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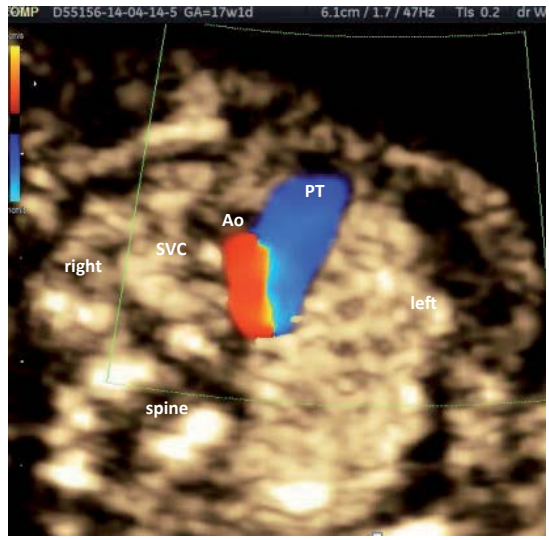

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Obesity as a risk factor of in-hospital outcomes in patients with endometrial cancer treated with laparoscopic surgical mode

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ABSTRACT

Objectives: Obesity has been suggested to have a negative influence on procedural outcomes of endometrial cancer laparoscopic treatment. Obesity and other possible risk factors of laparoscopic endometrial cancer treatment has not been precisely described in the literature. The aim of the study is to determine the factors that have the greatest influence on the course of laparoscopic surgery for endometrial cancer, with particular emphasis on the influence of obesity.

Material and methods: The study included 75 females who were treated for endometrial cancer by laparoscopic surgery. Preoperative body-mass index (BMI), waist circumference(WC), waist to hip ratio(WHR), and selected anatomical indices were measured. The duration of surgery and hospitalization stay, loss of hemoglobin, and procedural-related complications served as parameters of in-hospital outcomes.

Results: Multiple linear regression analysis indicate the body mass as most sensitive parameter of obesity which influence in-hospital outcomes in patients treated with laparoscopic procedure. Procedural-related complications occurred in the group of patients with significantly greater WC and BMI. Multiple linear regression indicates also histological grading (G1–G3), external conjugate, intertrochanteric distance as significant risk factors. The multiple linear regression analysis confirmed also that implementation of sentinel lymph node procedure is related with decreased hemoglobin loss in patients with cancer of endometrium compare to lymphadenectomy without sentinel node biopsy(Est.: 0.488; 95% CI: 0.083–0.892, p = 0.018).

Conclusions: The most sensitive risk factor of in-hospital outcomes in laparoscopic treatment of endometrial cancer is body mass. The implementation of the sentinel node procedure is associated with reduced surgery time and reduced hemoglobin loss.

Key words: obesity; endometrial cancer; risk factors; minimally invasive therapy; sentinel lymph node procedure; total laparoscopic histerectomy; perioperative outcomes

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INTRODUCTION

The most common malignant neoplasm of female reproductive organs is cancer of the endometrium. Incident rates of uterine cancer have increased over successive generations, especially in countries experiencing rapid socioeconomic transition [1]. The risk of developing endometrial cancer by 65 years of age in women ranges from 0.46% in low/middle developed countries and 0.92% in highly developed countries [2]. The prevalence of a number of the established risk factors appears to be rising in most parts of the world; obesity, in particular, has doubled in last 30 years globally [3]. While conducting a meta-analysis of 19 review works and prospective trials, it was found that each 5 kg/m^2 increase in BMI caused a significant increase in the risk of developing endometrial-type cancer (RR 1.59, 95% CI 1.50–1.68) [4]. In a review conducted among 380 patients with endometrial cancer, it was noted that morbid obesity was connected with higher mortality rate due to

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causes different than endometrial cancer or disease recurrence [5]. Traditionally, obesity was a contraindication to laparoscopic procedures and even constituted an exclusion criterion for laparoscopic surgery. Research published nearly two decades ago revealed that women qualified for laparoscopic management had a substantially lower BMI than those operated on using traditional procedures [6]. Further studies demonstrated that applying laparoscopic procedures in obese patients with endometrial cancer is safe and feasible [7–10]. In a recent study, there is evidence that the oncological efficiency of laparoscopic systematic lymphadenectomy is no less than open-type surgical treatment of patients experiencing intermediate to high-risk endometrial cancer [11]. It was also confirmed that sentinel nodemapping effectively up-staging patients with low or medium risk endometrial cancer and can also be used for high-risk histological types (serous cancer, clear cell carcinoma and carcinosarcoma) [12]. It is possible to distinguish factors modifying the perioperative course of endometrial cancer treatment with the laparoscopic method, taking into account various parameters of obesity, histological type, clinical stage of the cancer, type of lymphadenectomy, age of patients, comorbidities, pelvic anatomical parameters, number of previous abdominal operations. The factors with the greatest impact on the perioperative course of laparoscopic endometrial cancer has not been described in literature on the subject.

The objective of the study was to determine factors having the greatest influence on the course of laparoscopic surgery for endometrial cancer, with particular emphasis on the effect of obesity.

MATERIAL AND METHODS

This project was an observational prospective-type trial regarding treatment via laparoscopy. Seventy-five patients diagnosed with endometrial cancer qualified for total laparoscopic hysterectomy based on a histopathological examination of uterine scrapings were included in the study. The observation was carried out from January to August 2019.A pre-operative clinical interview was conducted which included questions about age, number of deliveries, education in years, previous abdominal surgery and comorbidities. The following parameters were determined in the preoperative examination: body height and mass, waist and hip circumference (cm) using a tape measure, as well as dimensions of the pelvic bone measured via a pelvis meter. In the study group, body mass index (BMI) and waist-hip ratio (WHR) were calculated for all participants. In accordance with the definition provided by the World Health Organization, obesity regards a BMI value ≥ 30 kg/m^2. Observation of patients covered the period from admission to hospital to discharge from the hospital and outpatient control in the event of postoperative complications. All participants gave informed consent prior to conducting the study. The study was approved by the ethics committee of the Rzeszów University — NO. 4/12/2011.

Eligibility criteria and treatment characteristics

The study included patients qualified for laparoscopic treatment who expressed informed consent for laparoscopic treatment and expressed informed consent to participate in the observational study. Patients were qualified for laparoscopic treatment in accordance with current Polish guidelines [13].Surgical treatment included: hysterectomy with adnexal removal, sentinel node procedure, pelvic and para-aortic lymphadenectomy. The sentinel node procedure was performed on 34 patients. When the sentinel node procedure was performed, 2 mL (1.0 mg/mL) of the dye was injected into the cervical stroma, divided between a superficial injection of 1–3 mm and a deep injection of 10–20 mm at 3 and 9 o'clock before entering the manipulator into the uterus. Before hysterectomy, the retroperitoneal spaces were developed and fluorescence imaging was used for sentinel node detection. Identified sentinel nodes were removed and submitted histopathological examination intraoperatively. Patients then underwent hysterectomy and bilateral salpingo-oophorectomy. According to sentinel lymph node procedure (SLNP), all suspicious lymph nodes were excised during the surgical procedure, regardless of mapping. If no lymph nodes were stained (without mapping) on one side of the pelvis, homologous unilateral pelvic lymphadenectomy was performed. Para-aortic lymphadenectomy was performed at the surgeon's discretion. If the sentinel node procedure was not performed, the patient was subjected to hysterectomy as well as bilateral salpingo-oophorectomy. Then patients underwent systematic pelvic and para-aortic lymphadenectomy in some intermediate-risk and all high-risk cases. In intermediate-risk cases(G1/G2 endometrioid cancer and myometrial invasion (MI) > 50% or G3 endometrioid cancer and MI < 50%) lymphadenectomy was considered. In high-risk cases (G3 endometrioid cancer and MI > 50%), in all cases of non-endometrioid cancer and all cases of clinical stage II, IIIA, IIIB, a lymphadenectomy was obligatorily performed [13, 14].

Study endpoints

In the perioperative period, the following selected parameters were monitored and recognized as predicators of in-hospital operative treatment outcomes: surgery duration of (/min), hemoglobin loss recognized as the difference in serum concentration level prior to surgical treatment and on the second day following surgery (in g/dL), the existence of procedure-related complications, and hospitalization duration (/days).

Statistical analysis

The continuous variables analysed in the study are expressed as mean ± standard deviation, while the categorical variables are presented as numbers and percentages. Normality of distribution was evaluated via the Shapiro-Wilk. Continuous variables in selected groups of patients were compared using the Welch test, Kruskal-Wallis test, and the Student's *t*-test when applicable. Categorical variables were compared with the chi square test. Univariate and multivariate linear regression models were applied for analysis of significant predictors regarding selected study endpoints. All potential predictors with clinical values were included into multiple regression modelling. Best models for prediction of hospitalization duration, procedure duration and hemoglobin loss were obtained using backward elimination with Akaike Information Criterion as a target. If two variables were highly correlated (correlation coefficient > 0.7), the strongest predictor was selected. Final results were presented as point estimates with 95% confidence intervals and p-values. R2 coefficients were calculated. Bootstrap model validation was performed with 1000 iterations. Model assessment was performed by examination of residuals. Statistical analysis was performed in R version 3.6.2 (R Foundation for Statistical Computing, Vienna, Austria, 2019). The p-value < 0.05 was considered statistically significant.

RESULTS

General characteristics

The study included 75 females treated for endometrial cancer in a laparoscopic way. There were 47 (62.7%) obese females in the current study (BMI ≥ 30 kg/m^2). Patients from the obese group were significantly older when compared to the non-obese patients (65.8 ± 6.2 vs 59.5 ± 8.3 years, p = 0.03). Obese patients originated more often from rural areas when compared to non-obese. However those difference was not significant (44.7% vs 32.1%, p = 0.28). While non-obese females were more often uniparous when compared to obese (28.5% vs 10.6%, p = 0.04). Obese females suffered more often from diabetes (40.4% vs 3.5%, p = 0.004), hypothyroidism (23.4% vs 0%, p = 0.005) and arrhythmias (19.1% vs 0%, p = 0.01) when compared to non-obese. The general patients' characteristics in the overall group of patients and according to the obesity status is presented in Table 1. There were no significant statistical differences in the type of procedures used in the groups of patients with and without obesity.

Selected antropometric and anatomical indices

Obese and non-obese females differ significantly in all the selected parameters of obesity, except for the height, which is presented in Table 2. While among anatomical parameters, all from the selected were longer among obese patients (intertrochanteric, interspinous, intercristal distance and external conjugate) when compared to non-obese, however statistical significance was achieved for intertrochanteric distance(36.08 ± 1.54 vs 35.07 ± 2.71 cm, p = 0.01) and intercristal distance (33.08 ± 2.27 vs 31.78 ± 2.78 cm, p = 0.03) (Tab. 2).

Tumor staging and grading

Most frequently, patients were diagnosed with stage I cancer (in accordance with the FIGO classification) and then underwent appropriate surgery (Tab. 3). Endometrioid cancer was the most frequent histopathological type (96%), and most diagnosed at first grade (58.7%). There were no significant differences between obese and non-obese patients (Tab. 3). While the percentage of females diagnosed at I A stage of FIGO classification was significantly higher among non-obese when compared to obese females (42.8% vs 12.7%, p = 0.03). This is presented in Table 3.

Duration of hospitalization

There was a significant difference in average hospitalization duration, which was notably longer for the obese female patients in comparison to the non-obese (7.1 ± 1.4 vs 5.4 ± 1.4 days, p < 0.001, Fig. 1C). Univariate regression analysis confirmed among predictors related to longer hospitalization time: greater waist circumference (p < 0.001), waist-hip ratio (p < 0.001), interspinous distance (p = 0.03), external conjugate (p = 0.001), higher grading (p = 0.03), procedural related complications (p = 0.003), diabetes (p = 0.01), hypothyreosis (p = 0.002) and anxiety disorders (p = 0.03). The multiple linear regression analysis confirmed among significant predictors of hospitalization time: body mass (Est.: 0.039; 95% CI: 0.022–0.056, p < 0.001) and external conjugate (Est.: 0.363; 95% CI: 0.123–0.603, p = 0.003) (Fig. 2).

Surgery duration

Surgical procedure duration was noted as significantly longer among the obese females when compared to non-obese females (98.1 ± 16.6 vs 80.4 ± 15.2 min., p = 0.003) (Fig. 1B). The univariate regression analysis revealed among factors related significantly to the longer operation time: waist-hip ratio (p < 0.001), intertrochanteric distance (p = 0.03), interspinous distance (p = 0.03), intercristal distance (p = 0.02), grading (p = 0.005), FIGO staging (p = 0.001), type of lymhadenectomy (p < 0.001), greater number of concomitant diseases (p = 0.01), presence of procedural related complications (p = 0.005), hypertension (p = 0.007), hypothyroidism (p = 0.008), heart failure (p = 0.02) and atrial fibrillation (p = 0.02). The significance was confirmed in multiple linear regression analysis for: body mass t (Est.: 0.473; 95% CI: 0.23–0.716, p < 0.001), intertrochanteric distance

Table 1. Patient's characteristics

Variable		Overall group treated by laparoscopy n = 75	Obese n = 47	Non-obese n = 28	p-value
Place of residency	Rural region	30 (40.0)	21 (44.7)	9 (32.1)	0.28
	Urban region	28 (37.3)	16 (34.0)	12 (42.8)	0.44
	Town > 50,000 residents	17 (22.7)	10 (21.2)	7 (25.0)	0.70
Menstrual status	Before menopause	9 (12.0)	5 (10.6)	4 (14.2)	0.63
	After menopause	66 (88)	42 (89.3)	24 (85.7)	0.63
Parity	Nulliparous	5 (7.0)	4 (8.5)	1 (3.5)	0.40
	Uniparous	13 (17.0)	5 (10.6)	8 (28.5)	0.04
	Multiparous	57 (76.0)	38 (80.8)	19 (67.8)	0.20
Co-morbidities	Diabetes mellitus	20 (26.7)	19 (40.4)	1 (3.5)	0.004
	Hypertension	34 (45.3)	25 (53.2)	9 (32.1)	0.07
	Coronary artery disease	10 (13.3)	8 (17.0)	2 (7.1)	0.22
	History of venous occlusive disease	3 (5.2)	3 (6.4)	0 (0)	0.17
	Arrhythmias	9 (12)	9 (19.1)	0 (0)	0.01
	Prior cerebral stroke	4 (5.3)	3 (6.3)	1 (3.5)	0.60
	Chronic heart failure	4 (5.3)	3 (6.3)	1 (3.5)	0.60
	Bronchial asthma	6 (8.0)	5 (3.2)	1 (3.5)	0.27
	Chronic pulmonary obstructive disease	8 (10.7)	5 (3.2)	3 (10.7)	0.99
	Hyperthyroidism	6 (8.0)	4 (8.5)	2 (7.1)	0.83
	Hypothyroidism	11 (14.7)	11 (23.4)	0 (0)	0.005
	Cholelithiasis	6 (8.4)	5 (10.6)	1 (3.5)	0.27
	Diathesis urica	4 (5.6)	2 (7.1)	2 (7.1)	0.59
	Osteoarthritis	9 (12.6)	6 (12.7)	3 (10.7)	0.79
	Chronic pancreatitis	8 (10.7)	6 (12.7)	2 (7.1)	0.44
	Chronic gastritis	6 (8.0)	4 (8.5)	2 (7.1)	0.83
	Peptic ulcer disease	6 (8.0)	5 (10.6)	1 (3.5)	0.27
	Anxiety disorders	4 (5.3)	4 (8.5)	0 (0)	0.11

Table 2. Selected antropometric and anatomical indices

Variable	Overal group n = 75	Obese n = 47	Non-obese n = 28	p-value
Weight [kg]	84.08 ± 20.30	94.25 ± 18.19	67.00 ± 8.23	< 0.001
Height [cm]	161.72 ± 8.72	161.59 ± 5.06	161.39 ± 4.63	0.86
Body-mass index [kg/m^2]	31.13 ± 7.29	35.99 ± 6.30	25.65 ± 2.60	< 0.001
Waist circumference [cm]	109.21 ± 18.78	118.34 ± 16.63	93.89 ± 9.69	< 0.001
Hip circumference [cm]	114.37 ± 20.20	122.76 ± 14.13	100.28 ± 20.65	< 0.001
Waist-hip ratio	0.94 ± 0.05	0.96 ± 0.04	0.90 ± 0.05	< 0.001
Intertrochanteric diameter [cm]	35.11 ± 4.37	36.08 ± 1.54	35.07 ± 2.71	0.01
Interspinous diameter [cm]	27.28 ± 1.94	27.48 ± 1.94	26.92 ± 1.86	0.23
Intercristal diameter [cm]	32.60 ± 2.57	33.08 ± 2.27	31.78 ± 2.78	0.03
External conjugate [cm]	21.86 ± 1.35	22.06 ± 1.19	21.53 ± 1.52	0.10

(Est.: 2.225; 95% CI: 0.109–4.341, p = 0.039) and FIGO staging class IIIC2 vs others (Est.: 39.963; 95% CI: 11.28–68.645, p = 0.007). This is presented in Figure 3.

Procedure-related hemoglobin loss

Values of mean hemoglobin loss were significantly higher during periprocedural time among obese compared to

Table 3. Tumor characteristics according to the obesity status

Variable			Overal group n = 75	Obese n = 47	Non-obese n = 28	p-value
Histopathological type	Endometrioid	G1	44 (58.7)	27 (57.4)	17 (60.7)	0.78
		G2	25 (33.3)	14 (29.8)	11 (39.2)	0.39
		G3	3 (4.0)	3 (6.4)	0 (0)	0.17
	Clear-cell		1 (1,3)	1 (2.1)	0 (0)	0.43
	Serous		1 (1,3)	1 (2.1)	0 (0)	0.43
	Adenosquamous		1 (1.3)	1 (2.1)	0 (0)	0.43
	Non-epithelial		0 (0)	0 (0)	0 (0)	–
Staging according to FIGO classification	Stage I					
	A		18 (24)	6 (12.7)	12 (42.8)	0.03
	B		35 (46.7)	24 (51.0)	11 (39.2)	0.32
	Stage II		13 (17.3)	9 (19.1)	4 (14.2)	0.59
	Stage III					
	A		3 (4.0)	2 (4.2)	1 (3.5)	0.88
	B		4 (5.3)	4 (8.5)	0 (0)	0.11
	C1		1 (2.1)	1 (2.1)	0 (0)	0.43
	C2		0 (0)	0 (0)	0 (0)	–
	Stage IV					
	A		1 (2.1)	1 (2.1)	0 (0)	0.43
	B		0 (0)	0 (0)	0 (0)	–

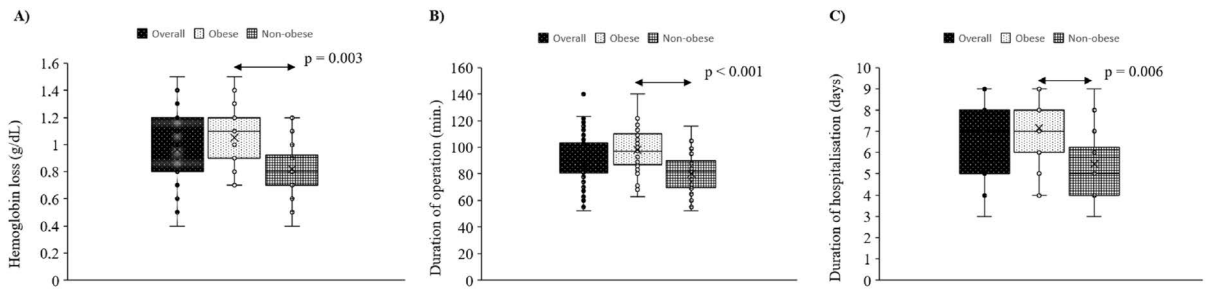

Figure 1. A. Duration of hospitalization according to the obesity status; **B.** Duration of the operation according to the obesity status; **C.** Haemoglobin loss after the procedure according to the obesity status

non-obese patients (1.05 ± 0.21 vs 0.82 ± 0.2 g/dL, p = 0.006) (Fig. 1A). The univariate regression analysis demonstrated that among significant predictors related to the greater hemoglobin loss during the procedure there were: tumor staging (p = 0.002), presence of procedural related complications (p < 0.001), diabetes (p = 0.05), hypothyroidism (p = 0.007) and heart failure (p = 0.007). The multiple linear regression analysis confirmed among factors significantly related to hemoglobin loss: body mass (Est.: 0.008; 95% CI: 0.006–0.011, p < 0.001), sentinel lymph node procedure (Est.: 0.488; 95% CI: 0.083–0.892, p = 0.018), pelvic lymphadenectomy (Est.: 0.535; 95% CI: 0.136–0.935, p = 0.009), and pelvic and para-aortic lymphadenectomy (Est.: 0.62; 95% CI: 0.197–1.044, p = 0.004) (Fig. 4).

Procedure-related complications

Five perioperative complications were noted: postoperative wound infection with impaired healing process in one of the patients, infection of vaginal wound with need of antibacterial systemic therapy in two patients, conversion to open surgery involved with abdominal obesity and pre-peritoneal entry and insufflation, omental damage and bleeding in one patient. All of these complications occurred in obese females. The differences in parameters of obesity between group with and without perioperative complications are statistically significant (BMI — 37.13 vs 37.43 p = 0.00002, WC — 106.91 vs 141.40 p = 0.00003, WHR — 0.93 vs 0.97 p = 0.004). We did not perform regression analysis due to the fact that were not able to create

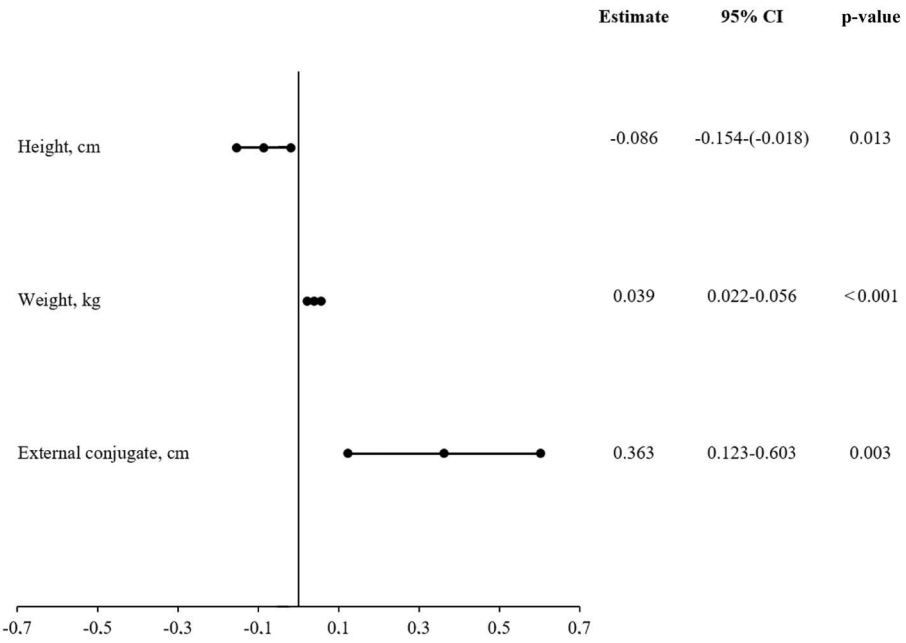

Figure 2. Predictors of the duration of hospitalization — multivariate linear regression analysis

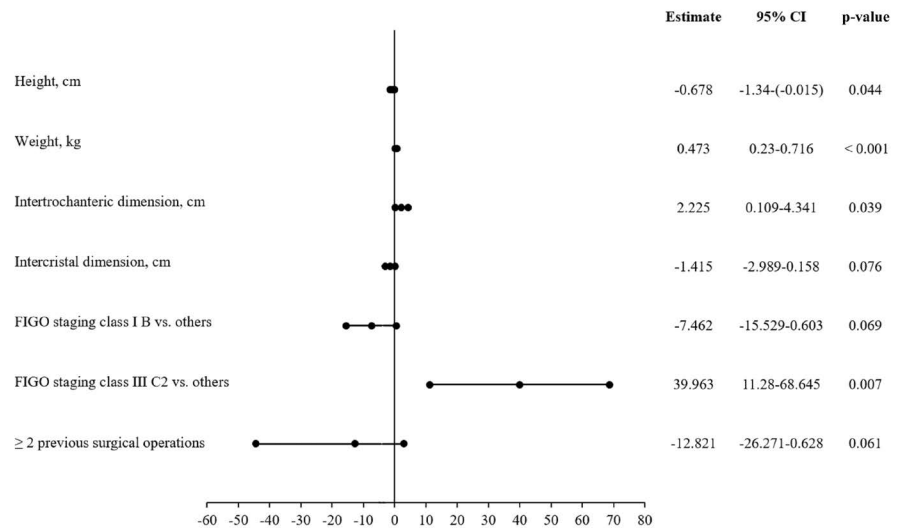

Figure 3. Predictors of the duration of operation — multivariate linear regression analysis

dedicated model, which was caused by lower number of complications in comparison to the number of assessed indices and number of their subclasses.

DISCUSSION

The general findings of this study are that patients with obesity experienced longer hospitalization as well as surgery duration, higher loss of hemoglobin during the periprocedural period. A further observation worth highlighting is that non-obese subjects were diagnosed with stage IA endometrial cancer (in accordance with FIGO classification) more frequently than obese patients. What is more, larger waist-hip ratio, higher grading and FIGO staging as well as greater range of lymphadenectomy were confirmed among the factors related to prolonged surgery time. Predictors of duration of hospitalization were greater waist circumference, waist-hip ratio, external conjugate, higher grading, and procedural related complications. A high correlation to hemoglobin loss were noticed for waist circumstance and BMI ($r = 0.58$ for WC and $r = 0.59$ for BMI). However, multiple

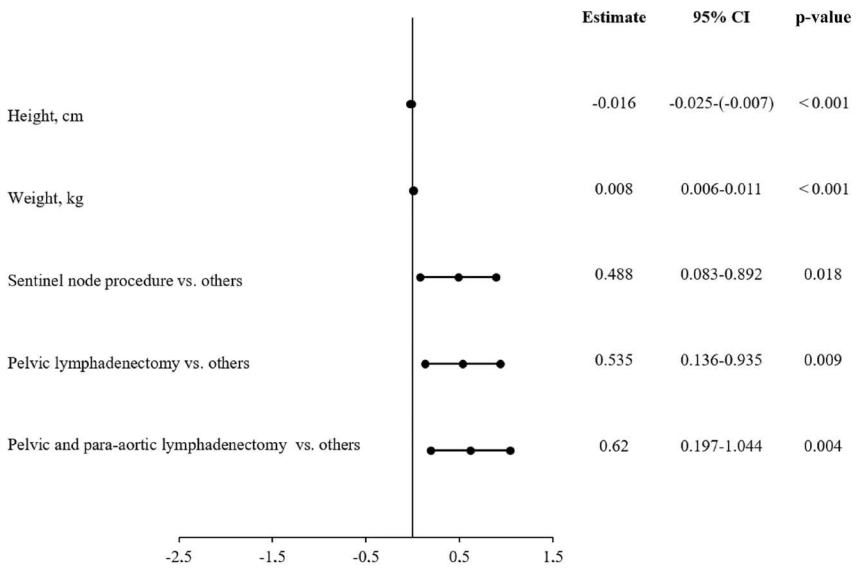

Figure 4. Predictors of the extent of haemoglobin loss according — multivariate linear regression analysis

linear regression analysis indicated weight and range of lymphadenectomy as a factors significantly related to hemoglobin loss. Patients with procedure-related complications were characterized by greater waist circumference and BMI. Multiple linear regression analysis indicated also that greater external conjugate was related to longer hospitalization and greater intertrochanteric distance was related to greater operative time. These observations may result from the fact that larger pelvic dimensions occurred in significantly more obese patients, or from the assumption that greater distances in laparoscopy hinder precision of surgery Yu et al. [10] noted that laparoscopic surgery is safe to use in morbidly obese women with endometrial cancer. Total laparoscopic hysterectomy with lymphadenectomy was also reported to be a safe procedure with benefits of application instead of laparotomy due to: shortened hospital stay, fewer complications, less hemoglobin loss and a better cosmetic result [15–17]. According to Malinowski et al. [18], a total laparoscopic hysterectomy with lymphadenectomy is a better alternative method than laparotomy that is characterized by a significantly smaller percentage of complications, better cosmetic results and a shorter hospital stay when performed by an experienced surgeon. Minimal access surgery appeared to be the preferred approach being associated with a lower pain score, a shorter hospitalization, and an earlier resumption of daily activities when compared with open surgery in randomized controlled trials [19, 20]. The average duration of surgery and hospitalization, as well as hemoglobin loss in the group subjected to endometrial cancer surgical treatment via laparoscopic procedures are similar to results achieved by other centers [15, 21]. In this trial, greater waist circumference may be connected with longer hospitalization and surgery duration. Among other natural explanations, the more complicated surgical procedure for obese compared to non-obese patients may be given. In the case of gynecological surgery via laparoscopy or using robotic apparatus, the navel may be considered a primary entry-point in the abdominal area for the reason that it is the thinnest part of the abdominal wall [22]. The navel's anatomic location: at aortic bifurcation level in non-obese females — is a significant characteristic point allowing the surgeon to more easily pinpoint critical intra-peritoneal structures during abdominal access via laparoscopy. Along with the increase in rates of obesity , particularly, the amount of women characterized by central adiposity what initiates a shift in this anatomic correlation. The navel is translocated caudally via the panniculus along with the increase in central adiposity, while the relationship between umbilicus and intra-peritoneal structures undergoes change. Abdominal-related obesity also causes an increase in entry depth and furthermore, increases the dangers of pre-peritoneal entry as well insufflation with following conversion to laparotomy. Nonetheless, overall risks related to injury for laparoscopic entry are low when performed by an experienced surgeon [23]. About 50% of all laparoscopy-related injuries occur at the time of initial abdominal trocar placement [24, 25]. The chances of laparoscopic injury may be higher among women with abdominal obesity. The left upper quadrant approach was first described by Palmer. It is frequently applied when entry via the umbilicus is challenging or contraindicated, or in cases when periumbilical adhesions, myomatous uteri (organ per-

foration risk), large ovarian cysts (mass rupture) are suspected, or in the two final trimesters of pregnancy (complication related to excessive bleeding) [22]. In the case of patients with abdominal obesity, the skin to peritoneum distance is increased. This may complicate initial trocar introduction. The advantages of visualizing open laparoscopy (Hasson technique) are restricted due to increased adiposity inherent among obese patients, which can further lead to difficulties in maintaining pneumoperitoneum [26]. Minimal abdominal invasive surgery may be challenging or hazardous in the case of overweight or obese subjects, especially when endometrial cancer is combined with abdominal obesity. The left upper quadrant entry can be a safe, reliable alternative for entry through the umbilical area in high-risk patients [27]. Greater waist circumference as well as BMI were noted in patients who experienced procedure-related complications. Complications following surgery may be early or late. The most commonly noted early complications after laparoscopic surgical gynecology are: conversion to open surgery, pre-peritoneal entry, subcutaneous edema, omental trauma, excessive bleeding, damage to the bladder, ureteral trauma, as well as intestinal perforation. The most frequently observed complications following surgical procedures include infection, difficulty in healing of the wound , thromboembolic and cardiovascular complications, respiratory and renal failure, gastrointestinal obstruction, disorders concerning urination and urogenital as well as intestinal fistulas. The co-morbidity rates regarding obesity and endometrial cancer can be linked with high procedure-related complications. Laparoscopic hysterectomy and bilateral salpingo-oophorectomy have been demonstrated to be the surgical technique of choice for women with endometrial cancer in three large randomized controlled trials [16, 17, 28]. Surgical staging is safe and feasible in a morbidly obese patient when using a minimally invasive approach. In addition, this approach is associated with lower estimated blood loss, length of hospital stay, and fewer perioperative complications. However, longer operating room time (minutes), estimated blood loss (mL) and length of hospital stay were associated with obese patients compared to non-obese [29]. In this study, a correlation was found between obesity (WC and BMI) and perioperative complication occurrence rate. There were statistically significant differences with regard to parameters for the comparative patient group experiencing complications (5 subjects). In the case of abdominal obesity, chronic inflammation or metabolic disturbances can also be considered as part of the reason for the observed complications following surgery, which may include: infection, difficulty in wound healing, circulatory or respiratory problems. In our trial, univariate regression analysis indicated that waist circumstance and waist-hip ratio have the highest predictive value for the analysed parameters for in-hospital outcomes among patients with endometrial cancer. However, multivariant regression indicates that body mass is the factor determining in-hospital outcomes. It is worth noting that the greater range of lymphadenectomy without sentinel lymph node procedure is a factor related to longer duration of operation and greater hemoglobin loss. The recent application of sentinel lymph node mapping has allowed for high feasibility and safety, as well accuracy in the evaluation of nodal metastasis. In a recent study, evidence could be found indicating that laparoscopic systematic lymphadenectomy is not of lower oncological efficient than open surgery when treating patients with intermediate- or high-risk endometrial cancer [31]. In a number of numerous studies, authors have come to the conclusion that sentinel lymph node mapping may be considered a precise alternative for systemic lymphadenectomy on determining the nodal spread in ECs at an early stage, while being cost-effective for treatment of patients low-risk endometrial cancer. In recent studies, it has also been shown that sentinel lymph node mapping allows upstaging in low- or intermediate-risk endometrial cancer patients for whom adjuvant therapy may be omitted. This strategy may be also applied in high-risk histological cancer types (serous carcinoma, clear cell carcinoma, and carcinosarcoma) [32]. Women with endometrial cancer staged with the sentinel lymph node procedure were more likely to undergo adjuvant treatment when compared to women staged with systemic lymphadenectomy. A decrease in surgery duration and a decreased rate of lymphatic edema strongly motivate the sentinel lymph biopsy concept in patients with high-risk endometrial cancer [33].Our study confirmed that implementation of sentinel lymph node procedure is related with reduced hemoglobin loss and operative time in patients with endometrial cancer compare to lymphadenectomy without sentinel node biopsy.

Limitations

This study may be considered developmental due to it being conducted on a small sample size. Furthermore, in the conducted analysis, attention was paid to evaluating trends and correlations between individual indicators and the results of treatment among a relatively small patient group.

CONCLUSIONS

Obesity is related to a longer duration of procedure and hospitalization, and greater hemoglobin loss associated with the laparoscopic treatment of endometrial cancer. Our study indicate the body mass as most sensitive parameter of obesity which influence in-hospital outcomes in patients treated with laparoscopic procedures. Abdominal obesity parameters, especially waist circumference significantly affect in-hospital treatment results. Some anatomical indices such

as intertrochanteric distance and external conjugate are also significant risk factors for laparoscopic treatment of endometrial cancer. There are statistically significant differences in parameters of obesity between two groups with or without procedural complications. Sentinel lymph node procedure is related with decreased operative time and hemoglobin loss.

Conflict of interest

The authors declare no conflict of interest.

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Contraception counselling during gynecology visit — does a questionnaire help?

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ABSTRACT

Objectives: Women are at risk of unplanned pregnancy and inappropriate choice of contraception if not given effective contraception counselling. We aimed to understand the contraceptive needs of women, improve effective contraception counselling promoting modern contraception methods during gynecology outpatient visit using a contraception counselling questionnaire.

Material and methods: All reproductive-age women over 18 were given Contraception Counselling Project Form to fill in while in the waiting room. The form consisted of 15 questions evaluating patients' characteristics and contraceptive method used. Physicians evaluated these forms during the examination and an appropriate method was chosen. Forms of pregnant, postmenopausal and sexually inactive patients as well as forms with more than one answer missing were excluded.

Results: 778 questionnaires were accepted for evaluation. 340 women (43.8%) used modern contraception, 112 (14.4%) used interrupted coitus, 3 (0.4%) used calendar method. 738 women could be given adequate contraception counselling by the physicians. 215 women among 323 women (66.5%) who did not use modern contraception and did not desire pregnancy, were convinced to use modern contraception and 103 (91.9%) among 112 women who used interrupted coitus for contraception were convinced to use modern contraception. There was a significant relationship between age, education, working state, parity, number and type of delivery, previous OCP usage, resources of contraception and the preferred contraception method.

Conclusions: More than half the women preferred to use modern contraception methods by means of contraception counselling questionnaire. Women's backgrounds significantly affected their choice of contraception method.

Key words: contraception; contraception counselling; oral contraception; intrauterine device

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INTRODUCTION

Contraception can be defined as the use of methods intended to prevent reproduction. Contraception can be categorized as modern or traditional. Modern methods of contraception include sterilization, intrauterine devices (IUD), subdermal implants, oral contraceptive pills, condoms and other barrier methods, injectable contraceptives, contraceptive patches, and vaginal rings [1]. Traditional methods of contraception include the rhythm method, withdrawal prior to ejaculation, lactational amenorrhea, and abstinence.

Contraception counselling is crucial in gynecology practice even in patients who do not apply for contraception counselling. In the outpatient clinic, time devoted for contraception counselling may be limited. Some patients express other complaints more often or physicians may concentrate on patients' complaints rather than counselling. The aims of the counselling are to educate women about contraception, select an appropriate method according to demand and preferences, prevent unintended pregnancy, and provide fertility when desired.

The American College of Obstetricians and Gynecologists advises to ask all women between ages 18–50 if pregnancy is desired over next year [2]. If pregnancy is not desired, appropriate contraception should be chosen according to state of health, personal values, and preferences. Even in countries with a high rate of contraception usage, almost 40% of women are at risk for unintended pregnancy [3]. In 2011, 45% of pregnancies in US were unintended [4]. Most sexually active women in US had used some form of contraception in their lifetime, but multiple barriers prevented women from obtaining contraceptives or using them effectively or consistently [5]. The main reasons for imperfect use of contraception were inappropriate counselling and incorrect choices of contraception method [6]. Rates of contraceptive use throughout

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Europe are high; 90% of women in Europe have been reported as using contraception [7]. However, in Europe, 45% of pregnancies are unintended and 64% of these result in abortion [8]. Almost half of these unintended pregnancies occur as a result of incorrect or inconsistent use of contraceptives [9]. Mean age at first birth is over 30 in Europe; thus most couples must use contraception for many years in order to avoid unintended pregnancy [10]. But different models of contraception care and contraception counselling exist across Europe which may not be adequate in some cases [11].

Alkema et al reported that contraceptive prevalence in Turkey increased from 62.2% in 1990 to 72.2% in 2010 with a decrease in the unmet need for contraception from 14.7% to 8.7% [12]. Modern contraceptive prevalence was reported between 20–40% [13]. Also, 51% of all women and 74% of the married women in the reproductive years use contraception with unintended pregnancy rate of 47.3% [14]. Only 33% of all women and 47% of married women use modern contraception. This might be due to inadequate counselling given to women regarding modern contraception methods. Kahramanoglu *et al* evaluated the differences in contraceptive choices before and after counselling Turkish women and suggested that contraceptive counselling significantly changed the contraceptive choices of women [15]. However, few studies have been published on how to implement contraceptive counselling to women [16–20].

Objectives

Our primary aim in this study was to screen out women who needed contraception counselling before they entered physicians' room with a form that they filled out while waiting and to evaluate the results. We evaluated whether effective contraceptive counselling increased the rate of modern contraceptive method usage among women who either did not use any contraception or used interrupted coitus for contraception. Our secondary aim was to evaluate the factors such as age, education, working state, parity, number and type of delivery, previous OCP usage, resources of contraception that influenced the preferred contraception method.

MATERIAL AND METHODS

Between June–December 2016, all reproductive-age women over 18 who applied to the gynecology clinic of Istanbul University Istanbul Faculty of Medicine Department of Obstetrics and Gynecology and who were mentally capable of filling out the questionnaire were given the contraception counselling form prepared by our institution. Ethics approval was obtained from the institutional ethics committee. Forms of patients who were postmenopausal, pregnant, or sexually inactive were excluded. Other exclusion criteria were being mentally incapable of filling out the form, being illiterate and not willing to participate in study.

Appendix 1. Contraception Counselling Form

1. Age		
2. Last Menstrual Period		
3. Have you ever delivered?	Yes	No
If your answer is yes		
4. How many deliveries?		
5. Time of last delivery?		
6. Are you lactating?		
7. Do you plan a pregnancy in the next 6 months?	Yes	No
8. Do you use a method to prevent pregnancy?	Yes	No
9. If your answer is yes, which method do you use?		
Oral contraceptive pills		
Intrauterine device		
Condom		
Interrupted coitus		
Tubal ligation		
Calendar method		
10. Have you ever used oral contraceptive pills and for how long?	Yes	No
11. Reason for quitting oral contraceptive pills?		
12. Do you smoke?	Yes	No
13. How long does your period last?		
14. Your weight and height?		
15. Do you have a diagnosed illness?	Yes	No
If yes, what is it?		

The contraception counselling form was formed by four gynecologists experienced in contraception counselling. The form consisted of 15 questions, including age, education, ongoing pregnancy or desire for pregnancy, parity, type of delivery, lactation, previously and currently used contraceptive method, reasons for not using contraception or changed method, sources of information regarding contraception, smoking, menstrual history, and history of diagnosed diseases (Appendix 1). Pilot testing was performed in ten women recruited from the gynecology outpatient clinic. Two experts interviewed the women after filling out the forms. There were no missing answers. The women thought that the questionnaire was applicable.

One thousand four hundred fifty-six women were recruited. The total number of women participating and the number of forms filled were 1000. Forms, which had more than one unanswered question were excluded. Forms in which the advised contraception method was not noted by the physicians were accepted as counselling not given. All participants filled out the forms by themselves in a designated private room while waiting and the patient and the physician evaluated the form in the examination room. Of the 1000 women, 87 forms were excluded because

Table 1. Demographic variables of women included in the study

	N = 778
Age	36.8 ± 8.1 (19-51)
Height	161.7 ± 6.3 cm (143–185 cm)
Weight	68.4 ± 13.3 kg (47–120 kg)
Parity	
Yes	609 (78.3%)
No	169 (21.8%)
Mean number of deliveries	2.1 ± 1.1 (1–9)
Type of Delivery	
Vaginal delivery	293 (48.1%)
Cesarean section	248 (40.7%)
Vaginal delivery+ Cesarean section	68 (11.2%)
Education Level	
Primary school	293 (37.7%)
Middle school	112 (14.4%)
High school	190 (24.4%)
University	157 (20.2%)
Higher degree	21 (2.7%)
No answer	5 (0.6%)
Working	
Yes	286 (36.8%)
No	492 (63.2%)
Aware of last menstrual period	
Yes	645 (82.9%)
No	133 (17.1%)
Lactation	
Yes	62 (8.0%)
No	716 (92.0%)
Smoking	
Yes	206 (26.5%)
No	572 (73.5%)
Plan of a pregnancy in the near future	
Yes	164 (21.1%)
No	591 (75.9%)
No answer	23 (3.0%)

46 women were postmenopausal/sexually inactive, and 41 women missed out more than one question. The number of women able to fill out the questionnaires completely was 823. Sixty women missed out one question and physicians did not counsel 30 patients although they filled out the form completely. One hundred thirty-five women were currently pregnant and were excluded. As a result, 778 forms were accepted for evaluation.

Physicians performed gynecologic examination on all patients. Menstrual irregularities, pelvic pain, vaginal discharge, breast diseases, abnormal PAP-smear results were assessed. PAP-smear and ultrasonography was performed when indicated. At the end of the examination, the form was examined by the physician and contraception counselling was given to patients.

Contraception counselling included types of contraceptive methods available in Turkey, their mechanisms of action, efficacy of each method, possible side effects, risk of cancer, effects on fertility, effects on menstrual cycle, and non-contraceptive benefits. Physicians advised most preferred contraceptive methods by Turkish women. These were copper-intrauterine device (Copper-IUD), levonorgestrel-releasing intrauterine device (LNG-IUD), combined oral contraceptives (OCP), progestin only pill, condom, bilateral tubal ligation (BTL), depot medroxyprogesterone acetate. Physicians used WHO medical eligibility criteria for contraception and ACOG guidelines for counselling [2, 21, 22]. At the end of the visit, method advised was noted on the form by the physician.

Statistical analysis

Statistical analysis was performed with Statistical Package for the Social Sciences (SPSS) version 21.0 (SPSS, Chicago, IL, USA) by a professional statistician. Data was expressed as mean ± standard deviation and frequencies. The relationship between factors that could affect choice of contraception and the contraception methods preferred by the women were analyzed using Pearson's correlation. Groups of preferred contraception methods were analyzed using Chi-square test for categorical variables and Kruskal-Wallis test for continuous dependent variables. A p value < 0.05 was considered as statistically significant.

RESULTS

Seven hundred seventy-eight forms were accepted for evaluation. Demographic variables are summarized in Table 1. Mean age was 36.8 ± 8.1. 609 (78.3%) women had delivered before. Mean number of deliveries was 2.1 ± 1.1. 48.9% of women delivered vaginally. 286 women (36.8%) were working. 164 (21.1%) women were planning a pregnancy soon, 23 women (2.9%) did not answer this question. 62 women (7.9%) were lactating.

Resources that patients had received information about contraception are summarized in Figure 1. 605 women (77.8%) recalled receiving information regarding contraception before. 399 women (65.9%) recalled receiving information from physicians, whereas only 2 women (0.3%) from newspapers.

Four hundred fifty-five (58.5%) women used a contraceptive method; 340 women (43.8%) used modern contracep-

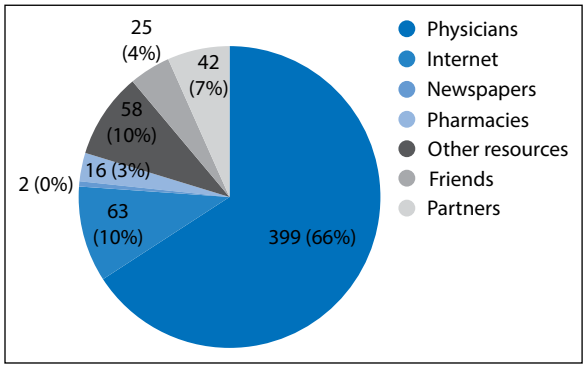

Figure 1. Distribution of resources that women had received information about contraception before

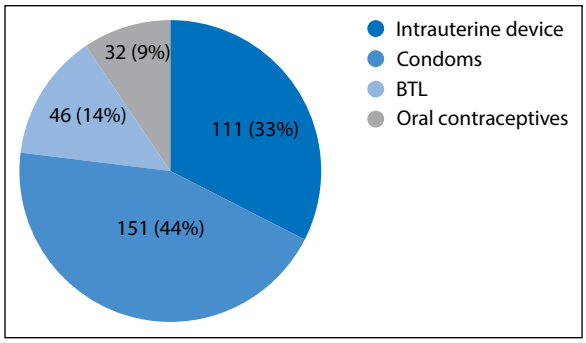

Figure 2. Distribution of contraception methods used by the women

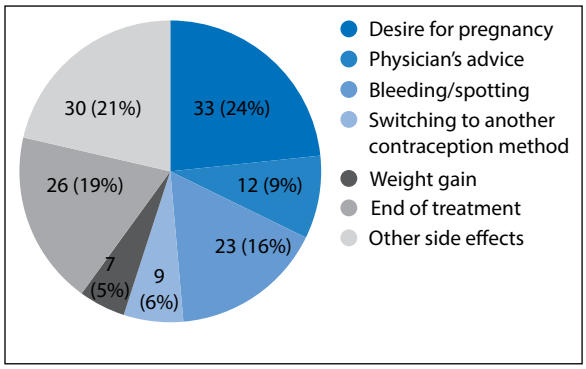

Figure 3. Reasons for stopping combined oral contraceptive usage

tive methods whereas 112 women (14.4%) used interrupted coitus and 3 women (0.4%) used the calendar method. The number of women that did not use any contraceptive method was 323 (41.5%). Distribution of modern contraceptive methods is summarized in Figure 2; 151 women (44.4%) used condoms whereas only 32 women (9.4%) used OCP. The patients without a pregnancy plan (9.7%) didn't use a contraceptive method and 22.9% of women without a pregnancy plan used interrupted coitus. One hundred seventy-eight (55.1%) women out of 323 women who did not use any contraceptive methods commented on the reason; main

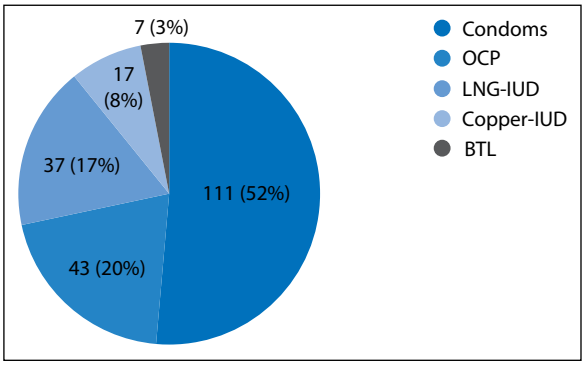

Figure 4. Distribution of the accepted contraception methods by the women who were convinced to use contraception after counselling (n = 215)

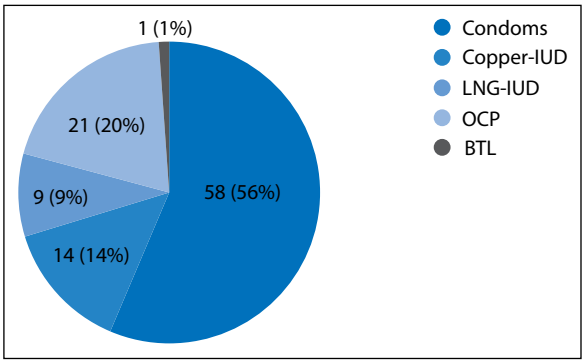

Figure 5. Distribution of accepted contraception method by the women who had used interrupted coitus before counselling (n = 103)

reasons were concern for side effects (n = 39), absence of a partner (n = 36), pregnancy plan (n = 82), difficulty of use (n = 10), and other reasons (n = 11).

Two hundred seventy-nine women (35.9%) had used OCP before, 177 (63.4%) had used OCP for contraception whereas 102 women (36.6%) due to physicians' prescriptions. Mean duration of usage was 23.8 ± 39.4 months. One hundred nineteen (42.7%) women had used OCP for less than 6 months. The majority of short-term users used OCP for medical reasons whereas most long-term users used for contraception. Reasons for ending OCP usage are summarized in Figure 3.

Among 438 women who did not use modern contraception or used interrupted coitus or calendar method for contraception, 115 women were planning pregnancy and 323 women remained who didn't use modern contraception and didn't desire a pregnancy. Also, 215 of the 323 women (66.5%) were convinced to use contraception. Contraceptive methods preferred by women after physician counselling are summarized in Figure 4. In addition, 103 (91.9%) among 112 women who used interrupted coitus for contraception were convinced to use modern contraception. Results are summarized in Figure 5. On the other hand, Copper-IUD was

switched to LNG-IUD in 24 women due to heavy menstrual bleeding.

When factors influencing the preferred contraception method were analyzed, there were significant relationships between age ($p < 0.001$), education level ($p = 0.017$), working state ($p = 0.016$), parity ($p < 0.001$), number ($p < 0.001$) and type of delivery ($p < 0.001$), previous OCP usage ($p = 0.001$), resources of contraception information ($p = 0.006$) and the preferred contraception method. Women who chose OCP were significantly younger than the women in the other groups ($p < 0.001$). Women over 40 years of age did not prefer to use OCP, but rather preferred IUD insertion. Most of the working women preferred OCP ($p = 0.016$). Women who chose OCP had a higher education level when compared to the women in the other groups ($p = 0.017$). Women who preferred BTL had higher number of children ($p < 0.001$). Most of the nulliparous women chose condoms and OCP. Nulliparous women did not prefer to use IUD; 97% of the women who chose IUD insertion were parous. Only 5 nulliparous women chose LNG-IUD insertion. More women who underwent BTL had a history of cesarean section when compared to other groups ($p < 0.001$). More women in the Copper-IUD and LNG-IUD groups had received information about contraception from physicians ($p = 0.006$). More women who chose condoms had received information from the web or their partners.

DISCUSSION

Due to high rate of unintended pregnancies, contraception counselling is crucial [23]. Time must be devoted to effective contraception counselling or other means should be provided in order to increase the efficacy especially in crowded outpatient clinics [24]. The World Health Organization (WHO) recommends that lifestyle issues and patient preferences should be considered when choosing the most appropriate contraception method for the women [21].

In our study, we showed that majority of women could effectively fill out the questionnaire by themselves and the physicians gave appropriate counselling to these women; only 30 women were not given effective counselling or counselling was not documented. After appropriate and individualized counselling, most of the women who used traditional contraceptive methods or did not use any method at all were convinced to use modern contraceptive methods.

This result is especially important considering the high number of primary school graduates in our study. Education level was highest in younger women aged 15–24 years. Caetano et al suggested that rates of unintended pregnancies were higher among younger women despite higher education level, which may be associated with inconsistent use of oral contraceptives [25]. In addition, 36.8% of the women were working in our study. As women's role in the society increases, contraception and planned timing of pregnancy becomes more important. In addition, busy schedules and life stressors may lead to inconsistent use of contraception and in these cases contraceptive counselling should include discussion of any potential barriers to adherence [25].

Most women in our study had received information about contraception previously. The main source of information was the physicians. In the TANCO study, 82% of the women stated that their healthcare provider was the most important person for contraception counselling compared with just 10% stating that their partner was the most important person [26]. Physician's role remains quite important in contraception counselling; physicians may direct women to individualized contraception methods according to women's preferences and needs. Therefore, incorporation of contraception counselling to daily practice of gynecologists is essential even when the women's gynecologist visits involve other problems. Dehlendorf et al evaluated a patient-centered decision support tool for contraception counselling [27]. Patients used this tablet-based decision support tool prior to family planning visit and contraceptive continuation, method of use, satisfaction, and unintended pregnancy were evaluated. Authors concluded that the method had no effect on contraception continuity, but increased experience of contraceptive counselling and informed decision-making. A recent systematic review of patient preferences for contraceptive counselling found that women value comprehensive education about methods, with a emphasis on education about side effects [28, 29]. Kahramanoglu et al. [15] evaluated women's choices about contraception before and after gynecologist counselling. Physicians and health care providers were the best source for information about contraception. Partner input also had an impact on contraceptive choice. Religious beliefs may affect choice of BTL. Authors also suggested that hardest prejudices to overcome were anxiety of insertion and removal of an IUD, fear of weight gain from OCP usage, religious beliefs in case of BTL. Influences from social media and/or friend were found to be important factors in determining choice of contraception method as well.

Most women in our study preferred condoms, followed by IUD. The rate of OCP usage for contraception is quite low in Turkey when compared to other developed countries. Indeed, 35% of women in our study had used OCP, but only 11% of women were using OCP at the time being. Most had used OCP for short periods. Main reasons for stopping other than pregnancy plan were side effects and switching to another contraception method. After counselling by using the questionnaire, the number of women preferring to use OCP increased. This emphasizes the importance of counselling in OCP usage and individualization of treatment in order to prevent side effects.

The majority of women using modern contraception preferred long-acting contraception. In the TANCO study involving 1089 physicians and 18521 women, 61% of the women were using oral contraceptives and only 9% were using long-acting contraceptive methods [26]. However 60% of the women stated that long-term contraception would be an option for them if they had received more information about it. In the Contraceptive CHOICE project, among 7637 women, 47% chose intrauterine systems whereas only 12% preferred OCP [30]. Cultural influences also affect the choice of contraception method.

Erfani and Yuksel-Kaptanoglu evaluated withdrawal method use in Iran and Turkey [31]. Lower education, poverty, having more than four children, and older age were associated with withdrawal use in Turkey. Authors suggested that family planning and reproductive health programs in Iran and Turkey should be aware of groups that have high rates of withdrawal and should encourage more effective contraceptive methods. Indeed, in our study 66.5% of women who did not use contraception and 83.5% of women who used interrupted coitus for contraception but didn't desire a pregnancy were convinced to use an effective method after contraception counselling with Contraception Counselling Form.

BTL has been a popular contraception method in Turkey. Forty-six women had undergone BTL and 7 women were convinced to undergo BTL in this study. The popularity of BTL is mostly due to high Cesarean section rates in Turkey and BTL is performed during Cesarean section when partners prefer. Laparoscopic BTL is also sometimes desired. In our study, we have shown that women may prefer laparoscopic BTL when they desire permanent contraception and are informed about the procedure. Eskicioglu et al evaluated regret state in women following BTL [32]. The rate of regret was 12–15%. Factors associated with regret were young age (age < 30), absence of spouse's support, not understanding permanent nature of procedure, lower education level, and thought of inability to have children in the future. Therefore, women and their partners must be thoroughly informed about nature of the procedure and misbelieved side effects in order to decrease rate of regret.

None of the couples used vasectomy in our study. Kısa et al, showed that more than 88% of Turkish men were not willing to have vasectomy and 35.4% thought that vasectomy had negative effect on marriage and health [33]. Sociocultural factors and misconceptions about vasectomy were main barriers for vasectomy use in Turkey.

In conclusion, contraception counselling using a questionnaire may aid in asking questions regarding method used or future use even if patients had come for other reasons to outpatient clinic and helps women to choose the best method. When considering that physicians were the most common source of information in our study, contraception counselling given to 97% of women applying for other reasons has been a success. Limitations of our study are lack of follow-up to evaluate usage of the preferred method, non-randomized nature of study, and lack of a control group. Education of women and adolescents regarding contraception, involvement of partners in counselling and support of all contraception methods by health insurance may aid in providing the most appropriate contraception. Contraception counselling using a questionnaire is an effective strategy to increase awareness about contraception both in women and physicians and to discuss about misconceptions aroused by society and social media about side effects.

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Twin pregnancy with a partial hydatidiform mole and a coexistent live fetus. Diagnostic and therapeutic dilemmas. A case report and the review of literature

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ABSTRACT

Objectives: We report the case of a twin pregnancy with a partial hydatidiform mole and a coexistent live fetus diagnosed in a 28-year-old primipara at 15 weeks of gestation and discuss the problems associated with the ultrasound diagnosis, histopathological examination of molar tissue samples and treatment.

Material and methods: A systematic research of the literature was conducted in PubMed database and Cochrane Library, including case reports and case series. A new case was also discussed. We collected data regarding the patient's serum human chorionic gonadotropin (hCG) level, initial symptoms, diagnosis and treatment.

Results: Most of the cases reported in the literature are those of a multiple pregnancy with complete hydatidiform mole (CHM) and a coexistent live fetus. The coexistence of a twin pregnancy with partial hydatidiform mole (PHM) and a live fetus in two separate amniotic sacs is extremely rare as a partial mole usually causes miscarriage of early pregnancy. Ultrasound is an important diagnostic tool, but the correct diagnosis is made only in 68% of cases. With further histological assessment of molar specimens and biochemical assays, the rates of correct early diagnoses should increase contributing to early therapeutic decisions and fewer adverse events.

Conclusions: The diagnosis, management, and monitoring of this condition will remain challenging because of its rarity. Because of that, all cases of a suspected multiple pregnancy with a hydatidiform mole and a coexistent live fetus should be referred to and managed at a tertiary center which specializes in the diagnosis and treatment of gestational trophoblastic disease.

Key words: hydatidiform mole; twin pregnancy; ultrasound; histopathological examination

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INTRODUCTION

The coexistence of a hydatidiform mole with a normal fetus is extremely rare with an incidence of 1/20 000 to 1/100,000 pregnancies [1–4]. In most cases, this is a complete hydatidiform mole (CHM). Partial hydatidiform mole (PHM) coexistent with a live fetus, in two separate amniotic sacs, is even less frequent since a partial molar pregnancy usually ends in early intrauterine death and miscarriage [5]. Diagnosis is by ultrasound, mostly in the second trimester, usually between 12 and 15 weeks [1, 3]. Even with advanced ultrasound technologies, correct diagnosis is made in approximately 68% of cases and first-trimester diagnoses are rare. Assessment of human chorionic gonadotropin (hCG) levels are less reliable in a multiple pregnancy. Magnetic resonance imaging (MRI) is useful in the diagnosis of a molar pregnancy with a coexisting live fetus as it visualizes two amniotic sacs and a separate normal placenta and additionally allows assessment for myometrial infiltration and parametrial involvement [6].

There are three possible variations of a twin molar pregnancy with a coexistent live fetus: 1. A dizygotic twin pregnancy with a complete mole and a live fetus of diploid karyotype; 2. A dizygotic twin pregnancy with a partial mole and a live diploid fetus in two separate amniotic sacs; 3. A monozygotic twin pregnancy with a partial mole and a live triploid fetus in a second amniotic sac [5].

This paper presents a case of a twin pregnancy with a partial hydatidiform mole and a coexistent live fetus and discusses problems associated with the ultrasound diagnosis, histopathological examination of molar tissue samples, and treatment.

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Case report

A 28-year-old primipara at 15 weeks of twin pregnancy was referred to the 1st Department of Obstetrics and Gynecology, Medical University of Warsaw from an antenatal clinic at her local hospital with a suspected hydatidiform mole and a coexistent live fetus in a second amniotic sac.

Pre-referral medical and obstetric history

The age at menarche 13 years. Before pregnancy, the patient received thyroid hormone replacement therapy for hypothyroidism. She had been trying to conceive for two years and ovulation induction was used in the last four cycles before conceiving. At 12 weeks of gestation, she was admitted to hospital with ovarian hyperstimulation syndrome. An ultrasound examination showed in the uterine cavity one live fetus whose measurements were consistent with gestational age of 11 weeks and five days. Seen behind the uterus, the ovaries were enlarged (the right measured 94 × 57 × 40 mm and the left 94 × 54 × 41 mm) with numerous follicles. There was some free fluid behind the uterus and between the coils of the intestine. There were no abnormalities detected on an abdominal ultrasound. The patient was prescribed anticoagulants and on day five was discharged home in good general condition. A first-trimester ultrasound performed one day later showed a normal development of a singleton pregnancy. The ovaries were enlarged as previously. After one week, the patient was readmitted to hospital for vaginal spotting. An ultrasound examination confirmed fetal cardiac activity and detected over the internal os a haematoma measuring 26 × 6 mm. A threatened miscarriage was diagnosed. The patient was prescribed progestins and antihaemorrhagic medication with a follow-up visit in 10 days when she was seen by her obstetrician. An ultrasound examination ten days later detected in the posterior uterine wall a 75 × 148 mm lesion with numerous fluid-filled spaces. The serum hCG level was over 1000,000 mIU/mL. The patient was referred to our Department.

On admission

Good general condition. On speculum examination a slight cervical bleeding. The size of the uterus corresponded with 25 weeks of gestation. Blood pressure 140/80, pulse 112/min, temperature 37.3°C. An ultrasound examination detected in the uterine cavity a live fetus 131g in weight, normal placenta and a cystic-solid lesion measuring 118 × 77 × 70 mm. The right ovary measured 100 × 60 × 58 mm and the left ovary 101 × 55 × 53 mm.

Blood tests: RBC 3.49 million/mm^3, Hb 11 g/dL, Ht 30.2%, WBC 8,600/mm^3, PLT 289 000/mm^3, hCG 1 601 660 mIU/mL, ALT 77 U/L, LDH 327 U/L, creatinine 0.62 mg/dL, potassium 4.2 mmol/L, sodium 136 mmol/L, TSH < 0.005 µIU/L, free FT3 7.61 pg/mL, free FT4 2.85 ng/dL, anti-TSH receptor antibodies < 0.8 IU/L, anti-TPO antibodies 1192.8 U/mL, INR 1.12, prothrombin time 12.4 s, prothrombin ratio (PR) 90%.

A multiple pregnancy with a CHM and a coexistent live fetus was diagnosed. In view of exceedingly high hCG levels, clinical hyperthyroidism confirmed by laboratory investigations and features of liver injury, the prognosis for pregnancy outcome was considered to be poor and the pregnancy threatened the mother's life and health. Termination of pregnancy was planned after prior institution of beta-blockers. The patient gave her informed written consent to surgical uterine evacuation, uterine curettage and hysterectomy, if necessary. The procedure was performed under general anaesthesia with antibiotic prophylaxis. The cervix of the uterus was dilated with Hegar dilators up to No 20. The molar tissue was aspirated under ultrasound guidance and next the fetus and placenta were removed. As the bleeding continued, curettage of the uterine cavity was performed, and oxytocin was given to induce haemostasis. The blood loss was estimated at ca. 2,000 mL. On the first postoperative day, the patient was well with normal vital signs. The uterus was well contracted with a moderate vaginal bleeding. Blood tests: RBC 3.05 million/mm^3, Hb 9.8 g/dL, Ht 26.2%, WBC 6 900/mm^3, PLT 232 000/mm^3, hCG 598 350 mIU/mL, ALT 53 U/L, AST 34 U/L, LDH 318 U/L. Lactation was suppressed. On the third postoperative day a slight vaginal bleeding persisted, and the patient had no complaints. On pelvic examination the uterus remained well contracted and painless. An ultrasound examination showed an empty uterus and the same appearance of the ovaries as on previous scans. The patient was discharged home in good general condition and advised to have hCG levels monitored every seven days (on discharge the serum hCG was 160 140 mIU/mL) and to continue medication for lactation suppression and beta-blockers.

Three weeks later the patient collected the histopathology report of a complete hydatidiform mole. The hCG was 6,660 mIU/mL and close to the level measured seven days earlier (6,672 mML). As the hCG levels failed to decrease, the patient was referred to her local oncology hospital where she was followed-up at one week intervals.

After a 3-month follow up, the patient was referred to the Center for Gestational Trophoblastic Disease at the Institute of Mother and Child. Based on the biochemical criteria (the plateau of hCG for the last four measurements) gestational trophoblastic neoplasia (GTN) was diagnosed. The molar specimens were re-examined at the Institute's Pathology Laboratory with the following findings: decidual and placental tissue fragments with features of oedematous degeneration of avascular villi, cistern-like villi present, mild focal atypia and partial degeneration of the trophoblast which corresponded with a partial hydatidiform mole.

As there were two different histopathological diagnoses (complete vs partial hydatidiform mole), immunohistochemical staining for p57KIP2 was additionally performed which was positive in the trophoblastic cells and confirmed the diagnosis of a partial hydatidiform mole.

A transvaginal ultrasound examination visualized an anteverted uterus with the AP diameter of 54 mm. The myometrial and endometrial echogenicity was homogenous, but in the posterior wall, adjacent to the internal os, a hyperechogenic lesion with visible vasculature, measuring 6 × 5 × 7 mm was detected. Both ovaries were normal. On Doppler ultrasonography the pulsatility index (PI) was 1.86 for the right uterine artery and 2.45 for the left uterine artery. There were no abnormalities detected on a chest x-ray.

The patient was classified as low-risk according to the FIGO criteria (score 2; antecedent pregnancy — abortion, score 1, pretreatment hCG between 10^3–10^4 mIU/L, score 1). MTX-FA (methotrexate/folinic acid) 8-day regimen, repeated every 2 weeks was prescribed (Tab. 1). The patient received chemotherapy in a total of 18 courses, including 3 courses of consolidation therapy**.** For the patient's convenience the treatment was administered in collaboration with her local hospital. The chemotherapy was well tolerated and occasional burning sensation in the oral cavity was relieved by symptomatic treatment, there were no cycle delays.

At present, the patient remains under close observation. The levels of hCG were monitored every 4 weeks for 6 months and then every 8 weeks for 12 months. The patient was advised to use effective contraception during that time.

DISCUSSION

The article presents difficulties in the diagnosis and treatment of a twin molar pregnancy with a coexistent normal live fetus. In the reported case, a molar pregnancy was first suspected as late as 15 weeks of gestation. Although the overall clinical and morphology picture was characteristic of a CHM, a PHM was identified by immunohistochemistry.

Table 1. Recommended single-agent chemotherapy regimens for gestational trophoblastic disease

MTX 0.4 mg/kg IM. or IV, on days 1, 2, 3, 4 and 5, repeat every 14 days
MTX 50 mg/m2 IM, repeat every 7 days
Dactinomycin 1.25 mg/m2 IV, repeat every 14 days
Dactinomycin 12 µg/kg IV on days 1, 2, 3, 4 and 5, repeat every 14 days
MTX 1 mg/kg (up to 70 mg) IM or IV, on days 1, 3, 5 and 7, repeat every 14 days + FA 0.1 mg/kg IM or IV, on days 2, 4, 6 and 8, repeat every 14 days
MTX 50 mg IM, on days 1, 3, 5 and 7, repeat every 14 days + FA 15 mg IM or IV, 30h after the start of MTX administration

FA — folinic acid; IM — intramuscular; IV — intravenous; MTX — methotrexate

At present, an ultrasound examination is the main imaging tool used to establish the diagnosis**.** The 'Swiss-cheese pattern' placenta separate from a normal-appearing placenta is pathognomonic [6]. When the normal appearance of the placenta is not visualized, a complete hydatidiform mole with a coexistent live fetus (CHMCF) may be misdiagnosed as a singleton pregnancy with a partial mole and a live fetus in one amniotic sac. Since the prognosis for pregnancy outcome is different in each case, visualization of a normal placenta often adjacent to a large molar placenta is of key importance for the correct diagnosis [7, 8]. PHM is more difficult to diagnose than CHM even in a singleton pregnancy due to the absence of the characteristic ultrasound features. The differential diagnosis should include a subchorionic haematoma, with a similar cystic-solid appearance and a mild trophoblast pathology of placental mesenchymal dysplasia coexistent with Beckwith-Wiedemann syndrome in the fetus [1, 2, 5].

Standard pathomorphologic assessment includes haematoxylin and eosin (H&E) staining and distinguishing the type of hydatidiform mole by morphology. In each case of a molar pregnancy a second opinion should be sought from another expert of pathomorphology laboratory, as we did in the reported case. Immunohistochemical staining for the protein p57KIP2, which is the product of the CDKNIC gene, is a reliable diagnostic tool. As CDKNIC is paternally imprinted and maternally expressed, the p57 staining is absent in CHM which lacks a maternal genome [9]. In the reported case, CHM was initially diagnosed by morphology alone and after reassessment of the molar tissue specimens at a tertiary medical center, the final diagnosis of PHM was established, confirmed by positive staining for p57KIP2.

The coexistence of a molar pregnancy and a live normal fetus carries a risk of severe fetal and maternal complications. The most common maternal complications include severe haemorrhage leading to anaemia, severe preeclampsia, hyperthyroidism and thromboembolic disorders [1, 4–6, 8]. Also common are such events as fetal growth retardation, intrauterine death, miscarriage or premature birth [1, 4, 7, 10]. Most of the cases reported in the literature are those of a multiple pregnancy with CHM and a coexistent live fetus. The coexistence of a multiple pregnancy with PHM and a live fetus in two separate amniotic sacs is extremely rare as a partial mole usually causes miscarriage of early pregnancy (10–20% of early spontaneous abortions) [3, 11].

The reported patient had severe hyperthyroidism and features of liver injury which were indications for pregnancy termination. In the past, the diagnosis of a molar pregnancy with a coexistent live fetus was an indication for an immediate therapeutic termination [4, 8]. Now, when a normal fetal development is confirmed by ultrasound and there are no maternal complications, analysis of the fetal karyotype is

recommended. Women who decide to proceed with their pregnancy should be aware that the chances of a successful outcome are approximately 40% [1, 2, 6]. A conservative approach is possible under close monitoring and when there are no maternal complications [3, 4, 6]. Decreasing hCG levels and absence of maternal complications are good predictors of a successful pregnancy outcome [12]. Abnormal fetal anatomy visualized by ultrasound or abnormal fetal karyotype are indications for termination. The risk for GTN in cases of a molar pregnancy with a coexistent live fetus ranges from 16 to 50% [1]. The development of invasive moles, choriocarcinomas or placental-site trophoblastic tumors has been reported [6]. The patient here reported developed GTN although she was finally diagnosed with PHM. The risk of GTN after surgical evacuation of CHM with a live fetus is significantly higher than the risk associated with evacuation of PHM in a multiple pregnancy (10–28% vs 3–5%) [5]. It is still unclear whether the continuation of pregnancy increases the risk for GTN [8]. According to many authors the duration of pregnancy has no effect on the development of GTN [1, 2, 4, 6, 13]. Also, there is no agreement concerning a more frequent occurrence of GTN after a twin pregnancy with CHM compared to a singleton pregnancy. Some authors found no differences in the incidence of GTN after a singleton complete molar pregnancy vs multiple molar pregnancy [2, 14]. Steller et al., however, observed the development of GTN in as many as 55% of women with a molar pregnancy with a coexistent fetus [15]. A national collaborative study in Japan found a considerably higher rate of subsequent GTN development in patients with CHMCF. Heavy vaginal bleeding and severe preeclampsia are substantial risk factors for subsequent GTN [13].

The patient we report had ovulation induction for the last four cycles before conceiving. Some authors find a higher risk for twin molar pregnancies subsequent to ovulation induction [5]. In a case series reported by Giorgione et al. [1] one third of the patients had had ovulation induction. It is suspected that ovulation induction may be associated with the appearance of ova without nuclei and thus increase the risk of molar pregnancy [16].

The method of termination if the woman does not wish to proceed with her pregnancy or maternal medical conditions exclude the use of a conservative approach is another dilemma**.** Most controversial is the management of a molar pregnancy in the second trimester. Since the pregnancy is advanced, termination by vaginal evacuation may be associated with massive bleeding. When choosing hysterotomy abortion, extreme fetal immaturity must be taken into consideration. In the case here reported, the cervix was mechanically dilated, and the uterus evacuated, with an estimated blood loss of 2 000 mL. Vaisbuch et al. used a similar procedure at 16 weeks gestation in a patient with early onset severe preeclampsia and thyreotoxicosis [8]. Braga et al. reported termination by hysterotomy of a pregnancy with CHMCF at 15 weeks gestation, due to the worsening of the mother's clinical condition with hCG levels of 1 881 508 mIU/mL [7]. Braga commented that uterine evacuation by aspiration is not possible after the 12th week of gestation due to the presence of a fetal skeleton. Also, the use of misoprostol is contraindicated as it may increase the likelihood of massive pulmonary thromboplastic embolization. After the first trimester, laparotomy and uterine evacuation by hysterotomy may be considered, especially when there are risk factors for adverse outcomes [7]. Close monitoring of hCG levels is mandatory after uterine evacuation of a molar pregnancy with a coexistent live fetus as it is after termination of a singleton pregnancy.

Differentiating of a complete mole from a partial mole is particularly important for choosing sufficient length of follow-up. With partial moles the risk of subsequent GTN is several-fold lower [17]. When a partial mole in a singleton pregnancy is evacuated, the patient needs to remain under observation for 4 weeks after the normalization of hCG. With a complete mole, hCG levels are monitored for up to 6 to 12 months, depending on the time of hCG normalization, within 8 weeks following evacuation or later than 8 weeks after evacuation.

Before starting the treatment of GTN, imaging studies should be performed to assess how advanced GTN is and to estimate the probability of single-agent chemotherapy failure. The patient here reported was classified as low-risk according to the FIGO criteria (score 2). MTX/FA 8-day regimen at a stable dose 50 mg/15mg was prescribed in view of its effectiveness and a manageable toxicity profile. FA given 30 h after MTX administration reduces MTX-associated haematological toxicity, but the time schedule of dosing must be strictly observed in order not to decrease the therapeutic effectiveness of MTX. Dactinomycin-based regimens have a less favourable adverse reaction profile with a higher incidence of nausea, vomiting and hair loss.

The hGG level was measured before each course of chemotherapy to assess response to treatment. During chemotherapy there is no need for imaging studies when the hCG levels gradually decrease. MTX/FA regimen was continued until hCG normalization and followed by three consolidation courses.

One important issue we encountered, was the correct assessment of hCG normalization which depends on the sensitivity of the laboratory test used. Several molecular variants of hCG present in serum include:

- intact hCG
- nicked intact hCG
- free β-subunit
- free α-subunit

- nicked free β-subunit
- β- subunit core fragment

In GTN, the percent ratios of free hCG β-subunit to total hCG vary depending on the degree of trophoblast differentiation from approximately 1% in PHM to 2.4% in CHM to 9% in choriocarcinoma. Carbohydrates account for approximately 30% of hCG mass and carbohydrate structure changes when they are synthesized by cancer cells. When the peptide chain is nicked, there is loss of biological activity and changes in the antigenicity of hCG. That is why a routine pregnancy test is less sensitive than the assays specifically designed to monitor hCG-secreting cancers. The use of hCG assays standardized to the World Health Organization (WHO) Fourth International Standard is recommended to minimize the risk of false negatives [18].

In the case here described, the hCG level before the 13th course of chemotherapy, measured outside the reference center, was 4.3 mIU/mL, which was considered as a negative result by the local center. The hCG level measured 14 days later at the reference center was 3.8 mIU/mL with the cut-off value of 1 mIU/mL. A shared treatment decision made by the patient and her doctor was to continue regular hCG measurements but using a more sensitive assay and to proceed with chemotherapy until hCG levels returned to normal, which was observed before the 16th course of chemotherapy. In line with the current recommendations for patients with low-risk GTN, three courses of consolidation chemotherapy were administered. A study from the UK and The Netherlands found two-fold lower relapse rates in low-risk GTN patients treated with three consolidation courses compared to patients treated with two consolidation courses [19]. After completing chemotherapy the patient must remain under observation and the hCG levels should be monitored with the measurements every month for six months after normalization, then every two months for up to 12 months post-normalization and finally every six months for up to 5 years. Patients are advised to use highly effective contraception in the first 12 months. In low-risk GTN the prognosis is good, there is a minor risk of recurrence and the complete remission rate is nearly 100%.

To sum up, a multiple pregnancy complicated by a hydatidiform mole carries a risk of severe maternal and fetal adverse events. It should be emphasized that in the reported case the ultrasound scans and the clinical presentation strongly suggested the presence of a complete mole with a coexistent live fetus, but the diagnosis of a partial mole was ultimately made histologically. With further advances in ultrasound technologies, histological assessment of molar specimens and biochemical assays, the rates of correct early diagnoses should increase contributing to early therapeutic decisions and fewer adverse events. Considering their exceptionally low frequency, all cases of a suspected multiple pregnancy with a hydatidiform mole and a coexistent live fetus should be referred to and managed at a tertiary center which specializes in the diagnosis and treatment of gestational trophoblastic disease.

Conflict of interest

All authors declare no conflict of interest.

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There are no funding issues as this is a case study coupled with review.

Ethical approval

All the procedures performed in this study were in accordance with the ethical standards of Ethics Committee of Warsaw Medical University and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The publication of this case report got permission of the patient.

Informed consent

Informed consent was obtained from the patient for publication of this article.

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Is weight just a number? Relationship between overweight, obesity and domains of sexual functioning among young women

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ABSTRACT

Objectives: Being overweight and obesity, one of the biggest health problems in developing countries, is known to affect reproductive health problems. More and more Polish women are struggling with infertility and sexual dysfunctions. Such complications are often diagnosed to be linked directly with patients' excess weight.
The main objectives of the study were to assess the influence of increased BMI (≥ 25.0) on sexual activity and the prevalence of sexual dysfunctions in overweight and obese women in Upper Silesia. Additionally, the occurrence of health problems existing along with obesity was analyzed.

Material and methods: The study was carried out at the Department of Pregnancy Pathology, Department of Woman's Health, School of Health Sciences in Katowice of Medical University of Silesia in Poland. From 526 examined patients, 38% had normal BMI (18.5–24.9), 27% were overweight (BMI 25–29.9) and 35% were obese (BMI score ≥ 30). The patients answered a completely self-administered questionnaire, which was divided into two parts. The first part consisted of general questions about the patient and her past medical history. The second part was the Polish version FSFI questionnaire. The results obtained from FSFI were analyzed using the STATISTICA program.

Results: Statistically significant ($p < 0.001$) reduction in the level of satisfaction was found in the group of obese women when compared to patients with BMI < 30. Also among obese patients the occurrence of sexual dysfunction (FSFI ≤ 26) was significantly increased ($p < 0.05$). A significantly higher number of patients from an average socio-economic situation suffered from sexual dysfunctions, when compared with patients from good a socio-economic group.

Conclusions: Obesity and being overweight lead to more frequent sexual dysfunctions, especially through prevalence of decreased level of sexual satisfaction. Sexual activity problems may be exacerbated by increased body weight in combination with its comorbidities such as insulin resistance, PCOS, obstetric difficulties and irregular menstruation. What is more, a worse socio-economic situation of women predisposes them to the occurrence of sexual dysfunctions.

Key words: obesity; sexuality; sexual dysfunction, physiological; sexual dysfunction, psychological; overweight

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INTRODUCTION

Obesity, or the pathological increase in the amount of adipose tissue has been widely discussed. Once considered a sign of high social status, nowadays it has become a pandemic that causes numerous health implications [1]. Overweight, assessed as BMI greater than or equal to 25 (Tab. 1), is an extremely common pre-obesity condition [2]. The World Health Organization (WHO) announced that in in 2016 almost 1.9 billion adults were overweight, while 650 million of them were already obese [3].

Obesity, defined as a body mass index (BMI) > 30 (Tab. 1), has become one of the biggest health problems in todays' societies in both developed and developing countries [3, 4].

Table 1. BMI classification [2]

BMI classification	
Underweight	< 18.5
Normal range	18.5–25.9
Overweight	≥ 25.0
Preobese	25.0–29.9
Obese	≥ 30.0
Class I	30.0–34.9
Class II	35.0–39.9
Class III	≥ 40.0

BMI — body mass index

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What is more, according to WHO data, the number of obese people has tripled over past 40 years [5].

Obesity is not just an aesthetic problem, it is also linked to a wide range of health problems such as type 2 Diabetes Mellitus, cardiovascular disease and atherogenic processes. Along with the above the oxidative stress (OS) is induced. Additionally, OS is associated with excessive production of adipokines, which further promotes the progression of the metabolic syndrome [6].

Obesity and being overweight directly affects reproductive health problems. According to WHO, positive reproductive health is a state when a woman's mental, physical and social well-being is satisfactory. It also refers to the proper functioning of the reproductive system and human reproductive functions. Reproductive health depends on many factors, being overweight and obesity definitely affect them negatively [7].

European Health Interview Survey (EHIS) states that from all European Union countries, the average for excess weight is 34.8%, and 15.4% for obesity. Similar tendencies were found in Poland [3]. The Bureau of Research of the Chancellery of the Sejm in 2017 reported that among 19.5 million of Polish women, 30.1% are overweight and 15.6% suffer from obesity [8, 9].

Reproductive age is on average between 15 and 49 years of age. There are over 10 million women at this age in Poland. It has been noticed that their procreative behaviors have changed over recent years. Women become pregnant later and are more often diagnosed with infertility and sexual dysfunctions [10].

The increased body mass index does not only influence the physical health, but also directly influences the mental and sexual health. Being overweight and obesity — visceral obesity in particular, are considered risk factors for sexual dysfunction [11]. Obesity affects several aspects of sexual function in otherwise healthy women, including arousal, lubrication, satisfaction, and orgasm [12].

Mental perception of one's appearance, well-known under the term of body image, is one of the most powerful influences of proper sexual health. It can be observed that that women who have higher Body Mass Index judge their bodies more skeptically [13]. Having said that, it leads to withdrawl from situations in which they could feel concerned about their appearance. Negative opinion about one's body image, including: appearance, health, normal functioning, loss of femininity or sexual attraction, can play a predictive role in development of anxiety and depression [14].

Objectives

The aim of the study was to analyze the influence of obesity and being overweight on sexual activity and the occurrence of sexual dysfunctions in women of Upper Silesia. In addition, the occurrence of diseases coexisting with obesity and factors such as age, marital status and socio-economic status were also taken into account.

MATERIAL AND METHODS

A longitudinal study was carried out at the Department of Pregnancy Pathology, Department of Woman's Health, School of Health Sciences in Katowice of Medical University of Silesia in Poland. The study included 526 patients in which 38% (n = 201) of them had the body mass index (BMI) in range between 18.5 and 24.9, what is assessed as normal BMI. 27% of patients (n = 140) had the BMI in range between 25 and 29.9, and were assessed as overweight. 35% (n = 185) patients were obese wit BMI score > 30. The median age of the studied group was 28 (IQR = 25–32). Exclusion criteria were: incorrectly completed questionnaire, missing data and lack of sexual activity. The university Ethics Committee waived the requirement for informed consent due to the anonymous and non-interventional nature of the study (KNW/0022/KB/68/19).

The full group characteristics are presented in Table 2.

Table 2. The main characteristics of the group

Characteristics		
Age	28	IQR 25–32
BMI		
Normal	201	(38%)
Overweight	140	(27%)
Obesity	185	(35%)
Marital status		
Married	337	(64%)
Informal relationship	163	(31%)
Single	26	(5%)
Education		
Basic	30	(6%)
Secondary	191	(36%)
Higher	305	(58%)
Place of residence		
Village	160	(30%)
Town < 50k	98	(19%)
City >50–200k	114	(22%)
City > 200k	154	(29%)
Economic situation		
Below the average	11	(2%)
Average	261	(50%)
Good	254	(40%)
Pregnancies		
None	89	(17%)
One	226	(43%)
More than one	211	(40%)
Given births		
None	126	(24%)
One	246	(47%)
More than one	154	(29%)

The symbol (%) indicates the percentage of the given data in the test population; IQR — interquartile range; BMI — body mass index

Table 3. Body mass index groups and sexual activity of women

	Normal (n = 201)	Overweight (n = 140)	Obesity (n = 185)	p value
FSFI	29.0 ± 4.9	29.4 ± 4.4	28.0 ± 6.2	> 0.05
Desire	4.2 ± 1.2	4.2 ± 1.1	4.2 ± 1.2	> 0.05
Arousal	4.8 ± 1.0	5.0 ± 0.9	4.7 ± 1.2	> 0.05
Lubrication	5.2 ± 0.9	5.3 ± 0.9	5.0 ± 1.2	> 0.05
Orgasm	4.7 ± 1.2	4.9 ± 1.2	4.4 ± 1.4	> 0.05
Satisfaction	5.2 ± 1.0	5.1 ± 0.9	4.7 ± 1.2	< 0.001
Pain	4.8 ± 1.2	5 ± 1.0	4.9 ± 1.2	> 0.05

FSFI — Female Sexual Function Index

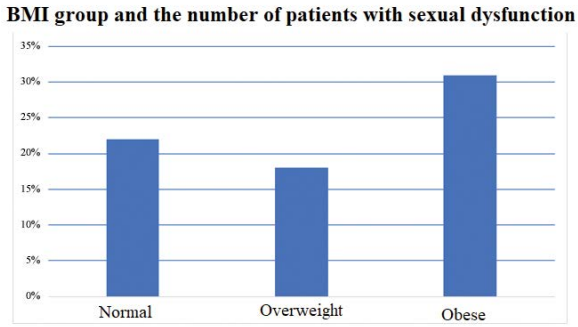

Figure 1. A significant increase in patients with sexual dysfunction in the group of obese women; BMI — body mass index

The completely self-administered questionnaire was provided to the patients at random while waiting for their routine medical check-ups. The first part contained general questions about the patient, as well as an analysis of her obstetric history and questions about coexisting diseases. The second part of the survey was the Polish version of the standardized Female Sexual Function Index (FSFI) questionnaire. It consists of 19 questions about six domains of sexual life: desire, sexual arousal, lubrication, orgasm, sexual satisfaction and pain related to sexual activity [15].

The results were obtained by performing calculations for FSFI according to the relevant instruction manual and using the STATISTICA program.

RESULTS

After analyzing the results, it turned out that in the domain of sexual satisfaction it has been possible to prove a statistically significant ($p < 0.001$) reduction in the level of satisfaction in the group of obese women in relation to women with normal body mass and those who were overweight. Assessing the remaining parameters — desire, sexual arousal, lubrication, orgasm and pain related to sexual activity, no statistically significant differences were noticed between any group: with a normal BMI, overweight or obese (Tab. 3).

Table 4. Influence of selected diseases and clinical situations on female sexuality

	No	Yes	p
Insulin resistance	29.1 ± 4.8	27.1 ± 6.9	< 0.05
PCOS	29.2 ± 4.9	27 0.0 ± 6.3	< 0.05
Gestational diabetes	28.9 ± 5.2	27.7 ± 5.8	> 0.05
Obstetric difficulties	29.4 ± 4.8	27 0.0 ± 6.2	< 0.001
Irregular menstruation	29.4 ± 4.8	27.6 ± 6 0.0	< 0.01

PCOS — Polycystic Ovary Syndrome

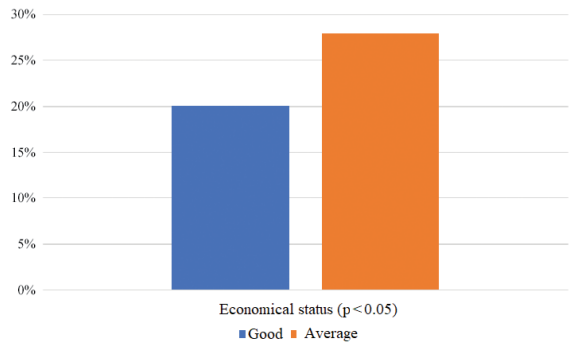

Figure 2. Economic situation in the family and the percentage of sexual dysfunction

However, by testing the groups for the number of patients with sexual dysfunction (FSFI ≤ 26) it was possible to show that obesity significantly increases the number of patients with this problem ($p < 0.05$). The results are shown in Figure 1.

In addition, the influence of selected diseases associated with abnormal body mass on sexual activity of the examined patients was examined (average FSFI score). A statistically significant result of the analysis was obtained for insulin resistance, PCOS, difficulties in getting pregnant and irregular menstruation. However, there was no relationship between sexual activity of women and the occurrence of gestational diabetes. The results are shown in Table 4.

An additional observation noted during the study is the fact that a worse socio-economic situation of women predisposes to the occurrence of sexual dysfunctions (Fig. 2). Sexual dysfunctions were detected in 28% of patients assessing their material status as average. Sexual dysfunctions are less common in a group assessing its economic socio-status as good and the frequency of their occurrence does not exceed 20% of respondents.

DISCUSSION

Sexuality is a complex process, coordinated by the nervous, vascular and hormonal systems. It includes family, social and religious beliefs and may be affected by health status, aging and personal experience [16]. The subject of sexuality

is closely related to the concept of sexual health. The World Human Organization, explains sexual health as a state of physical, emotional, mental and social well-being in relation to human's sexuality [17].

Studies on women's sexuality have been conducted for a relatively short time. Unfortunately, available literature on sexual dysfunctions and their links to weight and general health or other factors is quite limited.

The above study suggests the lack of evidence of obesity influence on sexual dysfunctions. However, being overweight and obesity significantly reduce the sense of sexual satisfaction. Our results correspond with ones obtained by Larsen et al. (2007) [18] and Kolotkin et al. (2006) [19].

Kolotkin et al. (2006) [19] explains these phenomena as an effect of an enhanced frequency of sexual difficulties attributed to patients' weight such as: lack of sexual enjoyment, lack of sexual desire, difficulty with sexual performance, and avoidance of sexual encounters. What is more, the obese commonly experience stigmatization, discrimination, and prejudice because of their weight. Such experiences often lead to the creation of a negative body image by obese people.

Negative body image (BI), especially often reported in women of reproductive age, can lead to many serious consequences. These include eating disorders, depression, unhealthy behavior related to weight control, smoking, reduced physical activity and a reduced health-related quality of life (QOL) [20].

What is more, women with poorer body image, particularly those who experience negative feelings about their physical appearance in a wide range of situations (*i.e.*, situational body image dysphoria), are more likely to report problems of sexual functioning than those who do not experience these types of dysphoria [17, 21]. Scheffers et al. (2018) indicate that in clinically depressed patients, body satisfaction, significantly improves after treatment such as cognitive-behavioral therapy [22, 23].

In our experiment, the sexual activity was significantly lower in groups with insulin resistance, PCOS, obstetric difficulties and irregular menstruation. Most of the mentioned entities are a component of the metabolic syndrome.

Metabolic syndrome is defined by a cluster of medical comorbidities including central obesity, insulin resistance, impaired glucose metabolism, dyslipidemia (hypertriglyceridemia, low high-density lipoprotein cholesterol), and systemic arterial hypertension [24].

Patients with PCOS are struggling with many problems that increase the risk of sexual dysfunction. This disease affects the external appearance — often occurring acne or hirsutism leading to a reduction in the sense of attractiveness, which is manifested by reduced interest in sexual life. The increased BMI of PCOS women results in a decrease in the sense of sexual satisfaction during relationships. Researchers admit that the lack of menstruation also predisposes to sexual dysfunctions, as in patients with normal menstruation sexual dysfunction are found much less frequently [25, 26]. This information is particularly important if one takes into account the fact that in adult women BMI > 25 kg/m^2 significantly increases the risk of menstrual disorders and ovulation, *i.e.* reduces the chances of pregnancy compared to the normal BMI group [27].

Obstetric difficulties may also influence the sexual activity. This subject is also strictly connected with the insulin resistance. It is widely known that the gestational diabetes mellitus may cause the fetus hypertrophy and a result more perinatal complications [20]. Moreover, Restall et al. (2014) states that clinically obese women (with BMI over 30) are more likely to gain excessive weigh during pregnancy when compared to women with a normal BMI. Restall et al. 2014 [28], leading to increased risks of high birthweight with associated risks, such as injuries.

Both, spontaneous injuries and the incision of the crotch performed during the labor affects sexual intercourse. Scientific research on the issue of episiotomy has proven its negative impact on the satisfaction with sexual life. In women who engage in sexual activity and who have had an episiotomy performed during childbirth, dyspareunia and secondary vaginismus is more commonly diagnosed [29–31].

Other disease entities were also correlated with the occurrence of sexual dysfunctions and obesity — in the study of the severity of migraine attacks in obese women, however, no significant compounds were found [32]. It is also suggested that sexual activity problems may be exacerbated by obstructive sleep apnea (OSA). OSA is described as repetitive episodes of upper respiratory tract obstruction, often reported in obese patients [33]. This can cause chronic fatigue, which is a known factor of reduced sexual desire. OSA may become an individual factor leading to sexual dysfunction, however this issue requires further research [34, 35].

The last correlation found in our experiment was the relation between a worse socio-economic situation of women and the more frequent occurrence of sexual dysfunctions. It is hard to explain this fact,however, various authors took that subject into consideration. Spinosa et al. (2019) suggest that lower socioeconomic status more often leads to psychological distress and subsequent emotional eating. Such behavior may lead to increased risk of obesity. At the same time, mentioned distress itself decrease the sexual satisfaction. What is more, obese people with good economic status are able to provide themselves a better healthcare and at the same time they cope better with the side effects of obesity [36, 37].

CONCLUSIONS

The presented study confirms higher incidence of sexual dysfunctions in obese and overweight women. However, there is no correlation between women's sexual activity and the BMI index. For the group with the highest BMI, however, a decreased level of sexual satisfaction was observed. A statistically significant result of the correlation analysis of comorbidities with increased body weight and sexual activity was obtained for insulin resistance, PCOS, obstetric difficulties and irregular menstruation. However, there was no relationship between sexual activity of women and the occurrence of gestational diabetes. The obtained results also suggest that the worse socio-economic situation of women predisposes to the occurrence of sexual dysfunctions.

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A randomized trial in comparison between planned cesarean and vaginal delivery on twin pregnancy

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ABSTRACT

Objective: We explored the planned cesarean to vaginal delivery at the risk of fetal or neonatal death or serious neonatal morbidity in women with twin pregnancies.

Material and methods: Three hundred and forty-three pregnant women were divided into planned cesarean delivery (PCD) and vaginal delivery (PVD) groups (208 vs 135). In the planned-cesarean-delivery group, the rate of cesarean delivery was 98.82%. Meanwhile, the rate of vaginal delivery was 51.27% in PVD group.

Results: Women in the PCD group delivered earlier than that in the PVD group. However, the composite primary outcome of the PCD group was like that of the PVD group. Certainly, the odds ratio of planned cesarean delivery and confidence interval of the PCD group was also like those of the PVD group.

Conclusions: The risk of fetal or neonatal death or serious neonatal morbidity of planned-vaginal-delivery was like those of planned-vaginal-delivery in pregnant women with twin pregnancies.

Key words: planned cesarean; vaginal delivery; twin pregnancy

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INTRODUCTION

Twin gestations accounts for 3% of all deliveries and has different risk characteristics than singleton gestations [1, 2]. It has been reported that in recent years, the cesarean section rate of multiple pregnancies has gradually increased to more than 70% [3]. The main reason for the rise of caesarean section (CS) rate in the world is maternal-choice CS (MCCS) [4]. Twin pregnancies appear to be an independent risk factor for cesarean births after induction of labor, but more than three-quarters of inductions culminated in vaginal delivery [5]. Implementation of the National Institute for Health and Care Excellence (NICE) guidance on the antenatal management of uncomplicated twin pregnancies contributed to significant reduction (>70%) in stillbirth has been noted in twin pregnancies in UK [6].

However, compared with singleton pregnancies, complications of gemellary pregnancies are obviously higher [7]. During gemellary pregnancies, it is more likely to have abortions, fetal malformations, polyhydramnios, preeclampsia and premature delivery, etc. [8]. During the stages of labor, complications such as dystocia, prolapse of cord and postpartum hemorrhage are more likely to occur [9]. As recent cesarean section rates in China are abnormally increasing, most gemellary pregnancies would be performed in the way of caesarean sections [10]. However, a gemellary pregnancy is not the absolute indication for cesarean delivery. Furthermore, when the heads of two fetuses or the first fetus head appears, vaginal delivery is principally feasible. Vaginal delivery is demanded by some gemellary pregnant women [11].

The selection of delivery time has no single standard by now. Generally, most gemellary pregnant women without complications would be admitted to hospital between the 36th~39th weeks [12]. The lowest fetal mortality and neonatal mortality rate occur between the 38th and 39th weeks, respectively. Consequently, it is generally suggested that gemellary pregnancies should be terminated before the 39th week. At present, caesarean sections are regarded as a relatively effective method for high risk pregnancy women and has been widely accepted and employed [13]. As society is constantly advancing and medical modes are continuously changing, rates of caesarean births are ascending steadily [14].

The Twin Birth Study, a recent randomized controlled trial of 2804 women with twin pregnancies, showed that the first twin presented in cephalic position to planned vaginal delivery or planned cesarean. All in all, there were

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no differences in neonatal and maternal outcome between the planned vaginal delivery and planned cesarean groups [15]. However, the design of the Twin Birth Study has always been controversial [16]. In this study, most women delivered shortly after the 32 weeks. Prematurity has a great influence on the neonatal outcomes, so it may include the influence of the way of full-term planned delivery. The subgroup of women that was randomized after 37 weeks was small and it was not clear which was the best method of delivery in twin pregnancy at term, although the less morbidity was observed after planned caesarean delivery. Whether the outcomes of the Twin Birth Study are completely applicable to other settings are still unknown [17].

Cesareans are not a physiological suitable means of pregnancy. As a traumatic surgery, it has many disadvantages and would bring about some problems for women. Besides, women after caesarean are more likely to have massive haemorrhaging, wound infection, scarred uterus or various complications [18]. As far as women who have subsequent pregnancies are concerned, they are confronted with the issue how to select their subsequent pregnancy methods [12]. This study was carried out to compare planned cesarean to vaginal delivery at the risk of fetal or neonatal death or serious neonatal morbidity in pregnant women with twin pregnancies.

MATERIAL AND METHODS

Study design

Women permitted to participate in the study had pregnancies with twins ranging from 32 weeks to 39 weeks, with the head of the first twin appearing earlier than the second during birth and with the two fetuses staying alive with weight from 1500 g to 4000 g, which was authenticated via ultrasonography within a week prior to randomization. Women were recruited with pregnancies as early as 32 weeks of gestation inasmuch as the number of women with twins intend to start a choice of the method of delivery at this time and a host of twins are born prematurely.

Study oversight

Women with the following conditions were excluded from the study: monoamniotic twins, the number of fetuses reduced at more than 13 weeks of gestation, anomalous fetus that is fatal, contraindication to labor or vaginal delivery, and prior participation in the Twin Birth Study.

Treatment

Our protocol, whose full text is available at NEJM.org, was approved by the research ethics committee at each participating center. All women participants, prior to the enrolment, provided the informed consent in written form. The first, second and last authors oversee the exactitude and integrity of all data and the correspondence of the report with integrity.

Those participating were distributed to planned cesarean delivery (PCD) and vaginal delivery (PVD) groups at random. Randomization was kept under control at the Centre for Mother, Infant, and Child Research at Sunnybrook Health Sciences Centre in Toronto with the assistance of a computerized program of randomization which was layered in line with parity (0 vs ≥ 1) and gestational age (224 days to 237 days, 238 days to 258 days, or 259 days to 272 days).

Table 1. Characteristics of pregnant woman at baseline

Characteristic	Cesarean deliver (n = 208)	Vaginal delivery (n = 135)
Previous cesarean section	7 (3.37%)	5 (3.70%)
Age ≥ 30-year age	87 (41.83%)	59 (43.70%)
Mean age	31.6 ± 0.9	31.9 ± 0.7
32nd week–33rd week	61 (29.32%)	41 (30.37%)
34th week–36th week	101 (48.56%)	67 (49.63%)
37th week–38th week	46 (22.12%)	27 (20.00%)
Fetal weight		
First twin	1179 ± 411	1184 ± 409
Second twin	1166 ± 406	1176 ± 405
Chorionicity		
Dichorionic and diamnionic	142 (68.27%)	91 (67.41%)
Monochorionic and diamnionic	57 (27.40%)	38 (28.15%)
Unknown	9 (4.32%)	6 (4.44%)
Not in labor	181 (87.02%)	119 (88.15%)
Membranes ruptured	11 (5.29%)	7 (5.19%)

Experienced staff members accumulated data from the medical records at each participating center and kept them on file, following labor, on standardized forms for data collection. Participating centers made an evaluation of the growth and well-being of fetuses by means of ultrasonography every four weeks at the minimum by stress free or biophysical profile test twice/week if need be. Preparations were made for possible cesarean sections within thirty minutes as the need arose; and at the time of planned vaginal delivery members in the hospital related to anesthesia, obstetrics and nursing were placed on standby.

Alternative delivery by way of either cesarean section (PCD group) or labor induction (PVD group) was organized between 264 to 272 days of gestation, so far as there was some evidence that at this gestational — age window perinatal conditions would yield the best possible results. Provided the first twin was brought into the world through vaginal means by a woman in the planned-cesarean group, the second twin would be delivered in the same manner, if logistically possible. In regards to women who were scheduled to have a vaginal delivery, it was expected that no less than 60% would give birth to both twins by vaginal means. At the time of delivery, there was a reassessment of the pregnancy; in case of a contraindication to labor or vaginal delivery, both twins would be born via caesarean section. Standard methods were utilized in case of induced labor, but for women with a previous caesarean section, advocacy of prostaglandins was not permitted.

Constant monitoring of the fetal heart rate by electronic means was approved in course of active labor. The obstetrician was authorized to make a decision regarding the application of oxytocin and epidural analgesia. Following the first twin birth, it would be advisable to make use of ultrasonography to examine the state of the second twin. In the event the twin would be born with the head appearing first, amniotomy was postponed until the head was engaged and natural vaginal delivery was planned, only when an unsatisfactory position necessitated the usage of forceps or vacuum extraction. Assuming the second twin did not remain in the cephalic presentation, the obstetrician was free to decide about the optimum method of delivery.

Those scheduled to have a vaginal delivery were accompanied by a competent obstetrician adept at vaginal twin delivery. This was interpreted a priori, an obstetrician who themselves had at vaginal twin delivery and whose department head saw eye to eye with this judgment. Prior to the recruitment at each center, a number code was assigned to each of the competent obstetricians who considered themselves qualified in vaginal twin birth, as well as their years of service with vaginal twin delivery and information was kept on file. In addition, collection of information about similar items for other clinicians present during delivery was also made.

Infants are born with positive-pressure ventilation, tracheal intubation, oxygen, intravenous therapy, blood transfusion, surfactant, or a combination of these therapies, if needed. An assessment of intracranial pathology was made by means of neonatal ultrasonography if so, specified in a clinical sense.

Outcomes

Regarding the current analysis, both mothers and their neonates were kept track of until 28 days after the delivery. The principal outcome was a combination of mortality of fetuses or neonates or life-threatening diseases for neonates. Assessment of neonatal mortality was made between day 1 and day 27 following the birth. Life-threatening diseases for neonates were interpreted as the following: birth trauma (spinal cord injury, basal or depressed skull fracture, fracture of a long bone, harm done to a peripheral nerve manifesting itself within 72 h after birth or at discharge, subdural or intracerebral hemorrhage substantiated through the agency of ultrasonography, CT, or MRI, APGAR score of no more than 4 to 5 min, coma, stupor, or slowed-down response to pain, minimum of two seizures before 72 h since birth, requirement of assisted ventilation by way of an endotracheal tube interpolated within 72 h following birth and kept in place for 24 h at the minimum, septicemia authenticated by way of blood culture or meningitis authenticated by means of cerebrospinal fluid culture within 72 h after birth, necrotizing enterocolitis, interpreted as intestinal perforation, pneumatosis intestinalis, or air in the portal vein diagnosed via surgery or radiography, bronchopulmonary dysplasia, interpreted as the requirement for additional oxygen at a postnatal gestational age of 36 weeks and authenticated by way of radiography, intraventricular hemorrhage or cystic periventricular leukomalacia. Data about newborn babies with the principal outcomes were evaluated with such information as the assigned group and mode of delivery (if applicable) kept dark by an adjudication committee.

Statistical analysis

Another result was an amalgam of death of a mother or mother's grave illness within 28 days following childbirth, interpreted as the following: death, hemorrhage (blood loss ≥ 1500 mL, need for blood transfusion, or need for dilation and curettage after delivery), laparotomy, genital tract injury (need for hysterectomy; vulvar or perineal hematoma requiring evacuation; broad-ligament hematoma authenticated by means of ultrasonography, CT, or MRI; intraoperative damage to the bladder, ureter, or bowel requiring repair; fistula involving the genital

Table 2. Characteristics of labor and delivery for pregnant woman

Characteristic	Cesarean deliver (n = 208)	Vaginal delivery (n = 135)
Mode of delivery		
Cesarean	187 (89.90%)	51 (37.77%)
Vaginal and cesarean	2 (0.96%)	7 (5.19%)
Vaginal for both	19 (9.13%)	77 (57.04%)
Timing of cesarean section		
Before the onset of labor	109 (52.40%)	19 (14.07%)
During labor	65 (31.25%)	42 (31.11%)
No cesarean section	34 (16.35%)	74 (54.81%)
Presentation at delivery		
Cephalic presentation		
Cephalic and noncephalic presentation	142 (68.27%)	91 (67.41%)
Noncephalic and cephalic or noncephalic presentation	57 (27.40%)	38 (28.15%)
Gestational age at delivery	9 (4.32%)	6 (4.44%)
Not in labor	181 (87.02%)	119 (88.15%)
Membranes ruptured	11 (5.29%)	7 (5.19%)
Gestational age at delivery of first twin		
Mean age		
32^{nd} week–33^{rd} week	11 (5.29%)	4 (2.96%)
34^{th} week–36^{th} week	84 (40.38%)	58 (42.96%)
37^{th} week–38^{th} week	109 (52.40%)	69 (51.11%)
> 39^{th} week	4 (1.92%)	4 (2.96%)
Time from randomization to delivery of first twin	12.2 ± 12.1 days	13.4 ± 12.2 days
Interval between deliveries	3.3 ± 9.6 min	10.2 ± 17.4 min
Use of antenatal glucocorticoids after randomization	25 (12.02%)	14 (10.37%)
Chorionicity at birth		
Dichorionic and diamnionic	149 (71.63%)	97 (71.85%)
Dichorionic and diamnionic	42 (20.19%)	30 (22.22%)
Dichorionic and diamnionic	1 (0.48%)	1 (0.74%)
Unknown	16 (7.69%)	7 (5.19%)
Use of anesthesia or analgesia	201 (96.63%)	95 (70.37%)
Regional	192 (95.52%)	73 (76.84%)
General	13 (6.47%)	6 (6.32%)
Other	4 (1.99%)	10 (10.52%)

tract; or third-degree or fourth-degree perineal laceration involving the anal sphincter or mucosa, thromboembolism requiring anticoagulant therapy, systemic infection, serious illness that is life-threatening, wound infection that calls for prolonged hospitalization, readmission to the hospital, or repeated treatment as an outpatient, wound dehiscence or breakdown; or other grievous maternal complication. Other detrimental factors except morbidity defined beforehand were supposed to be presented to the independent board for monitoring data and safety.

Subordinate results to be presented later encompassed death, an unsatisfactory neurodevelopmental outcome for children two years of age and troublesome urinary, fecal, or flatal incontinence for mothers two years following childbirth. There were additional results for mothers, inclusive of contentment with the mode of delivery, breast-feeding, quality of life, tiredness and melancholia.

The data are expressed as the mean ± standard deviation and conducted using SPSS 17.0 (SPSS, Inc., Chicago, IL, USA). Statistical analysis was performed where appropriate, and the Student-Newman-Keuls method was used for pairwise

Table 3. Pregnancies outcomes

Characteristic	Cesarean deliver (n = 208)	Vaginal delivery (n = 135)
No. of fetuses or infants included in analysis	418	271
Primary outcome	8 (1.91%)	6 (2.21%)
Gestational age		
32nd week–33rd week	6	4
34th week–36th week	2	2
37th week–38th week	0	0
Birth trauma	1	0
Long-bone fracture	0	2
Other bone fracture	1	0
Facial-nerve injury at 72 h of age or at discharge	0	1
Intracerebral hemorrhage	1	1
Apgar score < 4 at 5 min	1	4
Abnormal level of consciousness		
Stupor or decreased response to pain	4	2
Hyperalert, drowsy, or lethargic	0	1
Assisted ventilation for ≥ 24 h by means of endotracheal tube, inserted within 72 h after birth	0	2
Cystic periventricular leukomalacia	1	0

comparison. $P < 0.05$ was considered to indicate a statistically significant difference.

RESULTS

Characteristics of pregnant woman at baseline

There were 343 pregnant women who were randomly divided into PCD and PVD groups (208 vs 135) between October 2013 and March 2015. Table 1 showed that baseline characteristics of the two study groups were similar. The PCD group [162/208 (77.88%)] and the PVD group [108/135 (80.00%)] underwent randomization between 224 days and 258 days of gestation, respectively.

Characteristics of labor and delivery for pregnant woman

As shown in Table 2, the labor and delivery outcomes for all women were as follows: the planned-cesarean-delivery group, 187 (89.90%) pregnant women, 2 (0.96%) pregnant women and 19 (9.13%) pregnant women appeared cesarean for both infant, Vaginal and cesarean, and Vaginal for both, respectively; in the planned-vaginal delivery group, 51 (37.77%) pregnant women, 7 (5.19%) pregnant women and 77 (57.04%) pregnant women appeared cesarean for both infant, Vaginal and cesarean, and Vaginal for both, respectively. Timing of cesarean sections were higher in the planned-cesarean-delivery group than those in the planned-vaginal delivery group. There were no significant differences in other factors between the planned-vaginal delivery group and planned-vaginal delivery group.

Pregnancies outcomes

As shown in Table 3, the primary outcome was notably associated with gestational age at randomization. However, other factors between the PVD group and the PCD group were not related with primary outcome.

Pregnant outcomes

There was no significant difference in the frequency of the maternal composite outcome between the planned-cesarean-delivery and planned-delivery groups (Tab. 4). During the trial, all adverse events documented were measured composing the morbidity component of the primary outcome. However, there was no other adverse outcome reported to the data and safety monitoring board.

DISCUSSION

With the development of assisted reproductive technology, ratio of gemellary pregnancy worldwide is significantly increasing and distocia is more challenging to modern Obstetrics and Gynaecology [18]. In recent years, vaginal delivery rates of twins were decreasing while cesarean section rates were increasing year by year [19]. It was reported that in China, vaginal delivery rates of twins in 2010 were 78.45% [10]. As a result, how to select a suitable delivery method and reduce cesarean section rates is an issue that needs to be

Table 4. Pregnant outcomes

Characteristic	Cesarean deliver (n = 208)	Vaginal delivery (n = 135)
Death or serious maternal morbidity	14 (6.7%)	8 (5.93%)
Hemorrhage	14 (6.73%)	8 (5.93%)
Blood loss ≥ 1500 mL	5 (2.04%)	4 (2.96%)
Blood transfusion	12 (5.77%)	8 (5.93%)
Dilation and curettage of uterus after delivery	3 (1.44%)	3 (2.22%)
Laparotomy	2 (0.96%)	1 (0.74%)
Genital tract injury	1 (0.48%)	1 (0.74%)
Perineal third- or fourth-degree tear involving anal sphincter	0	1 (0.74%)
Thromboembolism requiring anticoagulant therapy	0	2 (1.48%)
Infection, excluding wound infection	2 (0.96%)	1 (0.74%)
Wound infection	7 (3.37%)	2 (1.48%)
Infection requiring prolongation of hospital stay	5 (2.04%)	2 (1.48%)
Infection requiring readmission to hospital	2 (0.96%)	1 (0.74%)
Infection requiring repeated treatment as an outpatient	5 (2.04%)	1 (0.74%)
Wound dehiscence or breakdown	14 (6.73%)	8 (5.93%)
Major serious or life-threatening medical illness	3 (1.44%)	0

solved urgently. In the present study, the results verified 162/208 (77.88%) pregnant women in the PCD group and 108/135 (80.00%) pregnant women in the PVD group underwent randomization between 224 days and 258 days of gestation.

When pregnant women feel hyperinflation in abdomen, expiatory dyspnea or serious illness, pregnancy should be terminated [20]. Furthermore, when women have premature rupture of fetal membranes or about to give birth during 28^{th}–34^{th} week, pregnancy should be terminated after fetal lung maturating [10]. Finally, pregnancy termination should be considered when complications occur, and pregnancy cannot be continued [13]. When the expected date of confinement reaches but delivery does not occur, women should be admitted to hospital and termination of the pregnancy should be considered [7]. Like a singleton pregnancy, delivery time of a gemellary pregnancy should comprehensively consider maternal complications and fetal situations in the uterus [21]. When the intrauterine environment is obviously not suitable to fetus growth and this condition cannot be improved by intrauterine therapy, it is the appropriate time to terminate the pregnancy [22]. Therefore, delivery time is dependent on specific conditions of pregnant women. Physician should communicate with women and their families as well as confirm gestational weeks. The present study showed that 87 (89.90%) pregnant women of the planned-cesarean-delivery group appeared cesarean for both infant and 77 (57.04%) pregnant women of the planned-vaginal delivery group appeared vaginal for both infants. The timing of cesarean sections were higher in the PCD group than those of the PVD group.

In recent years, with rapid advances of medical technology, cesarean techniques are significantly improving and rates of cesareans in China are continuous increasing [10]. However, cesareans may cause changes of uterus position or anteversion of uterus. As uterine contraction at uterine incision is weak, cesareans would seriously affect subsequent delivery [23]. Compared with normal labor, cesareans produce more bleeding and involution of uterus is slower [24]. Meanwhile, lactation and discharge of meconium for newborns delay while peak time of jaundice are later and more serious. Moreover, it would increase the possibilities of maternal and neonatal complications [25]. Consequently, the medical field is still confronted with the issue of how to select subsequent deliveries after a cesarean section. In the present study, significantly related to the primary outcome was gestational age at randomization in two groups.

In conclusion, these data indicate that there were no benefits of planned cesarean section with the delivery of twins between 32 and 38 weeks of gestation in comparison to planned vaginal delivery, if the first twin was in the cephalic presentation. The risk of fetal or neonatal death or serious neonatal morbidity of planned-vaginal-delivery was like those of planned-vaginal-delivery in pregnant woman with twin pregnancy.

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Secondary Postpartum Haemorrhage following vaginal delivery — a 3-year survey of causes and management

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ABSTRACT

Objectives: Secondary postpartum haemorrhage (PPH) is a serious complication of childbirth and a life-threatening condition that may lead to infertility amongst women during the reproductive age groups.

The objective of this study is to highlight the underlying causes of secondary PPH and outcomes for patients who delivered vaginally, with the aim of reducing maternal mortality and morbidity.

Material and Methods: This is a prospective cohort study conducted in the Department of Obstetrics and Gynaecology at AL-Yarmouk Teaching Hospital, Baghdad, Iraq. The study was conducted over a 3-year period from December 2015 to December 2018. Women who delivered vaginally with a gestational age of at least 24 weeks, with no previous caesarean or uterine scars, who were admitted to the hospital complaining of bleeding from their genital tracts after 24 hours of delivery, but prior to 6 weeks from delivery, were enrolled in the study. Patients received resuscitative measures and medical treatment and were observed regarding their response to medical treatment and whether they required surgical intervention. Types of management were also evaluated, and histopathological reviews were gathered and recorded for those who needed retained pieces of product evacuated or hysterectomies.

Results: Two hundred cases were analysed; the incidence of severe secondary postpartum haemorrhage was 60 per 10,000 deliveries. Endometritis was the leading cause (64% of patients), followed by retained placental pieces (13.5%); emergency hysterectomy was performed in 34.5% of patients. This study is novel because it is the first to shed light on secondary postpartum haemorrhage in unscarred uteri in Iraq.

Conclusions: Endometritis was the most common cause of secondary postpartum haemorrhage, and emergency hysterectomy was the most common strategy of treatment.

Key words: secondary postpartum haemorrhage; caesarean section; hysterectomy; endometritis

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INTRODUCTION

Complications of pregnancy and childbirth have been one of the leading causes of death and disability among women of reproductive age [1]. Postpartum haemorrhage (PPH) is an unusual complication following a vaginal delivery with an incidence of about 4% of all deliveries; it contributes to one-third of maternal mortalities in developing countries [2]. Secondary postpartum haemorrhage is any significant bleeding from a genital tract by any route (intra-abdominal or vaginal) that commences after the first 24 hours following delivery until the 6th weeks of puerperium. Because the estimated blood loss is difficult to assess, the diagnosis depends on the clinical evaluation of the patient [3]. The presentation varies from mild spotting or excessive lochia, which can be managed by medical treatment, to severe life-threating bleeding that requires surgical removal of a retained piece of tissue or a lifesaving hysterectomy to stop the bleeding and save the life of the mother [4]. The most common etiological factors are retaining a piece of placenta, endometritis, sub involution of placental bed, pseudoaneurysm of the uterine artery, arteriovenous malformation, dehiscent of the uterine scar and, rarely, gestational trophoblastic disease (GTD) [5]. Complications and consequences of secondary postpartum haemorrhage have importance to the researcher for assessing risks factors and preventive method spatially the alarming outcome of secondary PPH and subsequent effect in further fertility [6].

The aim of the study

The objective of this study is to evaluate the underlying causes of secondary PPH and the outcomes for patients.

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MATERIAL AND METHODS

This is a prospective cohort study that was done at the Department of Obstetrics and Gynaecology of AL-Yarmouk Teaching Hospital, Baghdad, Iraq. The study was conducted over a 3 year period from December 2015 to December 2018. The study protocol was approved by the Ethics Committee of the Medical College at Al-Mustansiriyah University, Iraq. Verbal consents were received from all participants.

Inclusion criteria

Women of any age who delivered vaginally with a gestational age of at least 24 weeks who were admitted to the hospital after 24 hours of delivery, but prior to 6 weeks from delivery, with complaints of heavy bleeding or with a history of repetitive attacks of irregular vaginal bleeding with unstable vital signs or with a drop in haemoglobin levels were enrolled in the study.

Exclusion criteria

All patients with prior scars, with previous uterine surgery, presenting with primary PPH, or presenting with placenta previa and accrete syndrome were excluded from the study.

A full history was obtained including age, parity, residence, educational level, modes of previous deliveries, intervals between pregnancies, history of medical diseases such as hypertension and diabetes mellitus, and gestational age. Place of delivery, time of presentations and any primary post-partum bleeding and amount of bleeding were also recorded. We conducted a systemic and local examination of each patient, including vital signs. Investigations included complete blood count, liver and renal function test, and high vaginal swab that was sent for culture and sensitivity. Ultrasounds were performed on all patients, and abnormalities were identified, such as retained pieces of product. All the patients received intravenous fluid, oxytocic drugs, tranexamic acid, blood and/or blood products and broad-spectrum antibiotics of the same type based the hospital's protocol, which includes clindamycin 900 mg three times per day and Garamycin (Gentamicin) 20 mg/kg per dose. Thereafter, each patient was observed regarding her response to medical treatment and whether she required surgical intervention. Additionally, histopathological specimens were sent for examination for cases of retained pieces of placenta and hysterectomy cases, and the records were collected and recorded.

Statistical analysis

Statistical Package for Social Sciences (SPSS version 25)* was used for data analysis. Categorical data were represented by frequencies and percentages. Associations between variables were measured using Pearson's Chi-square test. Results were considered statistically significant when the p-value equal to or less than 0.05.

*IBM Corp. Released in 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp

Table 1. General characteristics of the study group

Variable		No. (200)	%
Age (years)	< 20 years	37	18.5%
	20–29 years	65	32.5%
	30–39 years	83	41.5%
	40+ years	15	7.5%
Area of residence	Urban	92	46%
	Rural	108	54%
Education	Illiterate	59	29.5%
	Primary	73	36.5%
	Secondary	30	15%
	College & Higher	38	19%
BMI (Kg/m^2) at the time of presentation	Normal (18.5–24.9)	55	27.5%
	Overweight (25.0–29.9)	51	25.5%
	Obese (=> 30.0)	94	47%

RESULTS

During the study period, there were 33,000 live births in the Al-Yarmouk teaching hospital, which covers a wide area of Baghdad. The total number of vaginal deliveries was 17,830 (55%) while the total number of CS was 15,170 (45%). Two hundred patients were identified with severe secondary PPH following vaginal deliveries and required admission to the hospital, and the incidence was 6%. Of the study group, 83 (41.5%) were 30–39 years old, 108 (54%) were living in a rural area, more than one-third had primary school education and less than one-fifth had higher education. Most of the patients (47%) were obese (Tab. 1).

About 90 (45%) of women in the study group has a parity of 2–4. The babies delivered between 36-38 were 98 (49%). About 121 (60.5%) of the patients had no antenatal care. The most frequent medical disease during the index pregnancy was a history of anaemia, found in 87 women (43.5%). About three-quarters —149 (74.5%) — of the patients delivered in a hospital (whether our hospital or other hospitals). The onset of labour was spontaneous for 64% of study participants and induced for the remaining 36%. Prolonged labour was found in 87 (43.5%) of the patients and birth weight greater than 4 kg was found in 97 (48.5%) of the patients (Tab. 2).

The induction of labour was performed most frequently for premature pre-labour rupture of membrane (PPROM) (29.2%) or postdate pregnancy (25%) (Fig. 1).

Table 2. Pregnancy and delivery parameters of last pregnancy

Variable		No. (200)	%
Parity	1	78	39%
	2–4	90	45%
	≥ 5	32	16%
Gestational age	Less than 35	29	14.5%
	≥ 36–38	98	49%
	≥ 39–41	73	36.5%
Inter--pregnancy interval (years)	One	95	47.5%
	Two	76	38%
	More than 3	29	14.5%
Antenatal care (ANC)	Yes	79	39.5%
	No	121	60.5%
Medical disease during pregnancy	Anaemia	87	43.5%
	Hypertensive disorder	8	4%
	Diabetes mellitus	9	4.5%
	Coagulation disorder	5	2.5%
Place of delivery	Hospital	149	74.5%
	Home delivery	51	25.5%
Onset of labour	Spontaneous	128	64%
	Induced	72	36%
Prolonged labour		87	43.5%
Birth weight (Kg)	< 2.5	21	10.5%
	2.5–4	82	41%
	> 4	97	48.5%

Time of presentation after delivery varied and 44.5% presented 6–10 days following delivery. Nearly half of the patients (45.5%) had a history of primary PPH. PROM was found in 57 (28.5%) cases. On admission, 147 (73.5%) presented with shock, while 159 (79.5%) patients had a fever. On admission, maternal haemoglobin less than 7 was seen in 105 patients (52.5%). Hospitalization more than 5 days needed in 98 (49%). Readmission observed in 94 (47%) (Tab. 2).

All patients needed a transfusion of blood, blood product Factor VII and 149 (74.5%) needed a massive blood transfusion, (≥ 10 red blood units within 24 h, the transfusion of > 4 red blood units in 1 h) [7]. Additionally, 33 (16.5%) of cases responded to medical treatment (including Oxytocic drugs, antibiotics, tranexamic acid blood and or blood products and factor VII).

Vaginal exploration was done for the patients, which included removal of retained products of conception for 27 (13.5%), suturing of cervical tears for 18 (9%) and uterine balloon for 2 (1%). Laparotomies with the conservative of the uterus, including B lynch and internal iliac artery ligation, were required in 20 (10%) and 12 (6%) needed their ruptured uterus repaired. Emergency transabdominal hysterectomy without salpingo-oophorectomy was performed on 69 (34.5%) of the patients, and 19 (9.5%) need hysterectomy with internal iliac artery ligation. The major reason for performing a hysterectomy was the inability to stop bleeding using more conservative methods. All the specimens of the uterus and retained pieces of product

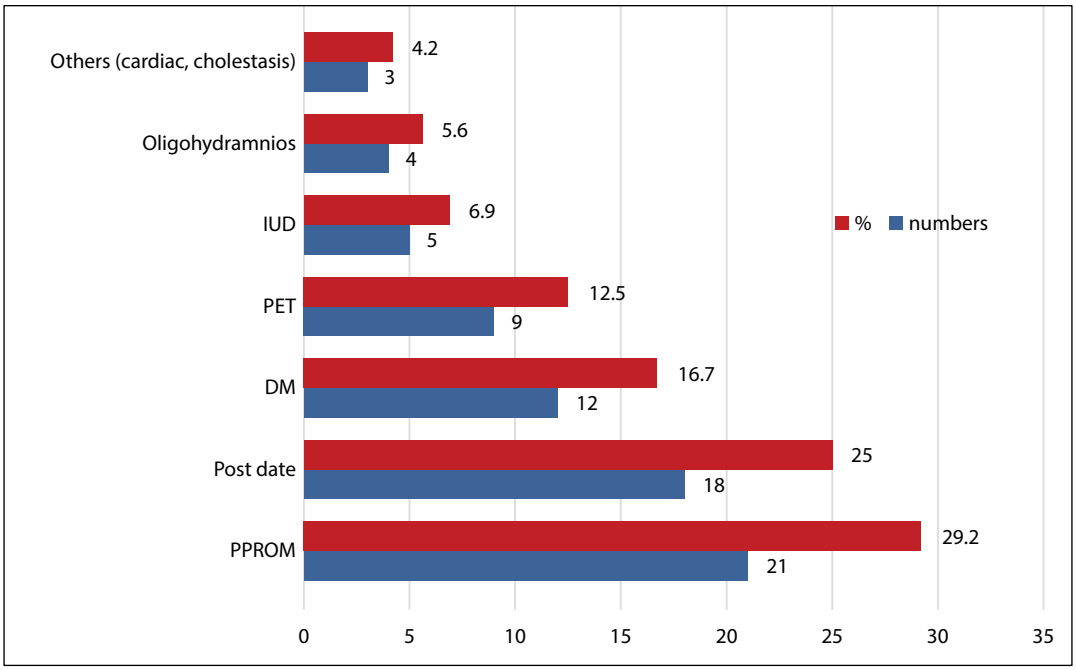

Figure 1. The indication of induction of labour

Table 3. Clinical evaluation at the time of admission

Variable		No.(200)	%
Time of presentation after delivery (days)	1–5	66	33%
	6–10	89	44.5%
	10–20	27	13.5%
	20–42	18	9%
History of primary PPH		91	45.5%
History of PROM		57	28.5%
Signs and symptoms	Shock	147	73.5%
	Fever	159	79.5%
Maternal haemoglobin on admission	Less than 7	105	52.5%
Hospitalization more than 5 days		98	49%
Readmission		94	47%

were sent for histopathology. Admission to RCU was 8.5% and the mortality rate was 1% (Tab. 3).

Endometritis was the leading cause of secondary PPH among the patients of this study (64%), followed by retained placental pieces (13.5%), 8% was due to cervical or vaginal tears, 4.5% was related to uterine atony, ruptured uterus was found in 3.5% of cases, coagulation or haematological disease in 3%, which was 4 cases of idiopathic thrombocytopenic purpura and 2 cases of Von Willebrand disease diseases, choriocarcinoma in 2.5% and the remaining 1% of cases had a different cause of the cause was not found (Fig. 2).

Table 4. Management modality of the study group

Types of intervention		Numbers	%
Massive blood transfusion		149	74.5%
Responded to conservative medical treatment (antibiotics, blood and blood product, factor 7, tranexamic acid)		33	16.5%
Vaginal exploration	Removal of retained products of conception	27	13.5%
	Cervical and or vaginal tears suturing	18	9%
	Uterine balloon	2	1%
Laparotomy with the conservation of the uterus	Repair of ruptured uterus	20	10%
	B lynch and internal iliac artery ligation	12	6%
Hysterectomy	Hysterectomy only	69	34.5%
	Hysterectomy with internal iliac artery ligation	19	9.5%
Admission to respiratory care unit		17	8.5%
Mortality		2	1%

DISCUSSION

One of the most challenging conditions to manage in obstetrics is a postpartum haemorrhage, which is considered one of the most important causes of maternal death and morbidity worldwide [6]. Optimal management and saving the life of the mother depend on the early diagnosis of this condition. Many studies have attempted to shed light on the management options available; for example, BUL — BUL S et al. [8]

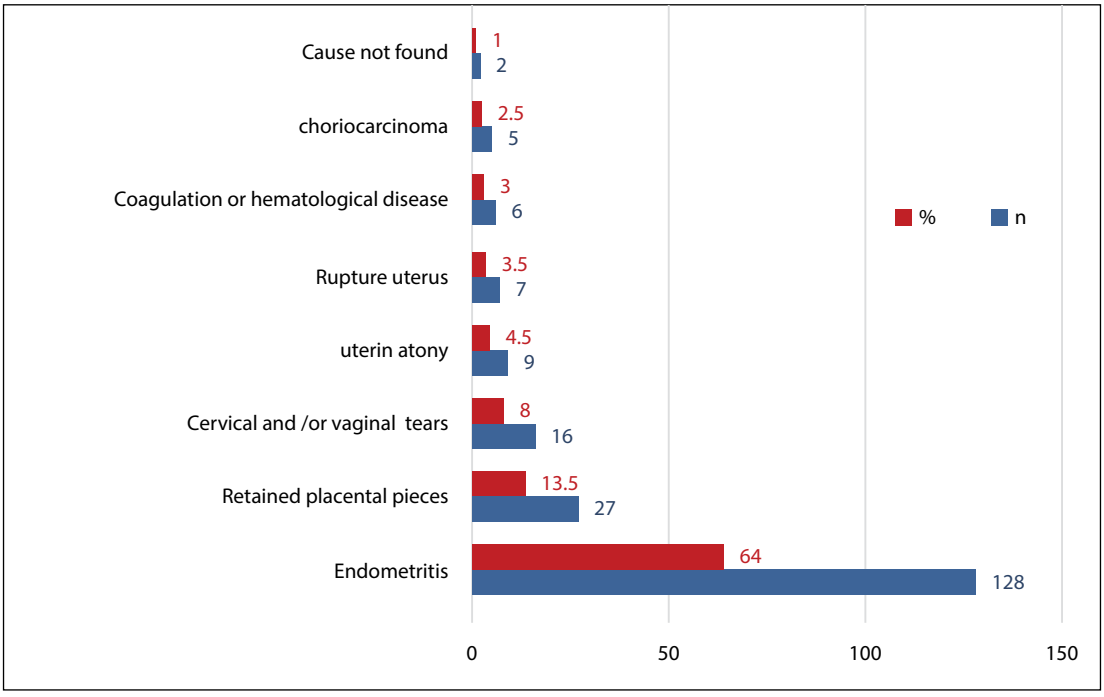

Figure 2. The causes of secondary PPH

found that the highest age group for women who presented with PPH was between 30 to 35 years — which we also found in this study —perhaps due to the higher parity in this age group. Most of the patients admitted to AL-Yarmouk hospital were from rural areas, which is similar to the previous study by Carrole et al. [8]. This finding may be related to a deficiency of talent and difficulty in attainment health care centres. Moreover, we found that women with BMIs of more than 30 Kg/m^2 were more at risk for secondary PPH, which agrees to some extent with a study done in 2013 [9]. Concomitantly, obese women tend to have longer first and second stages of labour compared to non-obese women, which considered one of the risk factors for postpartum haemorrhage. In this study, we observed secondary PPH more in multiparas women, although another study by Mulic-Lutvica et al. in 2009 [10] found that PPH was more common in primiparas women. Other studies [11, 12] reported the majority of grand multiparous women developed secondary postpartum haemorrhage. The differences among these study results may be related to geographic and ethnic differences and to the preference among most of the primigravida to deliver by a midwife. The present work revealed a higher incidence of secondary PPH among women who hadn't been booked or had irregular ANC, in agreement with the study by Ajenifuja, Ko et al., 2010 [13]. Anaemia was found to be prevalent in 43.5% of patients who developed secondary PPH, which was similar to a study by Khalil, Rozhan [14]. Our work observed that 149 of women who developed secondary PPH delivered in the hospital and 51 of women delivered at home, in contrast to a previous study by Jabbar, Shazia; 2019 [15] in which he found that most of the patients who developed secondary PPH delivered at home or in health facilities. This difference may be related to AL-Yarmok's status as a teaching hospital and tertiary centre that receives referral cases from all areas in our country. The time interval between delivery and onset of secondary PPH was 6–10 days for 44.5% of patients, which is similar to the finding published by Waseeqa Nigeen [16]. A history of primary PPH among women with secondary PPH in our current work was 45.5%, higher than the value cited by Dossou M et al. (19%), and it has been suggested that immediate PPH is a predictive factor of hysterectomy (4). Signs and symptoms of tachycardia and hypotension (shock) were founded most commonly, and we also observed more hysterectomies in patients who presented with severe hypotension and tachycardia, similar to a study by Kreshna H. M. et al.; 2011 [17], which may be due to patients ignoring bleeding, underestimating the amount of bleeding and delaying care. Those factors led them to endured an emergency hysterectomy to save their life. Fever was the most common symptom that led patients to seek medical advice and it was present in 159 (79%) of cases. This finding does not agree with the study done by Waseeqa Nigeen et al. [16]; 2017 in which he found that only fourteen (28%) of patients had a fever. This variation may be due to most of the patients not taking antibiotics even if needed after vaginal deliveries, increasing the incidence of endometritis; it is well known that fever is one of the symptoms that indicate infection. Maternal haemoglobin was low in most patients who presented with secondary PPH, and Waseeqa Nigeen et al.; 2017, [16] agree with the current study. This low level of haemoglobin is due to a massive amount of blood loss after vaginal delivery until the time of presentation. This study identified 98 (49%) who needed an admission of more than 5 days, in agreement with a study by Kamrun Nessa et al. conducted on 33 patients with a history of secondary PPH; 24 (73%) needed an admission of more than 5 days. This finding relates to surgical management and hysterectomies due to delays in seeking care rather than medical treatment, and this aggressive surgical intervention required longer hospitalizations [18]. We found a wide range of treatment modalities for the management of secondary PPH, ranging from medical to surgical, and about 33 (16.5%) patients responded to conservative management and 47 patients needed vaginal exploration after delivery. A study by Sheikh, Lumaan et al., 2011 [19] evaluated variable types of management protocols, which support our findings. This works described other management options and found that hysterectomy, as a lifesaving procedure, was required for 34.5% of patients, which was higher than a study done by Kittur et al., 2016 who found that the percentage of patients requiring a hysterectomy was only 6.9% [20]. This difference may be related to our study criteria, which included only vaginal deliveries, and to geographical variation and to the lack of other available facilities for controlling postpartum haemorrhage; such as embolization, an alternative to a hysterectomy, is not available in our radiological department. In this study, endometritis was the leading cause of secondary PPH among the patients (64%), followed by retained placental pieces (13.5%), which is not consistent with Kasap et al. [21] who did a retrospective descriptive study in North India for 6 months and found that retained products of contraception (RPOCs) was the leading cause (72% of patients) followed by endometritis (20%) [21]. This difference between our study and the other study might be due to a difference in sample size and our work included only women who delivered vaginally [22]. A limitation of the present study was that it was conducted in a single centre. Despite this limitation, this study presents new information from Iraq regarding secondary postpartum haemorrhage in unscarred uteri.

CONCLUSION

Endometritis was the most common cause of secondary PPH, and emergency hysterectomy was the management option for most patients.

RECOMMENDATIONS

Endometritis should be minimized in hospitals to decrease the risk of hysterectomies and the proper management of haemoglobin post-partum should be enforced.

Conflict of interest

No author has any potential conflicts of interest.

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The risk of hyperbilirubinemia in term neonates after placental transfusion — a randomized-blinded controlled trial

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ABSTRACT:

Objective: We aimed to demonstrate non-inferiority of delayed cord clamping (DCC) and cord milking (CM) in comparison to early cord clamping (ECC) in the incidence of hyperbilirubinemia requiring phototherapy.

Material and methods: 467 of maternal-foetal dyads were screened for eligibility. 389 term infants, of breastfeeding, non-smoking mothers were randomized to receive ECC (< 40 s), DCC (1–2 min) or CM (4 times towards the neonate). The primary outcome was defined as hyperbilirubinemia requiring phototherapy.

Results: 307 patients were included in the analysis. CM did not increase the risk of phototherapy RR 11.27 95% CI (0.80; 2.04). Similar results were achieved when comparing DCC and ECC, RR 1.29 95% CI (0.82; 2.05). This was also true for CM vs DCC, RR 0.99 95% CI (0.64; 1.52). The prevalence of total serum bilirubin (TSB) at 24–48 hours was 10.8 mg/dL; 10.33 mg/dL and 11.39 in ECC, CM and DCC group respectively. Transcutaneous bilirubin (TcB) levels at 24–48 h were 7.58 mg/dL, 7.89 mg/dL and 7.60 mg/dL in the ECC, CM and DCC respectively. None of the neonates met exchange transfusion criteria or symptomatic polycythaemia.

Conclusions: Our study suggests that placental transfusion is not associated with hyperbilirubinemia requiring phototherapy or exchange transfusion.

Key words: jaundice; hyperbilirubinemia; neonate; placental transfusion

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INTRODUCTION

Delayed cord clamping (DCC), also known as expectant or physiological cord clamping, has been a subject of extensive research for the last couple of years. It involves clamping the cord when pulsation has ceased or at least after 30–60 seconds, allowing for foetal blood transfer from the placenta to the infant [1]. Cord milking (CM), an alternative method, involves milking the cord towards the infants 4 times. These interventions, labeled as placental transfusion, can provide the infant with respectively up to 30% and 60% additional blood volume and red blood cells [2]. Numerous neonatal benefits of DCC have been suggested including increased haemoglobin and ferritin levels both at birth and at longer term [3]. Nevertheless, systematic reviews of DCC versus early or immediate cord clamping (ECC) reveal that it may also contribute to other neonatal outcomes including polycythaemia and hyperbilirubinemia [2–4].

A Cochrane review published in 2008 determined maternal and neonatal effects of different policies of cord clamping timing during the third stage of labour in term infants [3]. Eight trials examined jaundice requiring phototherapy. However, evidence for decreased risk of jaundice requiring phototherapy in the ECC group was based upon one unpublished trial. The variable did not reach statistical significance if this one trial was removed from the analysis. No difference was detected for polycythaemia. A meta-analysis published by Hutton provides contradictory results [5]. No significant differences were found between groups. Recently, a large study from Australia was published where the authors found that in preterm infants DCC did not increase the risk of hyperbilirubinemia [6]. Nevertheless, a systematic review from the same group showed that there was a significant increase in polycythaemia and jaundice [7]. It is important to note, that none of the reviews distinguished between DCC and CM, as opposed interventions to ECC. Based on numerous proven benefits, placental transfusion has been widely adopted in perinatal centres (personal communication) and is now part of both Polish and international guidelines on

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neonatal resuscitation [1]. A retrospective study published by Yang et al. has shown that implementing placental transfusion as a unit protocol did not increase the number of infants requiring phototherapy [8]. We are the first to report a prospective double blinded randomised controlled trial.

Objectives

The primary end point of this study was to evaluate if placental transfusion (delayed cord clamping or cord milking) increases the risk hyperbilirubinemia requiring phototherapy in term infants.

MATERIAL AND METHODS

We conducted a trial using observer blinded, balanced randomization (1:1:1), and included 3 parallel groups. We planned to demonstrate the non-inferiority of placental transfusion in comparison to ECC in regard to the incidence of hyperbilirubinemia requiring phototherapy.

Eligible participants were maternal-foetal dyads, in labour at 37–42 weeks of gestation. We recruited non-smoking mothers, willing to return for follow up visits, who declared to breastfeed for at least 6 months. Exclusion criteria included iso-immune haemolytic disease, sepsis, maternal Gilbert syndrome, birth asphyxia, need for resuscitation and serious maternal haemorrhage during delivery.

The study took place at a level III teaching hospital with approximately 3500 deliveries per year (2000 > 37 weeks of gestation) and 67 neonatal beds. During the trial, the local protocol on cord clamping had not been yet adjusted to the new International Liaison Committee on Resuscitation (ILCOR) guidelines [1].

A member of the recruitment team approached the mothers prior to delivery in the labour ward. He/she explained the study and obtained written consent for participating in the trial. The patient's medical record number (MRN) was registered on a secure web-based platform and demographic data was recorded. Maternal-foetal dyads, prior to delivery, were randomly assigned to receive ECC, DCC or CM. The midwife or obstetrician was informed about the allocated intervention preceding the delivery of the shoulders (spontaneous vaginal delivery), or head (caesarean section).

During vaginal deliveries midwifes were asked to maintain the infant at least 10 cm above the uterus until the cord is clamped, as this has been found to be most effective in obtaining adequate blood volumes [9, 10]. In cases of caesarean sections, the baby was placed on the mother's laps and swaddled in sterile towels to prevent heat loss. In the ECC and DCC group, the recruiter informed the team when 30 seconds or 2 minutes had passed. The attending labour ward staff clamped the cord afterwards.

If CM was applied the baby was placed about 20 cm below the level of the placenta, between the mother's thighs (during a vaginal delivery) or at the side of the mother, swaddled in sterile towels (during a caesarean delivery). Before starting the trial we piloted this procedure previously described by Rabe et al. [11]. We assumed that the placental would contain about 40% of total circulating foetal blood with about 10–15 mL present for placental transfusion in the umbilical vein, both during a vaginal and caesarean delivery [12]. If the cord was milked once at the speed of 20 cm/2 seconds, we were able to transfer approximately 10–13 mL of blood to the neonate. Under the assumption that the cord vein will rapidly refill itself, we assumed that milking the cord four times would give us 30–40 mL of blood. This amount is similar to the quantity of blood transfused to the neonate during DCC [11]. A member of the delivery team (vaginal delivery) or operating team (caesarean section) held the cord at the level of the introitus or caesarean wound and milked the cord four times towards the neonate counting out loud. The cord was clamped after the fourth milking.

The primary endpoint with respect to the risk of hyperbilirubinemia, was the number of neonates requiring phototherapy or exchange transfusion as defined by the American Academy of Paediatrics (AAP) guidelines [13]. Infants were assessed for the risk of developing hyperbilirubinemia or the need for exchange transfusion based on gestational age and risk factors as defined by Bhutani et al. [13]. If levels exceeded predefined thresholds, phototherapy was applied. In infants receiving treatment, bilirubin levels were reordered every 48 hours as per unit protocol.

The secondary objectives were to determine if DCC or CM compared to ECC, influenced the risk for polycythaemia during the first week of life, congenital anaemia, and readmission for hyperbilirubinemia during the first two weeks of life. Polycythaemia was defined as venous haematocrit of more than 65% or venous haemoglobin above 22 g/dL. Congenital anaemia was diagnosed in babies with cord haemoglobin < 12.5 g/dL [14]. The decision for readmission for hyperbilirubinemia was based on the AAP guidelines for initiating phototherapy [15].

Sample sizes were estimated based on proportions of neonates in need of phototherapy between groups reported by McDonald (8.8% and 4.1% of neonates with jaundice in the DCC and ECC group respectively) [16]. Initially we calculated that, to detect a higher prevalence of neonates requiring phototherapy in the DCC group with one-tailed α value of 0.05 and 80% power, 380 children should be enrolled in every group (1140 children in total). Unfortunately, we were only able to secure limited funds to complete the study, which forced us to significantly decrease the number of participants.

The patient's MRN was registered by one of the recruiters on a secure web-based platform, initial demographic data was recorded, and a random computer-generated treatment was allocated. Randomization was created by Blockrand

software (R Foundation for Statistical Computing, Vienna, Austria). Block randomization by delivery mode was applied. Patients were randomly assigned to ECC, DCC or CM in a 1:1:1 ratio. The block size was variable and concealed until primary endpoint analyses.

Due to the nature of the intervention, we could not take any measures to blind the intervention, however caregivers deciding on the initiation of phototherapy were blinded to intervention allocation. To prevent bias, members of the recruitment team did not participate in the further care of neonates on postnatal wards.

Venous cord blood samples were collected for each maternal-neonate dyad. Non-invasive transcutaneous bilirubin levels (TcB) were evaluated using a bilirubinometer (Bilicheck, Philips, Andover, MA, USA) every 24 hours during evening nursing rounds until discharge. The bilirubinometer was calibrated prior to every measurement, as per manufacture's recommendation. Venous samples for total serum bilirubin (TsB) were ordered on the discretion of the attending physician or if TcB extended recommended levels [17]. Olympus AU 480 (Beckman Coulter, Fullerton, CA, USA) was used to measure TsB. The analyser's calibration was checked with appropriate controls as per product guidelines.

Statistical comparison of baseline demographics between groups was performed using chi-squared test for frequency data. For continuous variables t-test was used when Shapiro-Wilk test did not rejected assumption of normality, otherwise Wilcoxon rank sum test was used. For the assessment of primary and secondary endpoints, 95% CI and p values for frequency data were calculated assuming normal approximation of a binomial distribution. To assess phototherapy duration and hospitalization duration, a comparison Wilcoxon rank sum test was used.

The local Bioethics Committee approved the study. Our study is registered with ClinicalTrials.gov.

RESULTS

Recruitment was conducted from January 2014 to June 2016. We approached 467 eligible women in labour and invited them to take part in the trial. Seventy-eight women either declined participation or were not enrolled for operative reasons. The remaining 389 maternal-foetal dyads were randomly assigned to 3 interventions (Fig. 1).

Compliance with allocated treatment was 96.9%, 91.5% and 90.1% in the ECC, CM and DCC groups respectively. Reasons for allocation deviation are presented in Fig1. Study groups were similar with respect to demographic and clinical variables (Tab. 1).

Primary outcomes

The primary analysis was planned as modified intention-to-treat (mITT) and included all patients, who were randomly assigned to procedures and passed inclusion and exclusion criteria. The initially planned number of patients was not achieved due to funding limitations. Forty-one infants were excluded from the analysis, including 26 neonates lost for follow-up or with incomplete data before assessment of eligibility criteria or reaching the primary endpoint (Fig. 1). In these cases, the reason for attrition was not known, which can lead to the bias.

The number of children who were randomized and passed inclusion/exclusion criteria was 109, 99 and 109 in ECC, CM and DCC group, respectively (Fig. 1).

To perform mITT analysis of the primary outcome, a single imputation method was planned to substitute missing data. Given the size of groups, the imputation could have substantial impact on the proportion of phototherapy which can lead to bias on estimated parameters but has little effect on the low power of the non-inferiority test, therefore per protocol primary outcome analysis was performed.

The percentage of neonates requiring phototherapy did not differ significantly between the ECC, CM and DCC group (23%, 29% and 29%, respectively). CM compared to ECC did not increase the risk of phototherapy, with a mean difference between two treatment arms of 6.2% and RR 1.27 95% CI (0.80; 2.04). Similar results were achieved when comparing DCC and ECC, with a mean difference of 6.6% and RR 1.29 95% CI (0.82; 2.05). This was also true for both methods of placental transfusion (CM vs DCC) RR 0.99 95% CI (0.64; 1.52) (Tab. 2).

For the non-inferiority analysis, the non-inferiority margin was set at 4% as the largest difference being clinically acceptable. We did not find published data regarding neonatal jaundice requiring phototherapy in neonates receiving cord milking, thus we assumed the same non-inferiority margin for all comparisons.

The non-inferiority of both therapies was assessed based on whether the pre-specified treatment effect falls within 95% one-tailed interval for the treatment effect, which is the same as the upper limit of a two-tailed 90% CI. The non-inferiority margin was within 90% of the two-tailed CI for the absolute risk difference between CM and ECC (–3.9; 16.3%) and for the absolute risk difference between DCC and ECC (–3.3%; 16.5%). Given that obtaining adequate sample size in our study was infeasible and the small statistical power of non-inferiority test (12% for CM vs ECC, and 13% for DCC vs ECC), a conclusive decision cannot be made about non-inferiority of CM and DCC procedures with respect to ECC.

Secondary outcomes

The prevalence of total serum bilirubin (TSB) at 24––48 hours was in all study groups. The average time (hours) of phototherapy was 58.0 in the ECC group, 49.1 in the CM group and 63.4 in the DCC group (Tab. 2). None of the patients had asymptomatic or symptomatic polycythaemia

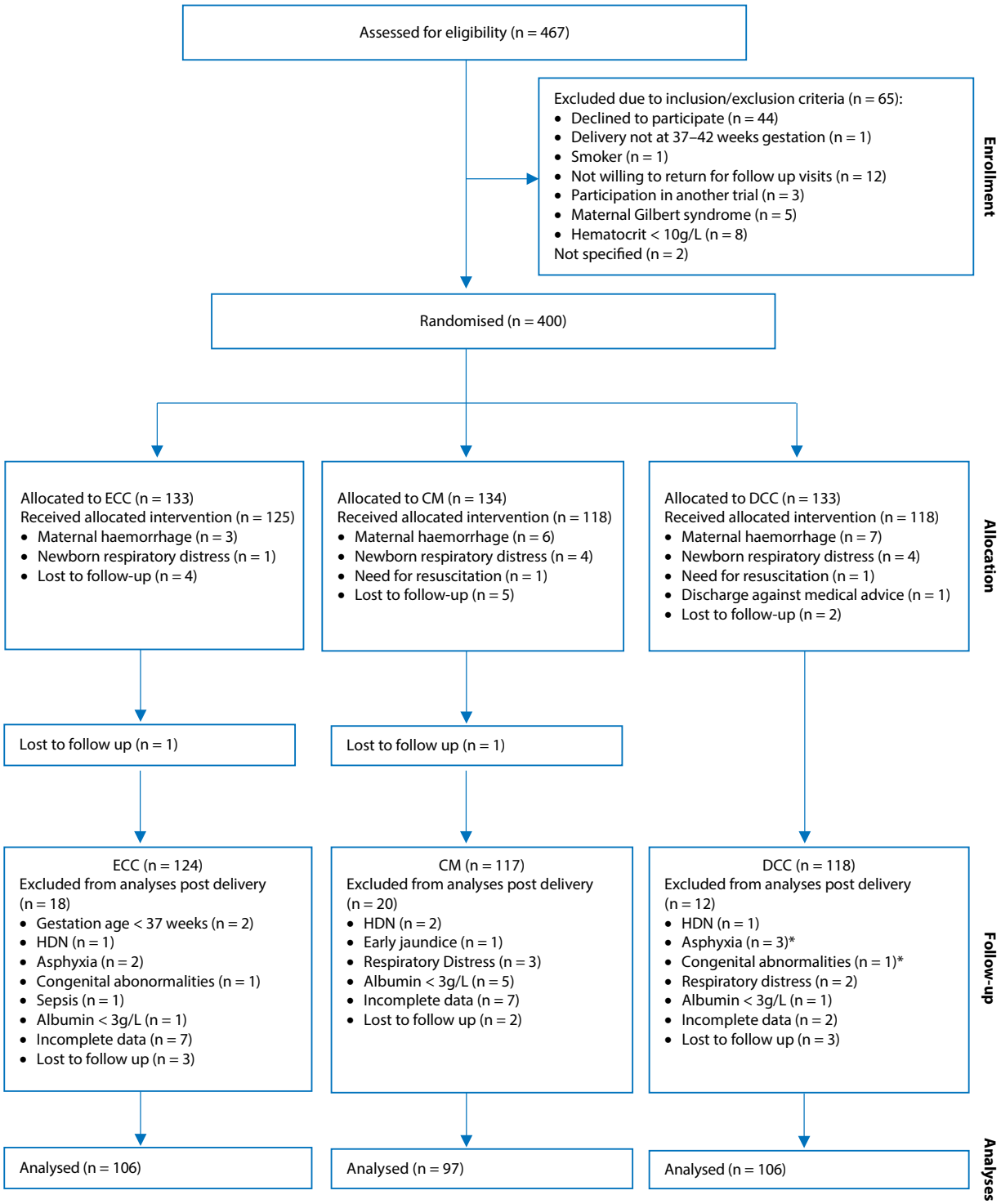

Figure 1. Randomization flow chart

(defined as a haematocrit > 65%). One infant in the ECC group (n = 26), none in the CM group (n = 24) and 5 neonates in the DCC group (n = 39) presented with venous haemoglobin above 22 g/dL (Tab. 2). One patient per group (CM and DCC) required a second course of phototherapy prior to discharge. On average, infants from ECC group were discharged home at 4.1 days, while infants from CM and DCC groups were hospitalized for 4.4 and 4.5 days, respectively.

DISCUSSION

A meta-analyses estimated a significant 47% reduction in the risk of anaemia and 33% reduction in the risk of iron

Table 1. Baseline demographics

	ECC (n = 106)	CM (n = 97)	DCC (n = 106)	CM vs ECC p value	DCC vs ECC p value	CM vs DCC p value
Gender, %						
Male	49.1%	43.3%	48.1%	0.411	0.891	0.492
Female	50.9%	56.7%	51.9%			
Mean (SD) birth weight, g	3503 (459)	3485 (399)	3551 (546)	0.767	0.493	0.328
Mean (SD) gestational age, wk	39.11 (0.99)	39.00 (1.01)	39.01 (1.07)	0.538	0.448	0.884
Method of childbirth, %						
Spontaneous vaginal delivery	53.8%	43.3%	48.1%	0.136	0.410	0.492
Caesarean section	46.2%	56.7%	51.9%			
Median APGAR1 (Q1, Q3)	10 (10, 10)	10 (10, 10)	10 (10, 10)			
Proportion APGAR1 < 10%	8.5%	8.2%	5.7%	0.950	0.422	0.468
Median APGAR5 (Q1, Q3)	10 (10, 10)	10 (10, 10)	10 (10, 10)			
Proportion APGAR5 < 10%	6.6%	5.2%	6.6%	0.662	1.000	0.662
Mean (SD) cord blood Hb, g/dL	16.80 (1.93)	16.33 (2.22)	16.62 (2.22)	0.072	0.263	0.406
Mean (SD) cord blood bilirubin, mg/dL	2.07 (0.63)	2.06 (0.55)	1.93 (0.49)	0.809	0.097	0.162
Maximum value	4.4	3.54	3.82			
Mean (SD) transcutaneous bilirubin (first 24 hours), mg/dL	4.20 (2.06)	4.19 (1.71)	3.99 (1.87)	0.995	0.581	0.499
Range (min; max)	[0; 10]	[1.2; 9.1]	[0; 8.7]			
Mean (SD) cord albumin, g/dL	3.50 (0.25)	3.48 (0.24)	3.44 (0.23)	0.644	0.083	0.197

ECC — early cord clamping; CM — cord milking; DCC — delayed cord clamping; IQR — interquadral; SD — standard deviation; Hb — hemoglobin

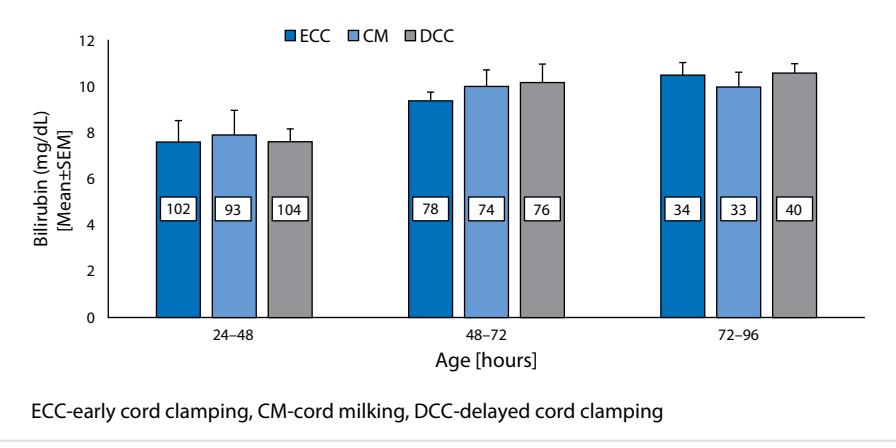

Figure 2. Transcutaneous bilirubin levels during the first 24–96 hours of life

deficiencies at ages 2 to 3 months in the DCC group [18–20]. Nonetheless, it is also important to understand, whether placental transfusion may also contribute for less favourable neonatal outcomes such as hyperbilirubinemia, (requiring phototherapy or exchange transfusion) and polycythaemia.

To our best knowledge, this is the first study, which was designed, to demonstrate that applying DCC or CM to term infants does not increase the risk of hyperbilirubinemia requiring phototherapy or exchange transfusion without harmful effects in comparison to ECC. The frequency of infants requiring phototherapy in CM or DCC groups was higher than in ECC group. However, due to small sample size, the non-inferiority analysis of the primary outcome was inconclusive. Perhaps, early cord clamping at only 30 seconds (similarly to previous authors), would have provided a larger difference in outcome data [21].

Postnatal hyperbilirubinemia is universal and manifests as neonate jaundice in over 60–80% of all neonates [13]. If left untreated, hyperbilirubinemia may progress to excessive levels that may be associated with evident bilirubin

Table 2. Primary and secondary outcomes

	ECC	CM	DCC	CM vs ECC		DCC vs ECC		CM vs DCC	
				RR (95% CI)	P Value	RR (95% CI)	P Value	RR (95% CI)	P Value
Primary analysis (hyperbilirubinaemia requiring phototherapy)									
First week of life (%)	24/106 (22.6)	28/97 (28.9)	31/106 (29.2)	1.27 (0.80; 2.04)	0.311	1.29 (0.82; 2.05)	0.274	0.99 (0.64; 1.52)	0.953
All phototherapies (%)	29/106 (27.4)	30/97 (30.9)	31/106 (29.2)	1.13 (0.74; 1.74)	0.576	1.07 (0.70; 1.64)	0.761	1.06 (0.70; 1.61)	0.794
Polycythaemia (%)	1/26 (3.8)	0/24 (0.0)	5/39 (12.8)	0.36 (0.02; 8.43)	0.509	3.33 (0.41; 26.92)	0.224	0.15 (0.01; 2.52)	0.114
Congenital anaemia (%)	0/104 (0.0)	3/95 (3.2)	2/106 (1.9)	7.66 (0.40; 146.31)	0.109	4.91 (0.24; 100.99)	0. 253	1.67 (0.29; 9.80)	0.564
Mean (SD) phototherapy duration, hours	58.0 (34.7)	49.1 (27.4)	63.4 (45.4)		0.242		0.678		0.152
Mean (SD), N, hospitalization duration, days	4.1 (1.8), 106	4.4 (1.9), 97	4.5 (2.3), 106		0.268		0.261		0.962
Feeding									
Breastfeeding only	53/54 (98.1%)	47/50 (94.0%)	51/55 (92.7%)	0.98 (0.94; 1.02)* 0.98 (0.94; 1.02)**	0.293* 0.299**	0.98 (0.94; 1.02)* 0.98 (0.95; 1.02)**	0.313* 0.322**	1.00 (0.94; 1.06)* 1.00 (0.95; 1.05)**	0.955* 0.946**
Formula feeding	0/54 (0.0%)	1/50 (2.0%)	1/55 (1.8%)						
Mixed	1/54 (1.9%)	2/50 (4.0%)	3/55 (5.5%)						

ECC — early cord clamping; CM — cord milking; DCC — delayed cord clamping; SD — standard deviation; RR — risk ratio; CI — confidence interval; *Breastfeeding only vs formula feeding comparison, **Breastfeeding and Mixed feeding vs formula feeding

neurotoxicity. Available results from other studies regarding "jaundice" and "jaundice needing phototherapy" (associated with DCC) can be misleading. First, no information is offered on how "clinical jaundice" was assessed on examination, and estimation of the degree of hyperbilirubinemia based solely on clinical examination can lead to errors [22–24]. A review on DCC revealed only 4 studies which assessed polycythaemia and hyperbilirubinemia during the first week of life as a second objective [25]. No information was provided on which hour of life the bilirubin levels were measured exactly. In our study, to avoid loss or delay in diagnosis we screened all participants for jaundice using a bilirubinometer. Furthermore, guidelines to treat jaundice have changed over time and none of the studies mentioned what threshold was used for administering phototherapy. No information is given whether staff responsible for phototherapy administration was blinded to the type of cord clamping intervention.

In view of the decrease sample size, our results may underestimate the true prevalence of hyperbilirubinemia requiring phototherapy. Additional subgroup analyses to identify the risk of readmission secondary for jaundice, anaemia and iron storages at 3 months of age will be a subject of a separate publication. Possible confounders such as maternal pre-gestational diabetes, iso-immune haemolytic disease, were not included in the analysis, which may alter the results.

CONCLUSIONS

With early detection of hyperbilirubinemia and prompt initiation of treatment following accepted guidelines, a possible elevated risk of bilirubin encephalopathy can be minimized, while preserving all potential benefits of the placental transfusion in term infants.

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Fetal upper mediastinum — normal and abnormal findings in obstetric ultrasound screening

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ABSTRACT

Fetal cardiac assessment is an integral part of the obstetric ultrasound. The inclusion of the outflow tracts and the three-vessel and tracheal view into the ultrasound screening enhances the detection rate for cardiovascular anomalies. Both, international and Polish guidelines recommend routine evaluation of the upper mediastinum. The aim of the study was to present the principles for assessing the structures of the upper mediastinum in normal conditions and to draw attention to the pathologies which may be visible in this plane.

Key words: upper mediastinum; three-vessel view; three-vessel and tracheal view; heart defects

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INTRODUCTION

Fetal cardiac assessment is an integral part of the obstetric ultrasound. In the early 1980s, the four-chamber view for congenital heart defects (CHD) screening was introduced [1, 2]. The early studies indicated an 80–87% sensitivity of this view for the detection of fetal heart defects [2, 3]. However, in the subsequent years, it turned out that single ventricle heart defects can be detected in the four-chamber view, but anomalies involving the outflow tracts and the great vessels may remain undetected [4, 5], and the sensitivity of the four-chamber view was re-estimated to be 30–60% [3–7]. In almost 70% of cases of the conotruncal anomalies, the four-chamber view is normal or almost normal [4, 9, 10]. The defects like tetralogy of Fallot (ToF), double outlet right ventricle (DORV), anomalies of the aortic arch, stenosis of the semilunar valves, common arterial trunk (CAT), and transposition of the great arteries (TGA) may have a normal four-chamber view but not the upper mediastinum view. Yoo et al. [10], proposed a three-vessel view (3VV) in the transverse plane of the fetal upper mediastinum as a simple way to detect anomalies of the ventricular outflow tracts and the great vessels. However, in this section the aortic arch cannot be assessed, which is also challenging in the classic long-axis view. In 1992, Achiron et al. [11], proposed a concept of the extended fetal echocardiogram, and recommended to incorporate the outflow tracts and the three-vessel and tracheal view (3VT) into screening for fetal cardiac defects [12]. A 3VT view enables to assess the anatomy of the great vessels in the mediastinum and, which is especially noteworthy, provides information about the aortic arch, its width, and its location in relation to the trachea. The inclusion of the 3VV and the 3VT view into the screening has led to increased sensitivity in detecting several congenital heart defects [10, 13–15]. In one prospective study, 70.8% of CHD cases presented at least one abnormality in 3VV and 3VT [15].

International ultrasound organizations such as the International Society of Ultrasound in Obstetrics and Gynecology (ISUOG) [16], and the American Heart Association [17], recommended to incorporate the upper mediastinum assessment in cardiac screening in order to detect anomalies of the outflow tracts and the great vessels. In Poland, the 2009 recommendations [18] as well as the 2012 and the 2015 guidelines of the Polish Society of Gynecologists and Obstetricians [10, 20], also include routine assessment of the vessels in the upper mediastinum during ultrasound examination. Hence, the aim of this study was to present the principles for assessing the structures of the upper mediastinum in normal conditions and to draw attention to the pathologies which may be visible in this section.

ANATOMY OF THE UPPER MEDIASTINUM

Starting from the four-chamber view and moving slightly cephalad, the outflow tracts are visible, followed by the structures of the upper mediastinum, with the image of the three vessels (three-vessel view, 3VV) (Fig. 1). In this section,

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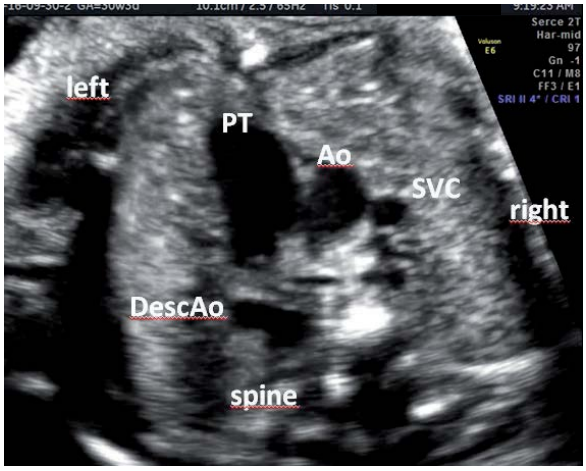


Figure 1. Three-vessel view: going from the anterior and left to the right and posterior side, the oblique cross-section of the pulmonary trunk, the transverse section of the ascending aorta and the superior vena cava can be seen; Ao — aorta; DescAo — descending aorta; PT —pulmonary trunk; SVC — superior vena cava

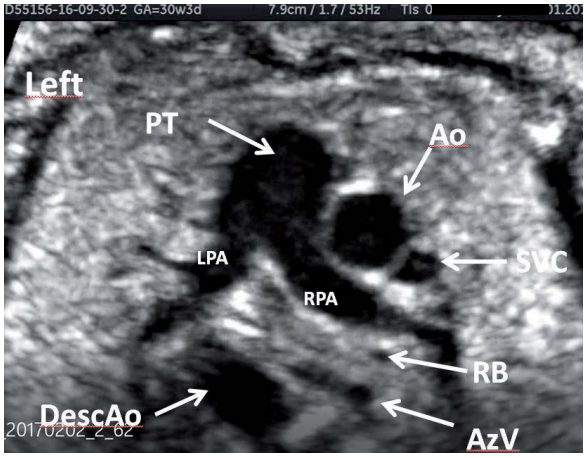


Figure 2. Branching of the pulmonary trunk to the left and right pulmonary arteries; Ao — aorta; AzV — azygos vein; DescAo — descending aorta; LPA — left pulmonary artery; PT — pulmonary trunk; RB — right bronchi; RPA — right pulmonary artery; SVC — superior vena cava

going from the anterior and left to the right and posterior side, the oblique cross-section of the pulmonary trunk, the transverse section of the ascending aorta and the right superior vena cava (SVC) can be seen. Under normal conditions, the pulmonary trunk is slightly wider than the aorta, while the aorta is wider than the superior vena cava. The 3VV also contains the cross-section of the descending aorta, which lies anterior and to the left of the spine. By gentle movement of the probe, it is possible to visualize the connection of the pulmonary trunk through the ductus arteriosus (DA) with the descending aorta as well as the branching of the pulmonary trunk to the left and right pulmonary arteries (Fig. 2). The right pulmonary artery goes straight to the

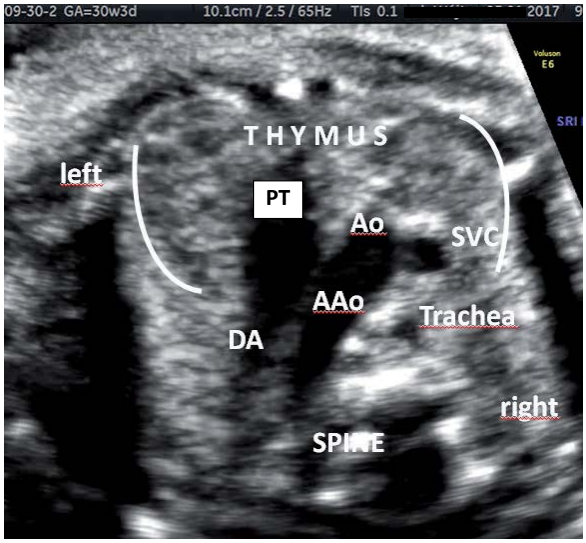


Figure 3. Three-vessel and tracheal view. The aortic arch and ductus arteriosus are running to the left of the trachea; left aortic arch; Ao — aorta; AAo — aortic arch; DA — ductus arteriosus; PT — pulmonary trunk; SVC — superior vena cava

right behind the descending aorta and the superior vena cava, while the left pulmonary artery runs to the left of and posterior to the aorta. At this level, the aortic and the ductal arches cannot be assessed. Only a small cephalad movement allows to visualize the aortic and the ductal arches as well as the localization of these vessels in relation to the trachea (Fig. 3). This plane is called the three-vessel and tracheal view (3VT). Normally, the large vessels in the upper mediastinum are arranged in a V shape directed to the left of the trachea and anterior to the spine. The left arm is formed by the pulmonary trunk that passes into DA and the right arm by the transverse part of the aortic arch, with the isthmus located to the left of the trachea [21]. To the right and more backward in relation to these vessels, a cross section of the superior vena cava, to which the azygous vein drains (often referred to as the 'azygous vein arch'), are seen (Fig. 4). The main advantage of this cross-section is the fact that the aortic and the ductal arches are visible together in any axial plane of the upper mediastinum, whereas the longitudinal demonstration of these arches is often limited and difficult to obtain.

In addition, the great vessels, *i.e.* the pulmonary trunk and the aorta, should not adhere to the anterior wall of the chest. Under normal conditions, going from the front of the chest to the back, the tissue which differs slightly from the lung tissue and which corresponds to the thymus, should be seen (Fig. 3, 4). Usually, the thymus has the same or less echogenicity as the lungs and contains hyperechogenic foci. However, thymus assessment can be problematic. Although various methods of assessing the presence and the measurements of the thymus have been proposed,

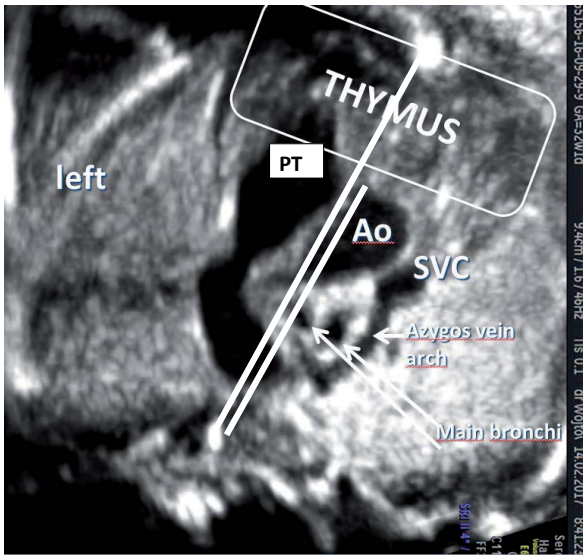


Figure 4. Three-vessel view with the azygous vein draining to the superior vena cava: azygos vein arch; Ao — aorta; AAo — aortic arch; DA — ductus arteriosus; PT — pulmonary trunk; SVC — superior vena cava

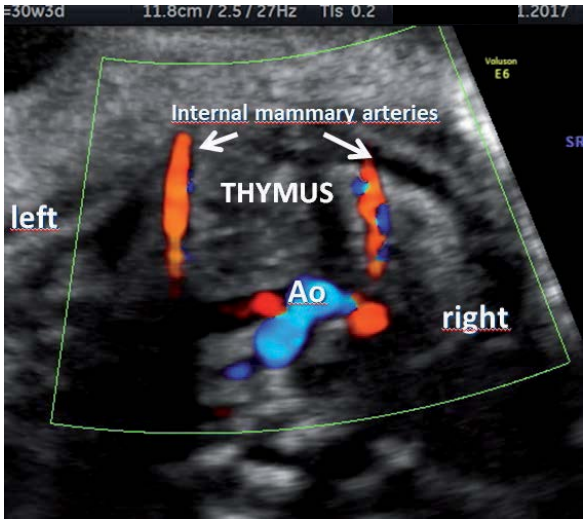


Figure 5. „Thy-box": thymus visible between internal mammary arteries on both sides; Ao — aorta

none could be described as the gold standard. The use of the internal mammary arteries, which are visible while using color Doppler ultrasonography with a low pulse repetition frequency on both sides of the thymus, has been proposed. These vessels, together with the ductal and the aortic arch on the posterior side and the sternum on the ventral side, form the so-called 'thy-box' [22] (Fig. 5). The 'thy-box' can be displayed in the fetus from the first to the third trimester of pregnancy. In turn, the size of the thymus can be assessed by measuring the transverse diameter, which increases with the advancement of the pregnancy, from an average of 12 mm at 19 weeks to 40 mm at 38 weeks of gestation [23]. The thymus diameter shows accelerated growth during pregnancy, with the diameter in millimeters being smaller than the gestational week in second and early third trimester, equal to the gestational age in weeks at 33 weeks, and larger later in pregnancy. During the second trimester, the thymus diameter in millimeters is equal to the abdomen circumference in centimeters. Another method of assessing the presence of the thymus and its size is calculation of the so called fetal thymic-thoracic ratio (TT-ratio), *i.e.* the ratio of the anteroposterior thymus diameter to the intrathoracic mediastinal diameter measured in the 3VT view (Fig. 4) [24]. In a study by Chaoui et al. [24], the TT-ratio did not show any statistically significant change during gestation, with a mean value of 0.44. It was observed that in more than 90% of fetuses with the 22q11 deletion the TT-ratio was < 0.3 [24].

More cephalad in the neighborhood with the posterior wall of the thymus and the anterior border of the aortic arch, the innominate or left brachiocephalic vein (LBCV) is seen. LBCV is formed by the confluence of the left jugular and left subclavian veins, and drains into the right superior vena cava [25]. A dilatation of LBCV was noticed in the supracardiac type of total anomalous pulmonary venous confluence and in the vein of Galen aneurysm [25]. Moreover, the absence of LBCV was observed in cases with a persistent left superior vena cava (LSVC) with a right superior vena cava (RSVC) [25].

Color Doppler assessment is a valuable supplement to the 2-dimensional ultrasound. Under normal conditions, the use of the color Doppler option allows the pulmonary trunk and the aorta to fill in one color, which means the flow is from the heart, giving the image of a 'blue V-sign' (Fig. 6A) or a 'red V-sign' (Fig. 6B), depending on the color marking the setting. This flow is laminar and additionally shows the shape of the vessels. Thus, the use of color Doppler improves the visualization of the vessels. In some conditions, blood flow in the vessels is more visible than the vessels themselves in 2D imaging, as is the case in women with obesity or in cases of unfavorable fetal position. The use of color Doppler confirms the presence of the pulmonary trunk and the aorta allowing to assess their shape, width, and direction of the blood flow, which is particularly valuable in detecting ductus arteriosus depending flow (retrograde flow). Color Doppler modality in a more cranial plane to the 3VT plane allows to visualize the aortic arch branches with the right subclavian artery course [26]. The right subclavian artery extends from the brachiocephalic trunk and is visible with color Doppler modality as a vessel running to the front and right to the trachea (Fig. 7).

Due to the high resolution of the probes, apart from the vascular structures in the upper mediastinum, it is also possible to visualize the esophagus behind the trachea and the trachea can be seen to its bifurcation (Fig. 4).

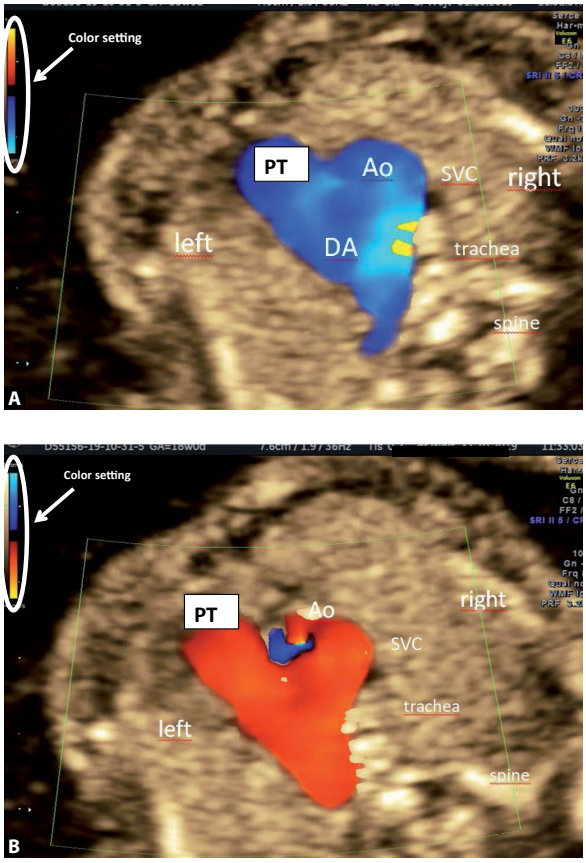


Figure 6. Color Doppler of the three-vessel and tracheal view depending on the setting; **A.** "blue V-sign" — color Doppler showed blood flow from the probe in blue; **B.** "red V-sign" — color Doppler showed blood flow from the probe in red; Ao — aorta; DA — ductus arteriosus; PT — pulmonary trunk; SVC — superior vena cava

Abnormalities Detected In The Upper Mediastinum

When assessing the upper mediastinum, the number of visible vessels, their size, shape, arrangement and alignment should always be determined [10]. In addition, attention should be paid to the possibility of pathological connections between the vessels, to the position of the transverse part of the aortic arch in relation to the trachea, and to the nature of the blood flow in the great vessels using color Doppler. It is also possible to assess pulmonary branching, ductus arteriosus width and the presence/absence of the thymus.

Abnormal number of vessels

An abnormal number of vessels may affect the arterial or the venous vessels, for example the presence of four instead of three vessels, as in the case of LSVC, which is located to the left of the pulmonary trunk (Fig. 8A). LSVC usually drains to the coronary sinus, which is dilated and visible in the left atrium at the four-chamber view. LSVC may be isolated or may be associated with hypoplasia of the left-sided structures, such as coarctation of the aorta

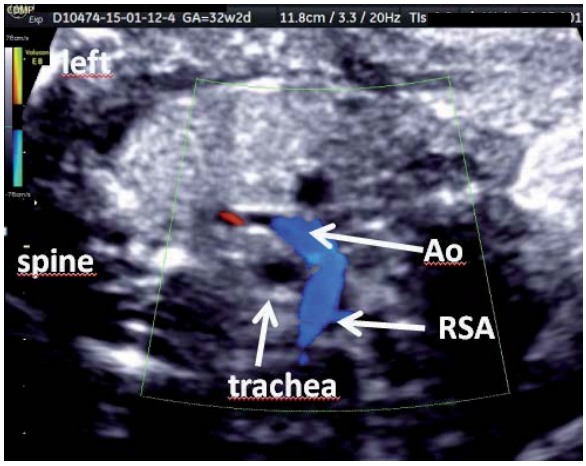


Figure 7. Right subclavian artery running to the front and right to the trachea; Ao — aorta; RSA — right subclavian artery

(Fig. 8A). In cases where LSVC and right SVC are persistent, the left brachiocephalic vein cannot usually be seen [25]. The diagnosis of persistent LSVC with the absent right SVC is a rarer and challenging condition. In such cases, three vessels, but going from the left to the right LSVC, the pulmonary artery and the aorta can be seen (Fig. 8B).

An abnormal number of vessels in the upper mediastinum, usually one large arterial vessel and the superior vena cava, is often found in complex heart defects, e.g. in case of TGA, DORV or ToF. In these cases, the two great vessels come out of the heart, but due to an abnormal arrangement or alignment of the outflow tracts, only one arterial and one venous vessel are observed in the upper mediastinum. Typically, the large arterial vessel in question is the aorta (Fig. 9), or the pulmonary artery with continuation in the ductal arch, while the aorta is hypoplastic and only visible when imaging with color Doppler, as in the case of hypoplastic left heart syndrome. A real anomaly in vessel numbers occurs in cases with a single arterial vessel coming out of the heart such as the CAT, or ToF with pulmonary atresia and an absent duct.

Abnormal vessel size

One of the vessels may be hypoplastic or dilated. Dilatation of one artery may be found in cases of stenosis of the semilunar valve as a post-stenotic dilatation of the artery. Dilatation of the aorta is seen in fetuses with Marfan syndrome and aneurysm of the ascending aorta [27] (Fig. 10A, 10B). In cases with ToF with absent pulmonary valve, a huge dilatation of the pulmonary trunk and pulmonary arteries with absent ductus arteriosus are observed. Also, the right SVC may be dilated due to increased blood flow from the azygos vein, which is visible in the rupture of the inferior vena cava with vena cava azygos continuation in cases of left isomerism or in supracardiac total anomalous pulmonary venous return or in the cases of vein of Galen aneurysm [14].

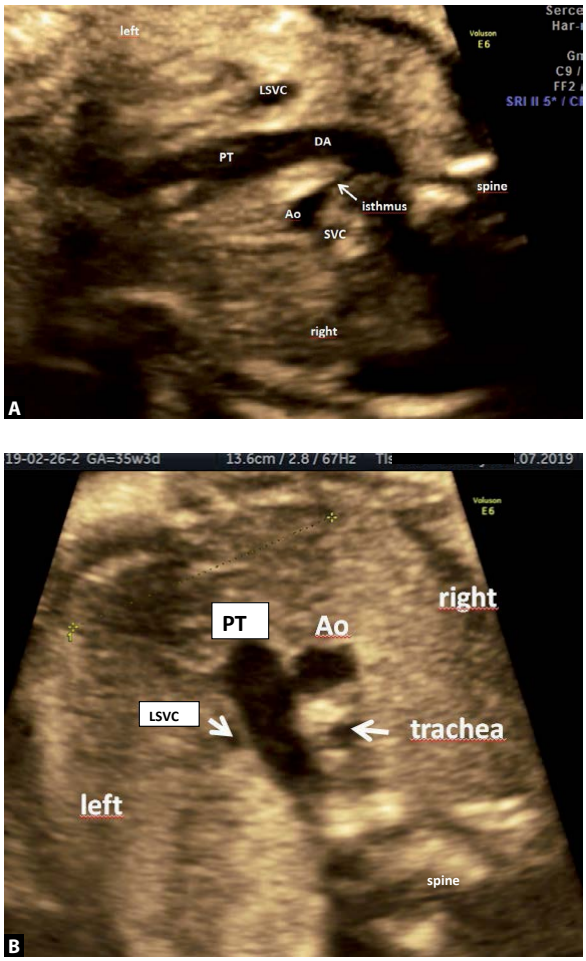


Figure 8. Persistent left superior vena cava (LSVC); **A.** LSVC located to the left of the pulmonary trunk with right superior vena cava located to the right of the aorta in a case of coarctation of the aorta; **B.** LSVC located to the left of the pulmonary trunk with absent right superior vena cava; Ao — aorta; LSVC — left superior vena cava; PT — pulmonary trunk; SVC — superior vena cava

Hypoplasia of the aorta with antegrade flow indicates aortic coarctation. A retrograde flow through a hypoplastic aortic arch is found in the hypoplastic left heart syndrome (Fig. 11A, 11B). The assessment of the aortic arch in the upper mediastinum is particularly valuable in suspected aortic coarctation. Aortic coarctation may be suspected if the dominance of the right ventricle in the four-chamber view and narrowing of the aortic arch and isthmus in the upper mediastinum with antegrade flow are observed [28]. Stenosis may also affect the pulmonary artery, as is the case in ToF, Ebstein anomaly or DORV.

Abnormal vessel alignment

Abnormal vessel alignment means that the three vessels are not positioned in a straight line, but the left-to-right order is preserved, most often due to the shifting of the ascending aorta forward, with or without the pulmonary

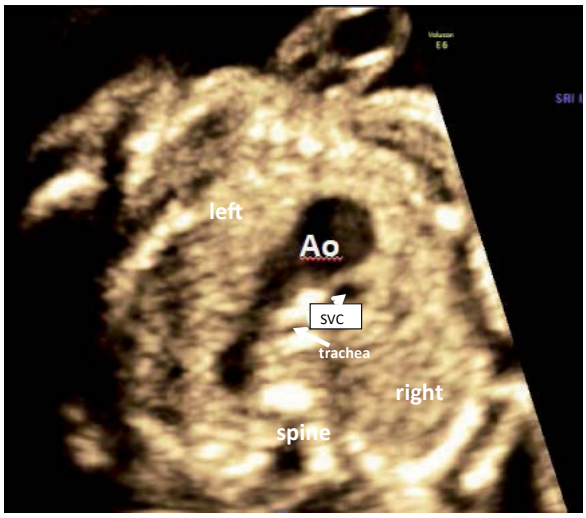


Figure 9. Upper mediastinum in tetralogy of Fallot with two vessels visible: ascending aorta (Ao) and superior vena cava (SVC). In aCGH confirmation of 22q11.2 deletion. Absent thymus

trunk shifting backwards. It could be seen in cases of perimembranous ventriculoseptal defect with malalignment of the aorta, as is the case in ToF [14]. Abnormal alignment can be observed in DORV (Fig. 12), where the great vessels can be seen side-by side and, less frequently, in transposition. In hypoplastic left heart syndrome and interruption of the aortic arch, the aorta can be shifted backwards. Importantly, abnormal vessel alignment is easier to detect in the three-vessel view than in the 3VT view.

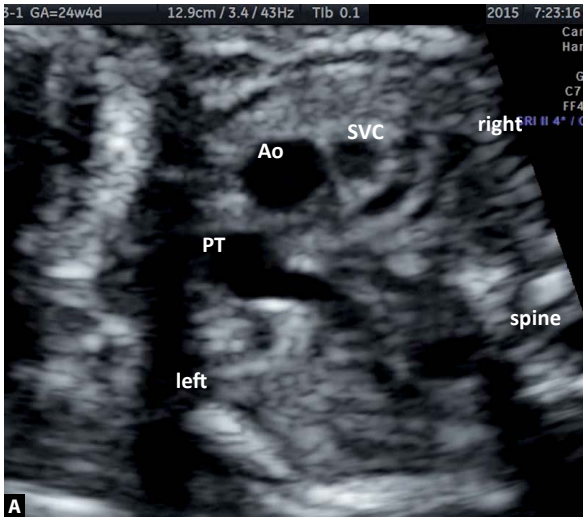
Abnormal vessel arrangement

Abnormal vessel arrangement, *i.e.* a complete distortion of the left–right order of the vessels, can be seen in the case of transposition of the great arteries (Fig. 13) as well as in DORV. In those disorders, the vessels are usually arranged in a triangle shape.

Abnormal vessel communications, branching and course

The upper mediastinum plane allows for the assessment of the aortic and ductal arches and the detection of pathological communications between these vessels, as is the case in the aortopulmonary window (Fig. 14). The communication may extend to the proximal or the distal part or may cover the entire length of the vessels. This defect is often associated with the interruption of the aortic arch.

Moreover, the relation to the trachea of the aortic and ductal arches can be assessed and cases of a right or a double aortic arch can be detected. Initially, during the early stage of embryonic development, a double aortic arch (DAA) is seen [29]. Normally, there is a regression between the rising of the right subclavian artery and the descending aorta



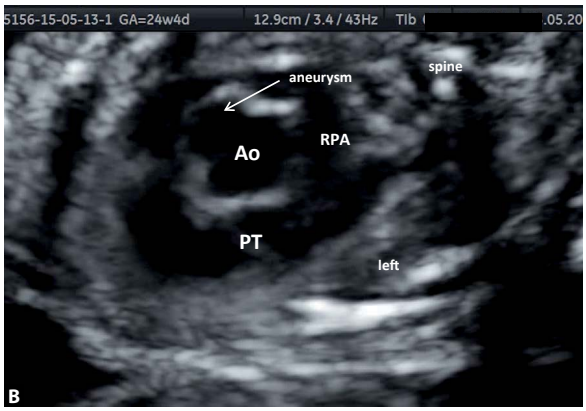
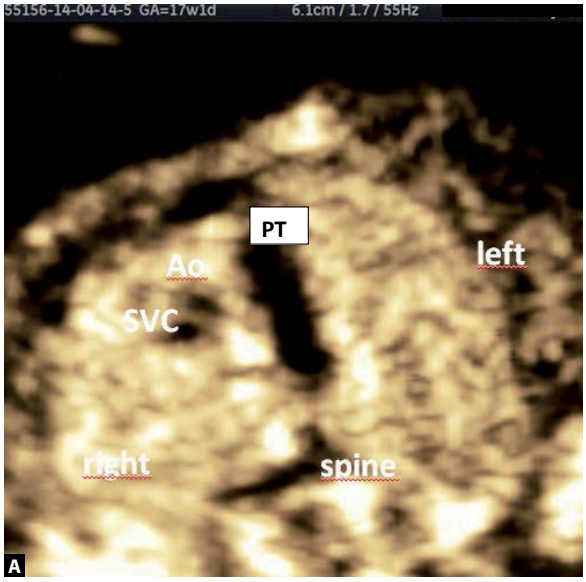


Figure 10. Upper mediastinum with an aneurysm of the ascending aorta in fetus with Marfan syndrome; **A.** Three-vessel view with dilatation of the aorta; **B.** Aneurysm of the ascending aorta; Ao — aorta; PT — pulmonary trunk; RPA — right pulmonary artery; SVC — superior vena cava

in the right-sided arch which also involves the right duct. As a result of this process, the left-sided aortic arch is formed [29]. If no regression occurs and both arches persist, DAA remains (Fig. 15).

From the anatomical point of view, the right aortic arch (RAA) is an anomaly in which the arch passes over the right instead of the left bronchus. *In utero* the visualization of the bronchus is difficult. The diagnosis of RAA is made on the basis of the course of the transverse aortic arch to the right of the trachea, which can be assessed in the upper mediastinum. Depending on the course of the DA in relation to the trachea we can distinguish two variants of the RAA. If the DA extends to the left and the aorta to the right of the trachea, then the vessels form a U shape (U sign) (Fig. 16). This variant is associated with aberrant left subclavian artery (ALSA), which forms a vascular ring. It could be isolated lesion, but cardiac anomalies have been reported in 10% to 50% of the cases [29, 30].



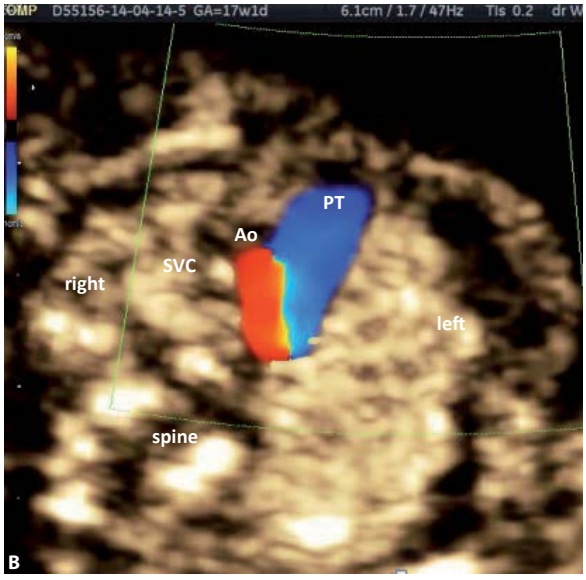


Figure 11. Upper mediastinum in hypoplastic left heart syndrome; **A.** Hypoplastic ascending aorta in 2D; **B.** A retrograde flow through a hypoplastic aortic arch; Ao — aorta; PT — pulmonary trunk; SVC — superior vena cava

The aorta and DA may lie to the right of the trachea, and then form a V shape (V sign) (Fig. 17). In such cases they do not form a vascular ring. In this variant usually a mirror image of the branching vessel is observed, with the brachiocephalic trunk being the first vessel to depart, followed by the right common carotid artery and the right subclavian artery [30].

Another pathology detected in the upper mediastinum is the absence or hypoplasia of the pulmonary arteries or abnormal branching from the aorta. Pulmonary arteries can be dilated in cases of ductus arteriosus constriction and aneurysmal dilatation of the pulmonary arteries is found

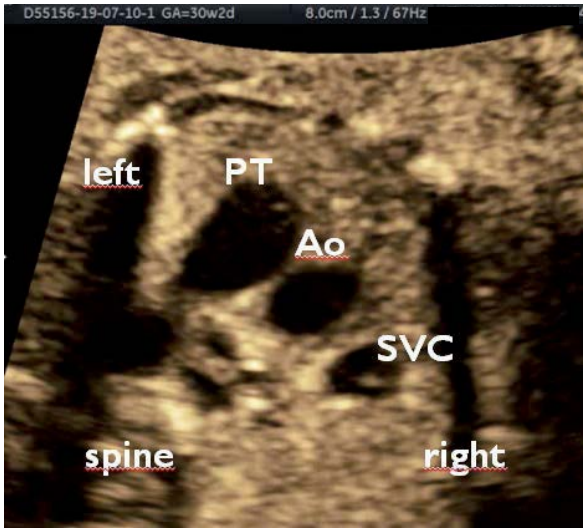


Figure 12. Abnormal vessel alignment in double outlet right ventricle. The left-to-right order is preserved, but the ascending aorta is shifted forward; Ao — aorta; PT — pulmonary trunk; SVC — superior vena cava

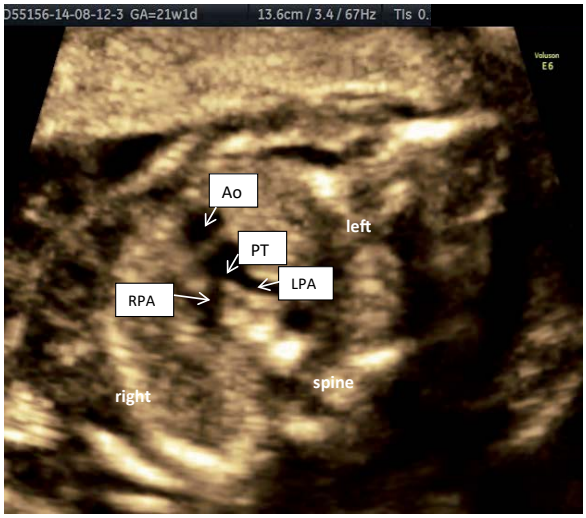


Figure 13. Abnormal vessel arrangement in transposition of the great arteries; vessels are arranged in a triangle shape; Ao — aorta; LPA — left pulmonary artery; PT — pulmonary trunk; RPA — right pulmonary artery

in tetralogy of Fallot, with absent pulmonary valve and ductus arteriosus. Variants of the standard view may be kinked, or the s-shaped ductal arch may become visible in late gestation.

Abnormalities detected in color Doppler modality

Cardiovascular defects detection rates can be increased by using the color Doppler modality. Color Doppler allows to detect stenosis, and absent or abnormal blood flow from the ductus arteriosus. The reversed flow in one of the arterial

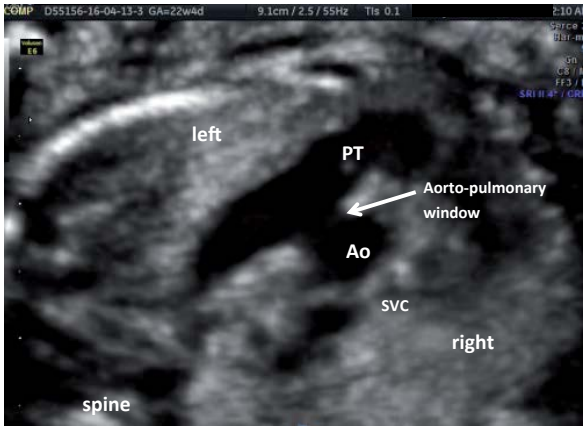


Figure 14. Upper mediastinum in a case of aorto-pulmonary window with interruption of the aortic arch: connection between aortic arch and pulmonary artery is visible. Absent thymus; in aCGH 22q11 deletion confirmation; Ao — aorta; PT — pulmonary trunk; SVC — superior vena cava

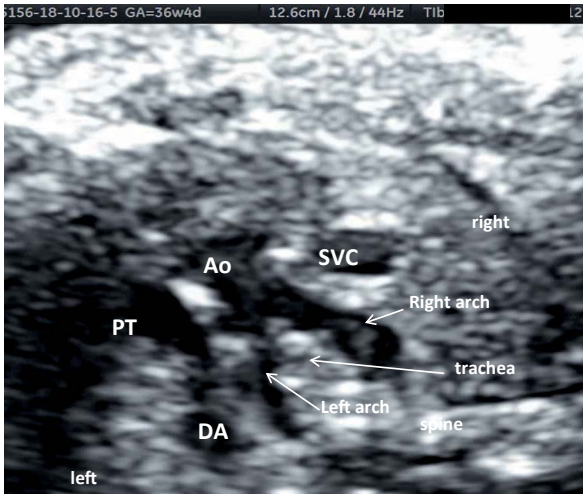


Figure 15. Double aortic arch; Ao — aorta; PT — pulmonary trunk; SVC — superior vena cava

vessels is a marker of ductal dependent heart defects and may be indicative of aortic atresia (Fig.11B), severe coarctation or interruption of the aortic arch or pulmonary atresia (Fig. 18). In turn, turbulent flow can be observed in 3VT view in cases of aortic stenosis and in fetuses with pulmonary stenosis. It is a result of increased velocity of the blood flow through a valve.

Color Doppler allows to detect an aberrant right subclavian artery (ARSA). ARSA, which presents as the last vessel extending from the aortic arch before the isthmus and running to the right, forward from the spine and behind the trachea and esophagus to the right arm, is present in nearly 1.5% of the population (Fig. 19) [26]. ARSA was found in over 20% of the fetuses with trisomy 21 and other chromosomal aberrations [31]. Therefore, it was treated as a marker of aneuploidy,

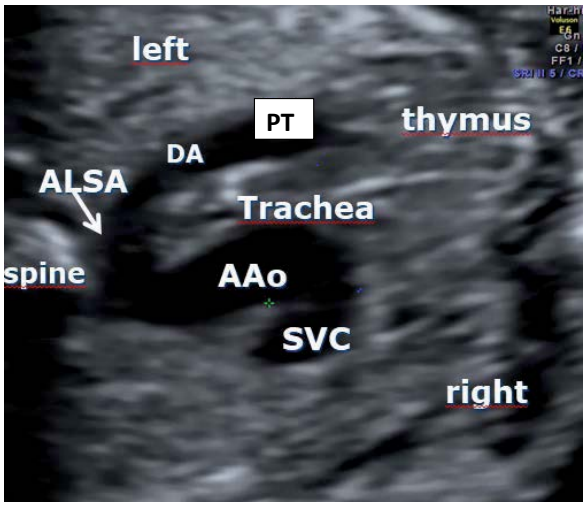


Figure 16. Three-vessel and tracheal view of the right aortic arch with aberrant left subclavian artery and left ductus arteriosus (the aortic arch forming U-shaped confluence with the ductus arteriosus); AAo — aortic arch; ALSA — aberrant left subclavian artery; DA — ductus arteriosus; PT — pulmonary trunk; SVC — superior vena cava

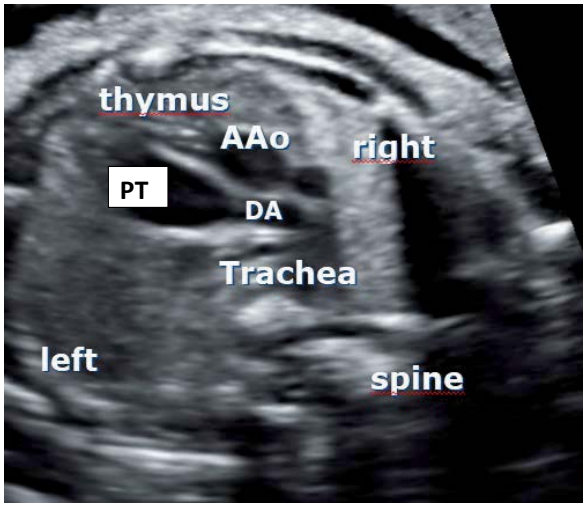


Figure 17. Three-vessel and tracheal view; right aortic arch with right ductus arteriosus (V-sign); AAo — aortic arch; DA — ductus arteriosus; PT — pulmonary trunk

increasing the risk by 10-fold [32]. However, the last study [33] showed that Down syndrome was present only in 0.4% of cases of isolated ARSA and authors concluded that isolated ARSA should be treated as a soft marker for Down syndrome.

Thymus hypoplasia

The thymus is the next organ which can be assessed in the upper mediastinum. The assessment of the thymus is important because thymic hypoplasia or agenesis (Fig. 9) is associated with the 22q11 deletion and with conotruncal anomalies and anomalies of the aortic arch [24]. Thymic hypoplasia is also a common finding in cases of pre-term pre-labor

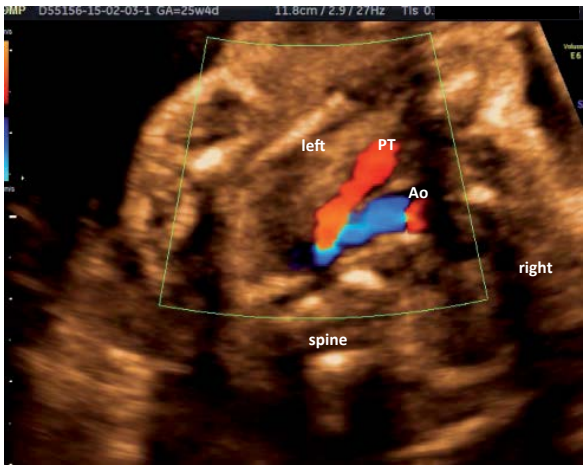


Figure 18. Reversed flow in pulmonary artery in case of pulmonary artery atresia; Ao — aorta; PT — pulmonary trunk

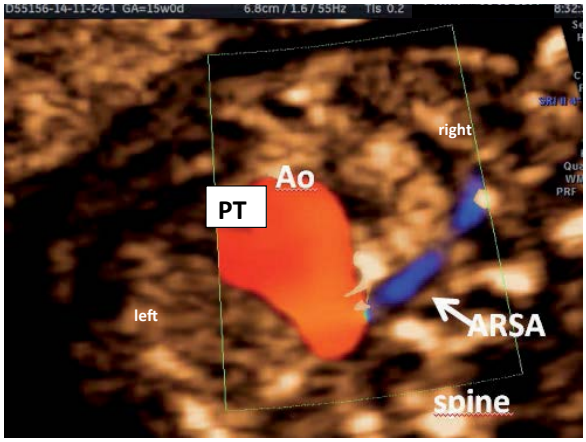


Figure 19. Three-vessel and tracheal view with aberrant right subclavian artery; Ao — aorta; ARSA — aberrant right subclavian artery; PT — pulmonary trunk

rupture of membranes, intrauterine growth restriction, maternal preeclampsia, and fetuses with Down syndrome and other aneuploidies. Thymic hypoplasia in those cases may be explained by the immune function impairment [34–36].

CONCLUSION

In summary, it should be emphasized that the abnormalities in the upper mediastinum may indicate the group of pathologies, but they do not allow to clearly determine the diagnosis. Only a comprehensive evaluation of the other planes as well as color and pulsed Doppler technique allow for a definite diagnosis. Nevertheless, the assessment of the 3VV and 3VT views increases the detection rate of fetal heart defects, especially in case of conotruncal and aortic arch anomalies. In addition, vascular and thymic abnormalities found in those planes signify the need to include genetic testing into the diagnostic process.

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Influenza vaccination in pregnancy — current data on safety and effectiveness

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ABSTRACT

Pregnant women are at risk of severe and complicated influenza, and so are children aged 2-5 years. Despite numerous recommendations, influenza vaccination coverage in pregnant women is still low. The trigger for this article was the development of new quadrivalent influenza vaccines along with the publication of new studies on the safety and effectiveness of inactivated influenza vaccines in pregnant women, administered also in the first trimester of pregnancy. The inactivated quadrivalent influenza vaccine is a safe and effective measure for preventing influenza in both mother and child. Live attenuated influenza vaccines are contraindicated in pregnant women, whereas inactivated influenza vaccines should be recommended to all pregnant women, either healthy or with comorbidities. Influenza vaccines can be administered during any pregnancy trimester, at least two weeks before delivery. The time of vaccination depends on vaccine availability; however, it should not be postponed unless there are significant medical contraindications.

Key words: effectiveness; influenza; pregnancy; safety; vaccine

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INTRODUCTION

According to the World Health Organization (WHO), 5–10% of the adult population and 10–20% of the children population become ill with influenza seasonally, and as many as 600,000 patients die of influenza or its complications globally [1]. Groups exposed to severe and complicated influenza involve children aged 2–5 years, senior citizens aged > 65, patients with chronic diseases (*e.g.* respiratory, circulatory, nervous and metabolic diseases) and pregnant women [1]. Observations made during the 20th century influenza pandemics show that pregnant women experience more severe influenza than the general population, and they are at a higher risk of complications, hospitalization (including intensive care treatment) and death [2]. During the Spanish flu pandemic, mortality in pregnant women was estimated at 27–45%, whereas the number of deaths during the influenza pandemic in 1957 and 1968 reached 70,000 and 30,000, respectively, whereby nearly half of the deaths were reported in pregnant women [2]. During the last influenza pandemic of 2009, the risk of influenza hospitalization in pregnant women with comorbidities was 7–8 times higher compared to the general population; the risk of complications was higher in the second and third trimester and the postpartum period (up to two weeks after the delivery), and as many as 5% of all deaths related to the influenza pandemic in the USA were reported in pregnant women [3–6].

A systematic review of 100 studies showed that the percentage of pregnant women hospitalized for influenza ranged from 5% to 87%, 0–22% of whom required intensive care treatment [4].

Recommendations for influenza vaccination during pregnancy were first published by the American Advisory Committee on Immunization Practices (ACIP) in 1997, and then extended in 2004 with a recommendation for influenza vaccinations in the first trimester [7]. Since 2005, the World Health Organization has been recommending vaccination for all pregnant women in a given influenza season [1]. Influenza vaccination during pregnancy is also recommended by the American College of Obstetricians and Gynecologists (ACOG) [8]. The Polish Immunization Schedule includes recommendations for influenza vaccinations in pregnant women and those planning pregnancy [9]. However, despite numerous recommendations, influenza vaccination coverage in pregnant women is still low in many low and middle income countries as well as many developed countries,

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which can be related to vaccine safety concerns of patients and medical workers, neglect of the disease severity and underestimation of the benefits of vaccination [7, 8].

The trigger for this publication was the development of new quadrivalent influenza vaccines along with new study results that have confirmed the effectiveness and safety of inactivated influenza vaccines in pregnant women (also in the first trimester).

WHY ARE PREGNANT WOMEN EXPOSED TO SEVERE AND COMPLICATED INFLUENZA?

Influenza incidence in pregnant women is the same as in the general population; however, disease severity and the risk of death in this group are higher [2–6]. The reason behind this phenomenon are changes in the immune system during pregnancy, such as impaired cellular immunity, which is crucial for combating viral infections [10]. Other changes that can be observed are related to humoral immunity, which is why during the influenza A (H1N1) pandemic of 2009, pregnant women with H1N1 influenza virus infection showed lower serum IgG2 levels compared to the infected non-pregnant women, and thus they were exposed to abnormal cytokine production and more severe and complicated influenza [10]. Influenza complications during pregnancy are often related to lung function changes (reduced lung capacity and reduced tidal volume), as well as hemodynamic changes in the circulatory system (increased cardiac output, increased oxygen consumption) [5, 10].

INFLUENZA COMPLICATIONS IN MOTHER AND CHILD

The most frequently reported maternal influenza complications include pneumonia and acute respiratory failure, which requires respiratory support, mechanical ventilation, or even ECMO [10]. Influenza during pregnancy has been reported to increase the risk of premature delivery (with all its consequences), miscarriage, intrauterine fetal death, and low birth weight, whereas maternal fever may cause fetal tachyarrhythmias [10–14]. During the 2009 influenza pandemic, it was observed that influenza during pregnancy increased the risk of fetal death or neonatal death, as well as the likelihood of cesarean section delivery [15–17]. The tragic effects of influenza during pregnancy (including mother's or newborn's death) have also been reported in Polish scientific literature [13].

It should be emphasized that newborns and infants are at risk of severe and complicated influenza. Although influenza infections in newborns are rarely reported, recent studies have indicated vertical transmission as a route of influenza transmission, besides droplet and contact transmission [17]. In a group of children with influenza under the age of 12 months, 4% required mechanical ventilation support and 10% required intensive care treatment (hospitalization risk was higher in children aged < 3 months as compared to those aged 6–12 months) [18].

INFLUENZA PREVENTION IN PREGNANT WOMEN

Non-specific influenza prevention measures in pregnant women include hand hygiene, the so-called "cough etiquette" and avoiding crowded places. Pre- and post-exposure pharmacological prophylaxis with neuraminidase inhibitors is also recommended [2, 4]. The only registered drug available on the Polish market is oseltamivir for oral administration (zanamivir for inhalation is registered but not available). However, it needs to be clearly stated that oseltamivir should be primarily used for the causal treatment of influenza and must not be abused in influenza prophylaxis due to the risk of developing drug resistance, and furthermore, it can cause adverse effects (mostly associated with the digestive system) as any other drug, which is why its effectiveness in influenza prevention is estimated at 80% [19].

The most important measure of preventing influenza in pregnant women is vaccination. Currently, split vaccines and subunit vaccines are recommended in this risk group, both administered intramuscularly or subcutaneously [7, 8]. Live attenuated influenza vaccines for intranasal administration are contraindicated during pregnancy [7, 8].

INFLUENZA VACCINE SAFETY IN PREGNANCY

Data on inactivated vaccines for seasonal influenza indicate that they are safe for both mother and child. A retrospective observational study by Nordin et al., conducted on a group 79,900 vaccinated and 148,000 unvaccinated pregnant women, showed that there was no increased risk of adverse vaccination reactions within 42 days after the vaccination [20]. Approximately 2.4 million pregnant women were vaccinated against influenza in the US in the 2009–2010 season, and no increased risk to mother or child was shown [20]. A detailed systematic review on influenza vaccine safety in pregnancy showed that inactivated influenza vaccines do not increase the risk of intrauterine fetal death, spontaneous miscarriage or the occurrence of birth defects in a child [21]. Data on the safety of influenza vaccines in pregnancy refer to inactivated vaccines with split virion or sub-unit vaccines without adjuvants (these vaccines are available in Poland). Currently, there is not enough data on the safety of adjuvanted vaccine, such as MF59 (squalene oil-based adjuvant used since 1997) and AS03 (a combination of tocopherol and squalene in an oil-in-water emulsion used during the 2009 pandemic), so as to recommend them for pregnant women [7, 8]. One retrospective study conducted on a group of pregnant women showed a higher incidence of gestational diabetes and eclampsia among

women who were administered an MF59 adjuvanted influenza vaccine [22]. In a randomized, controlled clinical trial comparing the MF59-adjuvanted vaccine in pregnant and non-pregnant women, a negligible tendency for a lower immune response was observed in pregnant women; 72% of women reported adverse reactions, 64% had local reactions and 26% had systemic reactions, the most common symptom being malaise [23]. AS03-adjuvanted influenza vaccine, which was administered to approximately 380,000 pregnant women, was associated with an increased risk of narcolepsy in children, which shows that oil emulsion-based adjuvants are not fully safe in less studied patient populations, such as children and pregnant women [24].

The number of studies on the effectiveness of vaccines based on recombinant hemagglutinin protein that is produced in insect cells (intended for American adults allergic to chicken egg protein) is also insufficient so as to recommend these vaccines for pregnant women [3].

Studies performed after the 2009 influenza pandemic have confirmed the safety of inactivated vaccines against influenza in pregnant women. In a randomized trial from the USA, Munoz et al. proved that two inactivated trivalent seasonal influenza vaccines are safe [21]. In an Australian cohort, no evidence on the increased occurrence of adverse reactions was found in vaccinated pregnant women as compared to non-pregnant women [25].

Recently, increasingly more scientific reports proving influenza vaccine safety in the first trimester have been published.

The effect of influenza vaccination on pregnancy and fetal development was assessed by Japanese researchers in the 2013/2014 season [26]. The following endpoints were considered: miscarriage, fetal death, preterm delivery, low birth weight and birth defects. Adverse delivery outcomes were reported for 641 (10%) of 6,387 unvaccinated pregnant women and 356 (9%) of 3,943 vaccinated pregnant women. Even considering potential confounding factors, vaccinations during pregnancy were not associated with a risk of adverse delivery outcomes (odds ratio 0.90, 95% confidence interval 0.76–1.07). Vaccinations in the first or second trimester showed no association with adverse delivery outcomes, while vaccination in the third trimester was associated with a reduced risk of adverse delivery outcomes (odds ratio 0.70, 95% confidence interval 0.51–0.98) [26]. Similar conclusions regarding the performance of vaccinations in the first trimester were also made by American researchers in a study from 2004–2013 [27]. A total of 52,856 children of vaccinated mothers were assessed with regard to their psychomotor development in the first 12 months of life and compared with 373,088 children of mothers who were not vaccinated in the first trimester. The incidence of structural birth defects (per 100 live births) was 1.6 in the group of children of vaccinated mothers compared to 1.5 in the group of children of unvaccinated mothers (corrected PR of 1.02, 95% CI 0.94–1.10) [27].

EFFECTIVENESS OF INFLUENZA VACCINATIONS IN PREGNANCY

The immunogenicity of influenza vaccines in pregnant women is comparable to that observed in non-pregnant women (*i.e.* the post-vaccination level of antibodies is comparable). Similar results were observed in the 1970s in the studies on A/New Jersey/8/76 monovalent vaccine, which showed no reduction in the number of vaccine antibodies in pregnant women compared to the general population [2]. During the 2009 pandemic, it was confirmed that the inactivated monovalent H1N1/2009pdm vaccine was immunogenic in pregnant women, although women who had previously been administered a seasonal vaccine showed a lower seroprotection rate [28].

The actual effectiveness of influenza vaccines during pregnancy has also been proven, along with vaccination benefits for both mother and child.

A randomized clinical trial entitled "Mother's Gift", which was conducted in Bangladesh by Zamana et al. [29] in 2004–2005, focused on the effectiveness of influenza vaccinations in the third trimester and the obtained results were compared with the numbers related to pneumococcal polysaccharide vaccinations (control group) [29]. It was found that the number of laboratory confirmed influenza cases decreased by 63% in children of mothers who were vaccinated during pregnancy (this effect was observed during the first 6 months of the child's life) [29]. Vaccinations in the third trimester resulted in a reduced number of infections with fever by 29% in infants and 36% in mothers [29].

Protective antibody levels were maintained in infants for 6 months, with an estimated half-life of 42–50 days. A higher level of IgA antibodies was also found in the breast milk of influenza-vaccinated pregnant mothers for 6 months [29].

A clinical study conducted by Thompson et al. [30] in two influenza seasons 2010–2012 showed that influenza vaccinations in pregnant women reduced the risk of acute respiratory symptoms associated with laboratory-confirmed influenza by approx 50%.

A quadrivalent influenza vaccine has been available since 2012, and it has replaced the trivalent vaccine. This vaccine contains two influenza A virus subtypes and two currently circulating influenza B virus strains (Victoria and Yamagata), whereas the trivalent vaccine contains only one of the influenza B virus strains. To assess the actual effectiveness of the quadrivalent inactivated split vaccine, a randomized, actively controlled blinded study on a group of 4,193 pregnant women in the third trimester was conducted in Mali from September 2011 to April 2013 [31]. The study involved

weekly medical visits, during which infants up to 6 months of age were tested for an influenza-like disease, and RT-PCR tests were made to identify laboratory-confirmed influenza [31]. The primary objectives of the study included: 1. Assessment of the effectiveness of the vaccine against the first laboratory-confirmed influenza episode in infants born to women vaccinated at any time before delivery; 2. Assessment of the effectiveness of the vaccine against the first laboratory-confirmed influenza episode in infants born to women vaccinated ≥ 14 days before delivery. The secondary purpose of the study was assessment of the effectiveness of the vaccine against the first laboratory-confirmed influenza episode in women (before and after delivery) [31]. Infants aged < 6 months, whose mothers had been vaccinated at any time during pregnancy, showed vaccination effectiveness of 33.1% (95% CI 3.7–53.9%), whereby the effectiveness against laboratory-confirmed influenza in the first 4 months of life was 67.9% (95% CI 35.1–85.3%). Infants < 6 months whose mothers were vaccinated ≥ 14 days before the delivery showed vaccine effectiveness of 37.3% (95% CI 7.6–57.8%); however, during the first 4 months of life the effectiveness was higher and reached 70.2% (95% CI 35.7–87.6%). Vaccine effectiveness in preventing laboratory-confirmed influenza in vaccinated women was estimated at 70.3% (95% CI 42.2–85.8%) [31].

The benefits of vaccinating pregnant women can be observed in the first six months of child's life. Since the influenza vaccine can be administered from the age of six months, infants cannot be vaccinated. Due to the functional immaturity of their immune system, infants, especially those aged > 6 months, suffer from influenza more frequently and are five times more likely to be hospitalized, as compared to infants aged 6–23 months [22].

In the light of the above statistics, a mother's vaccination protects a child who can become ill with influenza but is too young to be vaccinated. Vaccination results in the production of maternal antibodies which are transmitted to the child transplacentally and in breast milk. The degree and duration of the child protection are related to the level of maternal influenza antibody titers, which in turn depends on the time interval between vaccination and delivery [32]. How long the passively acquired antibodies persist in infants, it depends on their initial concentration in the umbilical cord blood; however, it is no longer than 6 months [32]. The effect of a mother's vaccination on a child has been evaluated in many studies. In a controlled comparative study from 2000–2009 (before H1N1 2009 pandemic), there were 90% fewer influenza-related hospitalizations in a group of infants aged < 6 months and born to influenza vaccinated mothers than in the group of children of non-vaccinated mothers [33]. Since no seroprotection was observed in children of mothers who had been vaccinated only 15 days before delivery, it can be assumed that vaccination against influenza should be performed at least 2 weeks before delivery to maximize the neonatal protection [33]. In a UK study, a mother's vaccination during pregnancy in the 2013/2014 season was effective for 71% infants under 6 months of age [34].

WHEN TO GET VACCINATED?

Influenza vaccination with an inactivated vaccine can be performed in any pregnancy trimester. In order to obtain optimal protection against influenza in both mother and child, it is recommended to perform a vaccination at least 2 weeks before the planned delivery. Later vaccination is safe but might not be effective enough (time between the production of antibodies and their transplacental transfer is too short). However, it should be emphasized that vaccination in this time is still beneficial and so is vaccination in the postpartum period, as part of the cocoon strategy. The strategy involves vaccinating people in the immediate environment of a patient (the newborn) who may become ill but cannot be vaccinated (because of being too young). Being part of the cocoon strategy, vaccinations in the immediate environment reduce the transmission of pathogens and the risk of becoming ill [35].

For many years, influenza vaccinations were recommended only when the vaccine composition recommended for a given season was available (most often in September). However, it should be emphasized that influenza vaccination can and should be performed during any autumn or winter month when there is increased influenza virus circulation. Postponement of the vaccination, caused *e.g.* by a delay in the vaccine development (which took place previously and was caused e.g. by the delay in the publication of the WHO vaccine composition recommendations for a given season or technological/production difficulties) does not adversely affect the effectiveness of vaccination. Furthermore, it can have a positive aspect. Antibodies have been shown to persist for up to 6 months and gradually disappear after the vaccination, which is why early vaccination may result in low levels of antibodies at the end of the influenza season [35]. In the case of patients at risk (*e.g.* patients with chronic respiratory, circulatory and metabolic diseases), vaccination is currently not recommended at the beginning of the season but later to ensure high antibody level throughout the influenza season [35].

CONCLUSIONS

Inactivated quadrivalent influenza vaccine is a safe and effective measure for preventing influenza in mothers and children. It can be recommended to all pregnant women, who are healthy or have comorbidities. The vaccine can be administered in any pregnancy trimester. The time of vac-

cination depends on the vaccine availability; however, it should not be postponed unless there are significant medical counterindications.

Conflict of interest

The authors declare no conflict of interests.

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VIA MEDICA

RECOMMENDATIONS

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Polish Society of Gynecologists and Obstetricians Recommendations on diagnosis and management of fetal growth restriction

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Recommendations present the current management, that may be modified and changed in certain cases, after a thorough analysis of a given clinical situation, which in the future may be the basis for their modification and actualization.

SUMMARY OF THE RECOMMENDATIONS

Definitions

Fetal Growth Restriction (FGR)— a synonim for intrauterine growth restriction (IUGR)

< 32 weeks — early-onset FGR; > 32 — late onset FGR
Hypotrophy — a term related to a newborn with growth restriction

Risk factors

Risk factors of growth restriction should be assessed in every woman at the beginning of pregnancy and at each following visit (Tab. 1A and 1B). Increased risk of FGR is diagnosed if, at least one major or three minor risk factors are present. Risk may also be determined using an algorithm combining ultrasound, medical history, and serum markers.

Confirming the gestational age

Each pregnant woman should undergo an ultrasound examination between 11–13 + 6 weeks of gestation, during which the crown-rump length is measured, and the date of delivery is determined. If there is no ultrasound examination at this time, the delivery date should be determined on the basis of HC and FL measurements in the second trimester of pregnancy.

Differential diagnosis

Suspicion of abnormal growth should be followed by a detailed work up to determine the potential cause (chromosomal abnormalities, infections, congenital anomalies, impaired blood flow in the uterine arteries, changes in the placenta).

Growth assessment

The recommended method of calculating the estimated fetal weight is the Hadlock equation. AC and HC measurements should be made using an ellipse to cover the outer contours of the abdomen and fetal head. Based on availability and accessibility, PSOGO recommends the use of

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Table 1A. Major risk factors for fetal growth restriction (adapted from RCOG — 13)

Maternal	Antiphospholipid syndrome	RR 6.2 (2.4–16.0)
	Diabetes-related angiopathy	OR 6 (1.5–2.3)
	Renal insufficiency	AOR 5.3 (2.8–10)
	Intense physical activity	AOR 3.3 (1.5–7.2)
	> 40 years of age	OR 3.2 (1.9–5.4)
	Cocaine	OR 3.2 (2.4–4.3)
	Maternal birthweight < 10 centile	OR 2.6 (2.3–3.0)
	Chronic hypertension	ARR 2.5 (2.1–2.9)
	Smoking >10 cigarettes/day	OR 2.2 (2.0–2.4)
Obstetric history	Birth of neonate with birthweight < 10 percentile	OR 3.9 (2.1–7.1)
Current pregnancy	Pre-eclampsia	AOR 2.7 (1.2–4.3)
	Threatened abortion accompanied by menstrual-like bleeding	AOR 2.6 (1.2–5.6)
	Pregnancy-induced hypertension – severe	RR 2.5 (2.3–2.8)
	Hyperechogenic bowel of the fetus in II trimester on ultrasound	AOR 2.1 (1.5–2.9)
Paternal	Paternal birthweight < 10 percentile	OR 3.5 (1.3–10.3)

RR — relative risk; OR — odds ratio; AOR — adjusted odds ratio

Table 1B. Minor risk factors for FGR (adapted from RCOG — 13)

Maternal	Primiparity	OR 1.9 (1.8–2.0)
	Diet low in fruit before pregnancy	AOR 1.9 (1.3–2.8)
	IVF	OR 1.6 (1.3–2.0)
	Obesity BMI ≥ 30	RR 1.5 (1.3–1.7)
	Maternal age > 35 years	OR 1.4 (1.1–1.8)
	Underweight BMI < 20	OR 1.2 (1.1–1.3)
	Overweight BMI 25–29.9	RR 1.2 (1.1–1.3)
Obstetric history	Mild pre-eclampsia	AOR 1.3 (1.2–1.4)
	Time between pregnancies < 6 months	AOR 1.3 (1.9–1.3)
	Time between pregnancies ≥ 60 months	AOR 1.3 (1.2–1.4)
Current pregnancy	Caffeine consumption ≥ 300 mg/daily in the III trimester	OR 1.9 (1.3-2.8)
	Pregnancy-induced hypertension – mild	RR 1.3 (1.3–1.4)

RR — relative risk; OR — odds ratio; AOR — adjusted odds ratio; IVF — in vitro fertilisation; BMI — body mass index

the Hadlock growth charts until the development and dissemination of growth standards for the Polish population.

Fundal height assessment should be performed in low-risk pregnancies starting from the 24th week of gestation.

Diagnosis and management

We recommend FGR diagnosis based on ultrasound criteria reported in the Delphi consensus. After the diagnosis, management is always individualized, and surveillance should incorporate all the available tools. Management is feasible in an outpatient setting. Hospitalization is indicated if FGR is accompanied by:

- oligohydramnios
- abnormal CTG tracings
- abnormal biophysical profile
- vaginal bleeding
- reduced or rapid fetal movements
- absent or reversed end diastolic flow in the umbilical artery
- CPR < 5 percentile
- absent or reversed end diastolic flow in the ductus venous
- other symptoms of fetal distress

Delivery

Choice of timing and mode of delivery depends on the severity of FGR, accompanying abnormalities in CTG trac-

Table 2. Comparison of early vs late fetal growth restriction

	Early FGR	Late FGR
Main problem	Management	Diagnosis
Placental changes	> 30%	< 30%
Cardiovascular reaction to hypoxia	Adaptation	No adaptation
Tolerance of hypoxia	High Natural history of disease established	Low Natural history of disease not established
Perinatal mortality	High, especially < 26 weeks of pregnancy	Low
Perinatal morbidity	High, especially < 26 weeks of gestation	Increased risk of perinatal complications. Risk of neonatal, childhood and adult morbidity unknown.

FGR — fetal growth restriction

ings and ultrasound assessment. In the absence of previous indications, delivery is recommended not later than week 37.

ABBREVIATIONS AND DEFINITIONS

AC — abdominal circumference
AEDV — absent end diastolic velocity
AGA — appropriate for gestational age — fetuses and neonates with estimated fetal weight and neonatal weight between the 10–90 percentile
AOR — adjusted odds ratio
APLS — antiphospholipid syndrome
ARR — adjusted relative risk
BMI — body mass index
BPD — biparietal diameter
CPR — cerebro-placental ratio
CRL — crown-rump-length
DV — Ductus Venous
Early-onset FGR — early onset growth restriction, onset before 32 weeks of gestation
FGR — fetal growth restriction — is the failure of the fetus to achieve the programmed birth weight after excluding internal factors (chromosomal aberrations, infections, birth defects)
FL — femur length
HC — head circumference
Hypotrophy - a term related to a newborn born with growth restriction
IUGR — intrauterine growth restriction —synonym of FGR
Late-onset FGR — late onset fetal growth restriction, onset after 32 weeks of gestation
LGA — large for gestational age — fetuses and neonates with estimated fetal weight and neonatal weight above the 90 centile
MCA — middle cerebral artery
OR — odds ratio
PIGF — placental growth factor
REDV — reverse end diastolic velocity
RR — relative risk
SGA — small-for-gestational-age — fetuses with estimated weight (EFW) on ultrasound between the 3rd and 10th percentile for gestational age without signs of growth failure or newborns with birth weight below the 10th percentile
TORCH —Toxoplasmosis, Rubella, Cytomegalovirus, Herpes simplex
UA — umbilical artery
UtA — uterine artery
ARSA — aberrant right subclavian artery

AIM

The aim of these recommendations is to present FGR management principles based on currently available scientific evidence and clinical experience.

INTRODUCTION

Fetal Growth Restriction (FGR) is a clinical situation in which the fetus does not reach its programmed birth weight [1]. Currently, there are two types of fetal growth restriction. Early-onset FGR before 32 weeks of gestation. Early FGR often coexists with maternal hypertension or connective tissue disease [2]. In the TRUFFLE study, pre-eclampsia was found in 75% of pregnancies included in the study [3]. Early FGR is an indication to refer the patient to a higher reference level and is primarily a challenge in terms of planning appropriate management. The natural course of the disease is relatively well understood. The GRIT and TRUFFLE studies analyzed the effectiveness of various diagnostic and therapeutic regimens and their impact on the outcomes of perinatal care (both early and late) [3–5]. According to experts, much more controversy exists around late FGR, which is defined as growth restriction that occurs after 32 weeks of gestation. In these cases, the primary problem is diagnosis in low-risk pregnancies, as in many countries, third trimester ultrasound examination in this group of women is not recommended (Tab. 2). FGR detection in low-risk pregnancies in many countries does not exceed 15% [2, 6, 7]. In Poland, it is currently recommended to perform an ultrasound scan in the third trimester

between 28–32 weeks of pregnancy and at term [8, 9]. In Poland, despite routine performance of the third trimester ultrasound, this detection rate is not much higher [10]. One of the greatest challenges of modern perinatology is the prevention of intrauterine deaths [11]. The experience from Great Britain shows that the identification of women with an increased risk of growth failure, staff training, the introduction of diagnostic and therapeutic recommendations and guidelines gives a chance to reduce perinatal mortality [12].

Risk factors

Risk factors for growth restriction should be assessed in every woman at the beginning of pregnancy and at each following visit. FGR risk factors can be classified as major or minor depending on the OR, AOR or RR (Tab. 1A and 1B). These are risk factors identified on the basis of maternal history and the course of current pregnancy. The diagnosis of an increased risk of FGR is based on the presence of at least one major risk factor or three minor risk factors [13]. The screening tests and preventive measures are described in detail later in the recommendations. A high risk of FGR in the first trimester of pregnancy is an indication to consider prophylactic administration of acetylsalicylic acid [14].

Pregnant women in Poland rarely admit to smoking. It is also difficult to obtain reliable information regarding their home exposure to cigarette smoke. According to data published for the Polish population, 12% of women continue to smoke during pregnancy [15]. Therefore, the risk should not be differentiated depending on the number of cigarettes smoked or the environmental exposure. If the patient reports that she had stopped smoking in the first trimester, we classify it as a major risk factor of FGR.

DIAGNOSIS AND MANAGEMENT

Differential diagnosis

Confirmation of gestational age

The basic criterion for the assessment and diagnosis of growth abnormalities is the correct determination of the duration of pregnancy. Measuring the CRL between 8 and 14 weeks of gestation is considered the most accurate method of assessing the duration of pregnancy [16]. Currently, according to the PSOGO recommendations, every pregnant woman should undergo an ultrasound examination between 11–13 + 6 weeks of gestation. In such a case, the measurement of the crown-rump length should be performed, and the date of delivery be determined on its basis. If the duration of pregnancy has been determined at that time, it should not be recalculated on the basis of subsequent ultrasound examinations. [8]. If data on CRL is unavailable, then the HC and FL measurements can be used to determine the duration of pregnancy in the second trimester [16].

Risk assessment of chromosomal abnormalities

One third of early-onset FGR may coexist with chromosomal abnormalities or genetic syndromes [17]. Therefore, if FGR is diagnosed before 24 weeks of gestation, the risk of chromosome aberrations should be verified. A detailed interview regarding what genetic and screening tests have been performed so far by the patient is helpful. The medical documentation should include an annotation whether the first trimester screening was performed in accordance with the recommendations of PSOGO. If not — it should be noted in the documentation whether this was discussed and offered to the patient.

The indications for invasive genetic testing in the case of FGR are as follows:

- Early FGR < 24 weeks
- Major structural defects accompanying FGR
- Presence of benign ultrasound markers indicating an increased risk of aneuploidy (nuchal fold thickening, ventriculomegaly, ARSA, choroid plexus cysts, incorrect hand position, septal defects, hyperechogenic bowel, shortened humerus, hypoplastic nasal bone < 10 percentile).

If the ultrasound examination does not show signs of placental insufficiency, and the patient has not had the first trimester screening in accordance with the FMF and PSOGO standards, or if, despite being at high risk, further screening was not performed (free fetal DNA testing), then amniocentesis or cordocentesis should be offered.

Diagnosis of TORCH infections

FGR suspicion should prompt diagnosis of cytomegaly, toxoplasmosis, rubella and herpes simplex. In Poland, routine malaria diagnosis is not recommended, although in selected cases, justified by medical history, it may be suggested.

Invasive diagnosis to confirm fetal infection should be considered individually. Amniocentesis should not be performed before 18 weeks of gestation and not earlier than 4 weeks after the onset of maternal symptoms. The indications for amniocentesis can be both the results of serological tests (the presence of specific IgM and IgG antibodies with low avidity of IgG antibodies) [18], as well as ultrasound assessment performed by an experienced professional or in a dedicated prenatal diagnosis center (cerebral, liver microcalcifications, ventriculomegaly, microcephaly, hepatomegaly, effusion in body cavities, fetal edema and placentomegaly) [19].

Anatomy assessment

FGR is an indication for a detailed assessment of fetal anatomy. The scope of ultrasound workup depends on the gestational age. Estimated fetal weight below the 3rd per-

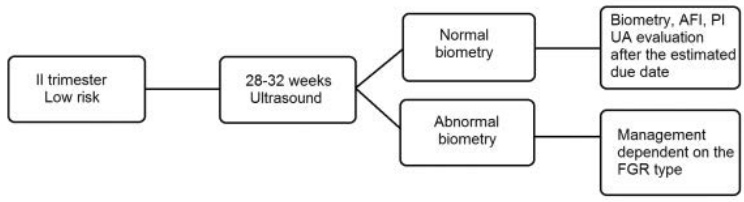

Figure 1. Low-risk pregnancy

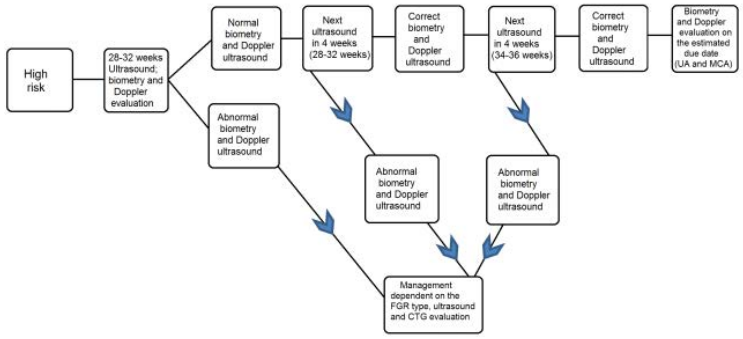

Figure 2. High-risk pregnancy

centile should include a detailed heart and central nervous system evaluation.

Growth assessment

In a low-risk pregnancy, fetal growth should be assessed at week 20–22; 28–32 weeks and after 40 weeks, in accordance with the current standard of perinatal care and the PSOGO recommendations [8, 9] (Fig. 1). In a high-risk pregnancy, fetal growth should be assessed: at week 20–22; at week 26–28; at week 34–38 and week 40 [8] (Fig. 2). In the case of FGR diagnosis, the frequency of ultrasound examinations depends on the severity of growth restriction. Fetal weight assessment should be made in accordance with the Hadlock II methodology, considering the BPD, HC, AC and FL measurements. The AC and HC measurements should be made using an ellipse and cover the external outline of the fetal soft tissues [16].

When assessing the fetal growth, the use of population growth charts is recommended [20]. The Z-score can also be used, but the percentile method is more readable for the recipients [21].

An alternative are customized growth charts, which allow calculation of the optimal birth weight for a given pregnancy, accounting for the mother's ethnic origin, her height and weight before pregnancy and parity [22]. However, in the light of previous reports, they do not demonstrate a predictive advantage. At the time of delivery, nearly 70% of fetuses with weight estimated between the 3rd and 10th centile is healthy, and their weight is exclusively constitutional (maternal constitutional conditions, race, fertility, BMI) [23]. When assessing the weight of the fetus and its centile, it is always worth paying attention to which specific measured parameter is responsible for the diagnosis of FGR. A low fetal weight percentile can sometimes be due to, for example, a relatively "shorter" FL measurement and may result in an unnecessary implementation of intensive care and invasive measures. At present, there are no recommendations to use customized growth charts for a given population, although it may be a more appropriate diagnostic method in the future [16]. Due to availability, PSOGO recommends using the Hadlock II algorithm until Polish population standard is developed and disseminated.

Fundal height measurement

The fundal height measurement is an approximate method of assessing the stage of pregnancy and the size of the fetus. The result is influenced by maternal obesity, parity and the obstetrician's experience. The assessment of fundal height can only be used as an indication for ultrasound assessment. It can be performed in low-risk pregnancies starting from the 24th week of gestation. It involves measuring the distance between the upper edge of the pubic symphysis and the floor of the uterus (SF, symphysis-fundal). The values and standard deviations of fundal height for a given gestational age according to Intergrowth are presented in Table 3. FGR is suspected when the SF measurement value is lower by 3 or more than 3 centimeters for a given gestational age [24]. This is an indication for an ultrasound

Table 3. Fundal height values for a given gestational age (SF) and the measurement value reduced by double the standard deviation (according to Intergrowth)

Gestational age [weeks]	Symphysis-fundal height (SF) [cm]	Fundal height — ≤ 2 standard deviation (SF — ≤ 2SD) [cm]
24	23.8	≤ 20.5
25	24.7	≤ 21.5
26	25.7	≤ 22.4
27	26.7	≤ 23.3
28	27.7	≤ 24.3
29	28.6	≤ 25.2
30	29.6	≤ 26.1
31	30.5	≤ 26.9
32	31.4	≤ 27.8
33	32.3	≤ 28.6
34	33.2	≤ 29.5
35	34.0	≤ 30.3
36	34.9	≤ 31.0
37	35.7	≤ 31.8
38	36.5	≤ 32.5
39	37.2	≤ 33.2
40	38.0	≤ 33.9
41	38.7	≤ 34.6
42	39.3	≤ 35.2

Table 4. Delphi criteria for diagnosis of early and late fetal growth restriction

Early FGR Gestational age ≤ 32 weeks	Late FGR Gestational age > 32 weeks
AC or EFW < 3 percentile or UA-AEDF	AC or EFW < 3 percentile
or	or 2/3 of criteria below
1. AC or EFW < 10 centile and 2. UtA-PI > 95 centile and/or 3. UA-PI > 95 centile	1. AC or EFW < 10 centile 2. AC or EFW drop > 2 quartile on the growth chart * 3. CPR < 5 centile or UA-PI > 95 percentile

*percentiles are not individualized, individual measurements of the fetus should be analyzed in each case of a low percentile; FGR — fetal growth restriction; AC — abdominal circumference; AEDF — no diastolic flow; CPR — cerebroplacental ratio; EFW — Estimated Fetal Weight; PI — pulsation indicator; UA — umbilical artery; UtA — uterine artery

examination. Fundal height assessment is not indicated in patients with pre-pregnancy BMI > 35 and in women with large uterine fibroids.

Delphi Criteria for FGR

In 2016, in order to standardize the diverse nomenclature, a definition of FGR was developed through an international consensus. This definition applies to fetuses with placental growth failure, after excluding congenital abnormalities, TORCH infections and chromosomal abnormalities. Fetal growth restriction has been classified into early and late onset FGR. The diagnostic criteria are presented in Table 4 [25].

As a rough measure, early-onset fetal growth restriction begins before 32 weeks of gestation. For diagnosis, one of the following parameters must be identified:

- abdominal circumference (AC) measured by ultrasound < 3 percentile at a given gestational age,
- estimated fetal weight (EFW) measured by ultrasound < 3 percentile at a given gestational age,
- absent umbilical artery end-diastolic flow (UA AEDV) regardless of the estimated fetal weight.

The last of the above-mentioned parameters indicates impaired placental flow, which allows to distinguish a group of children with potentially impaired growth in the following weeks of gestation. Early-onset FGR may also be suspected when AC or EFW are lower than the 10th centile at a given gestational age, and the umbilical artery (UA) and/or uterine artery (UtA) pulsation index (PI) is greater than the 95th centile at a given gestational age.

Late-onset fetal growth restriction begins after 32 weeks of gestation. The diagnosis is made by the occurrence of a single parameter:

- • abdominal circumference (AC) as measured by ultrasound < 3 centile for a given gestational age
- • estimated fetal weight (EFW) < 3 centile for a given gestational age.

The diagnosis of late FGR can also be made when the estimated fetal weight or abdominal circumference is below the 10th percentile and at least one of the following criteria is met:

- growth inhibition above 2 quartiles (more than 50 centiles)
- CPR value (quotient of PI in MCA and UA) < 5 percentile for a given gestational age
- UA PI > 95 percentile for a given gestational age

As in the case of early FGR, the last two of the above-mentioned parameters indicate the beginning of possible fetal hypoxia, brain-sparing and impaired placental flow, *i.e.* they allow for identification of the group of children with potentially impaired growth in the following weeks of pregnancy.

Early fetal growth restriction

The management of early FGR, the frequency of fetal monitoring and the route of delivery depends on severity of the disease. In the TRUFFLE study, which compared computer CTG analysis and the assessment of Doppler blood flow values in DV in monitoring the well-being of the fetus, 85% of children in the second year of life had no neurological complications, and only 1% had cerebral palsy [4]. The most important risk factor for neonatal complications, including

death, was prematurity. The rate of neurological complications was maintained at similar level regardless of the gestational age, but it was significantly lower in the study group where interventions were based on the blood flow in ductus venosus. The highest risk of intrauterine death regarded fetuses with FGR diagnosed before 26 weeks of gestation. Each day of intrauterine life between 26–29 weeks of gestation increases the chances of proper development by about 2%, while between 30–34 only by 1% [26]. There are 4 stages of early FGR [27]. Establishing the diagnosis requires a change in the supervision method and performing fetal biometry, assessment of the amniotic fluid volume and assessment of the blood flow in Doppler examination (UtA, UA, MCA and DV). The indications for termination of pregnancy consist of abnormal values of ultrasound indicators, CTG parameters and/or progressing symptoms of pre-eclampsia.

Stage I

Stage I is diagnosed when the estimated fetal weight or abdominal circumference are below the 3rd percentile or when the fetal weight is between the 3–10th centile, with an increased uterine artery pulsatility index (mean PI > 95th centile or CPR < 5th centile or MCA < 5th centile). In this case, the blood flow should be assessed once a week together with an assessment of the amniotic fluid volume, and from 34 weeks of gestation, a CTG should be performed once a week. Fetal weight should not be assessed more frequently than every 2 weeks. If the cerebroplacental ratio (CPR) is above the 5th centile, there is no need for an assessment of the ductus venous (DV) blood flow. If, however, it is below the 5th centile, the blood flow in DV should be assessed. Normal values are < 95 centile. The most important factor in predicting the fetus well-being in CTG is the assessment of short-term variability (STV) over a period of 40–60 minutes. Amniotic fluid volume can be assessed using both the maximum vertical pocket (MVP) and the amniotic fluid index (AFI). An incorrect MVP value is < 2 cm, and an incorrect AFI index < 5cm.

Stage II

Stage II is diagnosed in the absence of end-diastolic flow in the umbilical cord. It is estimated that the risk of intrauterine death in the absence of end-diastolic flow in the umbilical cord is more than three times increased — OR = 3.59, with a 95% CI 2.29–5.62 [28]. This is an indication for urgent hospitalization of the patient. It is optimal to implement intensive cardiotocographic monitoring. Ultrasound examination should be performed 2–3 times a week. Blood flow in UtA, UA, MCA and DV is evaluated. CPR < 5th percentile and MCA < 5th percentile, therefore symptoms of circulatory centralization, which are only adaptive symptoms of the fetus, are not an indication for termination of pregnancy. Persistence of the lack of late-diastolic blood flow is an indication for the administration of steroids and increased CTG surveillance. If during observation there is an absent a-wave or there is a reversed a-wave in the ductus venosus, then it is an indication for an immediate termination of pregnancy - the risk of death in this situation is OR = 12.39, with a 95% CI 8.49–18.06. In other cases, cardiotocographic supervision should be performed daily. With correct CTG, pregnancy should be ended after 34 weeks of gestation, after a previous steroid therapy.

Stage III

Stage III is diagnosed when a retrograde wave in the umbilical cord or PI in DV > 95 centile are found. In this case, the risk of intrauterine death is also high — OR = 7.15, with a 95% CI of 5.22–9.81. It is optimal to introduce increased cardiotocographic monitoring. Ultrasound examination should be performed in a hospital setting every 12–24 hours. Pregnancy should be ended by caesarean section, after a course of steroid therapy in the event of abnormal cardiotocographic records or persistent flow reversal.

Stage IV

Stage IV is diagnosed when an absence of A wave, reverse A wave in DV or incorrect values of the CTG records are found. The patient must be hospitalized immediately, be under constant cardiotocographic supervision and should be given steroids. This is an indication for urgent termination of pregnancy by caesarean section.

Regardless of the abnormal values of vascular flow measurements assessed in Doppler examination, an indication for termination of pregnancy is reduced to < 3.5 short-term variability for > 40 minutes or repeated decelerations in cardiotocographic tracings [29–31]. The optimal place of hospitalization is a tertiary perinatal care center. Hospitalization is indicated pending results of cardiotocographic tracings, ultrasound assessment, the patient's condition and the coexistence of hypertension and pre-eclampsia indicators. The diagnosis of pre-eclampsia increases the severity of FGR by one level. In case of diagnostic doubts, lack of experience in ultrasound evaluation, or lack of appropriate equipment, it is recommended to refer the patient at any stage of gestation to a reference center or to a perinatal medicine specialist to determine further management.

Hospitalization is indicated in each case of FGR complicated by oligohydramnios (MVP < 2 or AFI < 5), abnormal biophysical profile, suspicious CTG recording, vaginal bleeding, reduced fetal movements or lack of end-diastolic flow in the umbilical artery.

The assessment of fetal movements after 30 weeks of gestation, according to the PSOGO recommendations, should take place during the periods of fetus' highest activity

or after main meals (but not within the first hour after eating). The correct value is considered to be at least 4 movements within an hour or 10 movements within two hours [32].

Supervision of fetal well-being during hospitalization in a reference center should be based on recommendations to ensure appropriate supervision, consistent with current medical knowledge.

The route of delivery should always be chosen individually, considering obstetric conditions, risk factors and experience of medical personnel, but also an increased risk of chronic fetal hypoxia in the event of impaired fetal well-being with an indication for caesarean section. After the completion of 37 weeks of gestation, in the presence of indications for its termination and no contraindications to vaginal delivery, it is recommended to induce labor with continuous cardiotocographic monitoring. FGR is a contraindication to vaginal delivery in case of breech position of the fetus. In case of pregnancy with FGR and the need to deliver < 32 weeks, it is recommended to administer magnesium sulphate (MgSO4) for neuroprotection of the fetus.

Late fetal growth restriction

In the case of late-onset FGR, the biggest problem is its diagnosis and differentiation between the growth-restricted fetus and a constitutionally small fetus (SGA). The SGA fetus' growth potential is most likely inherited from its parents. Its growth parameters are within 3–10 percentile, but the blood flow in the uterine arteries, the umbilical cord, and the middle cerebral artery is normal. Such fetuses are, in most cases, healthy. Termination of pregnancy should occur at the time of delivery at the latest, in accordance with the PSOGO recommendations on labor induction [33].

Supervision of such fetus requires an evaluation of growth dynamics and the blood flow in the vessels every 2 weeks. In low-risk populations, the number of SGA diagnosed at term does not exceed 15%. In studies involving populations similar to the Polish one, despite of performing the commonly recommended examination between 28 and 32 weeks of gestation, the rate of such fetuses in low-risk pregnancies was 19%, and in high-risk pregnancies 47% [10]. Therefore, it is extremely important to select patients who require additional ultrasound examination between 32–40 weeks of gestation.

In late FGR, we rarely observe an abnormal blood flow spectrum in the uterine arteries, but Figueras et al. [27] showed that the evaluation of blood flow in these vessels, also in pregnancies over 32 weeks, allows for identification of fetuses with an increased risk of perinatal complications. In the DIGITAT study, AEDV was found in only 10% of patients, and the mean PI values in the umbilical cord ranged from 0.93–0.98 [34]. In late FGR, the most useful is the evaluation of CPR or MCA flow, and the values of these parameters < 5 percentile allow for identification of fetuses in which pregnancy should be terminated earlier [27]. Induction of labor at 37 weeks of gestation is indicated for fetuses with an estimated weight below the 3rd percentile or with an abdominal circumference below the 3rd percentile. Early termination of pregnancy should be considered in the presence of symptoms of pre-eclampsia, depending on the results of cardiotocography and ultrasound examinations. If CPR is < 5th percentile or MCA flow is < 5th percentile, the ductus venous blood flow should be assessed and the management like for early FGR should be introduced. The other indications for hospitalization, CTG surveillance, delivery route, counting fetal movements and assessment of the biophysical profile are the same as in early FGR. Regardless of whether we are dealing with late FGR or SGA, CTG and USG control should be implemented in the event of increased blood pressure, vaginal bleeding, uterine contractions and reduced fetal movements.

Screening tests and and general prevention

When compiling the management protocols, the authors considered different scenarios depending on whether the patient was screened and/or assessed for FGR risk in the first trimester of pregnancy. The scheme also assumes a situation when, despite the existing indications, the pregnant woman did not receive or did not start taking acetylsalicylic acid. The risk of FGR should be assessed at each stage of pregnancy. Scheme I presents the method of risk evaluation in the first and second trimesters of pregnancy, taking into account the lack of risk assessment based on ultrasound and biochemical parameters in the first trimester. In such case, it should be done based on the previously described risk factors (1A and 1B).

In a single pregnancy, the Polish Society of Gynecologists and Obstetricians recommends the use of prenatal screening between 11 and 13 + 6 weeks of pregnancy to evaluate the risk of early-onset FGR with Doppler evaluation of uterine blood flow (UtA), mean arterial pressure (MAP) and determine the value of placental growth factor (PlGF) in blood. In high-risk situations (> 1: 100), it is justified to start the administration of 150 mg of acetylsalicylic acid before 16 weeks of gestation and continue it until the 36th week [14] (Fig. 3).

According to the PSOGO standards, ultrasound examination should be performed at 11–14, 20 and 28–32 weeks of gestation. In a group at high risk of FGR and/or pre-eclampsia identified on the basis of the first trimester screening, a screening between 19–24 weeks of gestation should be considered using the patient's history and UtA PI, MAP, PlGF and sFlt-1 evaluation. Ultrasound assessment of growth should be performed according to the scheme outlined for high-risk pregnancies (High-risk pregnancy management scheme).

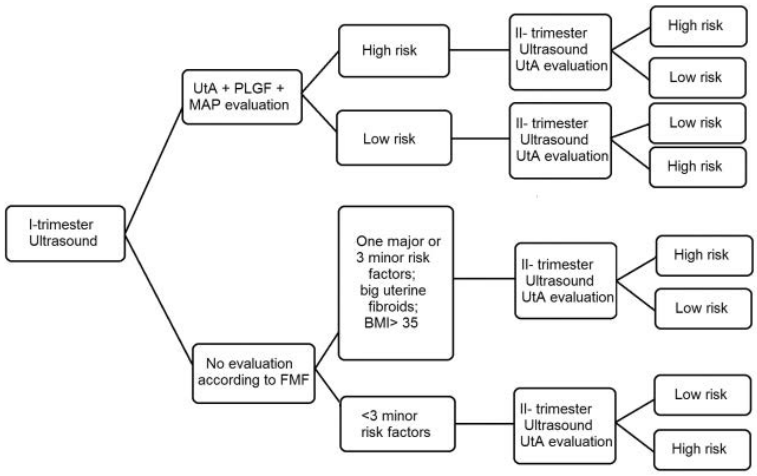

Figure 3. Scheme for risk assessment in the I/II trimester of pregnancy

However, in low-risk pregnancies, it may be considered to evaluate the uterine blood flow in the second and third trimesters. In the case of correct biometry and PI UtA> 95th percentile, we recommend an additional control of growth dynamics between 34-38.

Confirming the high risk of early-onset FGR/pre-eclampsia occurrence (> 1:100) entails an individualized approach in the form of every-day blood pressure measurements, weekly assessment of proteinuria and periodic evaluation of fetal biometry.

Placenta

Examination of the placenta: description of macroscopic changes in medical record documentation and possibly a histopathological examination.

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VIA MEDICA

RECOMMENDATIONS

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Polish Society of Gynecologists and Obstetricians recommendations on supplementation during pregnancy

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The recommendations present the current state of knowledge on the presented subject on the day of publication. The board of experts reserves the right to update the information in case of new significant scientific reports.

The board of experts undertook the analysis of literature, expert knowledge and clinical experience in matters of use of dietary supplementation in pregnancy.

INTRODUCTION

Progress in medicine allows for a better understanding of the purpose of dietary components in prophylaxis of civilization diseases and suggests that alimentation not only supplies energy and nutrients but provides compounds essential for proper functioning of the body as well [1].

Based on every day medical practice we can conclude that future mothers attach relatively substantial importance to their diet. They realize the importance of diet and its impact on the condition and development of the fetus. It is common among pregnant women to use dietary supplements, which often does not have any rational justification.

It is estimated that about 78–98% of pregnant women in the USA, Canada and Australia use dietary supplements [2]. There are no reliable data from Poland, but observations in obstetrical practice let us assume that the supplementation trend is very similar.

In literature there are contradictory reports regarding the safety and effectiveness of supplementation usage by pregnant women.

According to the WHO statement from 2016, as well as the majority of medical associations, a routine usage of multivitamin regimens by all pregnant women is not recommended. The basic source of microelements and vitamins should come from a well-balanced diet.

The following recommendations of the Polish Society of Gynecologists and Obstetricians present an up-to-date view on the importance of dietary supplementation in pregnancy in accordance with current knowledge and recommendations. We present five active substances — iron, folic acid, vitamin D, DHA acid and iodine, which are considered to be the basic elements useful in pregnancy supplementation. Presence of other microelements, vitamins and active substances in supplementation, therefore supplementing a normal diet is not recommended in a population of healthy women with no specified medical indications.

IRON

We talk about iron balance as a resultant of two factors: iron intake and loss. The total amount of this element in adults is about 4–5 g and is mostly present as a component of hemoglobin (75%), ferritin and hemosiderin (20%). In proper conditions there is a state of dynamic balance between the iron contained in hemoglobin and the storage and transport proteins.

Outside of pregnancy, a regular diet usually fully covers the daily requirement for iron. It increases during pregnancy daily by about 1 mg in the first trimester and 7.5 mg in the third trimester, which is the result of an increasing demand of a growing fetus, placenta and an increasing volume of the uterine muscle [3]. Iron deficiency is the most common cause of anemia in pregnancy.

The lower limit of hemoglobin in pregnancy defined by WHO is 11 g/dL (6.8 mmol/L). Anemia in pregnancy is defined by the level of Hgb below 11 g/dL in every trimester of pregnancy according to WHO [4]. Undoubtedly, it is quite a big interpretive simplification, though one giving the possibility of applying unified and proper treatment. When analyzing the necessity of iron supplementation, it is more useful to divide the normal range for hemoglobin depending on the

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trimester of pregnancy. CDC runs a simplified scheme of such range considering Hgb concentration < 11 g/dL in I and III trimester and Hgb < 10.5 g/dL in II trimester as reference ranges for diagnosing anemia in pregnancy [2, 5–7].

In „The Global Prevalence of Anemia in 2011" report, WHO states that in Europe anemia occurs in about 20–40% of all pregnant women aged 15–49, and it simultaneously recommends iron supplementation of all pregnant and planning pregnancy women, 30–60 mg daily to reduce the risk of perinatal complications, infections, low birth weight and preterm births.

The majority of scientific societies (Royal College of Obstetrics and Gynaecology (RCOG), Royal Australian and New Zealand College of Obstetrics and Gynaecology (RANZCOG), European Food Safety Authority (EFSA), Scientific Advisory Committee on Nutrition (SACN), British Society for Haematology, Obstetric Haematology group (BSH OHG) and British Committee for Standards in Haematology (BSCH) do not share this position, recommending iron supplementation only in case of deficiency.

The Polish Society of Gynecologists and Obstetricians shares this view. These recommendations result from the fact that, in recent years, it has been observed that there is a potential adverse effect of iron excess on the course of pregnancy and obstetric outcome. Iron takes part in the formation of reactive forms of oxygen and is responsible for development of insulin resistance and reduced insulin secretion by the pancreatic beta cells [11, 12]. Current research indicates a possible link between iron excess and risk of preeclampsia, especially among women supplementing iron before 16 weeks of gestation with normal Hgb concentration (Hgb > 13.2 g/dL at the beginning of the second trimester) [13–15].

In numerous studies, including two large meta-analyses, a correlation has been shown between the incidence of type two and gestational diabetes and the amount of iron stored in the body measured by iron concentration, hemoglobin and ferritin in blood serum [16–19].

Moreover, gestational diabetes has been shown to be more frequent in women supplementing iron that have normal hemoglobin levels [19, 20]. Helin et al. [21], showed that the occurrence of gestational diabetes was more frequent in a group of women with Hgb > 12 mg/dL with an average of 14.4 mg of iron in diet and an average of 27 mg in the form of Fe2+ supplements during preconception and in the first trimester.

The total iron requirement in pregnancy is about 1–1.2 g, of which approx. 500–600 mg participate in the development of pregnancy and the rest is the basic requirement of the body.

According to literature reports, it can be concluded that women with iron supplies of about 500 mg, which corresponds to ferritin concentration of about 60–70 mcg/L, most likely will not develop anemia nor iron deficiency in pregnancy, despite the lack of supplementation [3].

Complete iron depletion from the reserve iron storage is evidenced by ferritin concentration < 12 mcg/L [5].

With ferritin level < 60 mcg/L in women without anemia, oral iron supplementation can be considered in small doses up to about 30 mg daily after 16 weeks of gestation, for a longer period of time, which is related to the availability of storage and transport proteins [22].

It is also important to be aware of other possible, anemia causes during pregnancy, like chronic diseases, infectios, B12 vitamin deficiency or malignant tumors.

Considering the above, an insightful analysis of the mean corpuscular volume of erythrocytes (MCV) and ferritin concentration is recommended (Fig. 1), according to the diagram below. It allows appropriate implementation of dietary supplement with or without low dose iron (up to 30 mg) (Fig. 1).

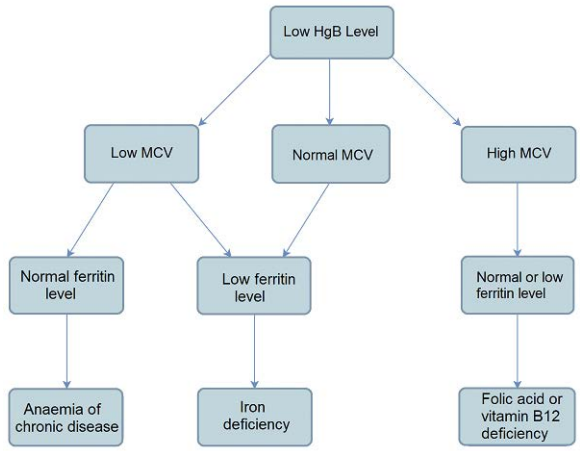

Figure 1. Management of anemia in pregnancy

The blood count test is a basic element of standard prenatal care. Its assessment should not only be based on the analysis of hemoglobin or hematocrit levels, but also MCV levels, which is an inherent parameter of the result. During anemia diagnostic tests it is recommended to examine the level of ferritin, which determines the necessity of introducing therapeutic doses of iron.

Summary

Taking into consideration the negative impact of both iron deficiency and excess on the course of pregnancy, obstetric results and possible causes of anemia in pregnancy other than iron deficiency, it is recommended to:

1. Assess blood count and ferritin concentration at the first prenatal visit and then the blood count at 15–20, 27–32,

33–37 and 38–39 weeks of gestation (in accordance with the Standard Management of Physiological Pregnancy — a regulation of the Polish Minister of Health),
2. Use iron regimens before 16 weeks of gestation in women with iron deficiency anemia (with Hgb < 11 g/dL and low ferritin level),
3. Allow iron supplementation up to 30 mg daily in women without anemia with ferritin level below 60 mcg/L after 16 weeks of gestation,
4. Use low oral doses of iron for longer period of time as treatment of iron deficiency anemia, and in the absence of improvement change to a preparation of higher proven availability or increase the dose and further observe the Fe levels,
5. Analyze the necessity of packed red cells transfusion in case of no response to high therapeutic doses of oral iron or Hgb < 7 g/dL.

DOCOSAHEXAENOIC ACID (DHA)

Concentration of lipids (fats) in the human central nervous system is about 60% of its dry mass, which puts it in the second place of lipid concentration in human body, right after the adipose tissue.

Lipids are the structural core (building material) of all biological membranes surrounding cells of living organisms, which have a major impact on the structure of membranes, their fluidity and elasticity.

Scietific studies show that high DHA concentration in membrane phospholipids affects the function, survivability and plasticity of neurons, and its deficiency or slow metabolism is certainly one of the causing factors of cognitive function decline, developing mental illnesses or neurodegenerative diseases [23] and is important for neuron protection against apoptosis induced by oxidative stress [24].

All these characteristics of membranes increase their „dynamics" in comparison with membranes built from phospholipids with a different building material [23].

An adequate DHA amount during pregnancy and lactation is therefore essential for preserving the proper development at cellular and neural level, and in consequence ensuring proper visual acuity and normal psychomotor development of the child. It also reduces the risk of depression incidence in the mother [3, 22].

Fetal DHA requirement is significantly increased in the third trimester of pregnancy. In published research, including meta-analyses, it was shown that omega-3 fatty acids supplementation reduces the risk of preeclampsia [25] and preterm birth [26–28].

In 2018 Olsen showed a 10-times higher risk of preterm birth before the 34 weeks of gestation in a group of women whose percentage of eicosapentaenoic acid (EPA) and DHA in the fatty acid pool was < 1.6% in comparison with women whose EPA and DHA percentage ≥ 1.8% (95% CI 6.80–15.79, p < 0.0001) [29].

Currently there are insufficient data to define target levels of DHA in blood serum, however the red blood cell (RBC) DHA level < 5% seems to have an effect of increasing the risk of preterm birth [29, 30].

The effect of omega-3 fatty acids on the reduction of the preterm birth risk is most likely the result of their anti-inflammatory properties.

One of the mechanisms for developing uterus contractions is the increase of connexin 43 and activation of myometrial receptors for oxytocin and prostaglandins. DHA stabilizes cell membranes by, *i.e.* modulation of Connexin 43 expression.

EPA competes with arachidonic acid (ARA), which is a source of E2 and F2 alpha prostaglandins.

The connection between consumption of fish and duration of pregnancy has been observed for many years, there are, however discrepancies in the recommended dose of polyunsaturated fatty acids.

Academy of Nutrition and Dietetics recommends supplementation of 500 mg of DHA daily for women that consume little amounts of fish, which is an equivalent of 2 portions of wild pacific salmon.

World Association of Perinatal Medicine recommends supplementation of at least 200 mg daily for all pregnant women [30].

Fish, algae and other seafood are a natural source of DHA, but one should keep in mind that fish can also be a source of environmental pollutants such as mercury, dioxins or polichlorinated biphenyls (PCBs). The highest levels of mercury are found in fish at the top of the food chain, such as shark, swordfish or tuna [31].

It seems justified that women at risk of DHEA deficiency, *i.e.* consuming low (lower than mentioned above) amount of fish, both during pregnancy and in the preconception period, should use polyunsaturated fatty acids in the form of supplements.

It is not entirely clear if increasing the DHA dose up to 600–1,000 mg daily brings benefits the further decline of the percentage of premature and very premature deliveries (< 34 weeks of gestation), but it is known that DHA supplementation in doses up to 2,100 mg per day is not associated with any side effects neither for the pregnant woman nor the fetus) [30].

The DOMInO study involving 2,399 women in singleton pregnancies has shown that the incidence of very premature deliveries (< 34 weeks of gestation) was higher in a group of women using placebo in comparison to women consuming 800 mg of DHA + 100mg of EPA per day (p = 0.03) [32].

In a multicenter Australian ORP study published in 2019, comprising of 5,486 women in singleton and multiple preg-

nancies, taking not more than 150 mg of DHA daily, a relevant statistical difference was not found in the incidence of very premature deliveries between women taking 900 mg of DHA per day additionally and a group of women also using vegetable oil containing only small amounts of DHA [33].

Currently the ADORE study is conducted in a group of 900–1,200 women and aims to compare the incidence of very premature deliveries in groups of pregnant women supplementing 200 and 1,000 mg of DHA per day. The study is expected to be completed in 2021[34].

Perhaps it will allow for determining the optimal dose of DHA supplementation in pregnancy.

Summary

Considering all available knowledge about DHA impact on the course of pregnancy and obstetric outcomes, it is currently recommended to:

1. Supplement at least 200 mg of DHA in all pregnant women,
2. Consider using higher doses of DHA in women consuming small amounts of fish during pregnancy and in the preconception period,
3. Use 1,000 mg of DHA daily in the group of women at risk of premature birth.

VITAMIN D

Vitamin D is a group of fat-soluble steroidal organic compounds. Two forms of vitamin D differing in the structure of the side chain are the most relevant ones: vitamin D2 (ergocalciferol) supplied to the human body with yeast and plant food and vitamin D3 (cholecalciferol) supplied with food of animal origin and produced in the skin under the influence of UV radiation [35].

Both D2 and D3 vitamins have no biological activity. It is only obtained through hydroxylation, which results in the formation of 1α, 25-dihydroxyvitamin D. The activation process takes place successively in the liver and then the kidneys, where both active forms of vitamin D2 and D3 [1α, 25-(OH) 2D2 and 1α, 25-(OH) 2D3] of identical biological properties are ultimately formed [36].

The role of vitamin D in regulating calcium and phosphorus levels in blood serum, maintaining the correct bone mineral density and its modulating effect on the function of the immune system has been commonly known. It cannot be ruled out that vitamin D deficiency may also play a role in the incidence of recurrent miscarriages, especially those of unspecified etiology [2].

Most randomized controlled trials have shown a positive effect of vitamin D on the course of pregnancy, however only when supplementation was started during placentation [37]. A precise effect of vitamin D on the process of placentation has not yet been explained.

It is known that 1.25(OH)2D affects the HOXA10 gene expression, responsible for uterine development in fetal life, development of endometrium, implantation and the trophoblast invasion into decidua [38].

A meta-analysis of 22 studies (consisting of 3,725 women in total) has indicated, that vitamin D supplementation in pregnancy in comparison with placebo, probably reduces the risk of **preeclampsia** [risk ratio (RR) 0.48, 95% confidence interval (CI) 0.30–0.79; 4 studies, 499 women], **gestational diabetes** (RR 0.51, 95% CI 0.27–0.97; 4 studies, 446 women) and **LBW** (< 2,500g) (RR 0.55, 95% CI 0.35–0.87; 5 studies, 697 women).

It is likely that vitamin D supplementation also reduces the risk of postpartum hemorrhage (RR 0.86%, 95% CI 0.51––0.91; 1 study, 1,134 women) [39]. Another meta-analysis comprising of 16 studies, 28,285 women in total, has shown a relationship between vitamin D deficiency in pregnancy and the incidence of SGA [40].

However, it should be emphasized that some of the quoted studies were not randomized.

The most relevant source of vitamin D for the human body is its synthesis through the skin. In Poland it is possible only from March to September and requires an exposure lasting at least half an hour without the use of sunscreen with UV filters [22]. Polish data, however, indicate a significant vitamin D deficiency in newborns regardless of the season when they were born [41].

In studies conducted in a group of pregnant women from the USA, Northern Europe and the Middle East it has been shown that 26–90% of them have vitamin D deficiency, defined as 1.25(OH)2D concentration < 50 mmol/ L [2]. Women with BMI > 30 are at particularly high risk of vitamin D deficiency. It is believed that their diet does not contain or contains not enough vitamin D. In most European countries and in the USA, supplementation of at least 600 IU of vitamin D per day is recommended. It is recognized that a dose of 1,500–2,500 IU in pregnancy and lactation could keep the vitamin D concentration in blood serum > 75 nmol/L. In most pregnant women it largely depends on their general health condition, individual diet and overall life hygiene. Choosing the correct dose of the supplement would be much easier after performing a blood test determining its actual concentration in the serum. Most often, for practical reasons for the purposes of laboratory diagnostics, the combined concentration of 25-OH-D2 and 25-OH-D3 is determined [42].

However, these tests go far beyond the standard perinatal care and are sometimes used for clinical trials developing conclusions disseminated later in recommendations.

The studies conducted so far have not shown any adverse effect of vitamin D supplementation in pregnancy up to 4,000 IU per day [37]. Assessment of vitamin D serum con-

centration in pregnant women would allow for selection of an individual dose which is particularly important in group of women at higher risk of 1.25(OH)2D deficiency, *i.e.* obese, with liver or kidney disease, chronic intestinal and thyroid gland diseases, or with diabetes, using antiepileptic or antiretroviral drugs [43]. Perhaps it would also allow for variation of the recommended dose in individual deficiency risk groups.

Summary

According to the current knowledge, it is recommended to:

1. Supplement 1,500–2,000 IU of vitamin D per day during pregnancy and lactation in women without factors suggesting vitamin D deficiency,
2. Adjust the vitamin D dose in pregnant women to its levels in the blood serum (optimal treatment),
3. Consider doses up to 4000 IU per day in women with high body mass index (BMI) > 30 kg/m^2 [44].

IODINE

During pregnancy the requirement for iodine increases, which is related to its loss through kidneys, deiodinase activity and fetal demand [22], however, the recommendations for supplementation of this element in pregnancy differ depending on the world region and the level of its deficiency in a given population. Significant iodine deficiency can be a cause of hypothyroidism in both pregnant woman and fetus, disorders of nerve myelination, CNS damage, mental retardation, hearing loss and deafness in newborns, as well as an increased risk of miscarriage and preterm deliveries.

However, such correlation was not observed in cases of mild and moderate deficiency i.e. with UIC (Urinary Iodine Concentration) in the range of 50–150 mcg/L [45, 46].

Iodine supplementation during the preconception period and in early pregnancy may reduce the risk of mental retardation of a newborn.

Despite the introduction of the WHO-recommended salt iodization programme, Europe still remains a region of iodine deficiency, with only 66% of children of school age having its adequate level. One should keep in mind that the requirement for iodine in pregnant women is approx. 1.5 times higher. In 2/3 of European countries, including Poland, it has been found that the median iodine level in pregnant women is below the norm, meaning that at least 50% of pregnant women in Poland suffer from iodine deficiency [47].

The best sources of iodine in diet are dairy products, eggs, fish and iodized salt. For women avoiding dairy products because of intolerance or by choice, or those limiting the intake of salt, providing a sufficient iodine supply without its supplementation is usually difficult to achieve.

It should also be mentioned that one of the elements that relatively easily displaces iodine from the organism is fluorine, commonly added to drinking water in many countries.

Numerous scientific studies directly point out the correlation between excessive consumption of this element and hypothyroidism, therefore an increased fluorine intake has an effect on elevated TSH levels. Hence, it is necessary in many cases to introduce iodine supplementation and target the consumption of mineral or spring water containing no controversial fluorine [48].

On the other hand, it should not be forgotten that an excess of iodine can cause thyroid function disorders, in the form of both hyperthyroidism and hypothyroidism, especially in women with anti-thyroid antibodies. Acute iodine poisoning may lead to gastrointestinal disturbance, cardiac disorders or even coma [45].

The publication made by Zhou and Condo has shown impaired psychomotor development of children at 18 months of age, assessed on the Bayley-III scale, both in case of supplementing too low (< 220 mcg/day) and too high (> 391 mcg/day) iodine doses before 20 weeks of gestation [49].

An ideal way to adjust the iodine dose to the needs of the individual pregnant women would be measuring the levels of anti-thyroid antibodies, thyroid hormones and renal iodine clearance, which should increase from 150 mcg/L up to 249 mcg/L during pregnancy. Abnormal TSH, fT3 and fT4 serum levels reflect thyroid dysfunction, while elevated thyroglobulin (Tg) level is an indirect indicator of iodine deficiency and iodine concentration in urine (UIC) > 499 mcg/L indicates its excessive intake [45].

Considering the difficulties in performing the above tests on a regular basis, the average requirement for iodine in pregnant women has been estimated in various regions of the world and the recommended dose of supplementation in pregnancy ranges from 150 mcg/day in Australia and New Zealand, 200 mcg/day in the European Union countries (EFSA) [50] to 220 mcg/day in the USA [2].

The maximum safe dose of iodine in the general population, which does not seem to cause adverse effects in healthy pregnant women, has been accepted to be 600 mcg/day in the EU countries and 1,100 mcg/day in the USA [45]. However, these doses seem too high because of high incidence of thyroid gland diseases in these areas [2].

Summary

In light of the latest research it is recommended to:

1. Supplement iodine in all pregnant women with no history of thyroid gland disease at a dose of 150–200 mcg per day,
2. Supplement iodine in women with thyroid gland disease while controlling thyroid hormones and the concentration of anti-thyroid antibodies.

FOLIC ACID

Folate participates in a number of chemical reactions responsible for transferring carbon units (OCM, one carbon metabolism), which consists of: folate transformations, homocysteine methylation and transsulfuration. These reactions play a key role in the synthesis of nucleic acids, proteins, reactive forms of oxygen and epigenetic regulation [51] (Fig. 2).

Homocysteine is an amino acid synthesized in all body cells from an exogenous amino acid — methionine, derived mostly from animal proteins. In the above homocysteine-methionine pathway, folic acid is involved (Fig. 3). Its deficiency may lead to hyperhomocysteinemia, defined as serum homocysteine concentration > 15 mcmol/L.

The main role of homocysteine is to rebuild damaged tissue, though it should not be forgotten that it also exhibits prothrombic properties.

Hyperhomocysteinemia, which occurs with folate deficiency can carry a number of adverse effects in homeostasis of both pregnant woman and the fetus. An elevated serum homocysteine concentration is considered to be a risk factor for development of many diseases, especially of the cardiovascular system and indirectly of dementia, as a result of atherosclerosis development in the cerebral vessels [51, 52]. It may also have an adverse effect on the course of pregnancy, impairing the blood supply to the placenta, which may lead to fetal growth restriction (FGR) or intrauterine death, as well as a negative impact on the development of the CNS of the fetus [51].

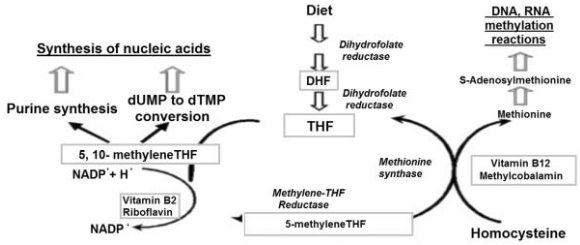

Figure 2. The effect of folic acid on homeostasis [51]

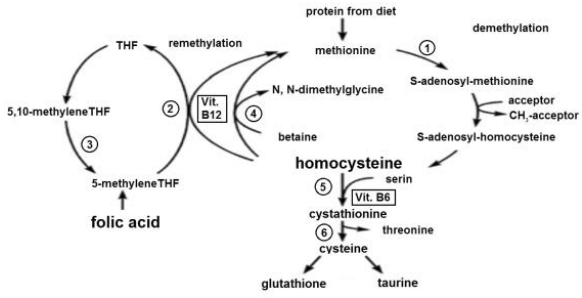

Figure 3. Homocysteine metabolism pathway [51]; 1 — methionine adenosyltransferase; 2 — methionine synthase; 3 — reductase 5, 10-methylenetetrahydrofolate (MTHFR); 4 — betaine-homocysteine methyltransferase; 5 — cystathionine βsyntase; 6 — γ-cystathionase [53]

An excessive consumption of animal proteins causes temporary increase in serum homocysteine levels. However, there is no convincing evidence that an increased methionine intake causes chronic elevation of homocysteine, especially in people with proper B vitamins intake, including folic acid. An unbalanced diet is a common cause of increase in homocysteine concentration, including vegetarian and vegan diets, with no additional, yet in this case, necessary supplementation of folic acid and other vitamins, especially the B complex. Modern food processing can also lead to a breakdown of a significant percentage (30–55%) of essential vitamins [53].

It is important to remember about other relevant causes of hyperhomocysteinemia, such as liver or kidney failure, diabetes, malignant tumors or using drugs like methotrexate (which inhibits dihydrofolate reductase), metformin (which affects the metabolism of B12 vitamin), cholestyramine (which reduces the absorption of B12 and folate), carbamazepine and valproic acid (which affect the folic acid metabolism), stimulants and genetically determined deficiency or lack of enzymes involved in homocysteine metabolism, especially of the cystathionine β-synthase (occurring 1/200–400 000 births) [53].

In recent years, possible contribution of another enzyme involved in folic acid metabolism and therefore homocysteine was pointed out — 5, 10-reductase methylenetetrahydrofolate (MTHFR). It is believed, that MTHFR activity can be moderately reduced in cases of commonly occurring polymorphic variants c.665C > T (known so far as c.677C > T) and c.1298A > C in the MTHFR gene (NM_005957). They are particularly common in white and Caucasian race, also in Poland, reaching up to 50% of general population.

Currently, however, there is no sufficiently documented evidence indicating significant impact of the mentioned variants on the incidence of high homocysteine concentration or neural tube defects [54]. There is no indication to use higher doses of folic acid or its active form in these cases. Considering the inverse correlation between homocysteine and folic acid serum levels it has been established that folic acid concentration > 10 nmol/L in blood serum and > 349 nmol/L in erythrocytes reflects its sufficient consumption in a healthy adult population. Based on randomized studies it has been established that daily requirement for folates, in this group, allowing for maintenance of the proper concentration in blood is 400 mcg, including 250 mcg for natural folates and 150 mcg for folic acid, respectively. To achieve the same level of folate in erythrocytes, pregnant women require an intake of about 600 mcg in the II and III trimesters, and about 500 mcg daily during lactation [50].

Folate deficiency can also result in impaired DNA synthesis and cell division, especially in rapidly growing tissues like bone marrow or fetal tissues. As a result of folic acid deficiency erythrocytes may form an abnormal nucleus, megaloblastic anemia as well as miscarriages and birth defects may develop, especially neural tube defects, which incidence is globally estimated at about 18.6/10,000 births [55].

Although the etiology of neural tube defects is multifactorial and both genetic and environmental factors take part in their formation, it is now known that one carbon metabolism plays a significant role in the process of neural tube closure. Mutations in genes coding enzymes participating in the OCM pathways are most certainly associated with the risk of natural tube defects (NTD) incidence.

However, despite of 30 years of research on genes involved in the process of neural tube closure, no simple correlation between mutations in specific genes and the incidence of NTD was found. Research carried out in the recent years indicate that the underlying cause of neural tube defects is polygenic and the risk of their occurrence increases with the accumulation of various mutations [55].

Neural tube closure occurs within 28 days after conception. Abnormalities in the course of this process result in formation of defects, such as anencephaly or spina bifida.

In 90% of cases, spina bifida is accompanied by type II Arnold-Chiari malformation, which involves displacement of the hindbrain structures to the spinal canal.

The correlation between folate deficiency and the incidence of NTD was discovered in 1965. CDC followed by issuing a recommendation in 1991 that women with prior NTD child should supplement 4 mg of folic acid per day for a strictly defined time, *i.e.* at least 4 weeks before the pregnancy and during its first 12 weeks. The recommendation was based on a research conducted on a group of 1,195 women with a history of NTD, in which the incidence of NTD in the next pregnancy was compared in a group of women using 4 mg of folic acid and in a folate-free group, finding a reduction of the NTD risk from 3.5% to 1% with no adverse effects [56].

Prolonged use of 4mg/d of folic acid may have potentially harmful effects on the fetus. A research by Johns Hopkins Bloomberg School of Public Health has shown that supplementing high doses of folates in pregnancy may increase the risk of autism in children. Due to the above report, in 2016 RCOG recommended using higher than 400 mcg/d doses of folic acid only in strictly defined groups of pregnant women and not longer than until 12 weeks of gestation [57].

In 2008, a study consisting of 700 women in India, Yajka and Deshpande showed possible effect of high folic acid concentration in erythrocytes of women at 28 weeks of gestation on the risk of developing insulin resistance in their offspring, measured by the HOMA-R index in 6-year-old children.

Excess of folic acid can also mask first symptoms of vitamin B12 deficiency-megaloblastic anemia [59, 60]. There have also been studies showing that using lower doses of folic acid for a longer period of time is effective in prophylaxis of neural tube defects [61–65].

However, selection of population groups in the above research does not authorize a change in the currently advocated use of 4 mg of folic acid in a group of patients with a history of NTD at least 4 weeks before planned conception and first 12 weeks of pregnancy.

Is should be remembered that although maternal folate deficiency may cause neural tube defects in the fetus, most NTDs occur in children whose mothers had normal levels of folic acid in blood serum. Exogenous folic acid prevents some neural tube defects most probably by epigenetic regulation (methylation) and regulation of cell division (purine synthesis).

Relevant environmental risk factors for NTD include: pregestational diabetes (risk 2–10 times higher), BMI > 30 (risk 1.4–3.5 higher), use of antiepileptic drugs (carbamazepine and valproic acid are associated with 1–2% of NTD risk), genetic conditions- neural tube defects in previous pregnancy or in a family history [66–70].

Serum folate level increases right after consumption and the effect lasts briefly, while the level in erythrocytes reflects the stored amount in the body better.

It has been shown that at RBC folate concentration of 1,000–1,300 nmol/L the risk of NTD is 7.9/10,000 pregnancies. Further increase of folate concentration in erythrocytes did not significantly reduce the risk [66] (Fig. 4).

In 1998, the FDA recommended fortifying foods with folic acid. Adding a dose of 0.4 mg of folate per 100 g to basic products (bread, pasta, flour) allowed an increase in the daily intake from 0.288 ± 195 mg to 0.550 ± 279 mg, which resulted in a decline of NTD incidence from 6.86 to 4.04/10,000 pregnancies. The above food enrichment was also introduced by countries like Canada, South Africa Chile, Saudi Arabia with a similar result.

In the EUROCAT study including 34 studies from 8 European countries where no food fortification was introduced and only supplementation of folic acid in preconception and early pregnancy was used between 1980 and 2001, such relevant reduction of NTD incidence was not obtained. The incidence of neural tube defects in those countries was 9.1/10,000 pregnancies. Furthermore, the research has indicated that folate supplementation in the preconception period does not exceed 50%. Though one should keep in mind that about 60% of all pregnancies is unplanned!

A 2017 in Germany study in a population of healthy, non-pregnant women, excluding women with diabetes, BMI > 30 or with chronic gastrointestinal diseases resulting in malabsorption such as colitis ulcerosa, Crohn's or

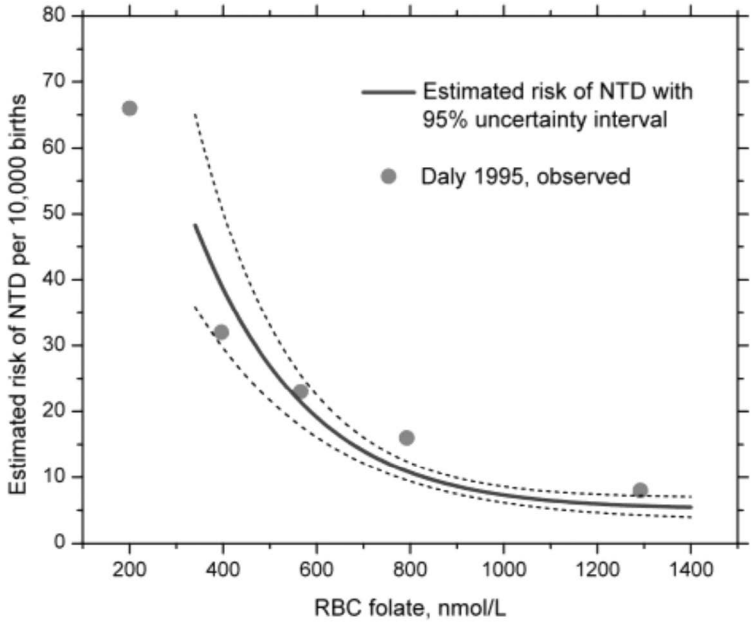

Figure 4. Red blood cell dependent risk of natural tube defects

celiac disease, has shown that 88% of them have folate concentration in RBC <906 nmol/l, 6% < 340 nmol/L, and the mean folate concentration was 640 nmol/L. Folic acid supplementation in a dose of 0.8 mg/d for 4 weeks allow for folate concentration in RBC > 906 nmol/L in 45%, while supplementation of 0.04 mg/d in the same period of time allowed for reaching > 906 nmol/L in only 31% of respondents. Extending the supplementation period to 8 weeks obtained the required dose in 83% of the 0.8 mg/d dose group and in 54% of the 0.4 mg/d dose group, respectively.

In a 2019 meta-analysis it has been shown that supplementation of 0.4 mcg/d of folate for about 36 weeks increases the folate levels in RBC by about 78% compared to the initial baseline and maintaining this concentration with further supplementation with the same dose, while the higher the increase, the lower the initial concentration.

For example, in case of folate concentration in RBC at 600 nmol/L, a 400 mcg/d dose causes an increase in folate concentration in RBC to 1,065 nmol/L within 9 months [72].

In a 2019 recommendation for food producers, the FDA established the optimal daily dose of consumed folate in the form of fortified food for the general population as 0.4 mg/d, 0.8 mg/d during pregnancy and lactation and the safe upper limit was established to be 1 mg [73].

In 2019 EFSA recommended the daily folate consumption to be 0.33 mg/d in a population of healthy men and non-pregnant women, 0.6 mg/d for pregnant women and 0.5 mg/d for breastfeeding women.

According to current research, the best solution to prevent the neural tube defects seems to be obligatory fortification of food with folic acid, which also is an appeal of the Polish Society of Gynecologists and Obstetricians.

The CDC and Institute of Medicine recommend that all women of reproductive-age intake at least 0.4 mg/d of folic acid in form of supplements, fortified food or the combination of both as an addition to a natural, folate-rich diet [56, 74].

Summary

According to the up-to-date knowledge, it is recommended to:

1. Use 0.4 mg/d of folic acid in all women of reproductive age, as a supplement to natural, folate-rich diet,
2. Supplement 0.4–0.8 mg/d of folic acid in the first trimester (before 12 weeks of gestation),
3. Supplement 0.6–0.8 mg/d of folic acid after 12 weeks of gestation and during lactation in a population of women with no additional risk factors,
4. Supplement 4 mg/d of folic acid in women with history of NTD in prior pregnancy, in a strictly defined period of time, *i.e.* at least 4 weeks before planned conception and during the first 12 weeks of pregnancy, then reduction of the dose to the levels of the general population,
5. Use 0.8 mg/d of folate for at least 3 months before planned conception and during pregnancy and lactation in women with high risk of folate deficiency and NTD:
   - with type I or II diabetes before pregnancy,
   - use of antiepileptic drugs, methotrexate, cholestyramine, metformin, sulfadiazine before or during pregnancy,

- using stimulants,
- with liver or kidney failure,
- with BMI > 30,
- after bariatric surgery or with gastrointestinal diseases resulting in malabsorption (Crohn's disease, colitis ulcerosa, celiac disease).

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Konferencja jest skierowana do wszystkich osób zainteresowanych tematyką. Sesje satelitarne firm farmaceutycznych, sesje firm farmaceutycznych oraz wystawy firm farmaceutycznych są skierowane tylko do osób uprawnionych do wystawiania recept lub osób prowadzących obrót produktami leczniczymi — podstawa prawna: Ustawa z dnia 6 września 2001 r. Prawo farmaceutyczne (Dz. U. z 2017 r. poz. 2211, z późn. zm.).