21 (38.9%)	1*
3500–3599 g	35 (24.8%)	23 (42.6%)	0.48 (0.22–1.04)
≥ 4000 g	6 (4.3%)	5 (9.3%)	0.43 (0.11–1.64)
Spontaneous onset labor			
present	74 (61.7%)	46 (38.3%)	1*
absent	67 (89.3%)	8 (10.7%)	5.21 (2.29–11.82)

*Reference category; OR — Odds Ratio; CI — Confidence interval; NVD — Normal vaginal delivery

by Bellows et al. [18], TOLAC patients before and after ACOG 2010 VBAC guidelines were compared; while the rate of hysterectomy in TOLAC attempts before guidelines was 1.1%, this rate was reported to be 0.1% after guidelines. This difference was found to be significant ($p = 0.03$).

In our study, mean postpartum mobilization and discharge time were found earlier and shorter respectively in successful TOLAC cases compared to ERCD cases ($p < 0.001$). Our data support the data of the National Institutes of Health stating that TOLAC is associated with a shorter hospitalization period [10].

In the literature, no randomized-controlled studies comparing neonatal outcomes with a high evidence level of TOLAC and ERCD are available. Data in some available studies are also controversial, however, when we evaluate generally, it is mentioned about the risk for sepsis and admission to NICU is increased in the TOLAC group and the risk for laceration-related birth injuries and TTN is increased in the ERCD group [19, 20]. In our study, no neonatal death was observed in our patients. The neonate of a patient developing uterine rupture was admitted to the NICU due to respiratory distress and discharged with full recovery after 14 days.

The uterine rupture is the complication causing the major concern for either patient or clinician in the TOLAC attempt. It has been reported in many studies that the risk of the uterine rupture increased markedly in the unsuccessful TOLAC attempt. Thus, we also observed that this risk increased 8.3-fold in women with unsuccessful TOLAC attempts. While this rate was reported to be 3.7-fold by Mc Mahon et al. [15], Landon et al. [21] reported this rate as 22.1-fold for the uterine rupture and as 14.8-fold dehiscence.

In our study, we determined that the factors affecting the success of TOLAC attempt as age, birth weight, the number of previous vaginal delivery and the presence of spontaneous onset of active-phase labor. When we take the 25–29 age range as a reference for maternal age, we observe that the likelihood of success of TOLAC attempt increases 2.18-fold in the age range of 20-24 years and 1.55-fold in the age range of 30–34 years. The success of the TOLAC attempt decreases under the age of 19-year-old and over the age of 35-year-old. When we take the patients without a previous vaginal delivery as a reference, while the likelihood of successful TOLAC attempt increases 3.33-fold in women with a previous vaginal delivery, this rate increases 2.07-fold in women with two or more previous vaginal deliveries. Again, similarly, we determined that the likelihood of successful TOLAC attempt increased 5.21-fold in women admitted to the delivery room due to the spontaneous onset of active-phase labor. These findings were also consistent

with the data of the study performed by Senturk et al. [22] and titled "factors associated with successful vaginal birth after the cesarean section". When we take the 3000–3499 g as a reference for birth weight, we observe that the likelihood of success of the TOLAC attempt increases 1.88-fold in the birth weight range of 2500–2999 g and the likelihood of success of TOLAC attempt progressively decreases over the birth weight of 3,500 and 4,000 g.

One of the major limitations of our study is having insufficient information from our patients about cesarean indication at previous cesarean delivery. Unknown indications about previous cesarean delivery which could be a factor increasing our TOLAC failure. The reason for this in the studies performed was reported to be an indication for the previous cesarean section that could not be repeated in subsequent pregnancies was a factor increasing TOLAC success [23, 24]. The other limitation of our study is the small numbers per groups which might lead to scarce adverse effects.

CONCLUSIONS

Developing countries like us have a high cesarean section rate. In our changing world our practice also needs to change for the better. Although it is impossible to predict TOLAC success yet, the maternal and perinatal outcomes of our study show that VBAC is a reliable mode of delivery in case of the creation of safe environments and meticulous selection of the candidates. To be able to prevent increasing cesarean rates, we think that the option of VBAC should be offered more frequently for selected appropriate patients.

Conflict of interest

All authors declare that they have no conflict of interest.

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Contemporary principles of diagnostic and therapeutic management in cervical and ovarian neuroendocrine tumors

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ABSTRACT

Enhancing knowledge about neuroendocrine neoplasms causes the need to improve management of these tumors. Although these tumors are rare in clinical practice, their biological diversity makes both diagnostics and therapy a challenge for contemporary oncology. The article discusses the latest developments in the diagnostic procedures and methods of treatment of the cervical and ovarian neuroendocrine tumors. Algorithms are presented to understand the differences in therapeutic management in these malignancies.

Key words: cervical neuroendocrine neoplasm; ovarian neuroendocrine neoplasm; carcinoid; management; small cell hypercalcemic ovarian tumor

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INTRODUCTION

Primary neuroendocrine neoplasms /tumors (NEN/NETs) of female genital organs require a separate approach due to extremely aggressive course. These tumors present as heterogeneous group with an incidence of about two percent of all female genital cancers [1, 2]. The cervix and ovaries are the most common locations of neuroendocrine tumors within the female reproductive system; only isolated cases have been described in the uterine corpus. NEN metastases from the gastrointestinal tract, lungs and thymus should be always excluded, especially in ovaries involvement. These tumors require an appropriate histopathological assessment and should be distinguished from other primary ovarian neoplasms, particularly granulosa cell tumor.

The terminology of neoplasm, commonly called carcinoid, has been changed since 2000 [3]. European Neuroendocrine Tumor Society, due to new opportunities in somatostatin receptor-targeted therapy within the neoplastic cells, distinguished two basic groups in NEN: low-grade neuroendocrine neoplasms/tumors (LG NENs/NETs) microscopically resembling carcinoids, and high-grade neuroendocrine neoplasms/tumors (HG NENs/NETs) with cancer morphology.

CERVICAL NENS

Nowadays, according to the WHO classification from 2014, cervical LG NENs are divided into the following groups [4]:

- low grade neuroendocrine tumors (TC, carcinoid tumor),
- low grade neuroendocrine tumors, G1
- low grade neuroendocrine tumors, (AC, atypical carcinoid tumor),
- low grade neuroendocrine tumors, G2.

Cervical HG NENs referred to as neuroendocrine carcinoma G3 (NEC) should be classified as tumors of the digestive system. The WHO classification distinguishes small cell neuroendocrine carcinoma (SCNEC) and large cell neuroendocrine carcinoma (LCNEC).

Cytological diagnostics

Pap smears are of little use in detecting early forms of the cervical NEN. Only for an experienced cytopathologist

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or pathologist, the cytological test raises suspicion of NEN. Chiang et al. recorded 57.5% normal smear in a group of 133 patients with SCNEC. The authors found that false negative results were significantly higher compared to squamous cell cervical cancer [5]. In another study, abnormal cytology was detected in 14–45.5% of cases [6]. Zhou et al. [7] presented an analysis of cytological smears from 11 patients with cervical NEN. In six cases, abnormal cells were found - in three patients non-specific cancer cells, in another three patients adenocarcinoma cells were diagnosed. Retrospective evaluation of seven smears, assessed initially as normal, showed abnormal cells in two patients. These cases were found to be false negative. Park et al. [8] observed abnormal cytology in 9 of 27 patients (33.33%) with cervical NEN. In two cases neuroendocrine tumor cells were detected in cytological smear; the others were diagnosed with squamous cell carcinoma (n = 2), HSIL (n = 3), ASCUS (n = 2). Kim et al. [9] attempted to determine the characteristic smear features for cervical SCNEC. They analyzed 13 cases of cervical SCNEC and compared them with squamous cell carcinoma, lymphoma and chronic cervicitis. Cytological changes useful in differential diagnosis were found: nuclear molding and smearing (100%), salt and pepper chromatin (100%), exudative and necrotic background (91.7%), various architectures including individual cells (83.3%), tight clusters (75%) and feathering and strip (50%), and inconspicuous nucleoli (75%).

Nonetheless cervical Pap smear test is insufficient for the diagnosis of NEN.

Histopathological and molecular diagnostics

Macroscopically cervical NENs are not different from squamous cell and adenocarcinoma. Diagnosis is based on a histopathological examination with immunohistochemical assay. Cervical NENs differentiate from squamous and glandular epithelium. Neuroendocrine tumors, especially low grade can produce various proteins and hormones like calcitonin, gastrin, serotonin, substance P, vasoactive intestinal peptide, pancreatic polypeptide, somatostatin and adrenocorticotrophic hormone. Nonetheless cervical NENs rarely demonstrate clinical symptoms. Carcinoid syndrome can be found in cases with liver metastases.

Microscopically LG NENs are characterized by organoid structures resembling carcinoids. Accordingly, to cell maturity they are divided into two subtypes [10]. LG NEN (G1) differs from LG NEN G2 in nuclear atypia, mitotic activity and the presence of focal thrombotic necrosis. Proliferation activity of Ki-67, which has significant predictive and prognostic value in the NEN of the digestive system, is not of that importance in the NEN of the cervix. Cervical HG NEC G3 resembles small- and large-cell lung cancers as far as microscopic image is concerned. They are characterized by high proliferation activity, extensive infiltration and necrosis.

Diagnosis of NEN requires confirmation of immunohistochemical (IHC) markers. Chromogranin A and synaptophysin are mandatory in every case. The expression of other markers like neuron- specific enolase (NSE) and CD56 may also be useful [4]. These markers are specific in 33 to 100% of small cell neuroendocrine tumors [10]. In some cases, particular in SCNENs, IHC expression of these markers may be weak.

Recently, Japanese researchers pointed out that insulinoma associated protein 1 (INSM 1) is more specific than other markers [11]. In addition, thyroid transcription factor 1 (TTF1) was found to be specific in SCNET in 33% to 84% [12]. Usefulness of TTF1 is limited, because it did not allow to distinguish SCNET from primary pulmonary NEN. Due to frequent coexistence of cervical NENs and HPV infection (especially high-risk 18 type) a positive reaction to p16 protein can be found. In the meta-analysis published by Castle et al. [13] HPV 16 and/or 18 infections was found in 85% of SCNENs and 88% of LCNENs. The activity of Ki-67 in cervical NETs is not obvious as in gastrointestinal tract and lung NENs. Moreover, in WHO classification 2014, the Ki-67 index was not included in the diagnostic criteria of cervical neuroendocrine tumors [4]. Among molecular abnormalities, mutations in the following genes are most common: c-myc (53%), p53 (26%), PIK3CA (18%). Loss of heterozygosity was found in approximately 30% of NETs of female reproductive system [10].

Imaging diagnostics

Chest, abdominal and pelvic computed tomography (CT) should be performed in each case of cervical NET. PET CT is also recommended. Pelvic MRI or a transrectal ultrasound (TRUSG) examination should be additionally performed in locally advanced disease. Accuracy of parametria involvement in tumors < 1 cm compared with the histopathological examination was 98.7% and 94.7% ($p < 0.219$), respectively [14]. MRI is the method of choice for staging cervical NETs in pregnant women, in cases of iodine contrast allergy or renal failure [15].

Somatostatin receptor scintigraphy (SRS) can be helpful in appropriate staging or searching for the primary lesion in well differentiated NENs due to overexpression of the somatostatin (SST) receptor. Other cervical NENs do not have significant expression of SST receptors. In these cases, positron emission tomography with fluorodeoxyglucose (FDG-PET) is an option. FDG-PET is used in staging and has prognostic significance in low differentiation NENs. It can also be used in identification of the primary tumor, assessment of treatment effectiveness or suspicion of relapse [16].

Clinical course, prognosis and treatment

LG NENs G1 and LG NENs G2

They account for 0.5 to 5% of all cervical cancers [17]. Primary LG NEN G1 is seldomly diagnosed. The metastatic

character of the tumor should always be excluded. The most common clinical symptom is vaginal bleeding. Symptoms of carcinoid syndrome are rarely manifested in these patients, although it is often possible to detect serum elevated concentrations of 5-hydroxyindoleacetic acid (5-HIAA). The clinical course of LG NEN G1 is difficult to predict due to its rare occurrence. LG NEN G2 is an extremely aggressive tumor. Between two to three-years overall survival range between 12.5 and 33%. Even early stage tumors may spread to distant locations through lymphatic drainage or blood. The treatment of LG NEN G2 is not standardized although total abdominal hysterectomy is proposed in a locally advanced tumor. Isolated liver metastases may be treated with transarterial chemoembolization (TACE) using streptozotocin and 5-fluorouracyl. It is more effective than systemic treatment with paclitaxel, cis- or carboplatin, which have been shown to be ineffective in the treatment of LG NEN G2 metastases. In cases of positive somatostatin receptor, treatment with somatostatin analogues can be used [10, 18].

HG NENs G3

The average age of patients with SCNEN ranges from 37 to 46 years. Lymphatic or blood metastases occur immediately even in early stages of disease. Perineural invasion is common. Staging is the most important prognostic factor. Postoperative histopathological examination revealed metastases in lymph nodes in 45–57% of cases and LVSI involvement in 80% of cases [19, 20]. The mean overall survival in stage I–IIA is 31 months, while in stage IIB - IVB it reaches 10 months. According to SEER data, five-years survival in early stages ranges from 30 to 60%, and in advanced stages is 0–17% [21]. The results of treatment are significantly worse than in other types of the cervical cancer. Five-year survival in SCNENs, squamous cell carcinoma and adenocarcinoma are 35.7%, 60.5% and 69.7% respectively [22]. Tumor size is also prognostic. Five-year survival in tumors ≤ 4 cm and > 4 cm was 76% and 18%, respectively.

As in other rare cancers, there is a lack of data on treatment based on randomized trials. The experience gathered during treatment of pulmonary NENs is used in therapy of gynecological NENs. At the moment of diagnosis of SCNEN metastases are often found, so treatment is usually multidisciplinary.

Incidence of LCNEN is less than SCNEN but it also has aggressive clinical course. Most patients with LCNEN die within the first three years since diagnosis. Embry et al. [23] analysed 63 patients with LCNENs and found that the average survival was 16.5 months (19 months — stage I, 17 months — stage II, 3 months — stage III, 1.5 moths — stage IV). Weak HER-2/Neu expression and strong EGFR expression appeared to be adverse prognostic factors. MD Anderson Cancer Center (MDACC) way of treatment of LCNENs is shown in Figure 1 [24]. MDACC is currently one of the leading institutions in developing diagnostic and treatment strategy of NENs of female reproductive system. Alternative management was shown by Gadducci et al. [19]. Their therapeutic chart is presented on Figure 2.

OVARIAN NENS

According to WHO 2014 classification ovarian neuroendocrine tumors are divided into two groups [4]. The first

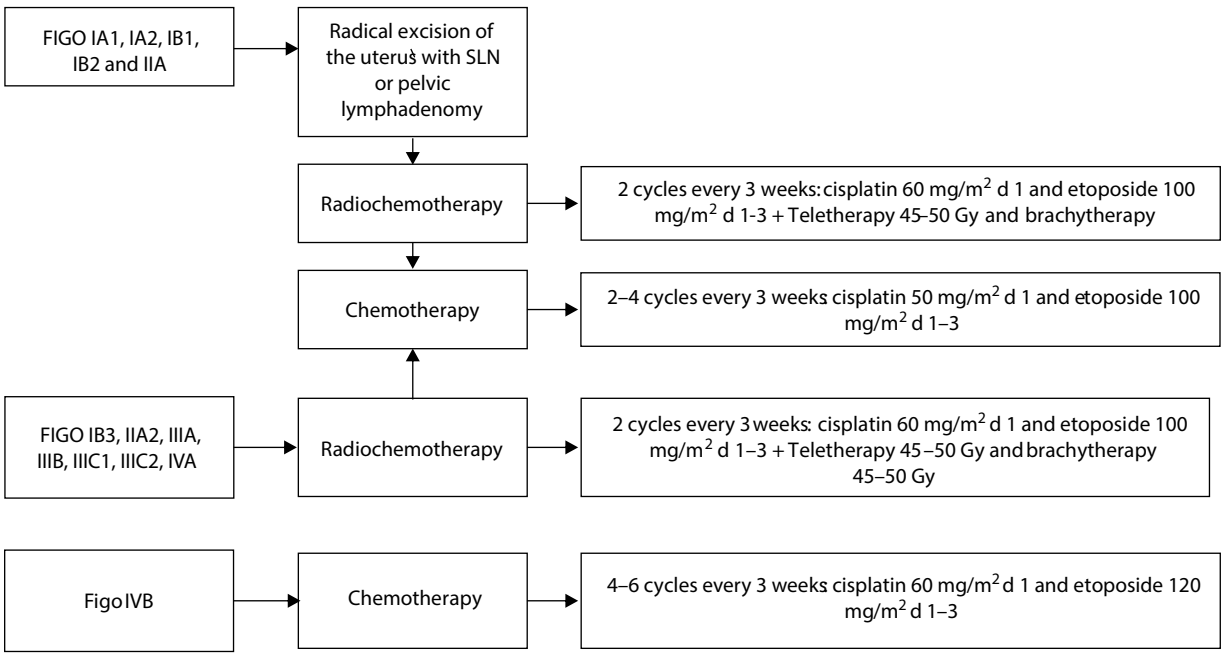

Figure 1. A therapeutic regimen in high grade cervical NETs adopted with recommendation of the MD Anderson Cancer Center

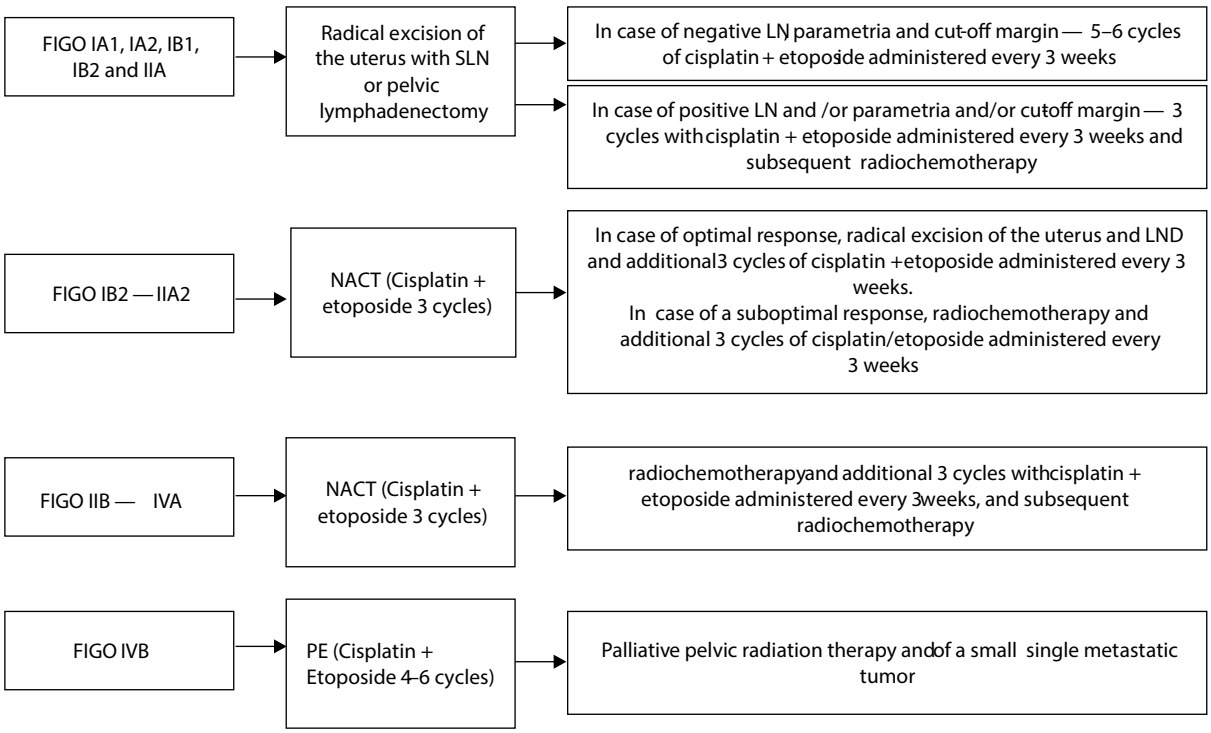

Figure 2. Therapeutic procedure scheme in high grade cervical NETs developed by Gadducci

group consists of low-grade neuroendocrine neoplasms resembling NEN of gastrointestinal system. They are identified as carcinoid (Carcinoid/Tumor carcinoid — TC) and correspond to low grade neuroendocrine tumors G1 (well differentiated neuroendocrine tumor/ low grade neuroendocrine tumor). The second category of ovarian NENs are poorly differentiated tumors (high grade NETs, HG NETs). The following types are found among HG NETs:

1. small cell carcinoma, hypercalcemic type (SCCHT),
2. small cell carcinoma, pulmonary type (SCCPT),
3. large cell neuroendocrine carcinoma (LCNEC).

LG NENS

Carcinoids (TC) are the most common ovarian NENs. They account for only five percent of all carcinoids and represent only 0.1% of all malignant ovarian neoplasms [17]. There are three types of TC:

a) a component of a mature teratoma
b) primary ovarian carcinoid
c) metastatic carcinoid

TC forming as a component of mature teratoma constitutes about 75% cases of ovarian carcinoids. It is usually found as unilateral lesion, but even in 15% of cases, mature cystic teratoma, mucinous tumor or Brenner tumor may be found in opposite site. Symptoms of carcinoid syndrome may occur in about 1/4 to 1/3 of cases. In the WHO classification 2014, ovarian carcinoids are included in the germinal ovarian tumors as teratoma with possibility of secretion of neuroendocrine substances that may cause carcinoid syndrome. Serotonin-derived molecule is secreted directly into the ovarian vein, bypasses the hepatic passage, and causes symptoms such as hot flushes, diarrheas, bronchospasm or edemas. Y peptide disturbs intestinal motility and leads to constipations. Other substances include pancreatic polypeptide, gastrin or glucagon [1, 25]. The average age at the moment of diagnosis TC is 55 years; most patients are women in perimenopause or menopause.

Primary ovarian carcinoid occurs in four microscopic types: insular, trabecular, mucinous and stromal. The insular type resembles neuroendocrine tumors of the middle segment of the archenteron, while the trabecular type imitates neuroendocrine neoplasms from the anterior and posterior sections of the archenteron. The mitotic figures are rare. Microscopic structure of the mucinous variant is akin to an appendix carcinoid and three histologic subtypes are distinguished: well differentiated, atypical and adenocarcinoid. Well differentiated tumors consist of goblet cells; however cuboidal or columnar cells may also occur. They infiltrate into the stroma or are located within the lakes of mucus. Atypical mucous carcinoid is formed by glandular, sieve or fine-cystic structures with moderate nuclear atypia. Histological structure of the adenocarcinoid is mixed of carcinoid and adenocarcinoma. Stromal carcinoid is compound of normal thyroid tissue and carcinoid, mostly trabecular type, rarely insular or mucinous.

Ovarian carcinoids are diagnosed in early clinical stage. Modlin et al. [18] analysed 113 cases of TC and found that

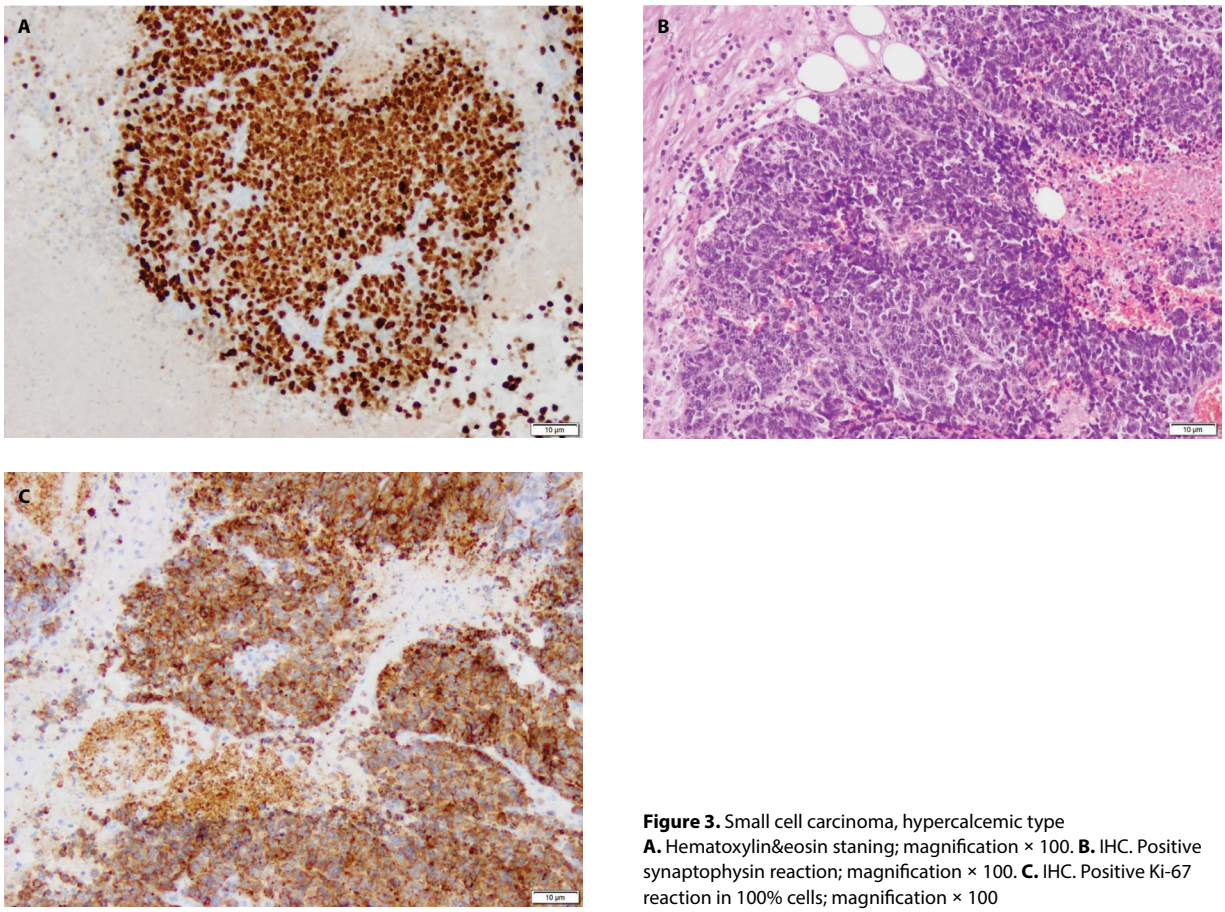

Figure 3. Small cell carcinoma, hypercalcemic type
A. Hematoxylin&eosin staning; magnification × 100. **B.** IHC. Positive synaptophysin reaction; magnification × 100. **C.** IHC. Positive Ki-67 reaction in 100% cells; magnification × 100

66% of these tumors are locally advanced. Patients diagnosed with TC have good prognosis. Survival in stage I is more than 90%, but in advanced stages does not exceed 33%. Carcinoid metastasis from gastrointestinal tract or lungs is mandatory. Implants outside the ovary, bilateral tumors, vessels infiltrations and the absence of teratoma elements indicate a metastatic character. Sometimes these tumors can be misdiagnosed as Brenner tumors, granulosa cell tumor or Sertoli-Leydig cells tumors. Surgery is the treatment of choice. Fertility sparing surgery is possible in patients with normal contralateral ovary and Ki-67 index does not exceed 5%.

HG NENS

These tumors are characterized by high mitotic activity and Ki-67 index usually above 30%. These features determine aggressive clinical course of HG ovarian NEN.

Small cell carcinoma, hypercalcemic type (Fig. 3) is an exceedingly rare and lethal tumor, mostly affecting young women (the average age is 24 years) with aggressive clinical course. It develops usually unilaterally; bilateral or hereditary forms are rare. The prognosis is extremely unfavorable. An advanced tumor with multiple metastases is found in about 50% of cases at the time of diagnosis. Symptoms of paraneoplastic hypercalcemia occur in 2/3 patients. This tumor can be misdiagnosed as granuloma, high grade ovarian cancer, dysgerminoma or other undifferentiated cancer. Kupryjańczyk et al. [26] described somatic and germinal mutations within the SMARCA4 gene, which causes a lack of BRG1 protein. This may be helpful in differentiating from other tumors.

In small cell carcinoma, pulmonary type, metastasis from primary pulmonary malignancy always must be excluded. It is extremely rare aggressive ovarian tumor with an incidence of < 1%, usually occurring in perimenopausal or postmenopausal women (the average age is 59 years). About 50% of cases occur bilaterally. It is diagnosed in advanced stages. Prognosis is poor. Patients sometimes demonstrate Cushing's syndrome-like symptoms.

Ovarian large cell carcinoma usually presents as unilateral lesion. An average age at the time of diagnosis is 48.5. It is a very rare form of cancer with an extremely aggressive clinical course. This neoplasm may co-exist with epithelial ovarian tumors such as mucinous borderline tumor, mucinous or serous cancers [27]. Symptoms and treatment of the disease are like these of ovarian cancer. The optimal surgery requires removal of all macroscopically lesions. An adjuvant chemotherapy is based on the regimens with cisplatin

and etoposide and minimum five cycles are recommended [23, 25, 27]. Treatment with somatostatin analogues can be considered in tumors with Ki-67 < 30% and SST receptors revealed in scintigraphy. In HG NETs with Ki-67 > 30% systemic treatment with cytotoxic drugs is mandatory.

SUMMARY

Neuroendocrine tumors of the cervix and ovaries are rare and require attentive histopathological diagnosis with immunohistochemical staining. The diagnosis should be always confirmed with chromogranin A and synaptophysin. The Ki-67 proliferation index is not always predictive or prognostic as in gastrointestinal neuroendocrine tumors. Ovarian carcinoids require differential diagnosis between primary ovarian cancers and metastases to ovaries, especially from the digestive system and pulmonary neoplasms. Treatment should be conducted by the most experienced oncology centers.

Conflicts of interest

The authors declare no conflict of interest.

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Chaos and cancers. Theories concerning carcinogenesis

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ABSTRACT

One of the most intriguing problems in biomedical sciences is the theory explaining cancer formation. It is known that cancer is the result of many molecular processes, the presence of oncogenic factors and the loss of apoptosis of affected cells. We currently have hypotheses based on carcinogenesis because of a single cell gene mutation, *i.e.* somatic mutation theory (SMT), or disorders in tissue architecture and intercellular communication called (TOFT) Tissue Organization Field Theory. An attempt to combine these separate and compatible cause and effect pathways into one unified theory of cancer transformation is the theory of chaotic adaptation. The new interpretative model is the systemic-evolution theory of cancer (SETOC) which postulates disintegration between the symbiosis of "energy" and "information" in normal cells. There are also epidemiological studies confirming that some types of cancer arise from viral infection. So, let us ask the question, can one hypothesis explain all the features of cancer?

Key words: carcinogenesis; somatic mutation theory; tissue organization field theory; chaotic adaptation; systemic-evolution theory of cancer; genome; chaos; information

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INTRODUCTION

Despite the spectacular contribution of molecular biology techniques in the field of carcinogenesis, the cancer mortality statistics do not show much difference. In the community of researchers of the process of neoplastic transformation, there is a debate regarding the insufficient methods of explaining this phenomenon. The purpose of our work is to present arguments, hypotheses and methodological assumptions describing the most current achievements in the context of the carcinogenesis dispute.

THE THEORIES AND EVALUATION OF THE IDES

For at least 30 years, the dominant theory of cancerogenesis was somatic mutation theory (SMT) [1]. It assumed that cancer is a clonal, cellular disorder, and its formation is a multistage process. It is characterized by the accumulation of changes in the genetic material in the cell — as a result of biological genotoxic mechanisms and epigenetic changes. The consequence of these changes is the accumulation of DNA mutations in tumor suppressor genes, microRNA genes, DNA repair genes or genes involved in cell cycle control and cell proliferation and apoptosis. In turn, epigenetic factors change the degree of DNA methylation and / or the conformation of chromatin, which is manifested by a change in the transcriptional activity of genes. Other factors important in the carcinogenesis process are also hereditary factors, immunology, hormonal status and external factors: chemicals, lifestyle, diet, cigarette smoke, sun exposure, radiation or viral, bacterial and other infections.

However, it should be emphasized that most cancers are histopathologically diverse and contain cytologically different clones resulting from genetic transformation from one transformed cell. It also seems that mutational changes are generally insufficient to cause cancer, because only a small proportion of cancers, in about 5%, arise as a result of mutations [2]. The theory of somatic mutations has never been able to explain how non-mutagenic factors are responsible for carcinogenesis. The somatic mutation model also ignores the fact that in every known case of cancer, not only individual genes can contain mutations, but also entire chromosomes that carry thousands of genes, can be duplicated, damaged, or structurally incorrect. Numerous experimental data suggest that this chaos at the chromosomal level is not

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only a side effect of carcinogenesis, but a direct cause and driving force of cancerous changes. Chromosomal mutations, which massively disturb the balance of thousands of genes, are sufficient to cause cellular instability [3]. Genetic instability may affect the enzymes which replicate DNA, enzymes which repair DNA, protein which affect chromosomal stability (histones, kinetochore proteins, spindle proteins) and proteins which control apoptosis and cell cycle regulation in response to DNA damage (p53 and pRb). The formation of micronuclei is also associated with chromosomal instability. Various molecular mechanisms are responsible for its formation, including double-stranded DNA breaks, impaired DNA repair response, improper DNA replication, DNA adduct-forming chemical or interference with mitosis [4]. Therefore, micronucleus formation usually acts as an index of genotoxic effects and chromosomal instability (both inherited and induced).

Therefore, carcinogens appear to act as „aneuploidies" rather than as mutagens. This fact explains why cancer cells, even within the same tumor, may have different combinations and changes in their chromosomes, making each cell a kind of new species for themselves, and their instability allows cancer cells to evolve new traits (phenotypes). The unusual variability of cancer cells and the huge variety of their phenotypes are the main reasons why tumors remain an unsolvable problem, both from a scientific and therapeutic point of view. The challenge, therefore, is to formulate a theory explaining how one normal cell, out of billions making up the human body, becomes chromosomally and phenotypically altered to cause a deadly cancer. Since each of the features of carcinogenesis that cannot be explained by a theory of mutation is associated with chromosomal changes, a chromosomal theory of cancer has been proposed that considers this inherent instability [5]. The SMT theory and the chromosomal theory are complemented by the theory called TOFT Tissue Organization Field Theory, which suggests that the origin and subsequent features of the cancer result from disorders in the microenvironment of the cell in the tissue in which the tumor is formed, lives and grows [6]. Molecular dialogue in this zone and cellular communication involves various host cells such as: endothelial cells, pericytes, immune cells, inflammatory cells, fibroblasts, soluble factors and structural components such as extracellular matrix, various proteins such as integrins, metalloproteinases, various factors growth and their receptors, as well as miRNA, oxygen, nutrient and other various chemical mediators [7]. Thus, the environment within the tumor and around the tumor becomes crucial for its growth, survival and impact on the host. According to the TOFT theory, tumorigenesis processes result from deregulation of interactions between cells and the microenvironment and disruption of cellular communication needed to maintain normal tissue structure, and DNA mutations are not primarily a necessary carcinogen [6]. During the neoplastic process, significant structural and functional changes occur at the border between cancer cells and neighboring host cells. However, the cancer is still localized in single cells. Therefore, in TOFT DNA mutations are the result and not the cause of disorders at the tissue level.

Nevertheless, no theory can explain all the features of cancer. In other words, different types of cancer are characterized by uncontrolled cell proliferation, genomic instability, DNA damage, or significant reprogramming of cellular energy metabolism. All cancer cells are insensitive to signals that inhibit proliferation, allow cancer cells to avoid immune destruction, thereby acquiring neoangiogenesis capabilities and activating invasion and metastasis [8].

Bedessem and Ruphy suggest that TOFT and SMT describe two separate and compatible cause and effect pathways and that these two theories are not contradictory but converge and complement each other in one unified theory of carcinogenesis — chaotic adaptation theory (CAT) [9]. The essence of this theory is the hypothesis that cancer arises from the adaptation of stem cells. The main pillars of the theory are chaos „adaptation „and" information". According to CAT theory, the development of cancer is strictly dependent on the microenvironment. Two researchers Tomasetti and Vogelstein have shown that spontaneous mutations occurring during the division of stem cells can lead to the formation of neoplastic changes in some tissues, and the risk of developing cancerogenic changes is correlated with the total number of normal self-renewing cells that maintain tissue in homeostasis [10].

Normal somatic stem cells (SSCs) are described as immature cells that have a dual ability to self-renew and differentiate. Their activity can be explained by natural selection acting based on SSC decisions in response to signals from other SSCs in the local microenvironment and from more diverse cells in the rest of the body [11]. On the other hand, SSCs have remarkable regulatory flexibility that allows them to operate in various external conditions. This ability to adapt to environmental changes is important for all organisms to maintain cellular functions [12]. SSC function is controlled by coordinated activation and / or inhibition of thousands of genes in a particular environment.

According to the hypothesis of chaotic adaptation theory, somatic stem cells (SSCs) receive information from daughter cells, which is transmitted to the SSC nucleus and a response is created. This phase was called the physiological phase [13]. The next phase is the tactical phase, in which as a result of adverse environmental changes, SSCs form cells of different phenotype, i.e. different shapes, different metabolism, etc. At this stage, mainly morphological atrophic and hypertrophic changes are observed. If the tactical phase

is not enough to protect the resulting daughter cells, the SSC genome jumps to the brink of chaos. This phase is called the chaos edge phase or the atavistic phase. This phase is pathomorphologically described as dysplasia or preneoplastic metaplasia, and phenotypes are referred to as atavistic phenotypes. If the SSC and daughter cells cannot adapt to an environment with increased energy flows, the systems go into the chaos or rescue phase (innovation phase). In this phase, SSCs become cancer stem cells. Delay in input signal transduction is a prerequisite for chaotic behavior [14, 15] These changes are „strategic" (fundamental changes in the current function of the cell). SSCs explore their own genotype spaces through ‚chaotic search'. Stochasticity and chaos are not identical. Chaotic sequences can be produced using deterministic algorithms [16].

The difference is important because differences in determined chaos are limited by the attractor, while true stochasticity is not limited. All chaotic innovations have their source in some genotype space. These innovations include molecules with new structures and biochemical functions. Chaos can act as a „heterogeneity engine" that allows cell populations to quickly study many phenotypes (different morphology, nuclear structure, chromatin architecture, metabolism, transmembrane potentials, etc.) [13]. Genomic chaos also refers to an increased rate of genome restructuring: changes in the number of chromosomes (aneuploidy), segmental rearrangement of chromosomes (translocations, duplications, inversions and deletions), instability of repetitive sequences and individual catastrophic events, e.g. the phenomenon of chromothripsis [14, 15]. Chromothripsis is a subtype of chaotic genome. It makes up roughly less than 10% of all different types of chaotic genomes examined [17]. The lack of experimental evidence of generating chaos at the intracellular level in vivo may indicate that during evolution the cell found a solution to this problem, namely the possibility of stabilizing the system in the presence of factors generating chaos [18]. Phenotypic diversity created by genomic chaos can be beneficial in a hostile environment, it is well established in ecology and population genetics.

The fact remains that, despite the chaos in the genome, which should generally lead to cell death, some chaotic genomes acquire the ability to survive and survive. About 45% of the human genome consists of transposable elements, which is a type of unauthorized recombination that does not require the homology of the nucleotide sequence of the DNA molecules involved. Transposable elements, which belong to the group of mobile genetic elements, due to their ability to move from one place in the genome to another, can cause large changes in the structure of the genome, i.e. inversions, deletions and duplications large DNA fragments. DNA transposition is commonly found in the human genome, but usually does not include coding sequences.

Liu et al. [19] presented evidence to support chaotic theory, showing that potential chaotic motifs are visible in the expression of certain genes in cancer cell lines.

Recently, Lou and Liu, propose the integrative theory for cancer, in which are three basic elements of cancer development — genetic alterations (cancer), metabolic imbalance (host) and immunological response (host) [20]. Cancer is a complex disease involving many changes in cell physiology and metabolism. According to Warburg the primary cause of cancer is a metabolic switch from oxidative to glycolytic metabolism. Damage the respiration and energy metabolism precedes and underlies the genome instability that accompanies tumor development [21]. According to Seyfried cancer is a mitochondrial metabolic disease [22]. The dysregulation of mitochondrial function is one the main component of the metabolic reprograming of cell. Abnormalities in the content and composition of mitochondria have been observed in different tumor tissues. The changes of metabolism can also trigger transcriptional programs alterations associated with the inflammatory milieu, acceleration cellular proliferation and metastasis [23].

The latest theory is the systemic-evolution theory of cancer (SETOC) which postulates two connected concepts. Breaking down the endosymbiosis between mitochondria and the information nucleus/cytoplasm. The evolution of the system of various cellular components because of long-term injuries leads to atavistic biological functions, dysplasia and then cancer [24]. Several studies show that destroying the communication between the mitochondria and nucleus makes the first dysfunctional and triggers carcinogenesis [25–27].

Epidemiological studies show that some of the cancers are caused by infection with a virus containing RNA-type genetic material (hepatitis c-HCV virus, retroviruses, *e.g.* HTLV-1) or DNA-type viruses [*i.e.* hepatitis B virus (HBV), Kaposi sarcoma herpesvirus (KSHV/HHV8, Merkel cell polyomavirus (MCV), Epstein-Barr virus (EBV)]. Cancer develops most often as a result of long-term infection. In addition, non-infectious cofactors, including age, genetics, environmental play an important role in the etiology of these cancers. Other factors and immunity *e.g.* dietary aflatoxin for HBV related hepatocellular carcinoma or host mutation predispose such as in genes encoding EVER1 and EVER2 for beta HPV-related epidermodysplasia verruciformis [28]. Individual human tumor viruses exert their malignant effects in different ways.

SUMMARY

In modern science, the existence of competing theories that differ in basic assumptions, but are based partly on

the same experimental data, is not unusual. The solution to a certain problem, in this case theories regarding the formation of tumors, can be analyzed by the thesis that it is impossible to specify or explain the theory through given experiments. The existence of significant theoretical differences between the processes presented above results from the huge amount of experimental data and the lack of unambiguous results confirming or negating the assumptions of the researchers. It is possible that soon, thanks to advances in molecular research on carcinogenesis, the problem of the formation and treatment of cancerous cell transformation will be partially solved [29].

Conflicts of interest

The authors declare no conflict of interest.

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Comparison of Polish and international guidelines on diet supplements in pregnancy — review

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ABSTRACT

Proper nutrition is an important element that determines the course of pregnancy. Unfortunately, the everyday diet is not always able to cover the increased in pregnancy essential vitamins and minerals requirements. Therefore, pregnant women often use dietary supplements. This study aimed to compare Polish and international recommendations regarding dietary supplementation during pregnancy. The Polish Society of Gynaecologists and Obstetricians (PSGO) recommends in every pregnant woman the dietary supplementation of folates, vitamin D and iodine.

Additionally, the benefits of iron supplementation in pregnant women with anemia or at high risk of developing anemia are also highlighted. In the light of Polish guidelines, the magnesium supplementation is recommended in the condition of its reduced level in blood. In the case of limited consumption of DHA (docosahexaenoic acid), Polish guidelines recommend in pregnant women's diet, at least 600 mg of DHA every day. Still, in case of the high risk of premature birth — at least 1000 mg DHA a day during the entire pregnancy period should be taken.

Key words: diet supplements; gestation; pregnancy; polish recommendations

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INTRODUCTION

Diet supplements cover a wide range of products which, due to their vast diversity, are hard to be precisely defined. Still, there is no consensus of international societies and scientific bodies regarding the definition of diet supplements, and the preparations that should be included in this group. Polish legal regulations specify that a diet supplement is "a food product whose purpose is to supplement the standard diet. Being a concentrated source of vitamins or mineral ingredients, or other substances demonstrating nutritious or other physiological effect, single or combined, traded in a form allowing dosing the substances, in the form of capsules, tablets, dragées, and other similar forms, pouches with powder, ampoules with liquid, bottles with a dropper, and other similar forms of liquids and powders intended for consumption in small, measured unit amounts, with the exclusion of medicinal products, as defined in the regulations of pharmaceutical law" [1]. However, other countries' regulations describe diet supplements very inhomogeneously, defining them as natural health products (NPH), supplementary medications, or nutritional supplements. A product which is considered a diet supplement in one country, and to which the regulations of food safety apply, in another may be a therapeutic mean or a substance subject to strict control, and pharmaceutical law may regulate its production. The situation is complicated even more by the traditional medicine of Far-East countries, which may consider a diet supplement a substance which is not admitted for trading in other countries [2]. It is also to believe that many dietary supplements which are traditionally considered beneficial for health are lacking reliable proof that they affect, or studies examining such products are very limited in number.

Moreover, we must remember that nowadays, diet supplements are mostly compound products that considerably hinder the definition of the potential effect of a given product on human's health [2]. The above issues indicate the need to introduce reliable research in line with

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evidence-based medicine (EBM) doctrine and concerning potential benefits of the use of diet supplements. This matter is particularly important in such a sensitive period as pregnancy, both from the developing child and maternal requirements, especially as regards the exposure to a metabolic disorder such as gestational diabetes.

The aim of this study is to compare Polish and international recommendations regarding dietary supplementation during pregnancy.

METHODS

This review was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement checklist. Data search of this review was performed in the Web of Science and PubMed databases ("all databases search"). The combinations of the following terms were used: "dietary supplementation" or "vitamins supplementation" or "minerals supplementation" or "supplementation" or "diet supplementation" or "DHA" or "folic acid" or "PUFA" or "iron" or "vitamin D" or "magnesium" or "zinc" and "pregnancy" or "gestation", or "polish society of gynecologists", "polish gynecologist society". The search criteria were narrowed down to articles with Polish affiliation. Papers with another affiliation were included exceptionally, only if provided important information essential to interpret included articles. The initial screening of title, abstract, and keyword were performed using the following filters: "supplementation", "vitamins", "minerals", "Polish recommendations", "polish society of gynecologists", "polish gynecologist society", "gestation", "pregnancy", "gestational". We systematically and thoroughly examined the reference lists of searched publications to identify both direct and indirect evidence to meet the aim of the review. We included papers from 2009 to December 2019. Only publications that were conducted human-only (both review and clinical trial) were included. We excluded case reports. Studies with data duplications, not in English or Polish, not with Polish affiliation, or published before 2009, were excluded.

From the Web of Science and PubMed databases ("all databases" search), 219 titles were found and assessed by two independent reviewers. After the titles were read, 117 abstracts were excluded. The remaining 102 articles were screened, and 91 were excluded. After the selection process, a total of 11 articles were included in the review (Fig. 1).

The Polish Society of Gynaecologists and Obstetricians (PSGO) informs that, besides the recommendation concerning supplementation of folates, currently there are no separate guidelines on supplementation of microelements and vitamins in patients with gestational diabetes. However, the need to supplement vitamins and microelements in pregnancy after bariatric surgeries and partial gastrectomy is emphasized [3, 4].

RESULTS

The results of the literature review of the Polish recommendations on the diet supplementation in pregnancy are presented in Table 1.

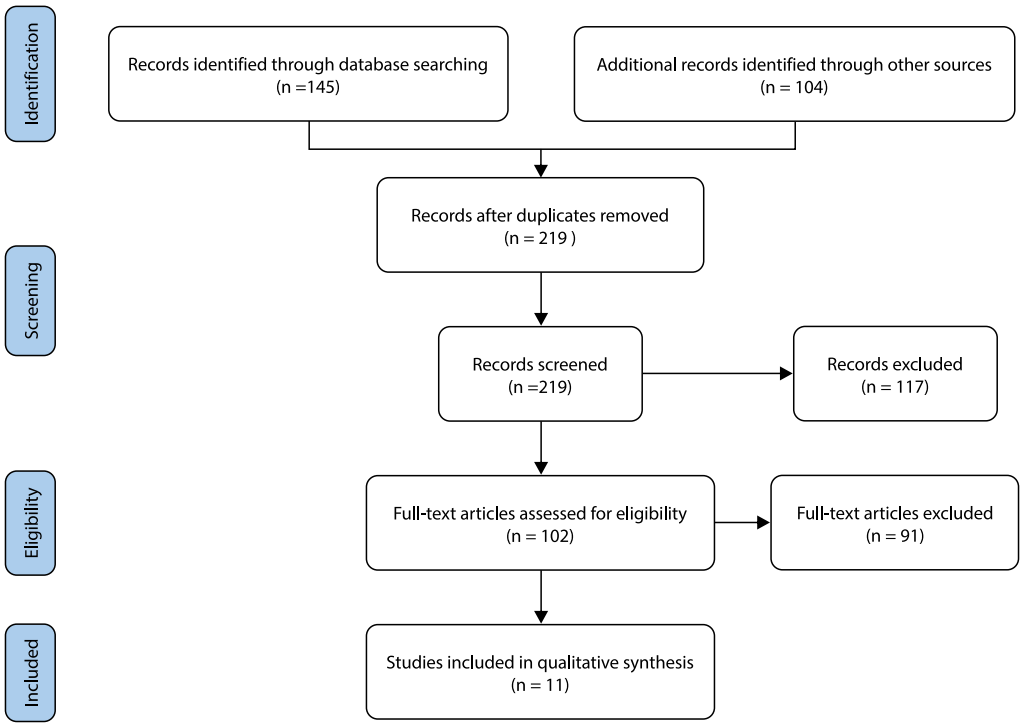

Figure 1. PRISMA flow chart

Table 1. Polish recommendations on the diet supplementation in pregnancy

No	Ref.	Supplementation recommendations
1	Wender-Ożegowska E, et al., 2018; [3]	Folic acid supplementation: • women planning pregnancy should start taking folic acid at least 12 weeks before pregnancy and continue using it during pregnancy, puerperium, and lactation • in women from the high-risk group (pre-pregnancy DM1 and DM2) the folates at a dose of 0.4 mg/day plus an additional 0.4 mg/day of active folates are recommended Vitamin D supplementation: • 1500–2000 IU/day
2	Wender-Ożegowska E, et al., 2012; [4]	In pregnant women who have undergone bariatric surgery, deficiencies of iron, folic acid, vitamin B12, and calcium should be corrected Supplementation should be continued during pregnancy and the postpartum period
3	Bomba-Opoń D, et al., 2017; [5]	Folic acid supplementation: • every woman in reproductive age should include products rich in folates in her diet, • the dose of folic acid depends on the risk of NTD (neural tube defects): — low risk: 0.4 mg/day, — intermediate risk (pre-diabetes DM1 or DM2, obesity, bariatric surgery, metformin use) — 0.8 mg/day, active folates at least 12 weeks before conception and during pregnancy, puerperium and lactation period, — high risk — 5 mg/day active folates in the preconception period and during the first trimester of pregnancy; 0.8 mg/d in the second and third trimester, and during the breastfeeding period • the active forms of folates and B12 vitamin supplementation are recommended
4	Polish Gynecological Society, 2014; [6]	Folic acid supplementation: • constant supplementation at least 6 weeks before conception until the end of organogenesis • the standard dose of folic acid 0.4 mg • higher doses in women with obesity, megaloblastic anemia, smokers, women using hormonal contraception, anti-epileptic drugs, hyperhomocysteinemia DHA supplementation: • 600 mg for women who consume small amounts of fish • up to 1000 mg for women at high risk of preterm labor Iron supplementation: • women with iron deficiency anemia: 30 mg/day before conception, and then, from the end of the 8th week of pregnancy, increase the dose to a maximum of 60–120 mg/day Iodine supplementation: • 200 mg/day Vitamin D supplementation: • 2000 IU/day for women planning to become pregnant and pregnant • the highest safe therapeutic dose: 10,000 IU Mg: • 600–1000 mg/day/depending on the indications
5	Poreba R, et al., 2011; [16]	Folic acid supplementation: • 0.4 mg of folic acid/active form/supplementation is recommended for women planning pregnancy for at least 6 weeks before it and until the end of the second trimester of pregnancy Iron supplementation: • women with a high risk of iron deficiency anemia or with anemia should be supplemented with the iron before conception and then, from the 9th week of pregnancy • standard daily doses: 18 mg/day before pregnancy, 26–27 mg in pregnancy, 20mg/day in breastfeeding period Vitamin D supplementation: • 800–1000µg/day /in women with vitamin D deficiency Magnesium supplementation: • 200–1000 mg/day /in women with magnesium deficiency Iodine supplementation: • 150 µg potassium iodide/in every pregnant woman DHA supplementation: • 200–300 mg/day DHA/in every pregnant woman
6	Dębski R, et al., 2013; [17]	Iron supplementation: • women with a high risk of iron deficiency anemia or with anemia should be supplemented with the iron before conception and then, from the 9th week of pregnancy, • standard daily doses: 18 mg/day before pregnancy, 26–27 mg in pregnancy, 20 mg/day in breastfeeding period
7	Horvath A, et al., 2007; [19]	DHA supplementation: • due to the low level of consumption in Poland • foods that are a natural source of omega-3 fatty, in women with low risk of preterm birth the supplementation at least 600 mg/day of DHA • throughout pregnancy should be considered • Women with a high risk of premature birth: at least 1000 mg DHA/day during all pregnancy period

→

Table 1. Polish recommendations on the diet supplementation in pregnancy, continued

No	Ref.	Supplementation recommendations
8	Charzewska J, et al., 2010; [20]	Vitamin D supplementation: • 800–1000 IU/d should be supplemented from the second trimester of pregnancy, if not adequate dietary supply and/or skin synthesis is provided
9	Płudowski P, et al., 2013; [21]	Vitamin D supplementation: • women who plan pregnancy should start/maintain Vitamin D supplementation as recommended for adult, • vitamin D supplementation of 1,500–2,000 IU/day (37.5–50.0 µg/day) should begin at least from the second trimester of pregnancy • gynecologists/obstetricians should consider starting Vitamin D supplementation for pregnant women soon after the pregnancy is confirmed; if feasible, periodical monitoring of serum 25(OH)D concentration should be done to define optimum dosage and to verify the efficacy of supplementation • the goal of supplementation is to achieve and maintain 25(OH)D concentration of 30–50 ng/mL (75–125 nmol/L)
10	Szybiński Z, 2012; [24]	Iodine supplementation: • obligatory iodization of household salt (20–40 mg KI/1 kg) and neonates' formula (10 µg/100 mL of milk) • additional supplementation for pregnant and breastfeeding women with 150–200 µg of iodine as pharmacotherapy
11	Bednarek W, et al., 2010; [32]	DHA supplementation: • women with low fish consumption and other sources of DHA: 500 mg of DHA/day for as little as the first month of pregnancy • women with a high risk of premature birth: 1000 mg DHA/day

NTD — neural tube defects; DHA — docosahexaenoic acid; DM1 — diabetes mellitus type 1; DM2 — diabetes mellitus type 2

The comparison of the Polish recommendations, American College of Obstetricians and Gynecologists (ACOG) recommendations and National Institute for Health and Care Excellence/Royal College of Obstetricians and Gynaecologists (NICE/RCOG) recommendations on the diet supplementation in pregnancy is presented in Table 2.

DISCUSSION

Folic acid supplementation during pregnancy

The essential diet supplement used in the preconception period and during pregnancy is folic acid. 5-methyltetrahydrofolate is an active form of folic acid in the body [5]. It is a coenzyme of nucleic acids transformations and a catalyst of blood formation processes. It is absorbed in the intestines. In blood circulation, it is bound to plasma proteins. A deficit in folic acid in the diet leads to the total consumption of its reserves within the body, as quickly as within four months [6]. Due to higher demand for folates during pregnancy, it may only be satisfied with well-composed diet [7]. In breastfeeding women, the requirement for folic acid is even higher than during pregnancy [8].

In a pregnant woman, the deficit in folic acid may result in megaloblastic anaemia. It is caused by the reduced rate of DNA synthesis process and a prolonged period of red blood cells maturing in the marrow [6]. Diagnosis of megaloblastic anaemia is the indication for the increase of the supplemented dose of folic acid. The increased dose of folic acid should also be implemented in patients who smoke, have previously taken anti-epileptics, methotrexate, sulfasalazine, colestyramine or hormonal contraceptives. Also, in patients with celiac disease, Leśniowski-Crohn's disease, ulcerative colitis, alcoholism, liver failure, kidney failure requiring dialysis, and patients with pre-eclampsia and/or IUGR (intrauterine growth restriction) in medical history. Women with hyperhomocysteinemia being the result of reduced activity of methylenetetrahydrofolate reductase (MTHFR) also require a higher supply of folic acid. The reasons for reduced MTHFR include different kinds of polymorphisms of MTHFR gene, among which the most frequent is polymorphism MTHFR 677 C > T, which occurs with the frequency reaching up to 50% in the Asian population [5, 6, 9]. Complications resulting from irregularities in the metabolic processes of folic acid, besides megaloblastic anaemia, include reoccurring miscarriages and pre-eclampsia [5, 10, 11].

For the foetus, folic acid deficiency may result in a range of defects of the central nervous system, heart defects, urinary system obstructive defects, cleft lip and palate, increased risk of Down syndrome, and increased risk of miscarriage and thrombosis. Moreover, disturbances in the metabolic processes of folates may result in the inhibition of intrauterine growth of foetus [5, 6, 11, 12].

A cofactor of metabolic processes of folic acid is B12 vitamin. The high concentration of folates with the coexisting insufficiency of B12 is particularly adverse. It may lead to hyperhomocysteinemia resulting in pregnancy complications. The use of too high doses of folic acids increases the risk of early pregnancy damage. It may cause the development of insulin resistance, type 2 diabetes, and obesity in a child [5]. Current guidelines indicate that application of folic acid in a dose higher than 5mg is not justified and may

Table 2. The comparison of the Polish recommendations, American College of Obstetricians and Gynecologists (ACOG) recommendations and National Institute for Health and Care Excellence/Royal College of Obstetricians and Gynaecologists (NICE/RCOG) recommendations on the diet supplementation in pregnancy

Supplementary recommendation	The Polish Society of Gynaecologists and Obstetricians (PSGO) [3, 5, 6, 24, 32]	American College of Obstetricians and Gynecologists (ACOG) [33, 34]	National Institute for Health and Care Excellence/ Royal College of Obstetricians and Gynaecologists (NICE/RCOG) [35–40]
Folic acid	every woman in reproductive age should include products rich in folates in her diet, the doses depend on the risk of NTD (neural tube defects): **low-risk** — 0.4 mg/day **intermediate risk** (pre-diabetes DM1 or DM2, obesity, bariatric surgery, metformin use) — 0.8 mg/day, active folates at least 12 weeks before conception and during pregnancy, puerperium and lactation period **high risk** — 5 mg/day active folates in the preconception period and during the first trimester of pregnancy; 0.8 mg/d in the second and third trimester, and during the breastfeeding period, the active forms of folates and B12 vitamin supplementation are recommended	all women capable of becoming pregnant should strive for intake of 400 µg (0.4 mg) of folic acid daily, in the form of a supplement, multivitamin, consumption of fortified foods, or a combination of the above. during pregnancy: 0.6 mg/day women who have had a previous NTD-affected pregnancy, who are themselves affected, have a first- or second-degree relative with a NTD, or who have DM1 should take 4 mg of folic acid commencing 3 months before conception and continuing throughout the first trimester	standard dose: 400 µg/day), ideally before conceiving and continue to 13th week of pregnancy women with high risk of NTD: 5 mg/day of folic acid
Iron	women with iron deficiency anemia: 30 mg/day before conception, and then, from the end of the 8th week of pregnancy, increase the dose to a maximum of 60–120 mg/day women with a high risk of iron deficiency anemia in pregnancy and breastfeeding period: 18 mg/day before conception, 26–27 mg/day during pregnancy, 20 mg/day during lactation	standard dose: 27 mg/day	iron supplementation should not be offered routinely to all pregnant women. it does not benefit the mother's or the baby's health and may have unpleasant maternal side effects
magnesium	200–1000 mg/day in women with a low level of magnesium in the blood serum or symptoms of magnesium deficiency	N/A	N/A
iodine	150–200 µg/day	200 µg/day	N/A
vitamin D	1500–2000 IU/day (4000 IU/day in women with obesity)	In pregnant women with increased risk of vitamin D deficiency, maternal serum 25-hydroxyvitamin D levels can be considered and should be interpreted in the context of the individual clinical circumstance when vitamin D deficiency is identified during pregnancy, 1.000–2.000 international units per day of vitamin D is safe	all pregnant and breastfeeding women — 10 micrograms/day women with high-risk of vitamin D deficiency: at least 1000 IU/d (women with increased skin pigmentation, reduced exposure to sunlight, or those who are socially excluded or obese) women with vitamin D deficiency — treatment for 4–6 weeks, either with cholecalciferol 20 000 IU/ week or ergocalciferol 10 000 IU/ twice a week, followed by standard supplementation
DHA	600 mg for women who consume small amounts of fish, up to 1000 mg for women at high risk of preterm labor,	N/A	N/A

N/A – not applicable; NTD — neural tube defects; DHA — docosahexaenoic acid; DM1 — diabetes mellitus type 1; DM2 — diabetes mellitus type 2

lower the seizure threshold [5, 13]. Folic acid supplementation should be avoided in elderly patients and in neoplastic diseases as it may intensify the oncogenesis [6].

Folic acid supplementation considerably reduces the risk of neural tube defect, heart defect, urinary system and limbs defect, cleft lip and palate, and pre-eclampsia [5]. Therefore, it is recommended by PSGO that every woman in reproductive age should include products rich in folates (e.g., lettuce, cabbage, nuts) and food enriched with this nutrient in her diet. PSGO has qualified patients with pre-diabetes, diabetes mellitus type 1 or type 2, obese patients, as well as women after bariatric surgery and patients using metformin as the group of intermediate risk of developing foetus defects. The previous studies have shown that both hyperglycaemia and insulin resistance may cause a disturbance in folates metabolism [5, 14]. For that group of women, PSGO recommends that folic acid should be supplemented at least 12 weeks before conception and continued during pregnancy, puerperium and lactation period. The recommended dose of folates for that population of patients is 0.8 mg/day, including active folates. PSGO recommends the use of preparations with documented composition and effect, and supplementation of B12 [3, 5].

If a patient with diabetes mellitus (DM) has given birth to a child with neural tube defect, according to PSGO guidelines, she belongs to the group of women with a high risk of giving birth to another child with neural tube defect. In such population, PSGO recommends folates supplementation in the dose of 5 mg a day in the preconception period and during the first trimester of pregnancy. In the second and third trimester, and during the breastfeeding period, the dose of folates should be reduced to 0.8 mg/day. It is recommended that active forms of folates and B12 vitamin supplementation are considered [5].

American College of Obstetricians and Gynecologists (ACOG) recommends that all women capable of becoming pregnant should strive for intake of 400 µg (0.4 mg) of folic acid daily, in the form of a supplement, multivitamin, consumption of fortified foods, or a combination of the above. The dose recommended during pregnancy is 0.6 mg/day. Women who have had a previous NTD-affected pregnancy, who are themselves affected, whose first- or second-degree relative has NTD, or suffering from DM1 should take 4 mg of folic acid commencing three months before conception and continuing throughout the first trimester [34].

National Institute for Health and Care Excellence/Royal College of Obstetricians and Gynaecologists (NICE/RCOG) recommends a standard dose of 400 µg/day of folic acid before conceive and continue the supplementation until 13th week of pregnancy. Women with high risk of NTD should take 5mg/day of folic acid [35, 37, 39].

Iron supplementation during pregnancy

Pregnant women often demonstrate iron deficiency anaemia and the so-called physiological anaemia resulting from haematocrit drop. Anaemia resulting from iron deficiency is recognised when the haemoglobin concentration is below 11 mg%. Anaemia during pregnancy leads to reduced tolerance to effort, tiredness and increased risk of premature birth. A drop in the iron content in feeding mother's milk may result in anaemia and reduced psychomotor development of the child [6]. Risk factors of iron deficiency in mother include vegetarian or vegan diet, heavy menstrual bleeding, lactation, malabsorption, and the pregnancy itself [6, 15].

In women who are not pregnant, iron content in the diet should amount to no less than 18 mg/day, during pregnancy 26–27 mg/day and 20 mg/day during lactation [16]. British Committee for Standards in Haematology indicates that iron supplementation is required in patients with haemoglobin level below 11.0 g% in the first trimester, below 10.5 g% in the second or third trimester, below 10 g% during puerperium or lactation period, or with ferritin level below 30 mg/L [17, 18]. Women with anaemia should start oral supplementation of iron during the pregnancy planning period. After the conception, they should begin iron supplementation after the eight weeks of pregnancy, in a daily dose of 30 mg. Afterwards, depending on the anaemia level, the dose should be increased to 60–120 mg/day. Iron supplementation before the eighth week of pregnancy may cause a high concentration of iron in vesicular fluid, which can harm the development of an embryo and cause developmental defects [6, 19]. Specialists emphasize that the most beneficial form of oral iron supplementation is supplying it in small doses over a long period. It is dependent on the metabolism of proteins responsible for iron transport in blood circulation. Moreover, during iron supplementation, it is essential to ensure proper supply of magnesium and B6 vitamin [6, 15]. Absorption of non-heme iron is assisted by vitamin C [17].

Iron supplementation is also recommended in women in the preconception period in which the risk of anaemia in the future is present. Moreover, PSGO recommends iron supplementation in pregnant women with the risk of iron deficiency anaemia and during the lactation. In the situations mentioned above the doses of iron supplement should be 18 mg before conception, 26–27 mg during pregnancy, and 20 mg during breastfeeding [6, 17].

PSGO experts recommend the use of iron bis-glycinate both to prevent and treat anaemia in obstetrics and gynaecology [17]. PSGO also points out to numerous benefits, including efficiency and the safety of use of low-dose heme iron preparations. PSGO emphasize that iron supplementa-

tion may be individually adjusted with the use of different preparations of various pharmacological properties [17].

ACOG recommends that pregnant women should take a standard dose: 27 mg/day of iron [33, 34]. NICE/RCOG states that iron supplementation should not be offered routinely to all pregnant women. Moreover, according to NICE/RCOG iron supplementation during pregnancy does not benefit the mother's or the baby's health and may even has unpleasant maternal side effects [35, 39].

Vitamin D supplementation during pregnancy

Vitamin D regulates calcium and phosphorus concentration in blood. It is responsible for mineral density of skeleton, reduces excessive proliferation, stimulates the development of cells in the hematopoietic system, and plays an immunomodulatory role [6]. Vitamin D is produced in human skin during exposure to sunlight. However, in Poland, such exposure is somewhat limited, which considerably reduces the production of vitamin D in the body [6]. Vitamin D insufficiency disturbs calcium and phosphate homeostasis and may be a cause of osteoporosis. Pregnant and lactating women are the group particularly susceptible to the inadequacy of that nutrient [6]. A correlation between vitamin D insufficiency and glucose tolerance disturbances and diabetes mellitus type 2 has been confirmed. Vitamin D insufficiency in Polish population is widespread [20]. Therefore, PSGO recommends the measurement of 25-OH-D3, especially in pregnant women with diabetes diagnosed during pregnancy, gestational diabetes in the early pregnancy, or obese pregnant women with hyperglycaemia during pregnancy. Standard recommended dose of vitamin D for a pregnant woman is 1.5–2 000 IU/d. Whereas, in an obese patient, it is recommended to use a daily dose of up to 4 000 IU/day [3, 21]. The highest clinically safe dose of vitamin D is 10 000 IU/day [6].

ACOG claims that when vitamin D deficiency is identified during pregnancy, a dose of 1 000–2 000 international units per day of vitamin D is safe [33]. NICE/RCOG recommends 10 micrograms/day of vitamin D to all pregnant and breastfeeding women. Women with high-risk of vitamin D deficiency should take at least 1 000 IU/day — these are women with increased skin pigmentation, reduced exposure to sunlight, or those who are socially excluded or obese. In women with vitamin D deficiency a 4–6 weeks-long treatment, either with cholecalciferol 20 000 IU/week or ergocalciferol 10 000 IU/twice a week, should be followed by standard supplementation [35–40].

Magnesium supplementation during pregnancy

Magnesium is responsible for the regulation of neuromuscular transmission and regulations of minerals management in the skeleton. Magnesium insufficiency increases muscle contractility demonstrated by painful contractions. It also leads to an elevated risk of arterial hypertension. Human body demand for this element is 6 mg/kg/day and doubles during pregnancy and breastfeeding period. Magnesium supplementation is recommended in the condition of its reduced concentration in blood, or case of clinical manifestations of the insufficiency. Magnesium is supplemented orally in a daily dose of 200 to 1000 mg, depending on the indications [6, 16, 22, 23].

No ACOG or NICE/RCOG recommendations on magnesium supplementation in pregnancy have been found.

Iodine supplementation during pregnancy

The risk of too low supply of iodine in the diet in Poland has become the basis for preventive supplementation of iodine in kitchen salt. Iodine demand during pregnancy increases and the recommendation for pregnant women to reduce salt content in their food may intensify the insufficiency [24, 25]. Iodine insufficiency may result in the occurrence of thyroid goitre, increased risk of central nervous system damage, hearing impairment, and mental disorders of the child. In a pregnant woman, hypothyroidism leads to an increased risk of premature birth and miscarriages. It may also result in hypothyroidism of the foetus and newborn child [24, 26].

In the first trimester of pregnancy, daily demand for iodine increases to about 200 µg. Breastfeeding is also the reason for the high need for this element. Recommended daily dose of iodine supplementation in pregnancy planning, pregnant and lactating women is 200 µg [6]. According to WHO (World Health Organisation), the treatment in pregnant and lactating women may amount to 200–500 µg [27].

ACOG recommends a daily dose of 200 µg of iodine during pregnancy [34].

Polyunsaturated fatty acids during pregnancy

PUFA (polyunsaturated fatty acids) are the components of phospholipid membranes. Proper supply of PUFA during pregnancy contributes to the extension of pregnancy duration, increased body mass of the newborn child without the risk of macrosomia, and reduced risk of premature birth [6]. It has been demonstrated that omega-3 acids supply minimises the occurrence of diabetes mellitus type 1, allergies and hypertension in adult life [28]. The most crucial omega-3 acid during pregnancy and lactating period is docosahexaenoic acid (DHA) present in seafood, algae, and fatty sea fish. Proper DHA supply during pregnancy and lactation results in undisturbed psychomotor development of the child. It also beneficially modifies the risk of postpartum depression in women. Favorable effects of DHA supply in pregnancy have been emphasized by European Food Safety Authority (EFSA) [6, 29]. PUFA supply demonstrates a positive impact on the cardiovascular system, reducing inflam-

matory condition in atherosclerotic plaques or decreasing triglyceride and low-density lipoprotein (LDL) cholesterol levels in blood [30].

PSGO recommends that in case of limited consumption of DHA in pregnant women's diet, at least 600 mg of DHA should be supplemented every day. In case of the high risk of premature birth — at least 1000 mg DHA a day during the entire pregnancy period should be taken. DHA supplementation is recommended at least from the 20th week of pregnancy [6, 31]. Considering the effect of DHA on the child's development, it is recommended to supplement DHA during breastfeeding period to maintain its optimal content in the milk. It is emphasized that DHA source should be safe and controlled, to prevent potential poisoning with heavy metals, dioxins and polychlorinated biphenyls (PCBs), resulting from impurities. The reliable source of DHA should be small fish and algae of the type Schizochytriumsp grown under artificial conditions [6, 15, 32].

The numerous studies have shown that DHA supplementation prolongs the duration of pregnancy and increases the birth weight of the child. The mechanisms of that phenomenon are based on reduced production of prostaglandins E2 and F2 by omega-3 acids and stabilization of cell membranes [15].

No current ACOG or NICE/RCOG recommendations on DHA supplementation in pregnancy have been found.

CONCLUSIONS

In the light of current Polish recommendation, the dietary supplementation of folates, vitamin D and iodine is recommended in every pregnant woman. Additionally, PSGO highlighted the benefits of iron supplementation in pregnant women with anaemia or at high risk of developing anaemia. Magnesium supplementation is needed in the condition of its reduced level in blood. In the case of limited consumption of DHA in pregnant women's diet and a group of pregnant women with a high risk of premature birth, DHA supplementation is also recommended.

PSGO, ACOG and NICE/RCOG recommend a standard dose of 0.4 mg/day of folic acid in women at low NTD risk. However, only PSGO considers a group of women at intermediate risk, in which a dose of 0.8 mg/day of active folates is recommended. In women at high NTD risk both PSGO and NICE/RCOG recommend 5 mg/day of folates, while in such case ACOG recommends 4 mg/day.

PSGO recommends iron supplementation during pregnancy and lactation depending on the woman's iron status, while ACOG advise a standard dose of 27 mg/day of iron. NICE/RCOG does not recommend iron supplementation routinely during pregnancy.

PSGO recommends 150–200 µg of iodine daily during pregnancy, similarly ACOG advices a daily dose of 200 ug of iodine. NICE/RCOG did not develop recommendations of iodine supply during pregnancy.

In relation to vitamin D supplementation in pregnancy PSGO advices 1500-2000 IU/day (4000 IU/day in women with obesity). Similarly, ACOG states that in vitamin D deficiency a dose of 1000–2000 IU of vitamin D per day is safe. NICE/RCOG recommends a dose of 10 micrograms/day of vitamin D to all pregnant and breastfeeding women; at least 1000 IU/day to women with high-risk of vitamin D deficiency; and 20 000 IU/week of cholecalciferol or 10 000 IU/twice a week of ergocalciferol, followed by standard supplementation to women with vitamin D deficiency.

Conflicts of interest

The authors declare no conflict of interest.

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Pelvic congestion syndrome — an enigmatic pathology and diagnostic challenge for doctors

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Key words: pelvic pain; pelvic congestion syndrome; pcs

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A 38-year-old patient, three vaginal deliveries in history, no previous surgeries or chronic diseases, was admitted to the Gynecological Department due to severe lower abdominal pain. The patient noticed chronic pain, located mainly in the lower left abdomen. The pain was non-cyclic, not connected with menses. It worsened in upright position and improved by recumbency. There were several episodes of severe exacerbation — mainly in the evening, which forced the patient to lie down and interfered with her daily activities. For two years the patient was seeking help from numerous specialists, starting from her general practitioner, having multiple consultations by surgeons, gastrologists and gynecologists and finishing on psychotherapy. During that time, a wide range of imaging examinations and laboratory tests were conducted. The results of full blood count, C-reactive protein, and other biochemical tests were within normal values. Transvaginal and transabdominal ultrasound examination presented no abnormalities and CT scan of abdominal and pelvic cavity was normal. During gynecological examination tenderness of the adnexa was noted, otherwise the examination was normal. The patient was offered different therapies — antibiotics, spasmolytics, painkillers, oral contraceptives, diagnostic laparoscopy (which did not reveal any pathology) and finally psychotherapy and antidepressants. For two years, without a final diagnosis and targeted treatment, the symptoms were getting worse, which affected the personal life of the patient.

Eventually, the patient presented to the gynecological emergency room in our hospital with another exacerbation episode. In transvaginal ultrasound both ovaries appeared normal, the uterus appeared normal, except for the presence of dilated arcuate veins in the myometrium (Fig. 1A). Dilated left parametrial plexus (Fig. 1B) and ovarian vein (Fig. 1C) was noticed with abnormal, very slow, reversed flow. When this area was compressed with the probe, the patient reported exactly the pain she has been suffering from. Finally, the underlying cause was identified, and the recognition stated — pelvic congestion syndrome (PCS). After the diagnosis, the patient was qualified for phlebography and embolization of the left ovarian vein. The abnormal veins were closed with the use of detachable coils and aethoxysclerol. Immediately after the procedure and at three months and six months follow-up the patient did not report any pain.

PCS is a poorly understood and frequently misdiagnosed disorder of the pelvic venous circulation. It is defined as incompetence of the pelvic veins, predominantly the left ovarian vein [1]. PCS typically affects women of reproductive age, who have had at least one child. PCS is one of the most often overlooked gynecological conditions. This is a multidisciplinary pathology, which could be diagnosed by various specialists. Ultrasound markers of PCS include dilated pelvic veins > 6 mm, slow (< 3 cm/s) or reversed flow within ovarian veins, polycystic changes within the ovaries, dilated veins within the myometrium [2, 3]. The low awareness of the disease among both doctors and patients is the main issue. PCS presents a typical clinical and radiological image, which could be detected by gynecologist as well as radiologist [4]. In patients suffering from chronic pelvic pain pelvic veins should be evaluated.

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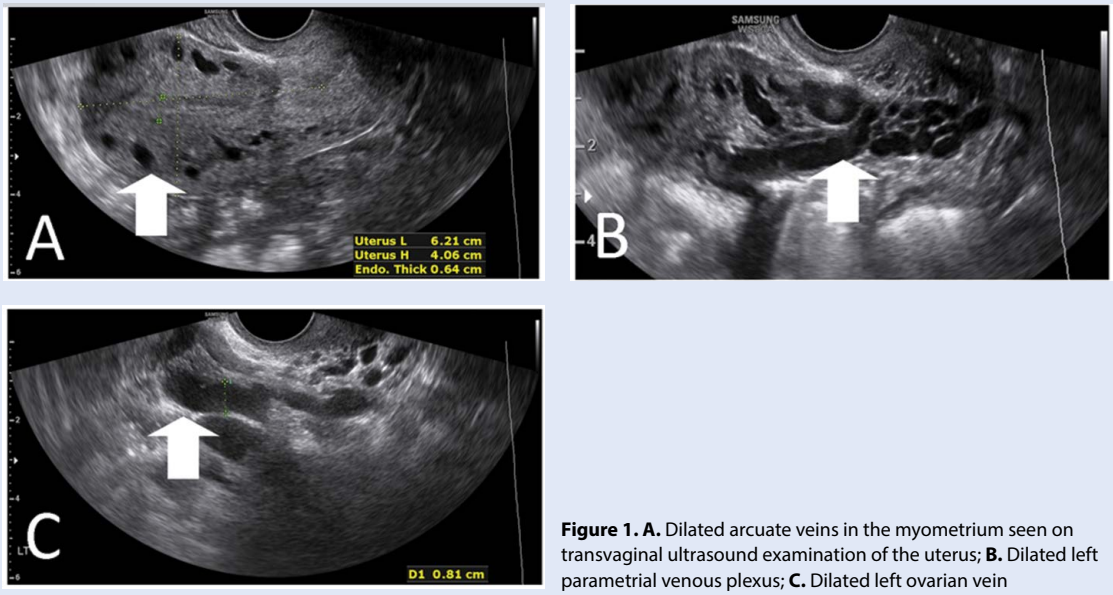

Figure 1. A. Dilated arcuate veins in the myometrium seen on transvaginal ultrasound examination of the uterus; **B.** Dilated left parametrial venous plexus; **C.** Dilated left ovarian vein

Conflicts of interest

The authors declare no conflict of interest.

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A successful vaginal myomectomy of cervical leiomyoma in early pregnancy

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ABSTRACT

The prevalence of clinically symptomatic cervical leiomyomas in pregnancy is lower than 0.1%. Surgical intervention is necessary in extremely rare cases and only few are described in the literature. This study presents a case of successful vaginal myomectomy in the 13th week of pregnancy followed by a delivery of a healthy neonate in term by cesarean section.

Key words: gynecologic surgical procedure; leiomyoma; pregnancy trimester; first

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INTRODUCTION

About five percent of uterine leiomyomas are located in the cervix. Cervical leiomyomas rarely grow to an extent which causes symptoms, including lower abdominal pain, abnormal urination, dyspareunia and obstructed labor. Large leiomyomas can extend out through the external cervical os, leading to contact bleeding. The prevalence of clinically symptomatic cervical leiomyomas in pregnancy is lower than 0.1% with a necessity of precipitate intervention in extremely rare cases [1].

CASE REPORT

A 31-year-old woman with a history of three vaginal deliveries and no miscarriages was admitted to the clinic in the eighth gestational week because of lower abdominal pain. Vaginal examination showed cervical bleeding of low intensity and a smooth, firm, movable tumor located in the cervix. A vaginal ultrasound showed features of a benign leiomyoma, with dimensions of 76 × 68 × 62 mm and a live fetus of CRL 39.5 mm in the uterus with no sign of subchorionic hematoma. There were no symptoms of anemia in the blood count performed on the admission, with HGB 13.0 g/dL, HCT 39%, RBC 4.57×10^6/uL and PLT 236×10^3/uL. After receiving conservative treatment with analgetic drugs administered intravenously and then orally, the patient was discharged with no symptoms.

She was readmitted in the 13th gestational week with severe abdominal pain and vaginal bleeding and was qualified for vaginal myomectomy in spinal anesthesia. The posterior wall of the cervix was incised and a total resection of a tumor of 10 cm in diameter was performed, with estimated blood loss of 200 mL. The ultrasound examination after the surgery confirmed a live fetus. The pathological examination of the specimen confirmed a benign leiomyoma. There were no complications in the postoperative period and the patient was discharged in good general condition.

The patient was admitted to the clinic in the 40th week of pregnancy with suspicious cardiotocography (CTG) tracings, including fetal tachycardia of 170 beats/min and increased variability. She was qualified for labor induction with oxytocin infusion. The patient reached 5 cm of dilation but was finally qualified for a cesarean section due to prolonged labor. A male neonate was born with birth weight of 3420 g and length of 53 cm, 9 points Apgar. There were no complications during the postpartum period and the patient and her infant were discharged four days after the cesarean section.

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DISCUSSION

There are few reports in the literature considering cervical leiomyomas and prolapsed submucosal leiomyomas complicating pregnancies and therefore there are no management recommendations established. Early surgical intervention should be considered in case of hemorrhage, infection, pain or urinary stasis [1]. Vaginal myomectomy in pregnancy carries a risk of hemorrhage, spontaneous abortion, premature rupture of membranes/delivery and hysterectomy. Regarding the presented case, the surgery performed on the cervix may also lead to difficulties in cervix dilation during vaginal labor. Obara et al. presented a case of a partial resection of a cervical leiomyoma in the 13th of pregnancy. Due to the thick base of the leiomyoma, they decided only to excise the myoma nucleus, having left a residual fragment of 3–4 cm of thickness. The patient had a vaginal delivery after oxytocin induction and mechanical dilatation of cervix in the 40th week of pregnancy [2]. Kilpatrick et al. [3] described two cases of vaginal myomectomies in pregnancy. The first one was performed in the 15th gestational week followed by a vaginal delivery in the 38th week. The second patient underwent the procedure in the 13th week of gestation, which was complicated by preterm premature rupture of membranes in the 16th gestational week [3].

To conclude, symptomatic cervical leiomyomas are rare findings in pregnancy and require meticulous attention and intervention only in case of absolute necessity.

Conflicts of interest

The authors declare no conflict of interest.

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