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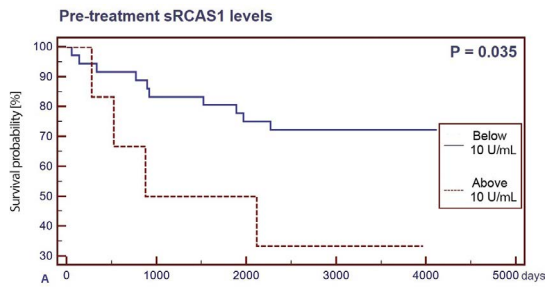

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Is copeptin a new potential biomarker of insulin resistance in polycystic ovary syndrome?

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ABSTRACT

Objectives: Copeptin has been reported to play an important role in metabolic response in women with PCOS. However, the optimal cut-off value for detecting subjects with insulin resistance (IR) remains undetermined. We investigated whether copeptin can serve as an indicator of IR and tried to determine the optimal cut-off value of plasma copeptin concentration in detecting subjects with PCOS and IR.

Material and methods: We carried out a case-control study on 158 women with PCOS and HOMA-IR < 2.5, 96 women with PCOS with HOMA-IR ≥ 2.5, and 70 healthy volunteers. Plasma copeptin, as well as hormonal, biochemical, metabolic, and IR parameters, were measured. To investigate whether copeptin allows IR to be predicted in PCOS, we used logistic regression models and ROC curve analysis.

Results: Median plasma copeptin concentration was the highest in the women with PCOS and HOMA-IR ≥ 2.5. Logistic regression analysis revealed that copeptin was the strongest predictor of HOMA ≥ 2.5 (OR: 53.34 CI 7.94–358.23, p < 0.01). Analysis of ROC curves indicated that the cut-off value above 4 pmol/L of plasma copeptin concentration had high (99%) specificity but very low (21%) sensitivity in diagnosing of IR (AUC 0.607 (95% CI 0.53–0.68.

Conclusions: Our findings suggest that copeptin is associated with IR in PCOS patients, but due to low sensitivity should not be considered as a marker of IR.

Key words: copeptin; PCOS; insulin resistance; metabolic syndrome; AVP

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INTRODUCTION

Polycystic ovary syndrome (PCOS) is a heterogeneous endocrine disease with an estimated occurrence rate of 5–10% in women of reproductive age [1]. Although metabolic disturbances, such as obesity and insulin resistance (IR), play an important role in the pathogenesis of PCOS, they do not currently form part of the diagnostic criteria. Approximately 50–60% of women with PCOS are overweight or obese, and IR is found in 50% of women with PCOS, irrespective of obesity [2]. Women with PCOS have increased cardiometabolic risk — that is, their risk of developing diabetes, hypertension, dyslipidemia, and cardiovascular disorders is greater than the risk within the population as a whole [3]. It is known that IR is the underlying cause for all these cardiovascular and metabolic disorders. Attention has recently been drawn to the role of arginine vasopressin (AVP) in controlling glucose homeostasis, the pathogenesis of IR, and the development of diabetes [4–6]. The activation of the hypothalamic-pituitary-adrenal (HPA) axis by AVP under chronic psychosocial stress stimulates the secretion of cortisol by activating V1a receptors, which interferes with insulin activity while stimulating glucagon secretion and glycogenolysis [7]. This process subsequently leads to an increase in blood glucose. By activating the V1b receptors on chromaffin cells in the adrenal medulla, AVP also increases epinephrine, which contributes to the development of hyperglycemia through glycogenolysis in the liver [7]. Increased AVP, as a result of the resistance of AVP to the V1a receptor, may also contrib-

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ute to IR and to the development of diabetes mellitus (DM) by stimulating the V1b receptor [8]. Because of its short half-life and instability, AVP is difficult to measure. Copeptin, the C-terminal fragment of provasopressin, is formed in the same quantities as AVP and, as a result of the processes that activate it, has been found to be a stable and sensitive surrogate marker for AVP release [9].

Recently, it has been demonstrated that plasma copeptin concentrations are elevated in plasma of PCOS patients. Copeptin thus appears to have an important role in metabolic response and in the subsequent development of atherosclerosis in insulin-resistant, hyperandrogenemic PCOS patients [10, 11]. However, the optimal cut-off value for detecting subjects with metabolic disorders remains undetermined.

Objectives

The main aim of the study was to investigate whether copeptin can serve as an indicator of IR, and secondly, to determine the optimal cut-off value of plasma copeptin concentration in detecting subjects with PCOS and IR.

MATERIAL AND METHODS

The study included 254 women with PCOS, aged 18–37 years, and hospitalized in the Department of Reproductive Medicine and Gynecology at the Pomeranian Medical University, Szczecin, and in the Infertility and Reproductive Endocrinology Division of Poznań University of Medical Sciences in the years 2010–2012. Women with PCOS were divided into two groups, depending on the presence of IR: the PCOS(+)IR group consisted of women with a homeostasis model assessment for IR index (HOMA-IR) ≥ 2.5, while the PCOS(-)IR group included only patients with HOMA-IR < 2.5. The study was approved by the Pomeranian Medical University Ethics Committee (No. KB-0012/41/11). The patients were informed of the plan and purpose of the study and gave their written informed consent.

The diagnosis of PCOS was confirmed when at least two of the three diagnostic criteria were present, according to the Rotterdam ESHRE/ASRM-sponsored PCOS Consensus Workshop Group [12]. Clinical hyperandrogenism was defined as a presence of hirsutism (a modified Ferriman-Gallwey score ≥ 8) with or without acne. Metabolic syndrome (MetS) was defined according to the IDF criteria by waist circumference > 80 cm and at least two of the remaining features: 1. Triglyceride (TG) level: ≥ 150 mg/dL or specific treatment for this lipid abnormality; 2. HDL cholesterol level: < 50 mg/dL or specific treatment for this lipid abnormality; 3. Systolic blood pressure ≥ 130 mmHg and diastolic blood pressure BP ≥ 85 mmHg, or treatment of previously diagnosed hypertension; 4. Fasting plasma glucose (FPG) ≥ 100 mg/dL or previously diagnosed type-2 diabetes [13].

The control group consisted of 70 healthy, normally menstruating, age-matched hospital staff and medical students. We included only those subjects who met the following inclusion criteria: eumenorrhea, no medical conditions requiring pharmacological treatment, and no apparent abnormalities in physical examination.

Assessment of clinical variables

The patients' BMIs were calculated from the weight and height measurements, based on the recommendations of the World Health Organization [14]. Waist and hip circumference measurements were also carried out. Blood pressure (BP) was measured using a standard mercury sphygmomanometer with an appropriate cuff size after a resting period of at least 30 min. Hypertension was defined according to the criteria of the Seventh Report of the Joint National Committee on the Prevention, Detection, Evaluation, and Treatment of High Blood Pressure as systolic BP ≥ 140 mmHg and diastolic BP ≥ 90 mmHg [15]. In the early follicular phase, between days 3 and 5 of the cycle, transvaginal ultrasound scans were performed in all patients. Polycystic morphology of ovaries was identified by the sonography according to the established criteria recommended in the literature [12].

Blood sample collection

Blood sampling was performed in the early follicular phase of the spontaneous or progesterone-induced menstrual cycle (between cycle days 3 and 5), after 12 h overnight fasting. Serum levels of FSH, LH, estradiol, prolactin, TSH, SHBG, and insulin were determined by specific electrochemiluminescence assays (automated Elecsys 2010 immunoanalyzer, Roche Diagnostics GmbH). The same method, with the use of Cobas 6000 equipment and Roche reagents, was applied to determine total testosterone levels. Levels of serum total cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL), and triglycerides (TG) were determined by semiautomated enzymatic methods (automated Cobas Integra 400Plus analyzer, Roche Diagnostics). The chemiluminescence method was used to determine the levels of androstenedione, DHEA-S, and hs-CRP with the use of Immulite equipment and Siemens reagents). The plasma glucose concentration was determined using the glucose oxidase/peroxidase method. All the basic hormonal and biochemical measurements were performed at the Central Laboratory of University Hospitals.

The free androgen index (FAI) was calculated as the serum testosterone (nmol/L) x 100/SHBG (nmol/L) ratio [16]. IR was diagnosed according to the homeostasis model assessment for IR index (HOMA-IR), and the value was calculated using the following formula: fasting plasma glucose (mmol/L) × fasting serum insulin (mU/mL)/ 22.5. The cut-off value for IR was HOMA-IR ≥ 2.5 [17].

Copeptin assay

Blood samples were taken into EDTA tubes and centrifuged at 3000 G for 10 min. After that, 500 µg of the obtained plasma was separated into a clean test tube with the addition of 5 µl aprotinin. The plasma samples were stored at -80°C until analysis. Copeptin levels were measured in duplicate using competitive enzyme immunoassay (#EK-065-3 Copeptin-Human EIA Kit, Phoenix Pharmaceuticals), carried out in line with the manufacturer's recommendations and using the average values from two measurements. The analytical sensitivity was 0.16 ng/mL. The coefficient of intra-assay repeatability was below 10%, whereas the coefficient of interassay repeatability for this test was < 15%. No cross-reactions were observed in this method.

Statistical analysis

Since the distributions of most quantitative variables were significantly different from normal, the difference between the groups was tested using the Kruskal-Wallis (test) ANOVA. The Fisher exact test was employed to compare qualitative variables. Where a significant difference was found in the Kruskal-Wallis test, the post hoc test with the Bonferroni adjustment was applied to determine the significant differences. The strength of the correlation between quantitative variables was measured using the Spearman rank correlation coefficient (Rs).

A variety of statistical methods were used to investigate whether copeptin can predict insulin resistance in PCOS. We first used linear and logistic regression models. Univariate linear regression analyses were performed with the copeptin level as the independent variable and HOMA-IR as the dependent variable. Subsequently, these associations were adjusted for covariates that could potentially confound in this association, using multivariable logistic regression models. Multivariable models were built stepwise and the following statistically significant parameters were included: age, BMI > 25 kg/m^2, SBP, HDL and copeptin > 4.0 pmol/L.

Secondly, a receiver operating characteristic (ROC) analysis was performed to assess the diagnostic value of copeptin as a marker of insulin resistance. P-values < 0.05 were considered statistically significant. Statistica 10 software (StatSoft, USA) was used for the calculations.

Additionally, to examine the possible correlation between copeptin concentration and the prevalence of MetS, the subjects were stratified by quartiles of copeptin concentration.

RESULTS

The baseline characteristics of the three study groups are shown in Table 1. The groups differed statistically in terms of anthropometric measurements (BMI, waist circumference, and WHR), chosen hormonal indices (SHBG, FAI), blood pressure, and HDL and LDL cholesterol. As might be expected, the PCOS(+)IR group had the highest fasting plasma glucose concentration and the highest fasting plasma insulin levels. Plasma copeptin concentration was the highest in the PCOS(+)IR group (median 1.64, interquartile range [IR 0.98–3.27] pmol/L), moderate in the PCOS(-)IR group (1.28 [IR 0.93–2/02] pmol/L), and the lowest (0.97 pmol/L [IR 0.76–1.14]) in the control group (p = 0.014). Interestingly, significant differences were found between studied groups regarding the prevalence of MetS, which was present in 37.5% of PCOS(+)IR, 10.1% of PCOS(-)IR, and 17.1% of controls.

Spearman rank correlation coefficient analysis showed no correlation between the plasma copeptin concentration and anthropometric measurements. Plasma copeptin was inversely correlated with FG score (-0.17; p < 0.01), and positively correlated with fasting insulin (0.18; p < 0.005), HOMA-IR (0.19; p < 0.005), and systolic and diastolic BP(0.14; p < 0.05; 0.17; p < 0.01). Even though the prevalence of MetS was different, we failed to find any correlation between MetS and copeptin (p = 0.4).

In the logistic regression model, the strongest predictor of elevated HOMA-IR ≥ 2.5 was copeptin (OR: 53.34 CI 7.94–358.23, p < 0.01). The others were BMI ≥ 25 m/kg^2 (OR: 4.22 CI: 1.85–9.64, p < 0.01) and SBP (OR: 1.02 CI: 1.00–1.05, p = 0.03). Age (OR: 0.86 CI: 0.80–0.93, p < 0.01) and HDL (OR: 0.96 CI: 0.93–0.98, p < 0.01) were negatively associated with HOMA-IR ≥ 2.5.

The ROC curve assessing the ability of copeptin to distinguish between women with and without IR had an AUC of 0.607 (95% CI 0.53–0.68) and a threshold value of 4 mmol/L or higher to identify insulin-resistant women in the PCOS group (Fig. 1). At this cut-off point, copeptin assay showed very high (99%) specificity to identify IR in women with PCOS, but low (21%) sensitivity.

DISCUSSION

Although IR and its metabolic consequences are not included in the diagnostic criteria of PCOS, it is well known that they play an important role in the pathogenesis of this disease. Copeptin, the C-terminal fragment of provasopressin, is formed in equal quantities as vasopressin (AVP) and, as a result of processes that activate it, has been suggested as a new and promising marker of IR and MetS. Until recently, it was believed that AVP's only role was its effect on the water-electrolyte balance of the body. It has since been shown that, in response to stress factors, AVP and corticotrophin-releasing hormone (CRH) stimulate the secretion of adrenocorticotrophic hormone (ACTH), which increases the secretion of adrenocortical hormones — mainly cortisol and, to a smaller extent, androgens and aldosterone [18,19]. Although under physiological condi-

Table 1. Clinical characteristics of the control, PCOS(-)IR, and PCOS(+)IR groups

	Controls n = 70	PCOS(-)IR [HOMA < 2.5] n = 158	PCOS(+)IR [HOMA ≥ 2.5] n = 96	p-value
Age [years]	28 (22–30)	28 (25–31)	26.5 (23–30.5)	ns
BMI [kg/m2]	25.3 (22.1–28.7)	22.7(20.7–26.5)	28.8 (24.8–32)	p < 0.001
Waist circumference [cm]	80.5 (71–91)	75 (69–85)	91 (78–101)	p < 0.001
WHR	0.79 (0.74–0.86)	0.78 (0.74–0.84)	0.83 (0.77–0.88)	p < 0.001
FSH [mIU/mL]	4.9 (3.96–6.25)	5.86 (5–6.84)	5.51 (4.74 -6.77)	ns
LH [mIU/mL]	6.04 (4.99–7.15)	9.32 (5.8–12.7)	7.74 (5.39–12.3)	ns
Estradiol [pg/mL]	47.1 (32.5–70)	46.4 (34.4–64.1)	43 (33.5–61.6)	ns
Prolactin [ng/mL]	15 (9.96–19.3)	13.8(9.85–18.8)	16(10.5–22.1)	ns
TSH [µIU/mL]	1.63 (1.2–2.05)	1.9 (1.29–2.45)	1.94 (1.31–2.46)	ns
Testosterone [ng/mL]	0.35 (0.25–0.46)	0.46 (0.33–0.56)	0.46 (0.35–0.61)	ns
SHBG [nmol/L]	55.4 (39.9–73.4)	45.73 (30.5–64.3)	28.3 (19.25–50.3)	p < 0.001
FAI	2.45 (1.34–3.57)	3.65 (2.18–5.48)	5.43 (3.48–9.17)	p < 0.001
DHEA-S [µg/dL]	159 (135–181)	247 (198–332)	287 (212–361)	ns
FG Score	0 (0–0)	8 (4–11)	8 (3–10)	ns
Fasting Glucose [mg/dL]	85 (81–89)	89 (83–94)	94.1 (88.7–98)	—
Fasting Insulin [µIU/mL]	6.83 (5.23–9.43)	5.97 (4.67–8.08)	14.8 (12.9–19.1)	—
HOMA - IR	1.42 (1.07–2.06)	1.33 (0.98–1.83)	3.51 (2.96–4.48)	—
Copeptin [pmol/L]	0.97 (0.76–1.14)	1.28 (0.93–2.02)	1.64 (0.98–3.27)	p < 0.05
SBP [mmHg]	120 (110–130)	120 (106–130)	130 (120–140)	p < 0.001
DBP [mmHg]	78.5 (70–85)	70 (60–80)	80 (70–85)	p < 0.001
Total Cholesterol [mg/dL]	165 (145–187)	186 (164–209)	188 (168–211)	ns
HDL Cholesterol [mg/dL]	59.5 (47–69)	66.5 (56–78)	51.5 (43.1–61.5)	p < 0.001
LDL Cholesterol [mg/dL]	99 (82–116)	102 (85.8–120)	110 (97–133)	p < 0.05
Triglycerides [mg/dL]	73 (55–99)	72 (57.9–94.1)	103 (72.2–142)	p < 0.001
Metabolic syndrome [%]	17.1%	10.1%	37.5%	p < 0.001
hs-CRP [mg/L]	1.3 (0.79–2.59)	1.31 (0.69–3.4)	2.05 (0.82–4.9)	ns

Values are expressed as medians (interquartile range); p-values were calculated using the Mann-Whitney post hoc U-test with the Bonferroni adjustment; p < 0.05 was considered statistically significant

tions CRH is a stronger stimulator of ACTH secretion, the synergistic effect of both neurohormones is over 30 times greater than that of CRH alone. It has been demonstrated that the role of AVP is greater under chronic stress. [19] There is an increase in the number of neurons expressing both CRH and AVP, and the amount of V1bR increases in the pituitary, with reduced CRH receptor. This effect is resistant to glucocorticoid feedback, suggesting crosstalk between the AVP and hypothalamic-pituitary-adrenal system that could be relevant to insulin resistance and diabetes development [20, 21]. Research on an animal model involving mice lacking V1aR showed display-impaired glucose tolerance and development of IR with increased AVP levels, whereas mice that lacked V1bR had lower fasting plasma glucose level and increased insulin sensitivity [22, 23]. Based on these studies, it is assumed that the abnormal effects on V1aR lead to increased AVP levels, which then stimulate VbR, leading to the development of disorders causing IR and diabetes. Saleem et al. [7] first report the cross-sectional association between high plasma copeptin levels, measures of IR, and the presence of MetS. The researchers reported that plasma copeptin levels correlate significantly with BMI, fasting plasma glucose, insulin level, HOMA-IR, and triglyceride level, and inversely with HDL-cholesterol. Furthermore, the multiple regression analysis that was adjusted for age and sex, plasma copeptin levels in the third and fourth quartiles were significantly associated with higher odds of having MetS. It has been estimated that the activation of the HPA axis by AVP in chromic psychosocial stress may be one of the mediators of its association with IR. It was concluded that such neuroendocrine dysregulation may lead to higher cortisol, decreased energy expenditure, increased appetite and food consumption, increased peripheral vascular resistance, and increased insulin levels. The reported study [7]

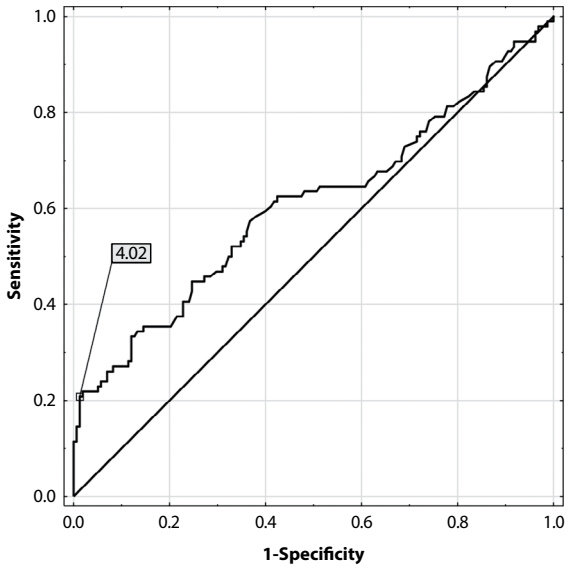

Figure 1. Receiver operating characteristics (ROC) curve assessing the ability of copeptin to distinguish between women with and without IR

included a large cohort that was much older than ours (with a mean age of 59 years) with familial hypertension and a relatively high prevalence of MetS (around 50%). In agreement with this study, we observed that plasma copeptin levels correlate with IR, but (unlike the results of Saleem et al.) not with full-blown MetS. Interestingly, a cross-sectional study extended the findings of Saleem et al. to a large population-based sample by showing that high copeptin levels are not only associated with the clustering of the MetS components, but that there is also an independent relationship with the core components of the syndrome — i.e., with hypertension and abdominal obesity [24]. Our results suggest that higher plasma copeptin levels are positively correlated with systolic and diastolic BP, but not with full-blown MetS. The differences may be due to significant differences in population characteristics. We speculate that absence of MetS among our subjects is due to the young age. Furthermore, we used different criteria (the IDF criteria) to diagnose MetS; these are more frequently used in Europe. Interestingly, Abbasi et al. have shown that the association of plasma copeptin with the risk of developing DM was stronger in women than in men, which contradicts the previous findings [24, 25]. Researchers have suggested that, because of lower tolerance to changes in AVP levels in women than in men, plasma copeptin both alone and along with the existing biomarkers such as glucose and hs-CRP significantly improved the risk prediction for diabetes in women, but not in men [26–28].

Our study aimed to assess the associations of copeptin concentration with well-known IR markers in women with PCOS. We have shown that plasma copeptin levels markedly increased in PCOS patients as compared with healthy women, with special emphasis on the PCOS(+)IR group. This finding is in agreement with the report of Karbek et al. [10], the only study published to date that had considered copeptin in PCOS. Other researchers have reported increased copeptin levels and their positive correlation with fasting insulin, triglyceride, free testosterone, HOMA-IR, and carotid intima media thickness. The above study [10] included only a relatively small group of forty women with PCOS and investigated the correlation between copeptin and the progression of atherosclerosis in PCOS patients. This study demonstrated that copeptin concentrations increase in PCOS patients and are associated with IR. However, the authors did not show whether copeptin can be an indicator of IR, nor did it determine the optimal cut-off value of plasma copeptin in detecting subjects with metabolic disorders. In agreement with the results of Krabek et al., plasma copeptin levels were significantly higher in PCOS than in the non-PCOS group and positively correlated with fasting insulin level, HOMA-IR, and FG score.

In a large prospective cohort study, Enhorning et al. reported that elevated copeptin predicts increased risk of DM independently of established clinical risk factors, including fasting glucose and insulin [8]. The association between copeptin at baseline and the incidence of DM was independent of the incidence of abdominal obesity and vice versa; it is thus possible that AVP independently triggers two different pathways leading to DM and abdominal obesity. Despite this, there is a possibility that the primary elevation of AVP caused by an increase in abdominal fat deposition can lead to the development of DM. Moreover, copeptin may better signal DM susceptibility earlier in the prediabetes state, which would be particularly useful in individuals with normal fasting glucose levels, who are likely to be less closely monitored than patients with impaired fasting glucose [4, 5]. Because PCOS is a risk factor for the development of type-2 DM, assessing the clinical utility of novel biomarkers such as copeptin would seem to be very important in this group of patients.

Our study showed copeptin to be associated with the risk of increased HOMA IR ≥ 2.5 in PCOS patients. The ROC analysis implies that copeptin levels above 4 pmol/L predict IR in PCOS patients with a specificity of 99%, meaning that almost all patients with that level and above have IR, however low sensitivity of 21% implies that 79% of IR women with PCOS may also have lower than 4 pmol/L copeptin levels. Therefore, copeptin cannot serve as a good marker for IR in our study group. Also, AUC value 0.607 reveals that copeptin levels are relatively weak surrogate of IR.

This study has some limitations. First, it was observational, so we could not establish the temporal changes in plasma copeptin, its relationship with preexisting metabolic

risk factors, or the future development of complications. Second, the number of individuals in the control group was relatively low, and larger studies are needed to confirm our findings. We did not measure either psychosocial stress in the participants or plasma levels of cortisol — the final mediator of a perturbed HPA axis. In our study, we did not use ambulatory BP measurement, which has been shown to be more useful than the causal or office BP measurement [29]. BP, if measured once during the day at a clinical examination, may give overestimated values in patients with white-coat syndrome. Finally, IR was reported based on HOMA-IR values. Although the gold standard for establishing IR is the euglycemic-hyperinsulinemic clamp, this elaborate procedure is not suitable as a screening method. The HOMA-IR calculation correlates very well with the euglycemic-hyperinsulinemic clamp result and is often used as a surrogate marker [30]. However, the cut-off or threshold values for HOMA-IR have not been established. It is well known that the development of IR occurs on a physiological continuum. Our choice of the value 2.5 is based on original HOMA research and previous work with PCOS patients [17, 31, 32].

CONCLUSIONS

Our data suggest that copeptin is associated with IR in PCOS patients, but copeptin measurements in plasma have very low sensitivity in detecting IR in this group of patients. Further work is necessary to improve our understanding of the role of AVP in IR and metabolic disorders in PCOS.

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Conflicts of interest

The authors report no conflicts of interest.

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Underestimation of breast cancer in intraductal papillomas treated with vacuum-assisted core needle biopsy

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ABSTRACT

Objectives: The aims of the study were as follows: 1) to determine the applicability of vacuum-assisted core needle biopsy in the diagnosis and management of intraductal papillomas of the breast; 2) to define factors which increase the risk for underestimation of breast cancer.

Material and methods: Between 2002–2017, a total of 222 cases of intraductal papillomas were diagnosed in one center (201 using vacuum-assisted core-needle ultrasound-guided biopsy and 21 using stereotactic biopsy). All patients underwent scheduled follow-up imaging.

Results: Pure papillomas were diagnosed in 158 women, whereas papillomas with atypia, in this case atypical ductal hyperplasia (ADH), were found in 29 subjects. In the latter group, 3 cases of invasive carcinoma and 5 cases of ductal carcinoma in situ (DCIS) were detected using open surgical biopsy. Breast cancer underestimation in that group of patients was 20%. Overall, ADH, whose presence increases the risk for BC by thirteen-fold as compared to other accompanying lesions, proved to be the most important predictive factor. Also, age, non-radical biopsy excision, and high BI-RADS ultrasound and mammogram scores increased the probability of malignancy. During the control follow-up, no cases of IP recurrence in the primary localization were observed in the group without open surgical biopsy.

Conclusions: Vacuum-assisted core needle biopsy is an efficient tool in the diagnosis and management of intraductal papillomas of the breast. Surgical excision is not indicated in cases when a pure intraductal papilloma, and data correlation between the diagnosis and the clinical presentation were confirmed. Regardless, caution is advised if residual lesions were left and in older populations. Open surgical biopsy should remain the standard of care in cases with atypia and discordance between clinical and pathology data.

Key words: intraductal papilloma; B3 breast lesions; vacuum-assisted core needle biopsy; breast carcinoma

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INTRODUCTION

Intraductal papillomas (IPs) of the breast are benign growths originating from the epithelium of the milk duct. Owing to their heterogeneity and the risk for coexisting malignant growths, IPs are classified as B3, i.e. lesions of uncertain malignant potential [1]. Their incidence has been estimated at 2–3% among the female population, but the risk increases to 40–70% in case of nipple discharge [2]. Papillomas may develop in women between the ages of 30 and 77 years [3], and have either central or peripheral presentation.

Central papillomas are typically single lesions and develop in older populations. They are localized within the large collective ducts and usually manifest as serous or serosanguinous nipple discharge [4]. The risk for developing breast cancer (BC) in women with central papillomas is comparable to the general population [5].

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Peripheral papillomas are diagnosed in approximately 10% of the cases. They usually develop in young women and rarely manifest as nipple discharge. Peripheral papillomas present as multiple, occasionally bilateral, lesions and correlate with elevated risk for developing invasive BC [4, 6].

Intraductal papillomas typically present as solid, hyperechogenic growths within the milk ducts, which may result in duct enlargement, or hyperechogenic, intracystic mural nodules. In extreme cases, IPs may completely obscure the lumen of the duct or the cyst, presenting as well-differentiated, hypochogenic solid masses with smooth contours [3, 6]. Often, IPs present as hypervascular solid masses on Doppler sonography [7]. On MMG, small IPs are usually invisible. Larger lesions present as well-differentiated, oval or round soft-tissue shadows [8], accompanied by non-suspicious microcalcifications in 25% of the cases [9]. On MRI, IPs range from normal images to irregular focal lesions, highly echogenic after the contrast agent has been administered intravenously, and exhibit the so-called wash-out effect, which is typical for malignant lesions [8, 10].

Histopathologic examination of core needle biopsy (CNB) specimens remains the gold standard for the diagnosis of intraductal papillomas. While the diagnosis of IPs at core needle biopsy is always associated with the need for open surgical biopsy [11–13], this is not the case for vacuum-assisted core needle biopsy (VAB). The possibility of performing the so-called therapeutic biopsy and including the affected women in the annual ultrasound control program is increasingly recommended [14, 15].

Objectives

The aim of the study was to determine the applicability of vacuum-assisted core needle biopsy in the management of intraductal papillomas of the breast and to identify the promoting factors for the risk of underestimation of malignant lesions.

MATERIAL AND METHODS

The study group included 222 women with IPs diagnosed using VAB, treated by a team of surgeons and gynecologists from a referral center for breast cancer between 2002–2017. The patients were selected from a group of women who were undergoing minimally-invasive diagnostic procedures due to changes in the breast. In total, 5113 biopsies (4083 USG-guided and 1030 MMG-guided) were performed at the time. All patients underwent an ultrasound examination of the breasts, with an additional mammogram if the subject was over 40 years of age (161 women). Between 2002–2006, VAB was performed using the Mammotome (ESS Johnson & Johnson) system, with 11 and 8G needles, whereas between 2006–2017 we used the Encor and Encor Enspire (Bard) system, with 10 and 7G needles. Tissue samples were fixed in 10% buffered formalin, and then sent for histopathologic evaluation to the Department of Pathology.

Macroscopic evaluation of the resection margins on ultrasound or MMG was performed and logged in the medical file of each patient. In 201 cases, the diagnosis was made using ultrasound-guided biopsy, and in 21 women as a result of stereotactic biopsy.

Retrospective analysis of lesion morphology on imaging, size on MMG and USG, localization (central ≤ 3cm from the nipple, and peripheral > 3cm from the nipple), lesion multifocality, categorization according to the BI-RADS classification (Breast Imaging-Reporting and Data System) [16], and macroscopic evaluation of the resection margins, was performed. The following were also taken into consideration: clinical symptoms (palpable tumor, nipple discharge, mastalgia), results of physical examination, menopausal status, positive personal and family history, and hormone therapy (hormonal contraceptives or HRT for over 5 years).

Patients with IP without atypia were followed-up after 6 months, and then every 12 months. Open surgical biopsy was routinely recommended in cases with atypia or suspicious clinical-pathologic correlation (38 women).

SAS 9.4 was used for statistical analysis. Continuous variables were presented as mean and standard deviation and medians. Frequencies of the categories were calculated for discrete and ordinal variables. T-test or Mann-Whitney test were used to compare continuous variables between the groups, chi-square test and Fisher's test were used to analyze the frequencies of discrete variables. Univariate and multivariate logistic regression models were used to analyze the correlations between potential risk factors and underestimation of malignant lesions. The p-value of < 0.05 was considered as statistically significant.

RESULTS

As far as all VAB are concerned, the rate of diagnosed papillomas was 4.3%, which corresponded to the group of 222 women aged 22–81 years (mean: 48.2 ± 12.8). Post-menopausal, asymptomatic women, with negative personal and family history of breast cancer constituted the vast majority of these cases. Detailed clinical characteristics of the study population are presented in Table 1.

In our study, IPs were predominantly (92.3%) single lesions, most often (60%) in the central localization, up to 3 cm from the nipple. On USG, the lesions were typically well-differentiated, hypervascular solid masses, 11.5 ± 6.2 mm in size (median 10 mm). On MMG, the lesions were most often described as shadows or focal asymmetric densities, 16.2 ± 12.2 mm in size (median 12.5 mm) (Fig. 1). The vast majority of the cases were classified as BI-RADS 4a on USG,

and only 5% presented features of highly suspicious lesions (BI-RADS 4c or 5) and (Fig. 2).

Detailed histopathologic results of all VAB are presented in Table 2.

Surgical intervention was performed in 38 (17.1%) women: 22 with ADH, 4 with radial scar, 2 with DCIS, and 1 with LCIS. In 10 cases of IPs without atypia, open surgical biopsy was also performed due to non-radical nature of the biopsy or lack of clinical-pathological correlation. The profile of biopsy diagnoses and histopathology results from the surgical excision is presented in Figure 3.

Notably, surgical management was abandoned in 3 cases of IPs with atypia. In 2 cases, the patients decided to discontinue that course of action, and in 1 case the decision was made because of the accompanying colon cancer spread.

In our study population, 3 (1.3%) cases of invasive carcinoma (subtypes: ductal, lobular, and tubular) and 5 (2.2%) cases of DCIS were found. The risk for underestimation of BC in patients with atypical ductal hyperplasia at biopsy was 20%: 8% (2/25) for invasive and 12% (3/25) for non-invasive carcinoma *in situ*. The probability of developing invasive carcinoma in IP patients with an intraductal tumor component was 50%, whereas the risk for DCIS in cases with pure papilloma was 0.6% (1/158).

Invasive carcinomas were diagnosed in 1 asymptomatic patient and 2 women with palpable tumors (aged 46, 61, and 66 years, respectively), and 2 subjects without positive family history. The tumors were solid (1 patient) or solid-cystic (2 patients), 12–40 mm in size. They were visible in both test and were classified as BIRADS 4c at USG and BIRADS 4 or 5 in MMG.

No correlations between the risk for BC underestimation and positive personal or family history, menopausal status, hormone therapy, lesion localization and patient complaints were found. However, a correlation was detected for older age (p = 0.0015, OR 1.7 for every 5 years) and the presence

Table 1. Clinical characteristics of the study population

	Yes		No	
	number [N]	rate [%]	number [N]	rate [%]
Positive family history of breast cancer	62	27.9	160	72.1
Personal history of breast cancer	3	1.4	219	98.6
Menopause	145	65.3	77	34.7
Hormonal therapy for > 5 years	36	16.2	186	83.8
Clinical symptoms	74	33.3	148	66.7
• palpable tumor	39	17.6	183	82.4
• nipple discharge	14	6.3	208	93.7
• sanguinous discharge	16	7.2	206	92.8
• pain complaints	14	6.3	208	93.7
• > 1 symptom	9	4.1	213	95.9
Peripheral localization > 3 cm from the nipple	89	40.1	133	59.9
Single lesion	205	92.3	17	7.6
Macroscopic assessment of resection margins	192	86.5	30	13.5

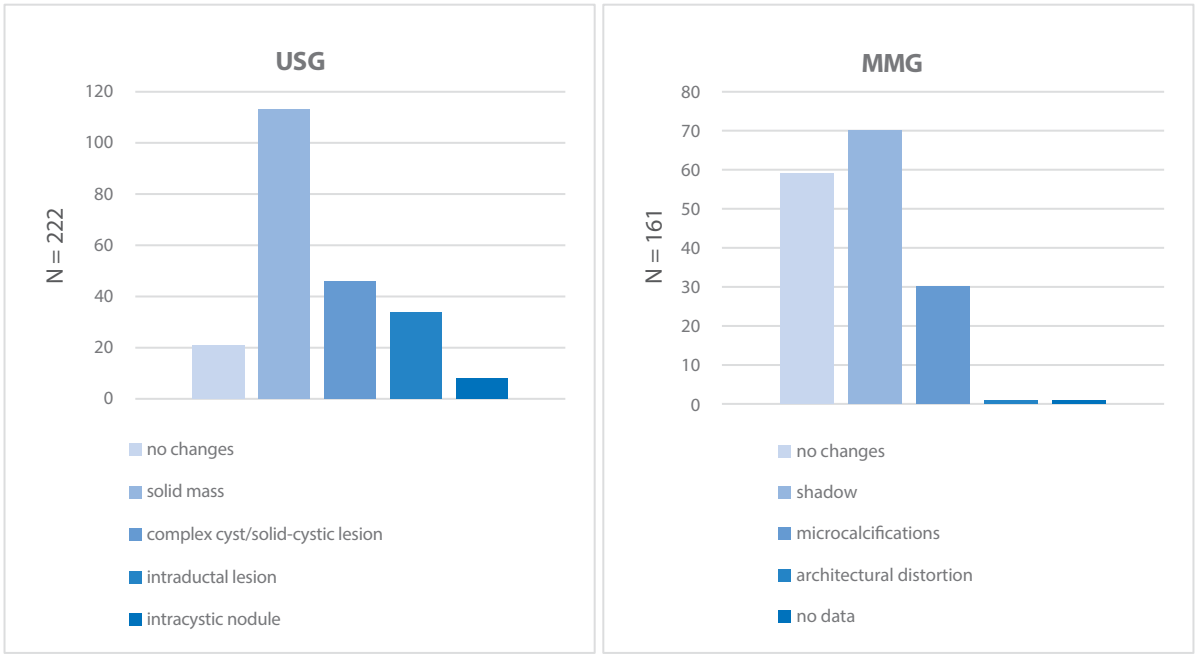

Figure 1. Morphology of the intraductal papillomas on imaging

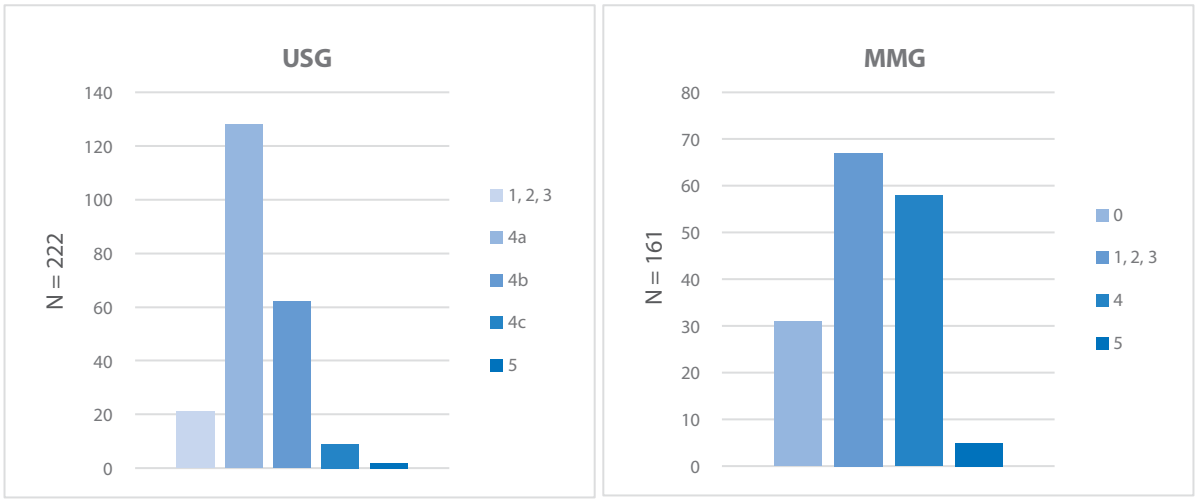

Figure 2. Categorization of the imaging results according to the BI-RADS classification [16] in the study population

Table 2. The spectrum of diagnoses accompanying IP in the specimens from vacuum-assisted core needle biopsy

Histopathologic diagnosis	number [N]	rate [%]
intraductal papilloma without atypia	158	70.3
atypical ductal hyperplasia (ADH)	25	11.3
fibroadenoma (FA)	20*	9.0
radial scars or complex sclerosing lesions	17*	7.7
lobular carcinoma in situ (LCIS)	2	0.9
ductal carcinoma in situ (DCIS)	2	0.9

*in 1 case intraductal papilloma was accompanied by FA and ADH, and in 1 case by ADH and radial scar

of atypia (p = 0.003, OR 16.2). The probability of BC diagnosis was also significantly higher (p < 0.001) in case of IP diagnosis at biopsy and BI-RADS classification (4c for USG and 4 or 5 for MMG). Identical results were obtained from the multivariate analysis (Tab. 3).

Macroscopic assessment revealed that all cases of DCIS and invasive carcinoma were detected after residual lesion biopsy. The overall risk for BC underestimation was 0% for the radical, and 26.7% for non-radical procedures. According to the Fisher's exact test, the p-value for that parameter was statistically significant (< 0.001).

In the group without surgical intervention, no cases of IP recurrence in the primary localization were found during the

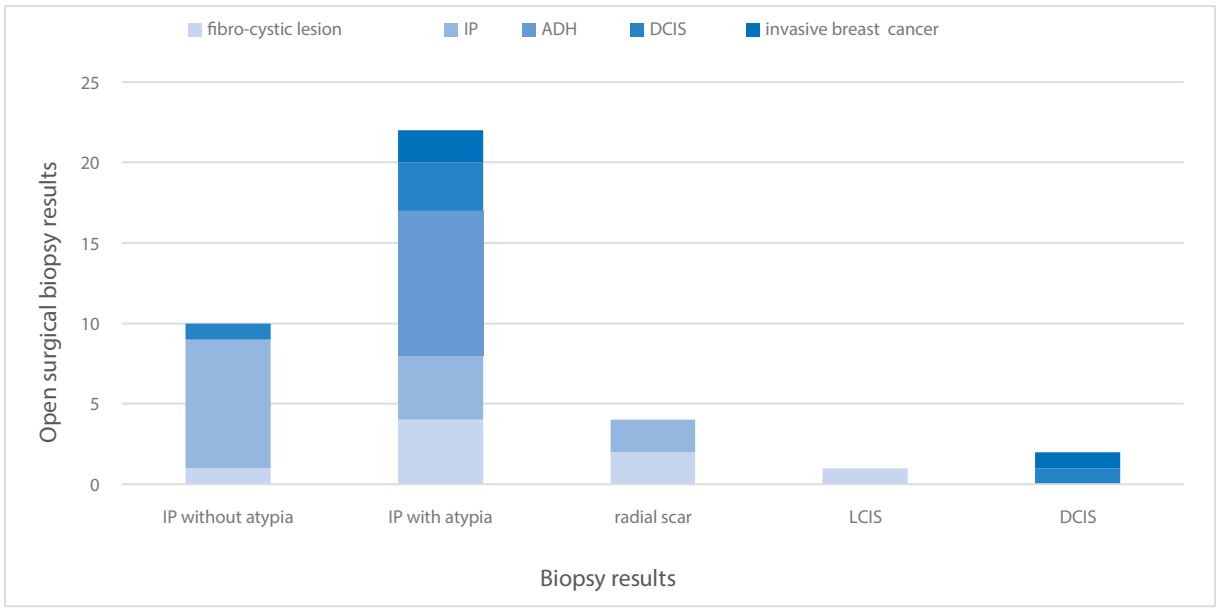

Figure 3. The profile for the final histopathologic diagnoses in the group after open surgical excision

Table 3. Contributing factors for BC underestimation in the study population based on the multivariate analysis

	p-value	OR
Age	0.029	1.7 (1.1, 2.9)
BI-RADS category	0.004	13.1 (2.3, 75.5)
Atypia	0.026	8.2 (1.3, 52.5)

follow-up control program (the control period ranged from 12 months to 16 years, mean: 28 months). New IPs in other localizations or in the other breast were found in 18 women and were again dissected using VAB. During the follow-up, 1 case of lobular carcinoma *in situ*, 1 of ductal carcinoma *in situ*, and 3 of invasive carcinomas in other localizations were diagnosed.

DISCUSSION

Intraductal papillomas belong to the heterogeneous group of lesions of uncertain malignant potential [17], which frequently presents a considerable diagnostic challenge. Due to their morphologic similarity to malignant lesions such as low-grade papillary DCIS, encapsulated papillary carcinoma, or solid papillary carcinoma, and the accompanying atypia, the diagnosis of IPs at CNB is associated with a certain risk for BC underestimation. In their 2012 meta-analysis of 34 studies from 1999–2012, Wen et al., demonstrated that the probability of IPs and an accompanying malignant process was 16.6% [18]. Therefore, until recently, open surgical biopsy was commonly performed to remove the lesions [19–21].

At present, medical advances and significant progress in the pathology-morphology diagnosis of the breasts, especially immunohistochemistry, allow for a more precise differentiation between various papillary growths [22]. Owing to that, the current underestimation of malignant BC at CNB ranges from 0.4 to 4% [23, 24]. Also, due to the development of minimally invasive techniques, e.g. VAB, the standards of management have changed and the indications for surgical interventions have been distinctly limited. The method in question allows to obtain an almost unlimited number of large specimens from one puncture site, and in case of pure papillomas it offers an equal in quality therapeutic option. As far as IPs with atypia are concerned, the risk for underestimation at CNB remains considerable, from 13 to 92% according to the available literature [25]. In light of the fact that VAB does not allow for a histological evaluation of the resection margins, open surgical biopsy is routinely recommended [14, 26, 27].

The risk for underestimation of a malignant process is notably smaller in case of vacuum-assisted CNB as compared to standard CNB, and has been estimated at 0%–2.6% [14, 28] versus 9–21% [15, 29] for pure IPs versus IPs with atypia [15, 29]. Our findings are consistent with the literature. The risk for BC underestimation was 0.6% at VAB. The accompanying atypical ductal hyperplasia, as compared to other histological diagnoses, increased the risk for malignancy by 13-fold, reaching 20%.

The role of atypical growths as the most important predictive factors for a malignant process was also emphasized in the meta-analysis by Wen [21], or later works by Shiino, Han, Kiran, Boufelli or Foley [12, 23–25, 30]. Current recommendations on diagnostic-therapeutic management still advise radical surgical approach in IPs with atypia, regardless of the biopsy technique [31]. Conservative management is allowed in strictly selected groups of patients [14, 27].

In our study, we detected an increased risk for underestimation in older populations, which is consistent with the reports by Foley et al., Rasmussen et al., and Yu et al. [30, 32, 33]. Therefore, caution is advised when recommending conservative management to that group of patients. On the other hand, we did not prove the predictive meaning of the accompanying clinical symptoms such as sanguine nipple discharge or multifocality of the lesions, which has been emphasized by Han et al. [23]. Also, similarly to Rasmussen, we found no correlation between the volume of the lesions at imaging and the risk for BC underestimation, which has been suggested by Boufelli et al., and Yu et al. [25, 33]. We believe it is not the volume of the lesion but the evaluation of sample representativeness and the results of clinical-pathological correlation which play the crucial role in the process. In our study, insufficient resection margins confirmed at follow-up control imaging and benign result of VAB in patients with high BI-RADS classification/scores, USG (at least 4c) and MMG (4 or 5) notably increased the risk for cancer underestimation. Similar correlations were presented by Wen et al., and Yu et al., for IPs and by Williams et al., for atypia [18, 33, 34].

We were not able to identify morphological features of the lesions on imaging which might become statistically significant predictors of benign or malignant nature of the change, which is consistent with the reports of Rasmussen et al. [32].

As no IP recurrence was observed during the follow-up period, it seems safe to assume that VAB is an effective method of IPs removal. However, due to the visible tendency for the development of new lesions in other localizations and increased BC incidence [13], we are of the opinion that the affected women should remain in the control follow-up program.

CONCLUSIONS

Vacuum-assisted core needle biopsy is an effective technique in the diagnosis and management of intraductal papillomas. Our findings, as well as the reports of other

authors, indicate that the diagnosis of pure papilloma and corresponding clinical presentation do not require further surgical intervention. That said, caution and careful monitoring are advised in older populations and cases with residual lesions. Radical surgical biopsy should remain the method of choice for all cases of IPs with atypia and lack of clinical-pathological correlation.

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Can preoperative magnetic resonance imaging replace intraoperative frozen sectioning in the evaluation of myometrial invasion for early-stage endometrial carcinoma?

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ABSTRACT

Objectives: To examine the performance of preoperative magnetic resonance imaging (MRI) and intraoperative frozen sectioning in the assessment of myometrial invasion during the early stages of endometrial cancer.

Material and methods: This retrospective study employed data from patients with endometrial cancer who were operated on between January 2013 and November 2018. Patients who underwent preoperative MRI and were of FIGO 2009 stage I were included in the study. Radiological staging and intraoperative staging by frozen sectioning were carried out. The data were analyzed to assess agreement of the overall results concerning myometrial invasion.

Results: In total, 222 patients were enrolled. Their mean age was 58.3 ± 8.5 years. The accuracy of MRI for the detection of myometrial invasion was 88.7% and its sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were 91.6%, 82.1%, 92.2%, and 80.9%, respectively, with a kappa coefficient of 0.734 (95% confidence interval [CI], 0.684–0.784; $p < 0.001$). The accuracy of intraoperative frozen sectioning was 94.4%, and its sensitivity, specificity, PPV, and NPV were 97.7%, 85.7%, 94.7%, and 93.4%, respectively, with a kappa coefficient of 0.856 (95% CI, 0.812–0.900; $p < 0.001$). No significant difference in accuracy was observed between MRI and frozen sectioning ($p = 0.057$). MRI and frozen sectioning were sensitive for the detection of myometrial invasion, according to receiver operating curve analyses (areas under the curve, 0.869 and 0.917, respectively; $p < 0.001$).

Conclusions: The assessment of myometrial invasion by preoperative MRI and intraoperative frozen sectioning during the early stages of endometrial carcinoma was highly accurate.

Key words: endometrial cancer; myometrial invasion; magnetic resonance imaging; MRI; frozen sectioning

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INTRODUCTION

Endometrial cancer is the most common gynecological malignancy in the United States and other developed countries [1]. As the majority of patients present with abnormal vaginal bleeding, particularly during the postmenopausal period, most cases are diagnosed in the early stages [2]. The prognosis for early-stage disease is generally excellent [3].

Surgical staging of endometrial cancer is necessary [2]. Disease staging provides insight about prognosis and adjuvant treatment [2]. The FIGO 2009 stage I subgroup is defined according to the depth of myometrial invasion (stage IA, no invasion or invasion < 50% of the myometrial thickness; stage IB, invasion ≥ 50% of the myometrial thickness) [4]. In addition, myometrial invasion determines the risks of extrauterine disease and lymph node metastasis [5]. Lymph node metastasis occurs in 30% of cases of deep myometrial invasion, but only 5% of cases with superficial myometrial invasion [5]. Systematic lymphadenectomy is advised as part of surgical staging for high-risk patients [2]. In contrast, previous reports indicate that systematic lymphadenectomy does not improve disease-free or overall survival during the early stages of the disease [6, 7]. Lymphadenectomy may

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cause complications, such as lymphedema and lymphocysts; thus, it should be avoided in low-risk patients [2]. The risk of recurrence can be estimated by assessing the depth of myometrial invasion during preoperative radiological evaluation or by intraoperative frozen sectioning.

Preoperative radiological examination has been used to assess endometrial cancer, and magnetic resonance imaging (MRI) is the recommended diagnostic imaging method [8]. The updated guidelines of European Society of Urogenital Radiology recommend MRI as the imaging modality of choice for the evaluation of disease extent in patients with newly diagnosed endometrial cancer [9]. The European Society for Medical Oncology (ESMO), European Society for Radiotherapy & Oncology (ESTRO), and European Society of Gynaecological Oncology (ESGO) recommend preoperative MRI for the evaluation of myometrial invasion in patients with stage 1 endometrial cancer [2]. Thus, MRI can be used to assess myometrial invasion during the early disease stage [8, 10, 11]. However, several studies have shown that the prediction of myometrial invasion using MRI alone can be difficult [12, 13].

Intraoperative examination modalities for endometrial tumors have been evaluated previously [14]. Tumor assessment by frozen sectioning has been found to have greater importance than gross examination [15]. However, the accuracy of frozen sectioning can be low [16]. Furthermore, some patients cannot be evaluated preoperatively by MRI, and low image quality may affect the ability to estimate disease extent preoperatively. In such situations, intraoperative frozen sectioning may play an important role. In addition, older patients and those with medical comorbidities, and younger patients who want to preserve their fertility, are not eligible for the operation [17]. Thus, preoperative evaluation is more important in these patients. Additionally, systematic lymphadenectomy and optimal staging cannot be performed in some patients because of the morbidity of lymphadenectomy and the extent of surgery [2, 18]. Preoperative clinical staging gains importance in these patient groups.

Unnecessary lymphadenectomy with complications and morbidity can be prevented by the preoperative and intraoperative evaluation of myometrial invasion during the early stages of the disease [10]. Under-staging can be avoided in high-risk patients [10], and inoperable cases can be staged clinically [2].

Objectives

The aim of this study was to examine the performance of preoperative MRI and intraoperative frozen sectioning in the assessment of myometrial invasion before surgical staging in patients with early-stage endometrial cancer in a high-volume tertiary cancer center employing experienced radiologists and pathologists in a gynecological oncology department.

MATERIAL AND METHODS

This retrospective study employed data from 337 patients with endometrial cancer who were diagnosed and operated on between January 2013 and November 2018 in a high-volume cancer center in western Turkey. Patients with advanced stages (≥ II) of the disease and those with synchronous tumors were excluded. Patients who did not undergo pelvic MRI and were scanned with abdominal computed tomography or positron emission tomography/computed tomography, cases that were diagnosed incidentally after hysterectomy and patients who were not performed frozen sectioning were excluded. In total, 222 patients who were diagnosed preoperatively by biopsy, underwent MRI in our center, and were optimally staged by gynecological oncologists, and performed frozen sectioning in our department were included in the study. This study was approved by the local institutional ethic committee.

All biopsy samples were obtained preoperatively by dilatation and curettage or pipelle sampling. Pelvic MRI was carried out with a 1.5 Tesla system (Siemens Avanto, Siemens Aera, GE Optima 360; Erlangen, Germany) and a six-channel body coil. The imaging protocol involved sagittal, axial, coronal, and oblique axial T2-weighted images without fat saturation, as well as precontrast and postcontrast (gadoteric acid, 0.1 mmol/kg) T1-weighted fat saturated images in the axial plane. One radiologist with 8 years of experience with pelvic MRI evaluated the images before surgery. The degree of myometrial invasion was interpreted as superficial or deep (≥ 50% of the myometrium). Radiological stages were assigned according to the imaging findings.

After a multidisciplinary tumor board examined the preoperative results, the patients underwent surgical staging by gynecological oncologists. Explorative laparotomy or laparoscopy was performed, followed by hysterectomy and bilateral salpingoophorectomy. The specimens were taken to the pathology department for frozen sectioning, according to the preoperative risk stratification of the endometrial cancer [2]. The lymph nodes were dissected according to the frozen sectioning results and preoperative risk group. Pathologists examined hysterectomy specimens using a longitudinal section of the endometrial cavity and uterine cervix, and a horizontal section from the uterine fundus, in each case. After placing the specimen over a film of optimal cutting temperature medium on a cryostat, the tumor was frozen, cut into 5-µm slices using a microtome, and then prepared for staining with hematoxylin and eosin for microscopic evaluation. Tumor histology, grade, and diameter, and depth of myometrial invasion (superficial or deep), were examined. The same pathologists with experience in gynecological oncology examined the slides used for the final pathological report. In cases of diagnostic discrepancy, another pathologist examined the slides. The tumor board evaluated the

Table 1. Clinical characteristics of the patients

Variables n [%]	N = 222
Age, mean ± SD	58.3 ± 8.5
Parity, median [range]	3 (0–10)
Menopausal Status Premenopausal Postmenopausal	 37 (16.7%) 185 (83.3%)
BMI, mean ± SD (kg/m^2) > 30 kg/m2 [n, %]	34.3 ± 6.0 169 (76.1%)
CA125, median (range) > 35 U/mL [n, %]	17 (2–800) 27 (12.2%)

SD — standard deviation; BMI — body mass index, kg/m2; CA 125 — cancer antigen 125, U/mL

postoperative results and final stages according to the FIGO 2009 classification to determine the optimal treatment [13]. No or < 50% myometrial invasion was considered to reflect stage IA, and ≥ 50% invasion was classified as stage IB, according to the FIGO 2009 classification [4].

The accuracy, specificity, sensitivity, positive predictive value (PPV), and negative predictive value (NPV) were calculated for the results of preoperative MRI and intraoperative frozen sectioning according to the final pathology results. The Cohen kappa statistic was used to examine the agreement of the overall results concerning myometrial invasion. Receiver operating characteristic (ROC) curves were used to evaluate the accuracy of the tests. SPSS software (ver. 21; SPSS Inc., Chicago, IL, USA) was used for the statistical analyses, and p-values < 0.05 were considered to be significant.

RESULTS

In total, 222 patients with stage 1 endometrial carcinoma were enrolled in this study. The clinical characteristics of the patients are shown in Table 1. The mean age of the patients was 58.3 ± 8.5 years. Most of the patients were postmenopausal (83.3%) and obese (body mass index > 30 kg/m^2; 76.1%). Twenty-seven (12.2%) patients had high (> 35 U/mL) preoperative levels of serum cancer antigen (CA) 125.

The surgical and histopathological results are summarized in Table 2. Approximately 64% of the patients were treated by laparotomy, and the majority (86.1%) of them underwent pelvic ± para-aortic lymphadenectomy. The most common tumor histological type was endometrioid, and 58.1% of the tumors were of grade 2. In total, 172 of 222 (77.5%) patients had tumor sizes > 2 cm. Lymphovascular space involvement (LVSI) was detected in 20.7% of the pathological specimens. The median sizes of tumors without and with LVSI were 3.5 (0.2–9) cm and 4.5 (2–8) cm, respectively (p = 0.001). According to the final pathological reports, 155 (69.8%) patients had stage IA and 67 (30.2%) had stage IB disease. The median dissected pelvic lymph node count was 12 (0–53).

Table 2. Surgical and histopathological characteristics of the patients

	n [%]
Surgery	
TAH + BS ± O	17 (7.7)
TLH/ Robotic Hysterectomy + BS ± O	36 (16.2)
TAH + BSO + Pelvic LND	41 (18.5)
TLH/ Robotic Hysterectomy + BSO + Pelvic LND	34 (15.3)
TAH + BSO + Pelvic LND + Para-aortic LND	85 (38.3)
TLH + BSO + Pelvic LND + Para-aortic LND	9 (4.0)
Tumor Histological Type	
Endometrioid	193 (86.9)
Serous/Clear Cell	8 (3.6)
Mixed*	14 (6.3)
Others (Carcinosarcoma, Adenosarcoma, ESS)	7 (3.2)
Tumor Grade	
1	65 (29.3)
2	129 (58.1)
3	28 (12.6)
Tumor Size, cm, median [range]	3,5 (0.2–9)
≤ 2 cm	50 (22.5)
> 2 cm	172 (77.5)
LVSI	
None	176 (79.3)
Present	46 (20.7)
FIGO Stage	
IA	155 (69.8)
IB	67 (30.2)
Pelvic LN Count, median	15 (2–53)
Para-aortic LN Count, median, [range]	9 (1–41)

TAH + BS ± O — total abdominal hysterectomy and bilateral salpingectomy with or without oophorectomy; TLH + BS ± O — total laparoscopic hysterectomy and bilateral salpingectomy with or without oophorectomy; TAH + BSO + Pelvic LND — total abdominal hysterectomy and bilateral salpingoophorectomy plus pelvic lymphadenectomy; TLH + BSO + Pelvic LND — total laparoscopic hysterectomy and bilateral salpingoophorectomy plus pelvic lymphadenectomy; TAH + BSO + Pelvic LND + Para-aortic LND — total abdominal hysterectomy and bilateral salpingoophorectomy plus pelvic and para-aortic lymphadenectomy; TLH + BSO Pelvic LND + Para-aortic LND — total laparoscopic hysterectomy and bilateral salpingoophorectomy plus pelvic and para-aortic lymphadenectomy; LN — lymph node
*endometrioid + mucinous, endometrioid + serous, endometrioid + clear cell
ESS — endometrial stromal sarcoma
LVSI — lymphovascular space invasion

The median time between MRI and operation was 21 (7–52) days. Tables 3 and 4 define the relationships of radiological staging and frozen sectioning to the final pathological results. Table 5 shows the results for combined consideration of MRI and frozen sectioning. The correlation of MRI

Table 3: Magnetic resonance imaging (MRI) and final pathological results[a]

		Stage		Total
		IA	IB	
MRI	IA	142 (64.0)	12 (5.4)	154 (69.4)
	IB	13 (5.9)	55 (2.8)	68 (30.6)
Total		155 (69.8)	67 (30.2)	222 (100)

[a] n, %

Table 4. Frozen sectioning and the final pathological results[a]

		Stage		Total
		IA	IB	
Frozen section	IA	126 (70.8)	7 (3.9)	133 (74.7)
	IB	3 (1.7)	42 (23.6)	45 (25.3)
Total		129 (72.5)	49 (27.5)	178 (100)

[a] n, %

Table 5. Preoperative magnetic resonance imaging (MRI) and additional intraoperative frozen sectioning and final pathological results[a]

		Stage		Total
		IA	IB	
MRI + Frozen section	IA	127 (71.4)	2 (1.1)	129 (72.4)
	IB	2 (1.1)	47 (26.4)	49 (27.5)
Total		129 (72.5)	49 (27.5)	178 (100)

[a] n, %

and frozen sectioning with the final pathological findings is shown in Table 6. The accuracy of MRI for the detection of myometrial invasion was 88.7%, and its sensitivity, specificity, PPV, and NPV were 91.6%, 82.1%, 92.2%, and 80.9%, respectively, with a kappa coefficient of 0.734 (95% confidence interval [CI], 0.684–0.784; $p < 0.001$). The accuracy of intraoperative frozen sectioning was 94.4%, and its sensitivity, specificity, PPV, and NPV were 97.7%, 85.7%, 94.7%, and 93.4%, respectively, with a kappa coefficient of 0.856 (95% CI, 0.812–0.900; $p < 0.001$). The rates of overdiagnosis were 8.4% for MRI and 2.3% for frozen sectioning. The rates of underdiagnosis were 17.9% for MRI and 14.3% for frozen sectioning. Preoperative MRI yielded 5.4% false-negative and 5.9% false-positive results for the prediction of deep myometrial invasion. The false-negative and false-positive ratios for frozen sectioning were 3.9% and 1.7%, respectively. No significant difference in accuracy was observed between MRI and frozen sectioning, according to McNemar's test ($p = 0.057$). When MRI and frozen sectioning were considered together, the accuracy was 97.8% and the sensitivity, specificity, PPV, and NPV were 98.5%, 95.9%, 98.5%, and 95.9%, respectively, with a kappa coefficient of 0.944 (95% CI, 0.916–0.972; $p = 0.028$).

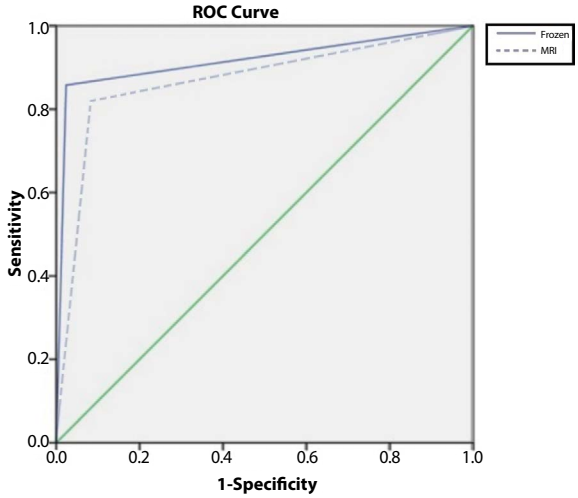

Figure 1. Receiver operating characteristic (ROC) curve for intraoperative frozen sectioning and magnetic resonance imaging (MRI) for the assessment of deep myometrial invasion (areas under the curve, 0.917 and 0.869, respectively; $p < 0.001$)

The ROC curves for the assessment of deep myometrial invasion are shown in Figure 1 for MRI and frozen sectioning. MRI and the frozen sectioning significantly detected myometrial invasion, according to the ROC curve analyses (areas under the curve, 0.869 and 0.917, respectively; $p < 0.001$).

DISCUSSION

Endometrial cancer is commonly diagnosed in postmenopausal women; the average age of patients in the United States is 63 years [3]. Most cases in our study group were postmenopausal and > 50 years of age, consistent with the literature. Obesity is an important risk factor for endometrial carcinoma [19]. The majority of the patients in our study group were obese, and the morbid obesity rate was high. Preoperative elevated serum CA 125 levels (> 35 U/mL) are associated with extrauterine disease [20]. Although the patients had early-stage disease, CA 125 levels were above the limit in 12.2% of cases in this study. Elevated CA 125 levels are correlated with increasing depth of myometrial invasion [20]. The median CA 125 level was higher in the deep myometrial invasion group, consistent with previous studies [20, 21].

Table 6: Correlation between preoperative magnetic resonance imaging (MRI) and intraoperative frozen sectioning and final pathological results

	Accuracy	Kappa Coefficient	Sensitivity	Specificity	PPV	NPV	Over-Diagnosis	Under-Diagnosis
MRI	88.7 %	0.734	91.6%	82.1%	92.2%	80.9%	8.4%	17.9%
Frozen Section	94.4 %	0.856	97.7%	85.7%	94.7%	93.4%	2.3%	14.3%
MRI + Frozen Section	97.8 %	0.944	98.5%	95.9%	98.5%	95.9%	1.6%	4.1%

PPV — positive predictive value; NPV— negative predictive value

Surgery for endometrial cancer can be performed with laparotomy or laparoscopy [22]. As minimally invasive surgery is recommended because of its lesser morbidity, the laparoscopic surgery rate is increasing with increases in minimally invasive surgical skills and facilities [22]. Only patients at high risk of recurrence should undergo lymphadenectomy [2]. This procedure can cause lower extremity lymphedema, lymphocysts, and surgical morbidities [4]. In this study, the risk classification was estimated using age, tumor histology, grade, and radiological and frozen sectioning findings. Although the patients in this study group had early-stage disease, pelvic or para-aortic lymphadenectomy was applied in the majority of cases. This pattern can be explained by the change in our approach since the January 2016 ESMO/ESTRO/ESGO consensus conference report, with no lymphadenectomy performed in a low-risk patient [2]. The majority of patients with endometrial cancer are diagnosed at the early stage [3]. All patients in this study were diagnosed at an early stage, and most cases were diagnosed as stage IA.

MRI is an appropriate imaging modality for the detection of myometrial invasion, extrauterine disease, and lymph node metastasis in patients with endometrial cancer [8]. Clinical staging can be estimated according to the radiological evaluation. Lin et al. [23] reported high sensitivity and specificity levels for MRI and an accuracy of 94%. However, other authors reported that the accuracy of MRI can be as low as 65% [24]. The sensitivity and accuracy levels obtained in this study were higher than in previous reports. The kappa coefficients also showed good correlations; thus, radiologists' experience is important for the interpretation of imaging results.

The intraoperative pathological examination of frozen-sectioned specimens is convenient for the detection of myometrial invasion [14, 15, 25]. However, Case et al. [16] reported that the accuracy of frozen sectioning is low (67%), posing a risk for under-staging, which can lead to suboptimal treatment, so they advised surgical staging for all patients with endometrial cancer. In our study, the accuracy of frozen sectioning was high, which is thought to be related to the skill level of the pathologists at our center, who have more than 10 years of experience in gyneco-pathology. In addition, a high correlation was observed between frozen sectioning findings and the final pathological results for deep myometrial invasion.

Tanaka et al. [26] and Kisu et al. [27] reported that frozen sectioning has a higher correlation rate than does MRI. They mentioned that diffusion-weighted MRI can have the same diagnostic precision as frozen sectioning [11]. In our study, the accuracies of MRI and frozen sectioning were similar. Additional frozen sectionings are recommended when MRI is positive or negative for the presence of myometrial invasion [27]. In our study, the correlation ratios were high when MRI and additional frozen sectioning results were interpreted together. In addition, over-diagnosis and under-diagnosis rates were lower with this approach.

Some patients cannot be operated on due to advanced age, morbid obesity, and/or medical comorbidities [2, 17]. In addition, some young patients wish to preserve their fertility [2, 28]. Thus, surgical staging cannot be performed and intra-abdominal or extrauterine spread of the disease cannot be seen in these cases. Clinical evaluation and preoperative MRI may be more important for these non-surgical patient groups.

A limitation of this study is its retrospective design. However, the high accuracy and correlation rates from a high-volume center, as well as the involvement of experienced radiologists and pathologists, support the importance of radiological and intraoperative evaluation. As diffusion-weighted MRI can increase the correlation rate, diffusion-weighted images have also been used recently.

CONCLUSIONS

The detection of myometrial invasion before surgery and the final pathology results reveal the need for lymphadenectomy to predict the prognosis, and are also thought to be very important for non-surgical patients. The assessment of myometrial invasion by preoperative MRI and intraoperative frozen sectioning during the early stages of endometrial carcinoma was highly accurate. Preoperative MRI can have the same diagnostic precision as frozen sectioning. The assessment of myometrial invasion by preoperative MRI and additional intraoperative frozen sectionings provided the most accurate results. So over-diagnosis and under-diagnosis rates were lower with this approach.

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The potential predictive value of serum sRCAS1 levels for overall survival in endometrial cancer

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ABSTRACT

Objectives: The main aim of the study was to evaluate the impact of levels of serum soluble receptor-binding cancer antigen expressed on SiSo cells (sRCAS1) on the overall survival (OS) rates in patients with endometrial cancer. Furthermore, we analyzed sRCAS1 levels according to the clinicopathological characteristics of the disease.

Material and methods: The study group comprised 43 patients who were being treated for endometrial cancer. We included 10 low-risk, 20 intermediate-risk and 13 high-risk endometrial cancers using the criteria of the European Society for Medical Oncology (ESMO), the European Society for Radiotherapy & Oncology (ESTRO) and the European Society of Gynaecological Oncology (ESGO). Serum sRCAS1 levels were obtained before and after surgery. Serum sRCAS1 levels were assessed using the ELISA method.

Results: In our univariate analysis, both the pre- and post-surgery high sRCAS1 groups of patients with endometrial cancer indicated a shortened OS. However, in our multivariate analysis, when patients' age and disease-related risk was taken into consideration, only the post-surgery sRCAS1 levels remained as independent prognostic factors of a poor OS. Pre-treatment serum sRCAS1 levels were statistically significantly higher than post-surgery sRCAS1 levels; however, the difference between pre- and post-surgery sRCAS1 levels did not influence the patients' OS rate. Pre- and post-surgery sRCAS1 levels did not differ according to tumor grade, stage of the disease or the disease-related risk group.

Conclusions: High post-surgery serum sRCAS1 levels seem to be an independent indicator of shortened overall survival in patients with endometrial cancer.

Key words: sRCAS1; RCAS1; receptor-binding cancer antigen expressed on SiSo cells; endometrial cancer; cancer immunology

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INTRODUCTION

Endometrial cancer is the most common gynecologic cancer and it is the fifth most common cancer in women. Due to the early manifestation of symptoms endometrial cancer possess favorable prognosis, and it is the fourteen cancer in terms of women's mortality [1, 2]. However, even in the cases of localized endometrial cancers (FIGO IA and IB), the 5-year survival rate is 88% for the former (IA) and 75% for the latter (IB) [3]. That means that a significant proportion of the risk factors of patients with early stage endometrial cancer have been underestimated. Endometrial cancer is predominantly diagnosed in elderly patients, who are more prone to the adverse outcomes of adjuvant therapy. Thus, adjusted risk stratification may mean that unnecessary adjuvant therapy is abandoned. On the other hand, the incidence of endometrial cancer is increasing and it is now increasingly being diagnosed in premenopausal women, and even in women younger than 40 years of age (5%) [1]. This group of premenopausal patients is at increased risk of long-term adverse outcomes of radiotherapy. Furthermore, due to the present trend in delayed childbearing, fertility-sparing has become an important consideration in the treatment

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of patients with endometrial cancer [4]. Adjuvant therapy in cases of endometrial cancer is still being debated [5]. Especially the exact role of adjuvant chemotherapy in higher risk patients is still not fully elucidated [6]. Thus, evaluation of all prognostic factors is required before any final decision about adjuvant management can be made [6].

Currently, the prognosis for endometrial cancer is predominantly based on the FIGO stage of the disease, the histopathological type of the tumor, histopathological grade and the lymphovascular space invasion (LVSI) status. Based on these aforementioned factors, the European Society for Medical Oncology (ESMO), the European Society for Radiotherapy & Oncology (ESTRO) and the European Society of Gynaecological Oncology (ESGO) proposed new categories of risk groups to guide adjuvant therapy in patients with endometrial cancer [6]. However, risk stratification may also be evaluated using biological markers of cancerogenesis. For instance, a pooled analysis of PORTEC trial results indicated high L1 cell adhesion molecule (L1CAM) expression as an independent predictor for poor overall survival [7].

Receptor-binding cancer antigen expressed on SiSo cells (RCAS1) was discovered in 1996 by Sonoda et al. [8] as a membrane protein present on cervical cancer cells. RCAS1 expression was found on a variety of cells, including T, B, and NK cells, and on macrophages, fibroblasts, and human neoplastic cells [9]. RCAS1 acts through the putative receptor, and its main function is related to the induction of selective immunosuppression. In the study by Nakashima et al. [10–12], authors showed that RCAS1 induces the arrest of cell growth and apoptosis in T, B and NK cells. Furthermore, immunohistochemical studies have shown an association between RCAS1 expression and the number of apoptotic lymphocytes and a negative correlation between RCAS1 expression and the quantity of tumor-infiltrating lymphocytes [13–15]. Despite the immunosuppressive activity of RCAS1, the protein can also contribute to tumor stroma remodelling creating a tumor-friendly microenvironment [16–18]. Specifically, RCAS1 interacts with noncancerous stromal cells (tumor associated macrophages, and cancer associated fibroblasts) to stimulate angiogenesis through VEGF, and its expression correlates with extracellular matrix proteases expression [16, 19–21].

RCAS1 can be secreted in the soluble form (sRCAS1) in the process of ectodomain shedding to the tumor microenvironment, and then to the blood system. Sonoda et al. [22], have shown that sRCAS1 also possesses an immunosuppressive capability, as it induces apoptosis of immune cells. Additionally, in their study of patients with cervical and endometrial cancer, Sonoda et al., showed there was a negative correlation between sRCAS1 and the number of peripheral blood lymphocytes [23].

Numerous studies have shown that tumor RCAS1 expression is an indicator of poor prognoses in patients with cancer [16, 24–29]. However, there is sparse data on serum sRCAS1 levels as a prognostic factor in human malignancies, and most of the data that does exist relates to the evaluation of short term outcomes [23]. From a clinical point of view, the most informative prognostic factors are those that influence patients' overall survival (OS) [28, 30]. To the best of our knowledge, there is no study evaluating the influence of serum sRCAS1 levels on the OS rates of patients with endometrial cancer.

Objectives

The main aim of our study was to evaluate the impact of pre- and post-surgery sRCAS1 levels on the overall survival rates in patients with endometrial cancer. Furthermore, we looked for correlations between sRCAS1 levels and clinicopathological features of the disease.

MATERIAL AND METHODS

Human subject

The study included 43 patients diagnosed with and treated for endometrial cancer. The median patient age was 65 and ranged from 43 to 84. The patients underwent treatment either in the Gynecology and Oncology Department of the Lukaszczyk Oncological Centerin Bydgoszcz or in the Gynecologic Oncology Department of the M. Sklodowska-Curie Memorial Institute in Krakow between 2007 and 2010. The patients were recruited consecutively from patients with newly diagnosed endometrial cancer admitted to our Departments for surgical treatment. Patients with significant co-morbidities, including, autoimmune connective tissue diseases or patients during immunosuppression, were excluded from the study. The study group included 37 patients with endometrioid adenocarcinomas, 2 with serous adenocarcinomas, one with adenosquamous carcinoma, one with clear-cell adenocarcinoma, one with carcinosarcoma and one with an undifferentiated carcinoma. The FIGO stages of the cancer patients were as follows: 1A — 11 patients; 1B — 22 patients; II — 2 patients; IIIA — 4 patients; IIIB —2 patients; and IIIC — 2 patients. Twenty-two tumors had G1 cancer, while 16 and 5 tumors were graded as G2 and G3 respectively. Using the combined consensual criteria of the European Society for Medical Oncology (ESMO), the European Society for Radiotherapy & Oncology (ESTRO) and European Society of Gynaecological Oncology (ESGO), the patients with endometrial cancers were divided into groups relating to the risk level of the disease. The study included 10 low-risk endometrial cancers (endometrioid type, grade 1–2, FIGO IA, LVSI negative), 20 intermediate-risk endometrial cancers (endometrioid type, grade 1–2, FIGO IB, LVSI negative), and 13 high-risk endometrial cancers (FIGO stage II or above, or non-endometrioid types). There were no "high-intermediate", "advanced" or "metastatic" risk groups among the endometrial cancers. For the survival analyses,

both low- and intermediate-risk cancers were included in a single subgroup.

We analyzed sRCAS1 levels in serum blood samples obtained both before and after surgery. Patients were treated with total abdominal hysterectomy with bilateral adnexectomy, and pelvic with/without paraaortic lymphadenectomy. Omentectomy was performed when serous endometrial adenocarcinoma was diagnosed. The low- and intermediate-risk group patients were either carefully followed-up postoperatively or they received brachytherapy. High-risk patients received chemoradiation.

Blood samples from patients treated surgically were collected directly prior to surgery and on the fourth day following hysterectomy. Blood samples were collected in a serum collection tube. A clot was permitted to form at room temperature for 30–60 minutes. The tube was placed on ice for 30 minutes to allow the clot to contract. The serum samples were then centrifuged at 3000x for 10 minutes at room temperature. Next, 1.0–2.0 mL samples were collected from the supernatants and stored at -80°C.

Each of the patients gave their written informed consent. Prior to the study, we obtained approval from the Jagiellonian University Ethical Committee (KBET/135/B/2007). Information on any patients who died was retrieved from the database of the Cuiavia-Pomerania and Lesser Poland National Health System of Poland. We analyzed patients' overall survival (OS) rates with respect to pre- and post-interventional sRCAS1 levels as well as with respect to the differences between pre- and post-surgery levels. The median follow-up period for patients was 1593 days (range 138–2468).

sRCAS1 levels assessment

The analysis of sRCAS1 concentrations in the serum samples was performed in the Department of Analytical Biochemistry, Faculty of Biochemistry, Biophysics, and Biotechnology, Jagiellonian University. We used a commercially avalible ELISA kit for sRCAS1 detection (Medical & Biological Laboratories Co. Ltd, Nagoya, Japan). Briefly, the diluted serum samples were pre-treated with neuraminidase and incubated in the wells of the plates coated with anti-human RCAS1 monoclonal antibodies. After washing, the wells were incubated with biotin conjugated anti-RCAS1 antibodies, and this procedure was followed by a second washing and incubation of the wells with a streptavidin-peroxidase conjugate. Following a third washing, color reaction was developed using the tetramethylbenzidine/hydrogen peroxide substrate. The reaction was stopped by acidification of the contents of the wells, and the plates were then read at 450 nm on a microplate reader. The plates were individually calibrated by a quantitative sRCAS1 reference standard provided by the manufacturer of the set and expressed in arbitrary units (U/mL). The correlation coefficient of the dose-response curves we obtained was above 0.99.

Statistical analysis

The distribution of variables in the study groups was verified using the Shapiro-Wilk test. Parametric or non-parametric tests were used for evaluation according to data distribution. The difference between pre- and post-surgery sRCAS1 levels was investigated using Wilcoxon matched-pairs test. The differences between sRCAS1 levels according to tumor grade were investigated with the use of Kruskal-Wallis test, both in pre- and post-intervention group. The differences in sRCAS1 levels between low/intermediate and high-risk patients, and between FIGO I and FIGO II/III stage disease were evaluated using Mann-Whitney test, both in pre-and post-intervention group. The correlation between patient age and sRCAS1 levels was evaluated using Spearman Rank correlation. Survival analysis was conducted using Kaplan-Meier survival curves. The cut-offs between "high" and "low" pre- and post-surgery sRCAS1 levels were determined following OS analyses; namely that we have analyzed different cut-offs, and the level with the lowest P-value was chosen. Multivariate survival analysis was conducted using Cox proportional-hazards regression with the stepwise entering method.

RESULTS

Survival analysis

Patients' pre-treatment sRCAS1 levels below 10 U/mL (36 women) were associated with statistically significant longer overall survival when compared with patients with pre-treatment sRCAS1 levels above 10 U/mL (7 women). Similarly, postoperative sRCAS1 levels below 8 U/mL (33 women) indicated longer OS when compared with patients with sRCAS1 levels above 8 U/mL (10 women). The variation of sRCAS1 levels after treatment was not associated with patients' survival. Serum sRCAS1 levels were found to be decreased more than 10% in 20 women, while 23 patients had either stable or increased sRCAS1 levels after treatment (this subgroup included patients either with a decrease of less than 10% or a stable level, or an increased sRCAS1 level). Patients with sRCAS1 levels decreasing more than 10% had median survival not significantly different from that of the rest of the group.

We have found the patient survival to be related with patients' age. Patients older than 65 (23 women) had significantly shortened survival when compared with patients younger than 65 (20 women).

Patients with high-risk endometrial cancers (13 patients) had significantly shortened survival when compared with the patients with low- and intermediate-risk endometrial cancers (30 patients). In the multivariate survival analysis, only postoperative sRCAS1 levels ($P = 0.03$), patients' ages ($P = 0.02$), and the risks group according to ESMO-ESGO-ESTRO criteria ($P = 0.02$) were independent predictors of patients' overall survival rates.

Survival curves are presented in Figure 1. The results of our analysis are summarized in Table 1.

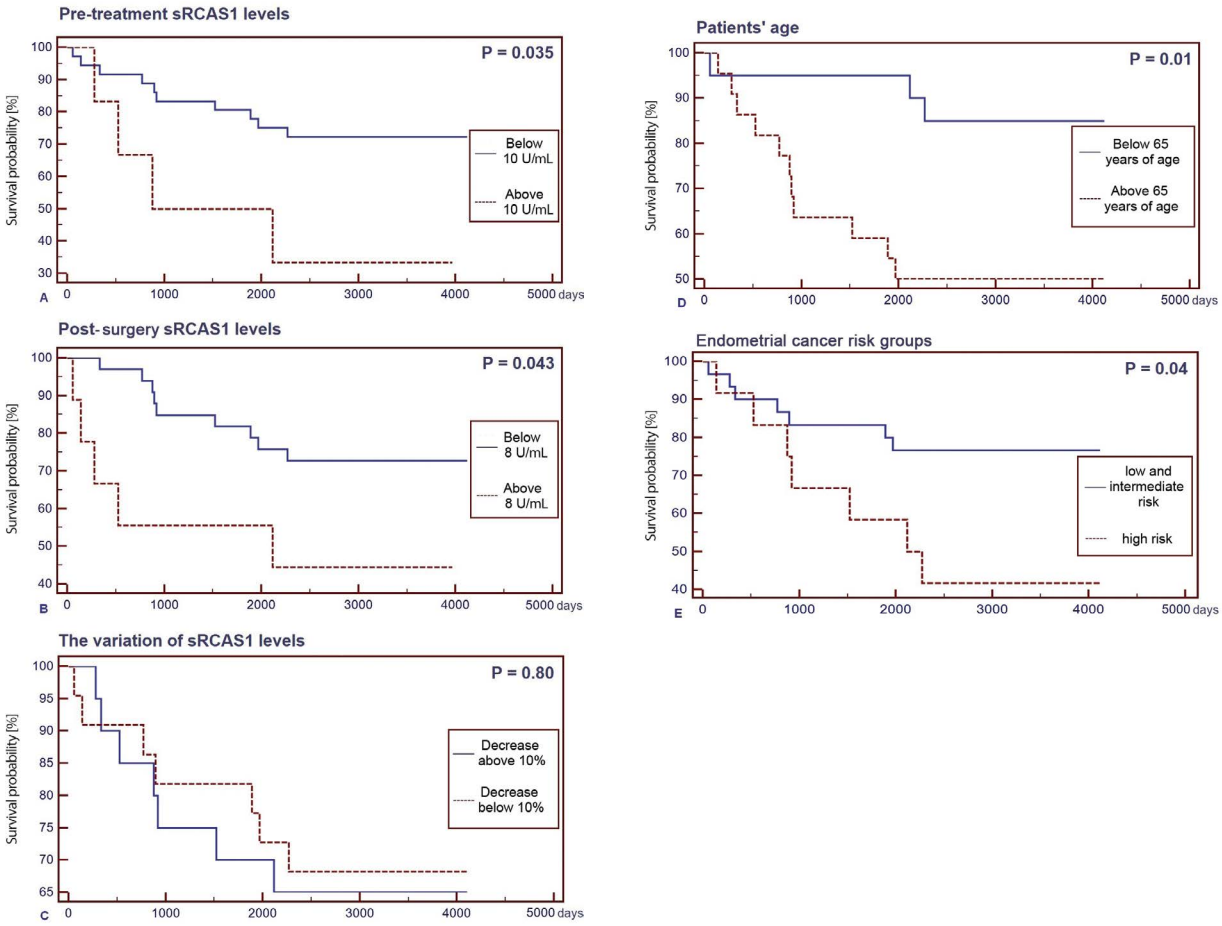

Figure 1. Analysis of patients' survival. **A)** Pre-treatment sRCAS1 levels. Group 1) below 10 U/mL (median survival: 3853 days, range 55–4117); Group 2) above 10 U/mL (1496 days, range 279–3967, P = 0.035). **B)** Postoperative sRCAS1 levels. Group 1) below 8 U/mL (median survival: 3855 days, range 336–4117); Group 2) above 8 U/mL (2116, range 55–3967; P = 0.043). **C)** Variation of sRCAS1 levels after treatment — the difference between postoperative and pre-surgery levels. Group 1) sRCAS1 levels decrease above 10% (median survival: 3889 days range 279–4104); Group 2) decrease below 10% and stable or increased sRCAS1 levels(3826 days, range 55–4117; P = 0.80). **D)** Survival according to patient age. Group 1) patients younger than 65 (median survival 3917 days, range 55–4117); Group 2) patients older than 65 (2854 days, range 138–4111, P = 0.01). **E)** Survival according to disease specific risk. Group 1) low- and intermediate-risk endometrial cancers (median survival: 3904 days, range 336–4084); Group 2) high-risk endometrial cancers (2975 days, range 55–4117; P = 0.04).

sRCAS1 levels and clinicopathological features of the disease

Pre-treatment serum sRCAS1 levels were statistically significantly higher than postoperative sRCAS1 levels (7.35 U/mL, range 3.40–66.16 compared with 6.85 U/mL, range 3.76–31.78, respectively; P = 0.0001).

We did not observe differences in pre- and post-surgery sRCAS1 levels regarding the grade of the tumor. Similarly, pre- and post-surgery sRCAS1 levels were not related either with FIGO stage of the disease or with the risk group. The results of the sRCAS1 assessment regarding the clinicopathological features of the disease we analyzed are summarized in Table 2.

The low-intermediate and high-risk groups of patients were not different in terms of patient age (60.4 ± SD 9.26 compared with 60.52 ± SD 10.34, respectively; P = 0.37).

Pre-treatment sRCAS1 levels were positively correlated with patients' age (R Spearman = 0.37, P = 0.01). Similarly, postoperative sRCAS1 levels were positively correlated with patients' ages (R Spearman = 0.36, P = 0.02).

DISCUSSION

In the present study, our univariate survival analysis has shown that high sRCAS1 levels in both pre- and postoperative patients were predictive factors of shortened survival rates for endometrial cancer patients. However, when other prognostic factors, like disease specific risk and patients' ages were taken into consideration, only high postoperative sRCAS1 levels was associated with patients' overall

Table 1. Survival analysis according to pre- and post-surgery serum sRCAS1 levels

Univariate Survival Analysis			
	Groups	**Survival**	**P-Value**
Pre-treatment sRCAS1 levels	below 10 U/mL (36 patients)	3853 days, range 55 –4117	P = 0.035
	above 10 U/mL (7 patients)	1496 days, range 279–3967	
Postoperative sRCAS1	below 8 U/mL (33 patients)	3855 days, range 336–4117	P = 0.043
	above 8 U/mL (10 patients)	2116, range 55–3967	
Variation insRCAS1 levels after treatment	decrease above 10% (20 patients)	3889 days, range 279–4104	P = 0.80
	decrease below 10% and stable or increased sRCAS1 levels (23 patients)	3826 days, range 55–4117	
Patients' age	older than 65 (23 patients)	2854 days, range 138–4111	P = 0.01
	younger than 65 (20 patients)	3917, range 55–4117	
Risk group	Low- and intermediate-risk (30 patients)	3904 days, range 336–4084	P = 0.04
	High-risk (13 patients)	2975 days, range 55–4117	
Multivariate Survival Analysis			
	P-value	95% CI	P-Value
Patients' age	P = 0.02	1.34–17.83	P = 0.0025
Risk group	P = 0.02	1.16-10.14	
Pre-treatment sRCAS1 levels	Not included		
Postoperative sRCAS1	P = 0.03	1.12–10.77	

Risk associated with the disease was stratified according to ESMO-ESGO-ESTRO criteria. We have used Cox proportional-hazards regression multivariate survival with the stepwise entering method. Pre-treatment sRCAS1 levels were not included in the calculation due to the nonsignificant impact on patients' survival rates in the multivariate analysis.

Table 2. Pre- and postoperative sRCAS1 levels according to the tumor grade, FIGO stage of the disease and the risk group related to endometrial cancer

	Pre-treatments sRCAS1 levels Median U/mL (range)	**P-Value**
G1	7.35 (4.16–10.75)	P = 0.23
G2	6.52 (3.40–66.16)	
G3	7.82 (6.56–31.23)	
FIGO I	6.94 (3.40–42.25)	P = 0.17
FIGO II - III	7.75 (3.91–66.16)	
Low- and intermediate-risk	6.96 (3.4-42.25)	P = 0.78
High-risk	7.69 (4.16–42.25)	
	Postoperative sRCAS1 levels Median U/mL (range)	**P-value**
G1	6.73 (3.76–17.15)	P = 0.73
G2	6.51 (3.76–31.78)	
G3	6.13 (5.80–23.08)	
FIGO I	6.69 (3.74–23.08)	P = 0.37
FIGO II - III	6.76 (5.54–31.78)	
Low- and intermediate-risk	6.56 (3.76–17.15)	P = 0.23
High-risk	6.75 (5.54–31.78)	

Risks groups associated with the disease were stratified according to ESMO-ESGO-ESTRO criteria

survival rates. Our results may indicate, that the intensity of the selective suppression of the host's immune system and the tumor stroma modulation related to RCAS1 function are reflected in the patients' prognoses. In an earlier research study, Sonoda et al. [31], showed that high tumor RCAS1 expression was associated with shortened OS. In that study, patients' survival was progressively correlated with the degree of RCAS1 expression. Similarly, RCAS1 expression was an independent prognostic factor in multivariate analysis [31]. From a clinical point of view, analysis of serum markers is more feasible and less subjective when compared with immunohistochemical tumor analysis. Additionally, serum sRCAS1 levels are also available for patients who are not operated upon. Thus, for practical purposes, serum sRCAS1 levels seem to be more a useful prognostic factor when compared with evaluations of tumor RCAS1 expression.

RCAS1 expression has been shown to progress from the normal endometrium, through premalignant lesions, to invasive carcinomas [32, 33]. Sonoda et al. [31], showed there is an association between RCAS1 expression in endometrial cancer and the clinical stage of the disease. Similarly, Zhou et al. [33], observed higher RCAS1 expression in endometrial cancer characterized by deep myometrial and vascular invasion. In an earlier study by Sonoda et al. [32], the authors reported that there was higher RCAS1 expression in grade 3

endometrial cancers when compared with grade 1 and 2 tumors. However, it seems that there is lack of association between serum sRCAS1 levels and the clinicopathological characteristics of endometrial cancer. Sonoda et al. [23], have evaluated serum sRCAS1 levels in fifty patients with endometrial cancer. These authors showed that there were higher pretreatment sRCAS1 levels in the patients with endometrial cancer compared with those of the healthy controls. However, serum sRCAS1 concentrations were not correlated with clinical stage, histologic type, grade, or lymph node metastasis [23]. This finding concurs with our observations. Namely, we did not observed differences between pre- and postoperative sRCAS1 levels according to tumor grade or the FIGO stage of the disease. Furthermore, in our study, we have found no association between sRCAS1 levels and the risk groups according to ESMO-ESGO-ESTRO criteria. This observation is very important, because it suggest that serum sRCAS1 levels may serve as a prognostic factor independent from clinical features of the disease. However, the results of our study should be interpreted with caution because of the small number of cases.

Sonoda et al. [23], showed there are decreased levels of sRCAS1 after successful treatment.We also observed decreased levels of sRCAS1 following hysterectomy. However, we did not observe any relationship between the degree of sRCAS1 level changes and the patients' prognoses. Therefore, we conclude that while sRCAS1 levels decrease after treatment for endometrial cancer, patients' prognoses are more related to the absolute levels of sRCAS1.

We observed a strong correlation between both pre- and postoperative sRCAS1 and patient age. In the study by Sonoda et al. [23], serum sRCAS1 levels were not associated with patient age. The possible explanation of this discrepancy is that Sonoda et al. studied a single group combining endometrial and cervical cancer patients, although these two cancers occur in different age groups. However, another study by Sonoda et al. [31], reported a strong and positive correlation between tumor RCAS1 immunoreactivity and patient age. Patients' age is in general regarded as a negative prognostic factor in endometrial cancer [34, 35]. Our results confirm this observation, because advanced age was associated with shortened survival. Although in our study sRCAS1 levels were correlated with patient age, in our multivariate analyses, both patient age and sRCAS1 levels were shown to be independent prognostic factors of patient OS.

In conclusion, we have found that elevated serum sRCAS1 were shown to be associated with shortened overall survival in patients with endometrial cancer. However, more prospective studies are needed to confirm or reject the hypothesis that the serum sRCAS1 levels could be used to predict the OS in women treated for endometrial cancer.

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Conflicts of interest

The authors declare no conflict of interests.

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The value of an initial drop in Human Chorionic Gonadotropin levels in predicting a response to methotrexate in women with low-risk Gestational Trophoblastic Neoplasia

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ABSTRACT

Objectives: The early identification of patients who are being treated for low-risk gestational trophoblastic neoplasia (LRGTN) with single-agent chemotherapy, who are at high risk of developing chemoresistance, is of crucial importance. The aim of our research was to evaluate the pretreatment beta subunit of human chorionic gonadotropin (βhCG) concentration and its decrease after the administration of the first course of methotrexate (MTX) in predicting later chemo-resistance to single-agent chemotherapy.

Material and methods: A total of 46 patients diagnosed with LRGTN treated with a 5-day methotrexate (MTX) regimen were retrospectively studied. 24 of the patients were successfully cured with only MTX therapy (MTX group). The disease was considered resistant in the remaining 22 patients who, after MTX therapy, required further chemotherapy with an EMA/CO regimen (EMA/CO group). To compare changes in the βhCG concentrations between the two courses of treatment (and the two groups), we calculated the percentage of decline. We determined the specificity and sensitivity of the initial βhCG level and its percentage decline, as a potential predictor of the need for a future EMA/CO regimen. For diagnostic purposes, βhCG levels were measured before the first and second administrations of MTX with a commercial ELISA kit.

Results: In the EMA/CO group, we found the initial βhCG level before the first MTX dose was higher (median = 6275 mIU/mL, range: 21.53–192.610.0 mIU/mL) than in the MTX group (median = 532 mIU/mL, range: 56.5 mIU/mL–360.397.0 mIU/mL) (p = 0.034, Mann-Whitney test). The percentage decreases in the βhCG values relative to the initial concentrations were higher in the MTX group (median decrease = 82.7%, range: from 13.3% to 99.9%) than in the EMA/CO group (median decrease = 71.1%, range: from an increase of 56.1% to a decrease of 97.1%) (p = 0.0079, Mann-Whitney test). An analysis of the ROC curves implied optimal cutoff values for the initial βHCG (6054 IU, sensitivity = 55%, specificity = 86%) and the percentage change in βhCG levels (decrease by 76.5%, sensitivity = 72%, specificity = 71%).

Conclusions:

1. Women with initially higher βhCG levels have a greater risk of developing MTX chemo resistance.
2. It would be advantageous to consider administering an EMA/CO regimen in women with LRGTN when their initial βhCG levels are greater than 6000.

Key words: methotrexate; predictive values of βhCG; gestational trophoblastic neoplasms

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INTRODUCTION

Gestational trophoblastic neoplasm (GTN) is a highly curable group of malignant pathologies that develop from trophoblastic cells [1]. It includes placental site trophoblastic tumors (PSTT), invasive moles, epithelial trophoblastic tumors (ETT) and choriocarcinomas. In recent years, one of the big challenges has been to find biomarkers for gestational trophoblastic disease (GTD) that could significantly improve the

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identification of patients who have a higher risk of developing more aggressive forms of the disease. Based on WHO criteria that consider epidemiological data, the course of disease has been qualified as either low-risk (LRGTN) or high-risk (HRGTN). Based on this same WHO risk-factor scoring system as modified by FIGO, patients diagnosed with GTN are classified as having either a low-risk or a high-risk of developing methotrexate (MTX) resistance. The FIGO Prognostic Scoring System is also designed to identify patients with a high risk of developing aggressive GTN [2]. Clinical features included in this scoring system are pretreatment beta subunit of human chorionic gonadotropin (βhCG) levels, form of preceding pregnancy, time since the last pregnancy, age, size of the tumor, site of the spread, number of metastases, and the drugs used that failed to treat the tumor. Due to varying dynamics of the disease, this staging system does not always work perfectly in practice. Whereas low-risk GTN patients (who have received < 5 points) are treated with single-agent chemotherapy, and for high-risk patients (who have received >= 7 vpoints) multi-agent chemotherapy is recommended. βhCG, though included in the WHO/FIGO criteria, is not the only decisive factor in determining future management. In practice, it may happen that patients with a relatively high βhCG levels are still qualified as have a low risk of the disease. Some patients, particularly those with high pre-treatment βhCG levels, who are assigned to the LRGTN group and are thus administered with a single-agent chemotherapy, in fact, later, require therapy conversion. Although the disease is highly sensitive to chemotherapy [3], early diagnosis and the best choice of treatment regimen are important for patients; and this may also shorten the treatment time, and consequently, its costs. If misdiagnosed at an early stage, malignant gestational trophoblastic disease may metastasize to distant organs. In addition, early diagnosis can permit early application of the appropriate treatment, which can increase the patient's chances of a faster recovery. Correct diagnosis can be obtained effortlessly using analysis of the concentration of human chorionic gonadotropin. But selecting the right treatment for the patient is more complicated. The application of a therapy that is too gentle can trigger drug resistance, whereas choosing a too-aggressive therapy increases the incidence of unwanted side effects and a premature disqualification of the patient from the therapy. Either discontinuing or disturbing treatment may also cause drug resistance, with the consequence of the patient remaining unhealed, and eventually, patient mortality. Almost 99% of low-risk patients respond to monotherapy, whereas 70% of medium-risk patients (who scored 5 and 6 points) do not respond to the first-line treatment and require an adjustment of their treatment regimen. About 25–30% of patients with GTN develop resistance to the first-line chemotherapy and require alteration of their therapy [3]. One of the most significant steps in the course of a GTN resistant therapy is choosing the right moment to apply the triple or multi-agent regimen. Until now, diagnosis of resistance to single agent treatment with MTX has been based on the rise or stagnation of serum βhCG levels during treatment, and (or) development of new metastases; however, no consensus on a defining guideline regarding the diagnosis of MTX resistance has been established [4]. Also, initially high levels of serum βhCG are a known risk factor of MTX treatment failure, though its dynamics during the treatment of MTX-sensitive and MTX-resistant patients still require some investigation. The aim of our study was to investigate whether initial differences in βhCG levels between the first and second doses of methotrexate are predictive of a future need for conversion to a multi-agent EMA/CO regimen.

MATERIAL AND METHODS

Patient Characteristics

A total of 46 patients diagnosed with low-risk GTN were retrospectively analyzed. All patients had been treated between November 2000 and September 2016 in the Department of Gynecology, Obstetrics and Gynecologic Oncology of the Poznan University of Medical Sciences, which is the Polish Reference Center for GTD. All women were initially qualified for a 5-day, single-agent therapy based on the WHO criteria (25 mg of Methotrexate once daily, administered intramuscularly). The pre-treatment evaluation of each patient included a physical examination, measuring the serum human chorionic gonadotropin levels, and conducting pelvic ultrasonography and chest radiography. Serum βhCG levels were evaluated before each chemotherapy cycle. Treatment was stopped if the βhCG levels normalized (≤ 1 mIU/mL) (MTX group). If there was an increase, a plateauing or a decrease of βhCG concentrations of less than 15% between any of the previous and following courses of MTX, the therapy was converted to a multi-agent regimen. At some point, 22 patients were considered resistant to the treatment of the 5-day MTX therapy and were subsequently treated with an EMA/CO regimen (EMA/CO group).

The study was conducted in accordance with the requirements of the Declaration of Helsinki and the study protocol was approved by the Ethical Review Board of the Poznan University of Medical Sciences, Poland (Decision No. 425/14).

Statistical analysis

Analysis of data was performed in R programming language (version 3.4.1) using RStudio (version 0.98.1060). The normality of the distribution was verified using the Shapiro test. Groups with a normal distribution were compared using the t-Student test. Groups with distributions that deviated from normal were compared using the Mann-Whitney test. The results were considered significant for p values < 0.05. P values are specified in the figures included in this paper. Plots were generated using ggplot2 and ggpubr R packages. P values were calculated

and added to the plots using the stat_compare_means() function. Boxplots were generated using the geom boxplot() function. Plot whiskers extend to the most extreme data point, within 1.5 times the interquartile range of the box. The upper and lower "hinges" correspond to the first and third quartiles. The central line in the boxplot represents the median. Dots in the plot were generated using the function geom_jitter() and correspond to the single measurements of individual patients. An R package plotROC was applied to produce receiver operating characteristics (ROC) curves and to calculate the area under the curve (AUC). The cutoff values were determined using the OptimalCutpoints R package based on the Youden index. The predictive performance of the markers were compared using the Delong test and were computed using the roc.test() function from the pROC R package.

RESULTS

The range of initial βhCG concentrations in the EMA/CO group members equaled 21.53 mIU/mL–192.610.0 mIU/mL. Before conversion to the EMA/CO therapy, patients received between 200 and 5050mg of MTX (between 1 and 16 methotrexate cycles were administered, with patients receiving 1, 2, 3, 4, 5, 7, 8 or 16 MTX courses). In the MTX group, 24 patients received between 3 and 10 administrations of methotrexate (the range of initial βhCG: 56.5mIU/mL–360.397.0 mIU/mL) and were successfully managed using MTX therapy (with an overall MTX dose of 375–900 mg) without further conversion to an EMA/CO regimen (MTX group).

We observed that the median of the initial βhCG levels before the onset of methotrexate therapy was higher in the EMA/CO (median = 6275) group than in the MTX (median = 532) group (p = 0.034, Mann-Whitney test, Fig. 1). To analyze the initial dynamics of βhCG, we plotted the corresponding concentrations at the first and second doses of methotrexate (Fig. 2A). To compare the decrease in βhCG levels between patients, we plotted the percentage change relative to the initial level at dose 1 of methotrexate (Fig. 2B). We observed that the average drop (the dashed line in Figure 2B) in the relative βhCG values was more pronounced in the MTX

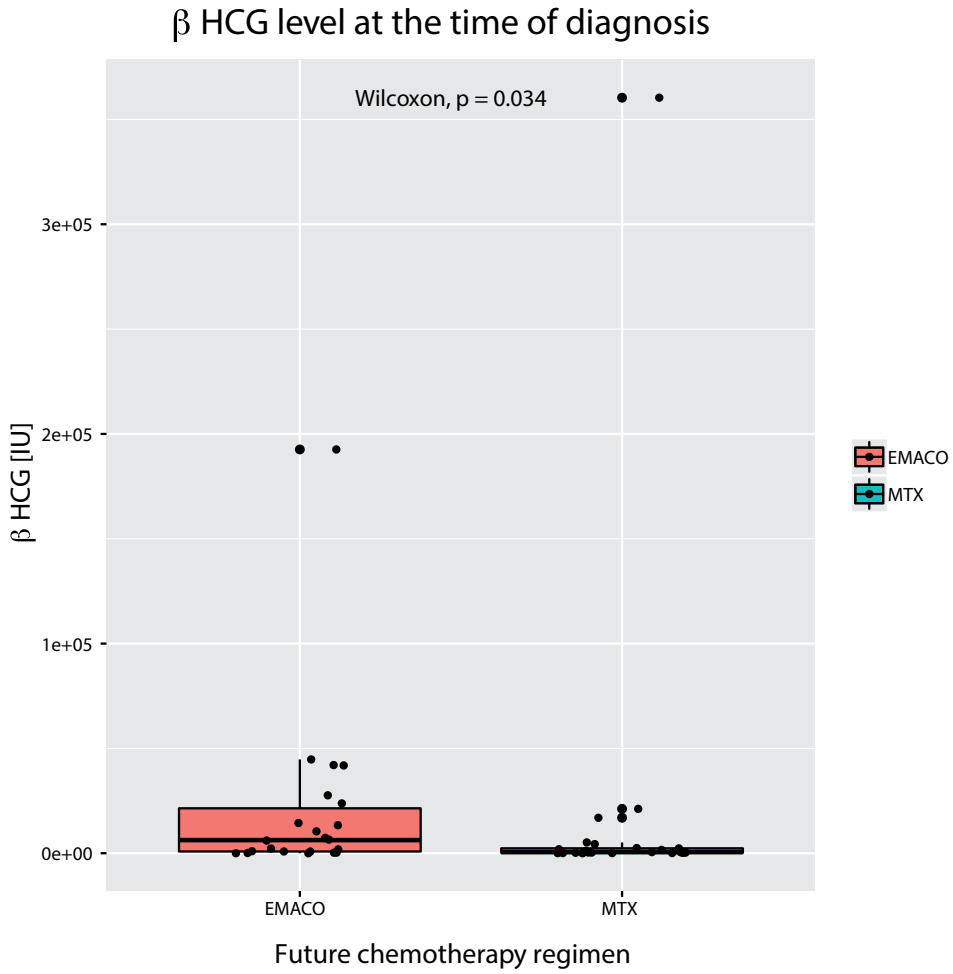

Figure 1. βhCG level at the time of diagnosis

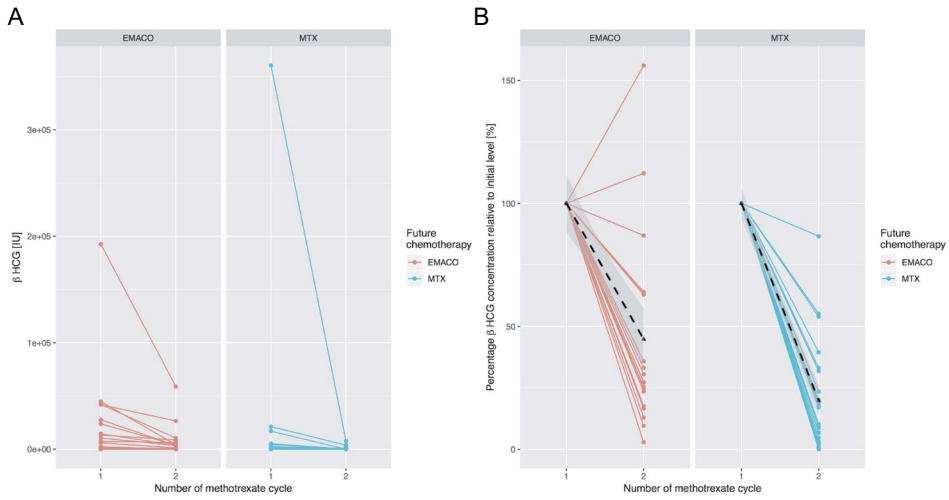

Figure 2. A. Concentrations of βhCG at the first and second doses of methotrexate **B.** The percentage change relative to the initial level at dose 1 of methotrexate

group. To determine whether that difference was relevant, we compared the percentage change in the βhCG levels between the EMA/CO and MTX groups. We demonstrated that the gradient in the relative βhCG values was more negative in the MTX (median decrease = 82.7%, range: 13.3–99.9%) group than in the EMA/CO (median decrease = 71.1%, range: from an increase of 56.1% to a decrease of 97.1%) group (p = 0.0079, Mann-Whitney test, Fig. 3). To evaluate the predictive value of those parameters we determined their specificity and sensitivity in predicting the future need for conversion to an EMA/CO regimen (Fig. 4A and 4B). An analysis of the ROC curves implied optimal cutoff values for the initial βhCG (6054 IU, sensitivity = 55%, specificity = 86%, based on Youden index) and the percentage change in the βhCG levels (a decrease of 76.5%, sensitivity = 72%, specificity = 71%, based on Youden index). The parameters of measuring the initial βhCG levels in comparison with the percentage changes in βhCG levels, and then comparing these results between the EMA/CO and MTX groups, showed that their predictive value did not differ (AUC for the initial βhCG and the percentage change in the βhCG levels were 0.68 and 0.74, respectively; DeLong test, p = 0.96). Altogether, we have shown that patients who will, in the future, be resistant to methotrexate and who will require an EMA/CO therapy (EMA/CO group) have a higher initial value of βhCG and a lower drop in the percentage of the βhCG value when measured between the first and second administrations of methotrexate.

DISCUSSION

Both defining and treating low-risk GTN remain somewhat controversial [4]. Tumor resistance is described as an increase in hCG levels or their stagnation over a 2 to 3-week period [5], although there is no internationally accepted consensus on the definition of drug resistance resulting from chemotherapy [6]. There is also no diagnostic tool available to predict chemoresistance and consequently to establish an appropriate treatment schema at the beginning of therapy.

In our study, we focused on only one factor (the regression of βhCG levels between the first and second doses of methotrexate) as the prognostic indicator of methotrexate resistance. We aimed to evaluate whether the patients, who would need converting to a single-agent therapy in the future, have a lower decrease in their βhCG levels between the first and second doses of MTX administered for LRGTN. MTX was the first agent used and is still the most common drug used in the treatment of LRGTN [7]. It has already been shown that a 5-day schema has minimal toxicity, and this compares favorably with the findings of other reports using similar methotrexate protocols [8–11]. Therefore, we used a 5-day regimen of methotrexate as the initial treatment for low-risk GTN. We noticed that the median initial βhCG level prior to the onset of methotrexate therapy was higher in the EMA/CO group than in the MTX group. Our research also revealed that patients who would become resistant to methotrexate in the future, and therefore require EMA/CO therapy, have a lower percentage decrease in their βhCG values when measured between the first and second administrations of methotrexate.

Several research projects on trophoblastic disease have concentrated on factors associated with hCG levels before. In one large study, the authors described the regression of serum hCG levels in patients with low-risk GTN who were successfully treated with MTX. The same authors revealed that serum hCG levels preceding the fourth and sixth single-agent chemotherapy courses proved to have excellent diagnostic

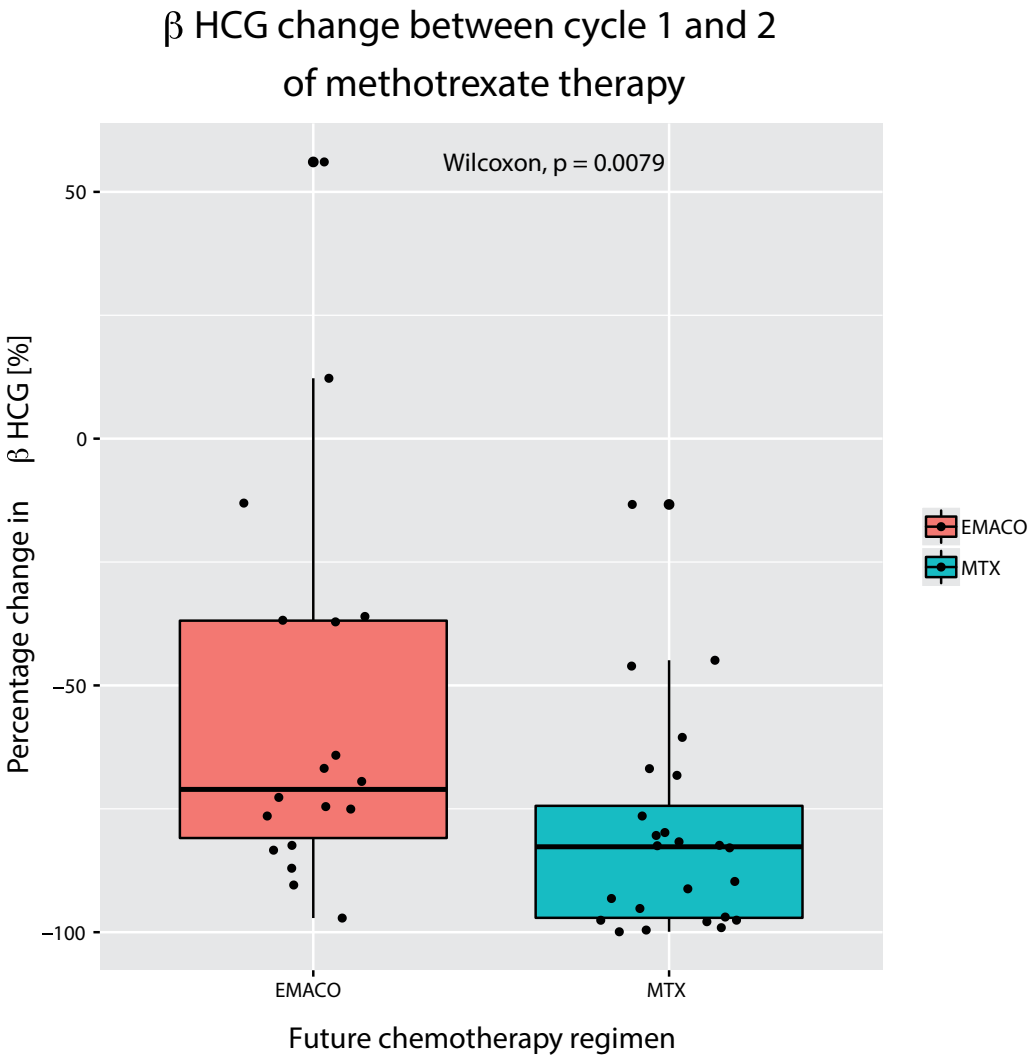

Figure 3. βhCG change between dose 1 and 2 of methotrexate therapy

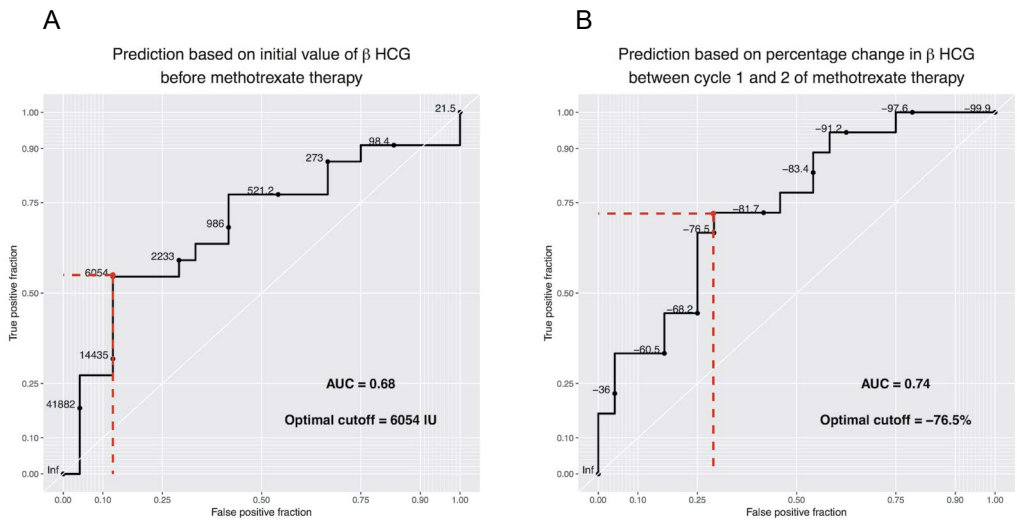

Figure 4. A. Prediction based on initial value of βhCG before methotrexate therapy **B.** Prediction based on percentage change in βhCG between cycle 1 and 2 of methotrexate therapy

accuracy for identifying resistance to single-agent chemotherapy, with an area under the curve (AUC) of 0.949 and 0.975, respectively, in the ROC curve analysis [12].

Maesta et al. [4] examined the time taken to achieve hCG remission in patients with low-risk postmolar GTN. The authors confirmed that a complete mole histology prior to GTN, the presence of metastatic disease, the use of a multi-agent therapy and a higher FIGO score were all independent factors associated with a longer time to hCG remission in patients with low-risk GTN. Chapman-Davis et al. [8] looked for the factors connected with resistance to single-agent methotrexate chemotherapy. Those authors described the presence of metastases, a clinicopathologic diagnosis of choriocarcinoma, higher FIGO/WHO scores and higher pretreatment hCG levels as factors associated with resistance to initial chemotherapy. In another research project, it was revealed that patients diagnosed with LRGTN and with a pre-treatment hCG > 400.000 IU/L should receive multi-agent chemotherapy (EMA/CO) from the onset of treatment due to a poor response to a methotrexate-folinic acid (MTX-FA) regimen [13]. Also, Soper et al [14], reported the influence of high pre-treatment hCG levels on a negative response for drug resistance, and this finding coincides with our own results.

You et al. [15–17] concentrated on finding a model for hCG that may be useful in predicting MTX resistance. Model-building is demanding and challenging, but the authors' results may have practical clinical application [17]. The NRG Oncology/Gynecologic Oncology Group-174 (GOG-174) trial showed the value of modelling the kinetic parameters of hCG decline regarding the resistance of the disease to a single-agent chemotherapy; and in fact, their results revealed that their modelling could predict the individual risk of such resistance [15]. In an earlier study, the same authors confirmed that it is possible to design an individual model for hCG decline curves using a kinetic population approach with LRGTN patients, and that derived parameters were strong early predictors of MTX resistance [16]. In their subsequent research, the same authors confirmed the superior predictive power of the kinetic population modelling approach. The authors showed that by using individually calculated modelling of the residual production of hCGres values, it was possible to accurately identify about 80% of the patients who would develop MTX resistance [17].

Further retrospective research based on a larger population of patients is desired to give results that will enable early and adequate treatment for patients with low-risk GTN. Identifying the prognostic factors associated with effective treatment choices may help avoid unnecessary prolongation of the therapy and therefore minimize the side effects of chemotherapy and treatment costs and reduce patient anxiety.

CONCLUSIONS

1. Women with initially higher βhCG levels have a greater risk of developing MTX chemo resistance.
2. It would be advantageous to consider administering an EMA/CO regimen in women with LRGTN when their initial βhCG levels are greater than 6000.

Author Contributions

Paulina Banach and Ewa Nowak-Markwitz designed the research; Paulina Banach and Ewa Nowak-Markwitz contributed important samples; Mikolaj Piotr Zaborowski performed the research; Paulina Banach, Natalia Izycka and Anna Romala collected data; Paulina Banach, Mikolaj Piotr Zaborowski and Ewa Nowak-Markwitz analyzed data; Paulina Banach, Mikolaj Piotr Zaborowski, Natalia Izycka, Anna Romala and Ewa Nowak-Markwitz wrote the paper; and all authors have read and approved the submitted manuscript.

Conflicts of Interest

The authors all declare they have no conflicts of interest.

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Long-term outcomes of prenatally diagnosed ventriculomegaly — 10 years of Polish tertiary centre experience

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ABSTRACT

Objectives: To estimate the prevalence, associated anomalies, and postnatal outcomes in infants prenatally diagnosed with ventriculomegaly.

Material and methods: All cases of ventriculomegaly that were examined and treated by the 1st Department of Obstetrics and Gynecology, at the Medical University of Warsaw, from August 2007 until November 2017 were included in this study. Ultrasound data, and information on perinatal outcomes and long-term postnatal follow up were retrospectively collected by a standardised telephone survey. Ventriculomegaly was diagnosed when the atrial width of the lateral ventricles was ≥ 10 mm. The cases analyzed were divided into two subgroups: isolated ventriculomegaly (IVM) and non-isolated ventriculomegaly (NIVM). Neurodevelopmental complications were differentiated as either moderate or severe and were compared within each group and between groups.

Results: There were 118 cases of prenatally diagnosed ventriculomegaly. Complete follow up records were collected for 54 cases (45.8%). IVM was diagnosed in 29/54 (53.7%) cases, while NIVM was diagnosed in the remaining 25 (46.3%). The mean ventricular width for IVM was 16.93 mm (range 10.0 mm–73.0 mm) and 14.08 mm (range 9.0 mm–27.1 mm) for NIVM ($p = 0.28$). The mean gestational age at delivery for the IVM cases was 36 + 4 weeks and in the NIVM group 33 + 4 weeks ($p = 0.022$). Mild VM (10–12 mm) was diagnosed in 22/54 cases (40.7%), moderate VM (13–15 mm) in 12/54 (22.3%) and severe (≥ 15 mm) in 20/54 (37%). Among the infants with IVM the rate of severe medical complications was 29.6% (8/28) and for NIVM 667% (8/12) ($p = 0.041$). Less severe medical conditions affected 6/28 of the infants with IVM (21.4%) vs 9/12 NIVM cases (75%) ($p = 0.012$).

Conclusions: In terms of prenatal diagnosis, treatment of ventriculomegaly remains challenging due to a lack of specific prognostic factors and the significant risk of neurodevelopmental disorders. Nevertheless, isolated ventriculomegaly has significantly better long-term outcomes compared with non-isolated ventriculomegaly. In our material, the rate of severe neurodevelopmental disorders in the non-isolated ventriculomegaly cases was associated with a 52% rate of adverse perinatal outcomes. On the other hand, less severe medical conditions occurred in 21.4% of the infants with IVM and in 75% of the NIVM cases. Furthermore, obstetrical data suggest that the risks of premature delivery and caesarean section are significantly higher in cases of non-isolated ventriculomegaly.

Key words: ventriculomegaly; ultrasound; neurodevelopment

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INTRODUCTION

The measurement of the posterior horns of the lateral ventricles has become an integral part of prenatal ultrasound screening. Ventriculomegaly (VM) is diagnosed when the atrial width is ≥ 10 mm and it remains one of the most common abnormalities detected prenatally. The prevalence range is 0.3 to 2% of foetuses [1]. To guard against false positive diagnoses, the wide variety of measurement techniques currently used ought to be replaced with a universal measurement protocol. The diagnosis of fetal ventriculomegaly may be described as either idiopathic or a symptom of genetic, infectious or anatomical disorders. Regardless of the primary cause, two groups may be distinguished: isolated (IVM) if there are no other abnormalities present, and non-isolated

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ventriculomegaly (NIVM) where there are other abnormalities present. To assess the severity of VM cases, most studies distinguish between "mild" (10–12 mm), "moderate" (13–15 mm) and "severe" (≥ 15 mm) ventriculomegaly [2]. Despite many studies undertaken by obstetricians and paediatricians that investigate the natural course of VM, the pregnancy and long-term neurodevelopment outcomes remain unknown in most cases. The prognoses of fetuses with VM are controversial because of the large variations in the study scales and follow-up criteria [1]. In this study, we retrospectively analysed and compared pregnancy outcomes, including long-term follow-up outcomes, in infants prenatally diagnosed with IVM and NIVM.

MATERIAL AND METHODS

The total number of cases (n = 118) that were diagnosed with VM and examined in the 1st Department of Obstetrics and Gynecology, Medical University of Warsaw (Poland) from August 2007 until November 2017 were included in this study. We retrospectively collected ultrasonographic data, and information on perinatal outcomes and long-term postnatal follow up. The ultrasound scans were performed by experienced senior ultrasonographers using the Aloka Prosound Alfa 10 system with transabdominal convex probe and the General Electric Voluson E6 BT13.05 system with transabdominal volumetric probe. VM was diagnosed when the atrial width of the lateral ventricle was ≥ 10 mm. Once VM was diagnosed, a detailed scan was performed to exclude associated intracranial or extracranial anomalies. The management protocol also included determination of gestational age, measurement of the contralateral ventricle (in cases of an asymmetrical VM, the larger diameter was considered), placental site, amniotic fluid volume and estimated fetal weight (according to the Hadlock formula). The cases were classified as "Isolated Ventriculomegaly" (IVM) if no associated anomaly was detected, or as "Non-Isolated Ventriculomegaly" (NIVM) which was defined as ultrasound findings of ventriculomegaly with other structural abnormalities or positive findings in TORCH screenings or karyotype examinations.

Medical records of all cases were carefully reviewed. Telephone interviews were used to obtain information about pregnancy outcomes and long-term neurodevelopmental follow-up. All parents were asked questions based on the same questionnaire that included seeking information on the children's: growth, neurological status, developmental status, locomotor activities, coordination, hearing and visual function, speech and socialisation capacities. Information on any current medical treatment or special medical care was also gathered.

Neurodevelopment disorders were divided into moderate and severe and compared within and between the IVM and NIVM groups. The types of moderate and severe disorders analysed in this paper are presented in Table 1.

Table 1. Types of moderate and severe complications reported in IVM and NIVM groups

System affected	Moderate symptoms	Severe symptoms
Central nervous system	Autism spectrum disorders	Tetraplegia
		Epilepsy
		Hydrocephalus
		Microcephaly
Motor function impairment	Increased muscle tension	Delayed psychomotor development
	Reduced muscle tension	Severe paralysis of the limbs
	Fine motor skills disorders	
	Flaccid paralysis of the limbs	
Vision/Hearing impairment	Nystagmus	Retinopathy
		Hearing impairment
		Speech impairment

Follow-up information and obstetrical data such as gestational age at the delivery, method of delivery and birthweight were analysed using SPSS 15.0 (SPSS Inc., Chicago, IL, USA). The chi-square test was applied, and differences were considered to be statistically significant at $p < 0.05$. Descriptive statistics were also used for analysis of ultrasonography details and the follow-up characteristics of all the cases.

RESULTS

Complete records were collected in 54 cases (45'8%). The high number of incomplete long-term follow-up data was due to inaccurate contact details in the records (i.e., either incorrect or missing telephone numbers). The mean maternal age at the time of the ultrasound scan was 30 years (range 20–45 years). Among the group of 54 fetuses affected with VM, 41/54 cases were singleton pregnancies (75.9%) and 13/54 in twins (24.1%). The mean gestational age at the time of referral/diagnosis was 27^{+0} weeks (range 18^{+0}–39^{+2} weeks). The study group was divided into two subgroups: IVM (isolated ventriculomegaly) and NIVM (non-isolated ventriculomegaly). The IVM group consisted of 29/54 fetuses (53.7%) and the NIVM group consisted of 25/54 cases (46.3%) (Fig. 1). The average gestational age at the time of diagnosis/counselling for IVM was 27^{+4} weeks (range: 18^{+6} 39^{+2}) and for NIVM, 26^{+1}weeks (range: 18^{+6}–39^{+0}).

The mean ventricular width for IVM was 16.93 mm (range 10.0 mm–73.0 mm) and for NIVM, 14.08 mm (range 9.0 mm–

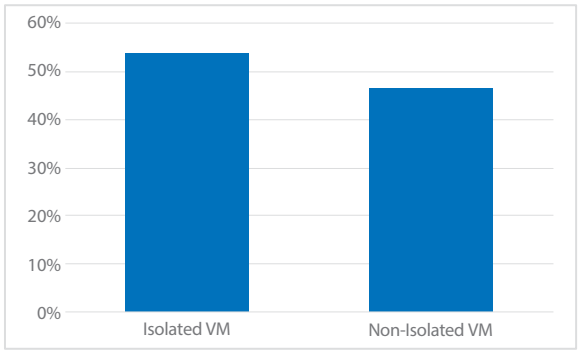

Figure 1. Prevalence of isolated vs. non-isolated ventriculomegaly in the study group

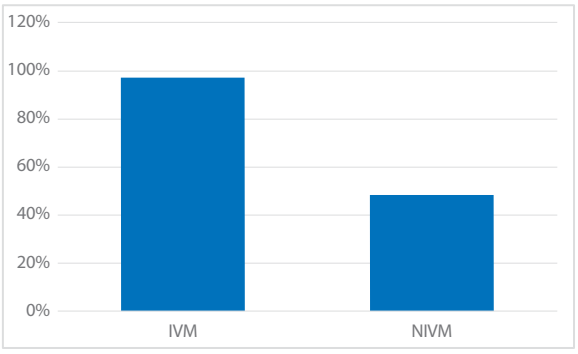

Figure 3. Survivors in the IVM and NIVM groups

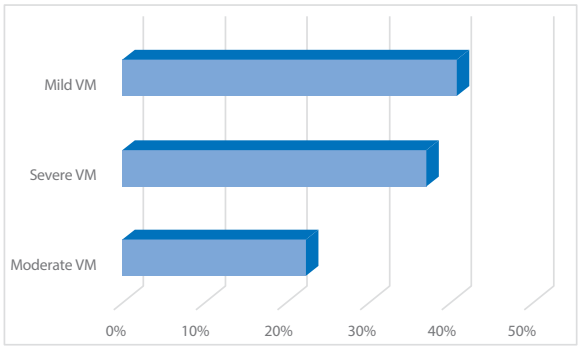

Figure 2. Ventriculomegaly severity range in the study group. (Mild VM: 10–12 mm; moderate VM: 13–15 mm; severe VM: ≥ 15 mm)

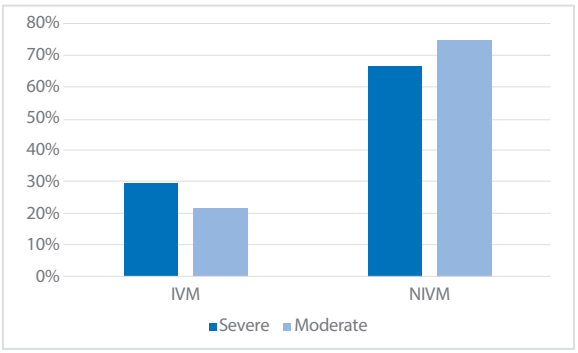

Figure 4. Prevalence of severe and moderate medical conditions diagnosed in the two subgroups

27.1 mm) (p = 0.28). Overall, mild VM (10–12 mm) was diagnosed in 22/54 cases (40.7%), moderate VM (13–15 mm) in 12/54 (22.3%), and severe (≥ 15 mm) in 20/54 (37%) (Fig. 2).

Multiple pregnancy rates were similar in both groups (27.6% vs 20.0% in IVM and NIVM respectively). The mean gestational age at delivery for IVM was 36^{+4} weeks and in the NIVM group 33^{+4} weeks (p = 0.022). The rate of preterm delivery < 34 weeks in IVM was 6/29 (21%) and in NIVM 8/25 (32%), and the difference between these was statistically significant (p = 0.027). The mean birth weight for IVM neonates was 2668 g vs 2129 g for the NIVM neonate, which showed a borderline statistical significance (p = 0.08).

The most frequent coexisting fetal abnormalities in the NIVM group were agenesis of corpus callosum, spina bifida, hydrocephalus, subarachnoid cyst, omphalocele, ventricular septal defect, diaphragmatic hernia, duodenal atresia, mega cisterna magna, talipes, kidney agenesis, and small for gestational age. There was one case of trisomy 13 (classified as NIVM).

Caesarean section rates in both groups were high amounting to 79.3% in the IVM group vs 77.3% in the NIVM group. The NIVM group was associated with a 52% rate of adverse perinatal outcomes. In 25 of the NIVM cases there were reported: 8/25 (32%) postnatal deaths, 2/25 (8%) stillbirths, and 3/25 (12%) spontaneous abortions. There was only 1/29 (3.4%) postnatal death in the IVM group. A total of 12 of 25 (48%) NIVM fetuses survived. (Fig. 3)

The average age of the children at the parental telephone interview was 23 months (range 6 weeks to 5 years). Among the surviving IVM infants, the rate of severe neurodevelopmental disorders (epilepsy, tetraplegia, speech or hearing impairment, microcephaly, hydrocephalus, delayed psychomotor development) was 29.6% (8/28), and among the NIVM survivors, 66.7% (8/12) (p = 0.041). The medical complications reported in both groups are listed in Table 1. Less severe medical conditions, such as motor function disorders, autism spectrum disorders, or reduced or increased muscle tension affected 6/28 of infants in the IVM group (21.4%) vs 9/12 of the NIVM cases (75%), which was statistically significant (p = 0.012) (Fig. 4).

DISCUSSION

The overall frequency of VM in the general population is approximately 0.3–2%. Most authors classify VM according to the three-degree classification, as either "mild" (10–12 mm), "moderate" (13–15 mm) or "severe" (≥ 15 mm) ventriculomegaly [2, 3]. In our study group, rates of mild VM (10–12 mm) and severe VM (≥ 15mm) were almost equal (40.7% and 37% respectively), while 22.3% were classified

as moderate VM (13–15 mm). In a larger group of 241 fetuses described by Chu et al. [1], the rate of moderate VM was comparable (23.2%), but in the same study the rate of mild VM was significantly higher that our result (62.7%). On the other hand, in that same paper, the rate of NIVM was high and reached 66% compared with 46.3% in our study group. Regardless of the severity of VM, follow-up scans are recommended as the risk of progression of ventricular dilatation is about 16% [4]. In most studies, progression of ventriculomegaly is defined as an increase in the ventricular measurement of more than 3 mm [5]. Several studies suggested the atrial width may determine the final outcome [6]. However, a large meta-analysis of pooled data did not demonstrate differences in the neurological outcomes between mild and moderate groups [4]. There is also a male predominance among fetuses with a mild VM diagnosis. It is noteworthy, that the female gender correlates significantly with worse neurodevelopmental outcomes [7].

There is wide variation in the reported incidence of neurodevelopmental delay, but several studies suggest this is around 11% [4, 7]. Weichert et al. [8] reported poor prognoses in 41% of cases. Another study reported handicap-free survival in just over one third of cases affected by severe isolated VM [9]. According to several other papers, a ventricular atrial width of > 15 mm is related to poor outcomes [6, 10, 11]. A large systematic review and meta-analysis revealed abnormal neurodevelopmental outcomes in 7% and 8% of mild and moderate VM cases, respectively, and in 58% of severe VM cases, suggesting the rate of neurodevelopmental delay for isolated mild and moderate VM is comparable to that of the general population [12].

We analysed 54 cases of VM diagnosed prenatally: 41 singleton (75.9%) and 13 twin pregnancies (24.1%). In a larger study group of 241 fetuses affected with VM, the multiple pregnancy rate was significantly lower than in our study — only 1.6% were twins [1]. The high incidence of multiple pregnancies in our group may be associated with the specific profile of the patients, because most of them were referred to a tertiary ultrasound department for an expert opinion. Moreover, many of the twin pregnancies in our study group remained under prenatal surveillance in the Multiple Pregnancies Out Patient Unit in our Department.

The mean maternal age in our study was 30 years, which was similar to that in the Gomez et al. study (29 years) [13]. The average gestational age at the time of delivery in the IVM group was significantly higher compared with that of the NIVM group (36^{+4} weeks vs. 33^{+4} weeks, respectively). This was most likely due to accompanying fetal abnormalities that increase the risk of preterm delivery or premature rupture of membranes (PROM), such as polyhydramnios in the course of abnormal fetal swallowing associated with central nervous system defects. Discordant rates of preterm deliveries resulted in the differences between the mean birth weights (2668 g vs 2129 g for the IVM and NIVM groups, respectively). Furthermore, there were surprisingly high rates of caesarean section in both groups — 79.3% in IVM and 77.3% in NIVM. A prevalence of caesarean deliveries in VM cases has also been reported by other authors. Hannon et al. [10] found an association between the final atrium measurement and mode of delivery with the odds of elective cesarean delivery being increased by 11% for each additional millimetre in atrial width. The most frequent indications for caesarean section in our group were: failure to progress, malpresentation, cephalopelvic disproportion, placenta praevia and hypertensive disorders. It must be underscored that the VM itself is not an indication for caesarean section. Pisapia et. al. [14] revealed that head circumference (HC) remains normal in most cases of VM. Only in cases with severe hydrocephaly causing abnormal intracranial pressure, resulting in increased head circumference (HC) above 400 mm, may qualify for elective caesarean section due to the high risk of obstetrical complications; however, there were no such cases in our study group.

The main goal of our study was to investigate the long-term neurological development outcomes following prenatal diagnosis of ventriculomegaly. In the group of infants with IVM, the rate of severe medical complications (epilepsy, tetraplegia, speech or hearing impairment, microcephaly, hydrocephalus or delayed psychomotor development) was 29.6% (8/28), while in the NIVM group the rate was 66.7% (8/12). We found a stronger association of poor prognosis with coexisting fetal abnormalities (NIVM) rather than with atrial width alone (the mean width for IVM was 16.93 mm and 14.08 mm for NIVM; $p = 0.28$). In the literature, mortality and impaired neurodevelopment in infants affected with VM differs between obstetrical and paediatric studies. Moreover, neurodevelopmental delay in preschool children is not rare, however reliable data on its precise prevalence are limited. In almost 10% of cases, associated anomalies are diagnosed in the postnatal period. Most infants with a prenatal diagnosis of IVM have normal neurological development at least in infancy and only 11% present some abnormalities [4].

Despite numerous studies, the perinatal outcomes and early adolescence neurodevelopment of infants affected with prenatally diagnosed VM remain unknown. Several studies investigating perinatal outcomes in cases affected with VM diagnosed prenatally revealed that any associated defect was related to significantly worse outcomes. The livebirth rates in NIVM cases is about 30–40% [10, 11]. This is consistent with our data, as a total of 12 out of 25 (48%) NIVM fetuses survived. On the other hand, in our IVM group, neonatal death occurred in only 3.4% of cases. The high rate of adverse perinatal outcomes in our material may be associated with the low number of pregnancy terminations (TOP) and the decision of patients to continue the gestation.

A major difficulty in prenatal diagnosis and treatment is related to the lack of a standardized and universal definition. A ventricular diameter of 10 mm correlates with more than two standard deviations of the normal, hence it qualifies as ventriculomegaly with most authors [15, 16]. Unfortunately, some clinicians tend to use the terms "ventriculomegaly" and "hydrocephalus" synonymously. However, even severe VM and the hydrocephalic state should be clearly differentiated. Besides significant dilatation of the ventricular system, hydrocephaly is associated with increased intracranial pressure. Unfortunately, though it is not possible to measure it antenatally, some indirect signs, such as dangling choroid plexuses or decreased volume and abnormal vascular flow pattern in subarachnoid vessels, may help achieve a differential diagnosis. Therefore, if there is no sign of increased intracranial pressure, the term "ventriculomegaly" should be used rather than "hydrocephalus". In selected cases, fetal MRI may have an additional diagnostic value; however, according to Malinger et. al., [17] a neurosonogram scan performed by an experienced sonographer has a similar accuracy to an MRI. In most cases neurosonography seems sufficient, especially with a transvaginal approach and vertex presentation, but MRI might be an extremely helpful imaging method in cases of poor visualisation or when a more detailed differential diagnostic tool is needed [15]. On the other hand, a large study involving third trimester MRI scans of 185 fetuses with moderate VM revealed information relevant enough to modify the obstetric management in 6% of cases [18]. In all cases of ventriculomegaly, the best available advanced neuroimaging should be offered as neurosonography has is highly accurate in the prenatal diagnosis of central nervous system abnormalities. It is noteworthy that approximately 40–60% of cases of ventriculomegaly have associated CNS or extra-CNS abnormalities [1, 7, 19, 20]. This is consistent with our data — NIVM were diagnosed with CNS or extra-CNS abnormalities in 25/54 cases (46.3%). There are several coexisting conditions leading to VM: meta-analysis by Gaglioti et al. [11] from 2009 points that abnormal turnover of cerebrospinal fluid (CSF), or congenital central nervous system defects such as agenesis of the corpus callosum, neuronal migration disorders, schizencephaly, vertical transmission of cytomegalovirus (CMV) or toxoplasmosis, intracranial haemorrhage and defects of the cerebral vessels may result in dilatation of the ventricular system. According to the literature, 9–12% of ventriculomegaly cases have an abnormal karyotype [1, 21]. On the other hand, a study by Melchiorre et al. [4] reports the rate of chromosomal abnormalities as 2.8%. In our group, there was only one case of trisomy 13. In the Melchiorre et al study, the group was screened for chromosomal abnormalities in the first trimester; whereas in our study, the single case of trisomy 13 was detected in the second trimester of pregnancy due to coexisting fetal abnormalities.

Study limitations

Several limitations of our study should be considered. The study was a retrospective analysis based on ultrasound reports, obstetrical data and paediatric follow-up. A precise protocol for interviewing parents by telephone was applied in every case. Most likely, in the instance of a higher rate of postnatal follow-up our results could have shed more light on the prenatal diagnosis of VM. Moreover, the paediatric follow-up was not evaluated by a paediatric neurologist and the infants' ages at the time of the telephone interview ranged from 6 weeks to 5 years. Considering the psychological impact of offspring's disease some of the data may be biased or inconclusive. On the other hand, this is the normal evaluation route from prenatal diagnosis to postnatal follow-up with retrospective studies.

CONCLUSIONS

Heterogenous aetiology and associated disorders suggest that in many cases VM should be considered as a symptom, not a disease itself. Despite the growing availability of different imaging techniques, a detailed ultrasound scan remains the first step and a reliable diagnostic tool. It has to be underscored that the measurement technique used plays a crucial role in the diagnostic process. Measurement of the atrium of the lateral ventricles on an axial transventricular plane, including the frontal horns and the cavum septi pellucidi, with symmetrical hemispheres is considered to be the most accurate [22]. Guidelines published by the International Society of Ultrasound in Obstetrics and Gynecology are based on the protocol by L. Guibaud, and this seems to provide the highest intra-observer reproducibility [23]. Once VM is diagnosed prenatally, associated CNS defects should be excluded. The most common associated CNS defects are agenesis of the corpus callosum (ACC) and spina bifida.

Due to unknown causes, prediction of postnatal neurodevelopment in fetuses affected with VM diagnosed prenatally is extremely unpredictable. Unfortunately, the results of studies in both obstetrical and paediatric fields are inconclusive. We are not able to precisely predict long-term follow up in individual cases. The available severity classifications and differentiating IVM from NIVM may help in prenatal counselling. Most of our results were like those available in the literature. Nonetheless, the obstetrical and paediatric data collected suggests that only a comprehensive prenatal diagnostic approach will help to determine the pregnancy outcome in each case.

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Continuous subcutaneous insulin infusion reduces neonatal risk in pregnant women with type 1 diabetes mellitus

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ABSTRACT

Objectives: An attempt was made to demonstrate the superiority of the treatment model using continuous subcutaneous insulin infusion (CSII) over multiple daily injections (MDI) of insulin in achieving a successful pregnancy outcome and good newborn's condition in patients with type 1 diabetes.

Material and methods: The study included 297 infants born to type 1 diabetic patients; 175 patients were treated with MDI and 122 with CSII.

Maternal metabolic control during pregnancy, gestational weight gain, insulin requirements, pregnancy outcome and neonatal status were compared between MDI and CSII arm.

The composite adverse neonatal outcome was diagnosed if at least one of the following was found: abnormal birth weight (LGA or SGA), congenital malformation, miscarriage, intrauterine fetal death, emergency CS due to fetal risk, iatrogenic prematurity, RDS, hypoglycemia, hyperbilirubinemia, and the postpartum pH in the umbilical artery ≤ 7.1.

Results: The studied groups did not differ regarding gestational week at delivery, a proportion of births at full term, preterm births, miscarriages, or late pregnancy losses (intrauterine fetal death > 22 weeks). Newborns of mothers treated with CSII showed lower incidence of neonatal complications (composite adverse neonatal outcome) compared to those of mothers treated with MDI (60% vs 74%, respectively; p = 0.01). We did not find any association between the mode of treatment and composite adverse maternal outcome.

Conclusions: The use of CSII in the treatment of pregnant women with type 1 diabetes was associated with reduced number of neonatal complications presented as neonatal composite outcome but had no influence on maternal outcome.

Key words: neonatal outcomes; pregestational diabetes mellitus; CSII; MDI

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INTRODUCTION

Short after insulin introduction, perinatal mortality of newborns among mothers with type 1 diabetes (T1DM) reached 40%. In the 1980s, it dropped to 5% in the most advanced centers due to modern medical treatments, with a further reduction to 1–2% that is reported today [1]. Apart from this substantial improvement, pregnancy in women with type 1 diabetes is still associated with an elevated feto-maternal risk. Unfortunately, we are still far from pregnancy outcomes in patients with T1DM being comparable to the general population.

The number of miscarriages and birth defects in the diabetic population remains 2 to 4 times higher than in the healthy population [2–5]. Maternal hyperglycemia in later pregnancy is a risk factor for late intrauterine fetal death, which is 2 to 5 times higher than in the rest of the population. Moreover, small vessels disease, characteristic for long-lasting diabetes also induces changes in placental

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micro vessels, resulting in placental insufficiency that also contributes to an increased proportion of fetal demise [6]. Fetal macrosomia, occurring in 25–42% of newborns, is a consequence of increased glucose and lipid transfer and selective transport of amino acids through the placenta in the second half of pregnancy. Subsequent fetal hyperinsulinemia results in hypertrophy and hyperplasia of fetal cells [7]. Fetal hyperinsulinemia also inhibits the stimulating effects of cortisol and lowers lecithin levels, resulting in an impaired synthesis of surfactant and causing delayed fetal lung maturation. This impairment can manifest as respiratory distress syndrome (RDS) that occurs 4 to 6 times more often in that group of neonates and can also happen in deliveries at term. RDS coexists with other symptoms of diabetic fetopathy: hypoglycemia, polycythemia, and hyperbilirubinemia [8]. New data also link maternal diabetes to remote health risks in the offspring such as type 2 diabetes and obesity in later life, by altering intrauterine development and growth [9].

Objectives

An attempt was made to demonstrate the superiority of the treatment model using continuous subcutaneous insulin infusion (CSII) over multiple daily injections (MDI) of insulin in achieving a successful pregnancy outcome and good newborn's condition in patients with type 1 diabetes.

MATERIAL AND METHODS

A retrospective analysis based on medical records of the pregnancies and their outcome, and neonates born from 297 pregnant women with T1DM. Patients who developed type 1 diabetes at least one year before conception, with single pregnancy and were given obstetric care before the 15th week of gestation were included in the study. Participants were referred from local diabetic units for antenatal care with a diagnosis of type 1 diabetes set at a baseline by practitioners who initiated medical therapy. For perinatal risk assessment, we used modified White's classification of diabetes during pregnancy [10]. We compared the course of pregnancy, pregnancy outcome, and the newborn status in both groups, taking into account the efficacy of the two investigated treatment methods.

All patients were treated with functional intensive insulin therapy using recombinant human insulins or short-acting insulin analogues according to the uniform procedure of the study center.

We allocated our patients to two groups, according to the type of insulin therapy used:

1. The group of patients treated with multiple daily insulin injections; N = 175.
2. The group of patients treated with continuous subcutaneous insulin infusion; N = 122.

Each patient referred to the unit in early pregnancy between 2010 to 2015 for further antenatal care, was offered to continue MDI or to participate in appropriate training on CSII. In patients who completed the training, we commenced treatment with CSII. None of the participants used the continuous glucose monitoring system (CGMS).

According to the center's protocol, the patients were hospitalized at least once during each trimester and were also seen in the outpatient clinic for combined diabetes and obstetrics antenatal care, which enabled data collection throughout the entire pregnancy.

We used the following criteria for good diabetes control during pregnancy: glycated hemoglobin ≤ 6.1% (43 mmol/mol), fasting glucose 60–90 mg/dL (3.3–5.0 mmol/L), glycemia one hour after a meal < 120mg/dL (6.7 mmol/L) and nocturnal glycemia > 60 mg/dL (3.3 mmol/L), in accordance to the recommendations of the Polish Diabetes Association (PTD) of 2011 [11]. Patients kept self-monitoring diaries with commercially available glucometers determining capillary blood glucose levels. We diagnosed hypoglycemic events if glucose concentration was below 40 mg/dL (2.2 mmol/L). Postprandial hyperglycemia was defined as a glycemia above 140 mg/dL (7.8 mmol/L) one hour after a meal.

We retrieved the following pieces of information from medical notes of the participants: patient age, age at diabetes onset, duration of illness, gestational age and body mass index (BMI) at the first antenatal visit, number of previous births, vascular complications like nephro- and retinopathy, and prepregnancy hypertension.

In subsequent trimesters, we monitored selected biochemical parameters evaluated at the Central Laboratory of the Hospital and daily glucose profiles performed by patients using glucometers for self-control during hospitalization.

From the medical records, we retrieved the following feto-maternal pregnancy outcomes: gestational age at delivery, mode of delivery, indications for caesarean sections, miscarriages and intrauterine deaths after 22nd gestational week. Women who lost their pregnancies within four weeks after enrollment were excluded from the analysis.

In newborns, we analyzed: birth weight, Apgar score at 1 and 5 minutes, pH from umbilical artery, birth weight (LGA; birthweight > 90th percentile according to local growth charts for normal population, customized for gestational age at delivery and sex; SGA; birthweight < 10th percentile according to local growth charts for normal population, customized for gestational age at delivery and sex). We also recorded RDS, hyperbilirubinemia, hypoglycemia, and congenital malformations.

We defined the following abnormalities as malformations: cardiovascular defects (ventricular septal defect (VSD)

and atrial septal defect (ASD), transposition of the great arteries (TGA), and coarctation of the aorta), caudal regression syndrome, and defects of the neural tube in the form of encephalocele [12]. We did not include newborns who have been diagnosed with patent foramen ovale because its prevalence was similar to this seen in the general population. Therefore, it could not be attributed to the maternal disease [13].

We defined a composite adverse neonatal outcome as abnormal birth weight (LGA or SGA), presence of congenital malformation, miscarriage, intrauterine fetal death, emergency CS due to fetal risk, iatrogenic prematurity, RDS, hypoglycemia, hyperbilirubinemia, and the postpartum pH in the umbilical artery ≤ 7.1 [14].

The composite adverse maternal outcome was recorded if at least one of the following occurred: newly diagnosed gestational hypertension, preeclampsia, emergency cc due to maternal risk, a progression of vascular complications or diagnosis of vascular complications de novo, excessive gestational weight gain.

For the statistical analysis, we used tests appropriate for the distribution of the variables. Quantitative variables with normal distribution were presented as mean ± SD or as median with minimum and maximum values for variables with nonparametric distribution. The chi^2 test was used to compare the characteristics of the unrelated nominal variables. The Mann-Whitney test was used to compare the unrelated ordinal values. Logistic regression models were made to demonstrate the significance of the impact of the independent parameters on the occurrence of the studied endpoint. A relative risk analysis was performed to compare the two treatment methods. P values below 0.05 were considered significant. Statistical calculations were performed using Microsoft Excel 2010, Statistica 7.1, and SPSS 14.0.

RESULTS

Characteristics of participants did not show statistically significant differences in age, the onset of care, or baseline BMI between the groups. Pregnant women in the CSII arm were significantly younger when diagnosed with T1DM, had a significantly longer history of the disease and were significantly more likely to plan their pregnancies, comparing to the MDI arm. The CSII- group also included significantly more patients with long-lasting diabetes with vascular changes in comparison to the MDI group. (Tab. 1).

Daily insulin requirements and gestational weight gain were similar between the groups. We observed an improvement in metabolic control regardless of the type of therapy. A longitudinal analysis of HbA1c showed a significant reduction in this parameter across the trimesters, irrespectively of the method of treatment. Also, mean daily glucose levels, fasting, postprandial and nocturnal glycemia improved in both arms. It is notable that fasting and nocturnal glycemia in the CSII group remained in the target range according to recommendations, but the results of MDI patients were higher [11]. We did not find differences in the number of hypoglycemic episodes during pregnancy among pregnant women from both groups. However, CSII treatment was associated with a significantly lower incidence of postprandial hyperglycemia in the second (15% vs 4.5%) and in the third (22.5% vs 7.7%) trimester compared to the MDI group (Tab. 2).

The studied groups did not differ regarding gestational week at delivery, a proportion of births at full term, preterm births, miscarriages, or late pregnancy losses. However, we noted a trend for the increased number of preterm births and intrauterine deaths in MDI arm (Tab. 3). In our cohort, we evaluated the composite adverse neonatal outcome between the groups and noted significantly reduced proportion of neonatal complications in the CSII group ($p < 0.01$) (Tab. 4). Maternal age, participant age when diagnosed with the disease and pregnancy planning (characteristics that differed significantly between the MDI and CSII groups, see Table 1) did not significantly correlate with composite neonatal outcome. Birth weight and Apgar scores were not statistically different, but we noted a trend for a higher first-minute Apgar score in CSII arm.

In the logistic regression model, we confirmed that duration of diabetes, the first-trimester body weight, glycated haemoglobin in the first and second trimesters, and insulin requirement in the last trimester were significant predictors

Table 1. Characteristics of the studied groups

Analyzed parameter	MDI N = 175	CSII N = 122	p
Age of the pregnant woman [years]	28.0 ± 4.9	27.9 ± 4.5	0.96*
Disease onset [years]	17.9 ± 8.2	14.5 ± 6.9	0.001*
Diabetes duration [years]	10.2 ± 6.8	13.5 ± 8.4	0.0004*
Onset of diabetes care [w.g.]	7.7 ± 2.6	7.4 ± 2.4	0.40*
Body weight at the beginning of care [kg]	67.1 ± 13.2	65.8 ± 11.3	0.58*
Weight gain during pregnancy [kg]	12.58	12.06	0.50*
BMI at the beginning of care [kg/m^2]	24.5 ± 4.5	23.8 ± 3.4	0.31*
Patients planning pregnancy [N; %]	55 (30)	55(45)	0.02**
Patients with nephropathy [N; %]	13 (7)	13 (11)	0.33**
Patients with diabetic retinopathy [N; %]	25 (14)	20 (16)	0.62**
Patients with chronic hypertension [N; %]	19 (11)	12 (10)	0.77**

* Mann-Whitney test, ** Chi^2 test

Table 2. Metabolic control of patients in both studied groups

Analyzed parameter	MDI N = 175	CSII N = 122	p
Trimester I of pregnancy			
HbA1c [%] HbA1c [mmol/mol]	7.5 ± 1.9 58 ± 20.9	7.3 ± 1.4 56 ± 15.4	0.61*
Postprandial hyperglycemia ≥ 140 mg/dL [N; %]	110 (27)***	86 (27.5)***	0.68**
Trimester II of pregnancy			
HbA1c [%] HbA1c [mmol/mol]	6.1 ± 1.0 43 ± 11	6.0 ± 0.9 42 ± 10	0.97*
Postprandial hyperglycemia ≥ 140 mg/dL [N; %]	53 (15)***	14 (4.5)***	0.0001**
Trimester II of pregnancy			
HbA1c [%] HbA1c [mmol/mol]	6.5 ± 1.1 48 ± 12	6.3 ± 0.7 45 ± 8	0.67*
Postprandial hyperglycemia ≥ 140 [mg/dL]	64 (22.5)***	21 (7.7)***	0.0001**

* Mann-Whitney test, ** Chi^2 test, *** % calculated for the number of all measurements from a given group in a given trimester.
In the second trimester, calculations were made for MDI N = 165, CSII N = 120 (miscarriage excluded) and in the third trimester, calculations were made for MDI N = 161, CSII N = 119 (intrauterine death excluded)

Table 3. Pregnancy outcome

Analyzed parameter	MDI N = 175	CSII N = 122	p
Gestational age at delivery [w.g.]	37.5 ± 2.0	37.5 ± 1.9	0.63*
Births at full term [N; %]	131 (73)	95 (77.5)	0.64*
Late preterm births: GA 34–37 [N; %]	17 (9)	19 (15.5)	0.18*
Preterm births: GA ≤ 33 + 6 [N; %]	13 (7)	5 (4)	0.35*
Miscarriages: GA < 22 [N; %]	10 (9)	2 (2)	0.15*
Intrauterine deaths below 22nd gestational week [N; %]	4 (2)	1 (1)	0.90*

* Chi^2 test

of excessive fetal birth weight in the studied population (Tab. 5). In a separate analysis the proportion of LGA newborns was similar between the arms.

Late pregnancy loss (intrauterine death) occurred in five patients in the studied population. Four cases recorded in the MDI arm occurred in patients with an inadequate metabolic control throughout the whole pregnancy (mean HbA1c in a subgroup of 9.7%) or noncomplying (not reporting for scheduled antenatal check-ups in the referral center). A single case noted in the CSII arm occurred in a well-controlled woman with long-lasting diabetes and coexisting diabetic kidney disease which is an independent risk factor for unfavorable neonatal outcome.

We did not note any association between the mode of treatment end composite adverse maternal outcome.

Table 4. Status of newborns

Analyzed parameter	MDI N = 161	CSII N = 119	p
Birth weight [g]	3480 ± 750	3430 ± 680	0.58*
Apgar score in the first min. of life [median, min-max]	8 [1–10]	8 [1–10]	0.06*
Apgar score in the fifth min. of life [median, min-max]	9 [1–10]	9 [1–10]	0.38*
Composite adverse neonatal outcome [N; %]	119 (74)	72 (60)	0.01**

Miscarriages and intrauterine death excluded from the analysis
Composite adverse neonatal outcome: abnormal birth weight (LGA or SGA) malformation, miscarriage, intrauterine fetal death, emergency CS due to fetal risk, iatrogenic prematurity, RDS, hypoglycemia, hyperbilirubinemia, and the postpartum pH in the umbilical artery ≤ 7.1.
* Mann-Whitney test, ** Chi^2 test

Table 5. Predictors of LGA

Analyzed parameter	OR	(95% OR)	p
Diabetes duration [years]	0.95	(0.92–0.99)	0.02
Body weight in trimester I [kg]	0.22	(0.08–0.57)	0.00
HbA1c in trimester I [%]	1.99	(1.09–3.62)	0.00
HbA1c in trimester II [%]	0.29	(0.18–0.48)	0.01
Insulin requirement in trimester III (kg/body weight)	2.63	(1.05–6.63)	0.04

DISCUSSION

Hormonal changes, mainly increasing concentrations of anti-insulin factors, can lead to significant fluctuations in glucose levels, even in patients whose metabolism is considered well-controlled before pregnancy. Moreover, during normal pregnancy maternal body operates on lower glucose levels due to natural hormonal adaptations that give a fetus a priority in an access to maternal glucose [15]. Therefore, close monitoring of both maternal and fetal well-being is mandatory, as there is a higher risk of miscarriage, congenital malformations, early and late intrauterine death, and fetal growth disorders that can occur even at nearly normal glycemic levels [10, 11, 16].

The current standards concerning antenatal care for women with diabetes recommend the use of intensive functional insulin therapy in this population. Taking into account the patient's clinical condition, technical ability, and compliance, we have two options for administering insulin: using MDI or CSII.

Carbohydrate metabolism changes in the pregnant woman and the pregnancy itself becomes a diabetogenic factor, altering the hormonal homeostasis. There is a worsening of carbohydrate tolerance, increased peripheral insulin resistance, and thus impaired action of exogenous insulin [17, 18]. Pregnant women must be aware, however, that continuous adding extra insulin doses to achieve normo-

glycemia is a vicious cycle that raises insulin resistance. This wrong habit also leads to an excessive gestational body weight gain and adds to dangerous changes in lipid profile. This way, inappropriate insulin dose also contributes to metabolic changes that often lead to excessive fetal growth, despite apparently good metabolic control [19].

An important problem during pregnancy complicated by pregestational diabetes is the abnormal growth of the fetus which can manifest as excessive (LGA) or restricted (SGA) growth. Excessive fetal growth is caused mainly by fetal hyperinsulinemia, resulting from maternal hyperglycemia [20]. However, studies on metabolic control during pregnancy as a predictor of growth disorders provide contradictory results, whether it is more influenced by the average glycemia or pre- or postprandial glycemia. Some authors confirm that elevated HbA1c levels are a significant risk indicator of LGA [21, 22]. Combs et al. [23] deny, however, the importance of average glycemia, and point out especially on postprandial hyperglycemia. In recent reports, LGA newborns are predominant in pregnancies complicated by mild hyperglycemia and maternal obesity, whereas the increased prevalence of SGA is characteristic for pregnancies complicated by diabetic microangiopathy, especially diabetic kidney disease, as well as hypertension and preeclampsia [24, 25]. These observations demonstrate the contribution of factors other than glycemia to fetal growth abnormalities, i.e. obesity and accompanying lipid disorders and the role of vascular complications. Also, in our cohort, we did not find any significant differences between the mean birth weight in the MDI-group and those of the CSII group Our results are consistent with the results of Cypryk et al. [26], who did not show the effect of type of insulin therapy on an occurrence of either LGA and SGA in their group. It should be noted, however, that in the CSII, the proportion of LGA was a few percent lower than in the MDI group, while the percentage of SGA was very similar in both groups although the CSII group consisted of patients with more complicated diabetes. The lack of significant differences in the incidence of growth disorders does not, however, make it possible to unequivocally demonstrate the superiority of any of the analyzed methods of intensive functional insulin therapy. However, due to the fact that the percentage of all growth disorders was lower in the CSII group, it seems that this model of treatment may contribute to a reduction in the incidence of these disorders.

In the logistic regression model, the predictors of LGA were: duration of diabetes, patient body weight in the first trimester, glycated haemoglobin in the first and second trimesters, and insulin requirement in the last trimester of pregnancy. These associations provide an additional proof that in an appropriately controlled pregnant woman, the occurrence of excessive fetal birth weight depends on many factors and the fact that the insulin requirement in the third trimester of pregnancy was the most potent predictor confirms the role of insulin resistance in inducing excessive growth. Low body weight in pregnant women seems to correlate with the fact that these patients often pay less attention to later weight gain in pregnancy than overweight patients, and we know that excessive weight gain is also a factor inducing excessive fetal growth.

Assessment of pregnancy outcomes including newborn birth weight, week of delivery, and the mode of delivery, did not show statistically significant differences between the MDI and CSII groups, which is in agreement with the results of other authors [18, 27–29]. The timing and mode of delivery in patients with T1DM remains a subject to extensive discussion. In the absence of indications resulting from vascular complications, fetal macrosomia, or birth defects, there are no indications for scheduled cesarean section [11]. The situation can change completely intrapartum when symptoms of fetal or maternal risks can occur suddenly. Neff et al. showed a significant difference in the higher proportion of pregnancies completed by cesarean section in CSII patients. However, this was a group of patients with a significantly longer disease history and was, therefore, more burdened by vascular complications [30]. In our cohort, we did not find any significant difference in the proportion of physiological labours, labours with interventions, or cesarean section.

Most of the available reports show no effect of the used therapy on the newborn status after birth [18, 26, 30, 31]. Tylaviya et al. [32] demonstrated that the only significant parameter is the Apgar score, which was higher in CSII mothers. Several reasons make any epidemiological analysis of pregnancy outcomes in diabetic mothers challenging: first, CSII is a relatively new modality in diabetes treatment, and only limited amount of data from small cohorts of pregnant women is available. Second, due to a general improvement in antenatal care seen in the last decades in the settings where specific needs of pregnant women are appropriately addressed, some of the perinatal complications (e,g. late intrauterine death or intrapartum complications) became rare anyway. Therefore, prospective intervention trials adequately powered to track rare complications in a population of pregnant women suffering from the disease complicating ca. 1% of pregnancies would be trying even if running such research in a frame of multicenter cooperation. In our cohort, we found a significantly reduced number of overall neonatal complications, defined as a composite adverse neonatal outcome, in the CSII arm. Although this difference lost statistical significance after controlling for the confounded, it still remains a possible relevant clinical finding. The reasons for this advantage should be sought in facilitated glycemic control with the use of insulin pump that accurately adjusts

the dose of both the basal insulin and the type and dose of prandial boluses [33]. Continuous infusion allows for a more flexible and stable administration of basal insulin achieving nocturnal and early-morning normoglycemia more efficiently than long-acting insulin boluses administered with a pen at night. Also, reduced number of hyperglycemia noted in our CSII arm could suggest improved glycemic variability, i.e. diminished short-term glucose fluctuations that can translate into a better endothelial function in placenta and more stable placental transfer of nutrients. All this contributes to the optimization of treatment and the achievement of better metabolic control that alleviates or substantially reduces potent adverse effects of hyperglycemia on the fetus [18, 27, 34].

CONCLUSIONS

Treatment of type 1 diabetic pregnant women with a personal insulin pump allows for the optimization of therapy and precise titration of the basal insulin dose and the type and size of the prandial boluses.

As a result, we note a decreased incidence of hyperglycemia, which seems to reduce the risk of composite adverse neonatal outcome and early postpartum complications in the offspring in this group of patients.

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The clinical usefulness of biochemical (free β-hCG, PAPP-A) and ultrasound (nuchal translucency) parameters in prenatal screening of trisomy 21 in the first trimester of pregnancy

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ABSTRACT

Objectives: The aim of the study was to analyze the correlation of multiples of the normal median of PAPP-A, free β-hCG levels and nuchal translucency values in prenatal, first trimester screening of trisomy 21 in pregnant women.

Material and methods: 251 pregnant women underwent antenatal screening at 11–13^{+6} weeks of pregnancy which was composed of the measurement of free β-human chorionic gonadotropin (β-hCG) and pregnancy-associated plasma protein (PAPP-A) levels in the maternal serum and an ultrasound assessment of nuchal translucency (NT). The pregnant women with a high risk of trisomy 21 (≥ 1:300) were given amniocentesis to verify fetal defects. There were 217 cases of normal fetal karyotype and 34 cases of trisomy 21. PAPP-A, β-hCGMoM and NT values were analyzed for the predefined ranges.

Results: 85% cases of trisomy 21 had elevated free β-hCGMoM (> 1.5) and only 53% of these had a PAPP-AMoM result below 0.5 ($p < 0.05$). Analysis of NT in selected ranges of β-hCG (> 1.5) and PAPP-AMoM (< 0.05), which are typical for Down Syndrome values, showed that not all fetuses with Down Syndrome presented with an increased NT. Respectively 44.15% and 26.5% of fetuses presented with increased NT. Characteristic for trisomy 21, a correlation with all 1st trimester screening tests' parameters occurred in only 23.5% of cases. In 53% of cases the results were atypical.

Conclusions: The PAPP-A and β-hCG values in the selected MoM ranges did not shown a correlation to the NT measurement, therefore they are independent factors in the diagnosis of trisomy 21. Simultaneous biochemical and ultrasound testing is an indispensable condition for prenatal diagnosis of trisomy 21 in the 1st trimester of pregnancy.

Key words: PAPP-A; free β-hCG; nuchal translucency (NT); prenatal screening; trisomy 21

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INTRODUCTION

Prenatal screening that include non-invasive diagnostic tests enable assessment of the risk of fetal chromosomal aberrations and may reduce the use of invasive procedures associated with the 0.5–1.0% risk of miscarriage [1–4]. Since the 1990s, measuring maternal serum free beta human chorionic gonadotropin (β-hCG) and pregnancy associated plasma protein (PAPP-A) levels has been included in first-trimester prenatal screening carried out at 11–13^{+6} weeks of gestation alongside a fetal ultrasound assessment that includes nuchal translucency (NT) measurement. This, according to different authors, enables the detection of approximately 80–90% of all trisomy 21 cases [1, 2, 5–11]. The measured concentrations of either PAPP-A or free β-hCG are converted into the multiples of the median (MoM) appropriate to the gestational age of each pregnancy. The MoM value is obtained by dividing

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an individual's marker concentration by the median level of that marker for the entire population at the same gestational age in that laboratory. In a healthy pregnancy, the maternal serum PAPP-A level increases exponentially, whereas the free β-hCG level drops, after an initial increase, in the period between 10 and 14 gestational weeks [12]. According to FMF and Polish Society of Gynecologists and Obstetricians recommendations, a PAPP-A MoM below 0.5, free β-hCG MoM above 1.5, and a nuchal translucency increase in weeks 11–13^{+6} of gestation are typical of fetal trisomy 21 [7–11, 13–15].

The debate on the utility of combined ultrasound and biochemistry testing and the role of such screening in detecting chromosomal aberrations has been ongoing for over 20 years. Therefore, a detailed analysis was conceived to assess the association between the individual parameters and to determine whether the magnitude of PAPP-A level reduction and free β-hCG level elevation are of clinical significance in Down Syndrome risk calculation.

Aim

The aim of the study was to analyze the correlation in multiples of the normal median of biochemical parameters in maternal serum — PAPP-A and free β-hCG — as well as nuchal translucency values in the 11–13^{+6} weeks of gestation in patients with cytogenetically confirmed trisomy 21.

MATERIAL AND METHODS

The study included a group of 251 pregnant women aged 18 to 46 years (mean age of 35.9 years), with a mean BMI of 23.44, who were patients at the Ultrasonography and Prenatal Imaging Clinic of the Gynaecology and Obstetrics Hospital of Poznan University of Medical Sciences. All women with an increased risk of trisomy 21 (≥ 1:300) in the 1st trimester screening test (double test), had genetic amniocentesis to assess the fetal karyotype, in accordance with recommendations of the Ultrasonography Division of the Polish Society of Gynecologists and Obstetricians.

Assessment of the occurrence of chromosomal aberrations was carried out using the routine antenatal scan at 11–13^{+6} gestational weeks, which consisted of ultrasound fetal assessment with a maternal serum assay of PAPP-A and free β-hCG.

Ultrasound examination included assessment of the risk markers of the most common chromosomal aberrations (trisomy 21, 18, 13) — crown-rump length (CRL) of 45–85 mm, nuchal translucency (NT), fetal heart rate, and blood flow in the ductus venosus with fetal anatomy and chorion [1, 2, 16].

Maternal serum concentrations of free β-hCG and PAPP-A were determined using an immunofluorometric assay on the Delfia Xpress analyzer (Perkin-Elmer Life and Analytical Sciences, Waltham, USA). The reaction surface was coated with specific antibodies directed against the respective PAPP-A and β-hCG antigen determinant. Then, antibodies to other antigenic determinants of the parameters were studied, labeled with fluorochrome (Europium), and added to be able to read the concentrations of the determined parameters. The resulting complex was read at 612 nm.

The risk of trisomy 21 was calculated based on the measured biochemical markers and ultrasound parameters using ©2000–2016 Astraia software (Astraia Software Gmbh, Occamstr. 20, 80802 Munich, Germany) [1, 13, 16].

Participants with an elevated risk of trisomy 21 (< 1:300) were offered amniocentesis in line with the recommendation of the Ultrasonography Division of the Polish Society of Gynecologists and Obstetricians. It consisted of abdominal collection of approximately 20 mL of amniotic fluid, then amniocytes — amniotic fluid cells were cultured in a special media. In the cytogenic preparations obtained after the culture, metaphases colored by the G-band method were analyzed to assess the karyotype.

Patients were sub-divided into two groups according to the occurrence of fetal defects: group I — pregnant women with a normal karyotype; and group II — pregnant women with trisomy 21 in fetuses.

In both groups a detailed analysis of the PAPP-A and free β-hCG MoM values was carried out to determine their correlation with the risk of trisomy 21. The following PAPP-A MoM ranges were determined: 0.001–0.500; 0.501–0.900; and above 0.901. Similarly, the following free β-hCG MoM ranges were determined: 0.001–1.000; 1.001–1.500; 1.501–2.000; and above 2.000.

The nuchal translucency (NT) values of the fetuses in the group with trisomy 21, that were classified into the predefined ranges of 1.0–2.0 mm, 2.1–3.0 mm, 3.1–5.0 mm, 5.1–8.0 mm, and above 8.1 mm, were analyzed for PAPP-A MoM of 0.001–0.500 and above 0.500 and free β-hCG MoM of 0.001–1.500 and above 1.500.

Statistical analysis was carried out using the PQStat bundle. Normality of distribution was verified using the Kolmogorov–Smirnov test, Lillefors test and Shapiro-Wilk test. The ROC analysis of the assessed classifiers (PAPP-A MoM and β-hCG MoM) enabled us to distinguish between participants with fetal trisomy 21 and those with normal fetal karyotype.

RESULTS

Of all patients who underwent cytogenetic evaluation, 217 were diagnosed with normal fetal karyotype and 34 cases were diagnosed with trisomy 21. In the group with normal karyotype results, the patients ≥ 35 years old accounted for 68.8% of the trisomy 21 cases and 31.2% were < 35 years. The age distribution was similar in the group with fetal trisomy 21, with 67.6% of the women aged ≥ 35 years and 32.3% aged < 35 years. In the study group overall, the age of the pregnant women had no significance on the results of the study and this parameter was discarded as an assessment criterion.

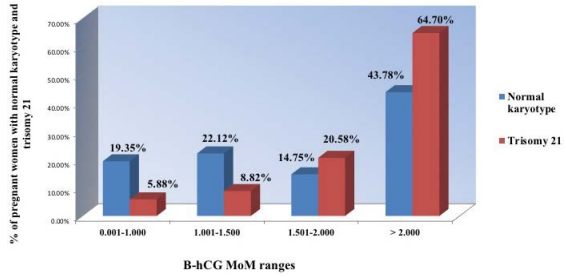

Figure 1. Cases of fetal euploidy and trisomy 21 in the analyzed free β-hCG MoM ranges

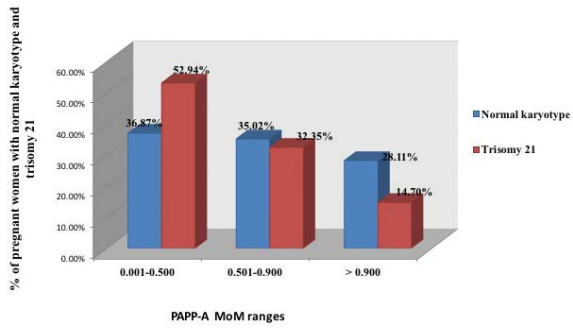

Figure 2. Cases of fetal euploidy and trisomy 21 in the analyzed PAPP-A MoM ranges

The mean β-hCG MoM = 2.894, with SD ± 1.665 in 34 cases of fetal trisomy 21, was higher than in the group with normal karyotype results β-hCG MoM = 1.979, with SD ± 1.569 ($p < 0.05$).

A detailed analysis of free β-hCG MoM demonstrated that the maternal serum free β-hCG MoM was above 1.5 in most of the fetal trisomy 21 cases (85.28%). At the same time, 58.53% of the participants with free β-hCG MoM above 1.5 had normal fetal karyotype, including 43.78% of the cases with free β-hCG MoM above 2.0 (64.70% for fetuses with trisomy 21).

Cases of confirmed fetal trisomy 21 constituted only a small part (14.7%) of the subgroup with free β-hCG MoM below 1.5. 41.50% were cases with normal fetal karyotype (Fig. 1).

The mean PAPP-A MoM in cases of confirmed fetal trisomy 21 was significantly lower than in cases of fetal euploidy (0.539 ± 0.281 vs. 0.691 ± 0.45, $p < .05$).

The PAPP-A MoM analysis demonstrated the largest proportion (52.94%) of trisomy 21 cases in a subgroup with PAPP-A MoM ranging between 0.001 and 0.500. At the same time, the euploidy cases comprised 36.87% of that subgroup.

A subgroup with PAPP-A MoM above 0.501 consisted of trisomy 21 cases in 47.05% of the subjects and euploidy cases in 63.13% of the subjects (Fig. 2).

The ROC analysis for the assessed classifiers (PAPP-A MoM and β-hCG MoM) enabled us to distinguish between participants with fetal trisomy 21 and those with normal fetal karyotype (Fig. 3 and 4).

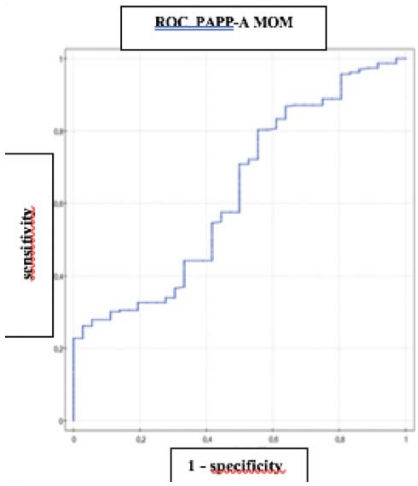

Figure 3. ROC curve - sensitivity and specificity of PAPP-A MoM to distinguish between cases of trisomy 21 and euploidy

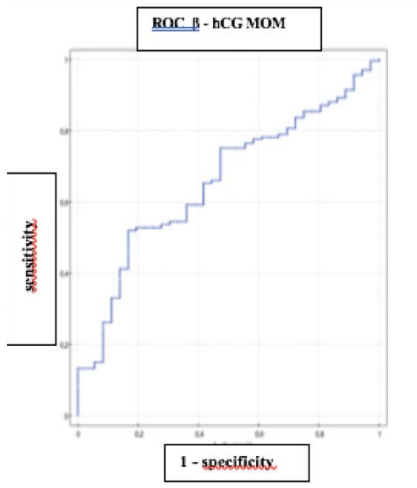

Figure 4. ROC curve - sensitivity and specificity of β-hCG MoM to distinguish between cases of trisomy 21 and euploidy

The cut-off value of PAPP-A MoM was 0.463. Its sensitivity and specificity were 70.8% and 50%, respectively. A decrease of PAPP-A MoM below the cut-off value increases the marker's sensitivity and the likelihood of trisomy 21. The cut-off value of free β-hCGMoM was 2.17. Its sensitivity and specificity were 75.1% and 52.8%, respectively. An increase in the free β-hCG MoM above the cut-off value increases the likelihood of trisomy 21 (Tab. 1).

In cases of confirmed fetal trisomy 21, nuchal translucency was significantly higher than in cases of euploidy (3.9 mm ± 1.893 vs. 2.2 mm ± 0.938).

The next stage was to analyze the fetal nuchal translucency in selected PAPP-A MoM ranges. It was demonstrated that among the cases of known fetal trisomy 21, only 26.5% of fetuses had NT over 3.1 mm if the maternal serum PAPP-A MoM fell within the range 0.001-0.500.

Table 1. ROC analysis — (cut-off point, sensitivity, specificity, area under the curve — AUC, statistical significance level — p) PAPP-A MoM and β-hCG MoM for classifiers differentiating between participants with fetal trisomy 21 and normal fetal karyotype

Variable	Cut-off point	Sensitivity [%]	Specificity [%]	AUC	p
PAPP-A MoM	0.463	70.8	50.0	0.63	0.013
β-hCGMoM	2.71	75.1	52.8	0.656	0.003

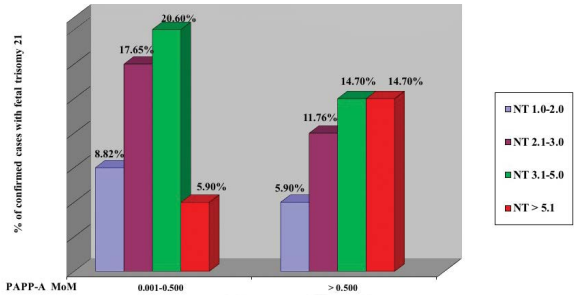

Figure 5. NT analysis for selected PAPP-A MoM ranges in participants with known fetal trisomy 21

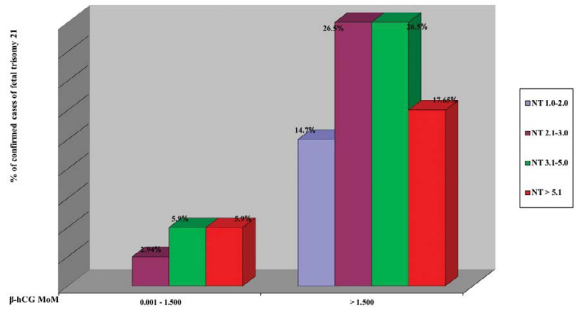

Figure 6. NT analysis for selected bHCG MoM ranges in participants with known fetal trisomy 21

Also, 26.5% of fetuses with known trisomy 21 and maternal serum PAPP-A MoM below 0.500 did not present with increased NT; instead, PAPP-A MoM was the only aneuploidy indicator.

Furthermore, 17.66% of fetuses with known trisomy 21 and maternal serum PAPP-A MoM above 0.500 did not present with increased NT as compared with 29.4% of fetuses with NT over 3.1 mm in the same subgroup. Among these cases, only the increased NT sub-set was indicative of Down Syndrome risk (Fig. 5).

Among the confirmed cases of fetal trisomy 21, in a subgroup of participants with free β-hCG MoM over 1.5, an NT increase over 3.1 mm was demonstrated in 44.15% of cases, as compared with 41.2% of cases with an NT below 3.0 mm. On the other hand, in a subgroup of participants with free β-hCGMoM below 1.5, an NT increase over 3.1 mm was demonstrated in 11.8% of cases, as compared with 2.94% of cases with an NT below 3.0 mm (Fig. 6).

The combined analysis of biochemical parameters and nuchal translucency in the group with fetal trisomy 21 showed that 23.5% of pregnant women had PAPP-A MoM < 0.5 and > 1.5 β-hCG MoM with an increased NT. Also, 23.5% of cases of this group presented with typical trisomy 21 biochemical parameters without an NT increase.

Among the confirmed trisomy 21 cases, there were 18 cases (53%) of atypical PAPP-A and free β-hCG MoM values, combined with the absence of simultaneous PAPP-A MoM reduction and free β-hCG MoM elevation, which typically indicates a high risk of Down Syndrome. A combination of normal PAPP-A MoM (of about 1.0) and elevated free β-hCGMoM (above 1.5) was shown in 38.2% (n = 13) of known trisomy 21 cases; and in addition, 61.5% of these fetuses had an increased nuchal translucency. A combination of normal free β-hCG MoM and reduced PAPP-A MoM (below 0.5) was shown in 8.8% of known trisomy 21 cases; and in addition, 66.7% of these fetuses had an increased nuchal translucency. The two remaining cases of trisomy 21 had reduced PAPP-A MoM combined with reduced free β-hCGMoM, and normal PAPP-A MoM combined with reduced free β-hCGMoM, respectively. Nuchal translucency was increased in both cases. (Tab. 2 and 3).

The presented results prove that the biochemical values and nuchal translucency, as parameters, are independent of each other in the diagnosis of trisomy 21.

DISCUSSION

Non-invasive, first-trimester prenatal screening encompassing a combination of maternal serum biochemistry assays (free β-hCG and PAPP-A) and ultrasound-assessed nuchal translucency (NT) enables accurate identification of approximately 90% of chromosomal abnormalities with 5% false positive results [7, 8, 13, 16]. The results of individual tests may not always correlate with each other as per the current standards; however, the ultimate output will indicate an increased risk of aneuploidy. We have observed this in our sample of known trisomy 21 cases. The preliminary data analysis showed no significant differences between the mean free β-hCG and PAPP-A MoM levels obtained in our sample of known trisomy 21 cases and those reported by other authors [8, 9, 12, 14, 17].

The main aim of our study was to determine the distribution of trisomy 21 cases in individual free β-hCG and PAPP-A MoM ranges. A detailed analysis indicated that most cases of trisomy

Table 2. Atypical PAPP-A MoM, β-hCG MoM and NT in pregnant women with diagnosed fetal trisomy 21

No.	PAPP-A MoM	free B-hCG MoM	NT	Karyotype	Double marker test risk estimate
1.	0.885	5.468	6	47, XY, + 21	1 : 2
2.	0.844	1.750	5.5	47, XY, + 21	1 : 12
3.	0.334	1.236	8	47, XY, + 21	1 : 2
4.	0.568	1.095	2.5	47, XX, + 21	1 : 108
5.	1.035	3.924	6.0	47, XX, + 21	1 : 2
6.	0.676	0.715	6	47, XX, + 21	1 : 3
7.	0.904	9.304	2.7	47, XX, + 21	1 :4
8.	0.782	1.895	4	47, XX, + 21	1 : 2
9.	0.947	2.714	8.6	47, XY, + 21	1 : 4
10.	0.915	1.858	2.5	47, XY, + 21	1 : 128
11.	0.973	0.788	4.8	47, XY, + 21	1 : 4
12.	0.837	2.053	4.2	47, XX, inv(9)(p12q13), + 21	1 : 4
13.	0.806	3.773	4	47, XY, + 21	1:4
14.	0.839	3.547	1.6	47, XX, + 21, 21 pss	1 : 29
15.	0.318	1.442	5	46, XX, der(14; 21)(q10; q10), + 21	1 : 2

Table 3. Atypical PAPP-A and free β-hCG MoM values in pregnant women with confirmed fetal trisomy 21

PAPP-A and free β-hCGMoM value analysis	No. of cases with trisomy 21	% of all trisomy 21 cases detected antenatally
normal PAPP-A MoM and free β-hCGMoM ≥ 1.5	13	38.2
PAPP-A MoM < 0.5 and normal free β-hCGMoM	3	8.8
decreased both PAPP-A MoM and free β-hCGMoM	1	2.9
normal PAPP-A MoM and decreased free β-hCGMoM	1	2.9

21 detected during antenatal screening, as seen in previous studies, had free β-hCGMoM over 1.5 (85.28%), but only 53% of these had PAPP-A MoM below 0.5. The correlation of all components of the characteristics in the screening test for the risk of trisomy 21 (< 0.5 PAPP-A MoM and > 1.5 β-hCG MoM) and increased NT, occurred in only 23.5% of the pregnant women. In all cases with prenatally diagnosed 21 fetal trisomy, the evidence of risk was increased in the screening test. Our findings prove the benefit of antenatal screening in helping to identify high-risk cases for Down Syndrome [18].

The analysis of free β-hCG and PAPP-A MoM values in cases with known fetal trisomy 21 identified 53% (n-18) atypical cases with biochemical test results and their configuration different from those typically seen in fetal trisomy 21. The most common atypical configuration was a normal PAPP-A MoM (of approximately 1.0) combined with an elevated free β-hCGMoM (above 1.5). Most fetuses in this subgroup presented with an increased NT. In such cases, the free β-hCGMoM and increased NT were the indicators of trisomy 21. Furthermore, there were 2.9% cases with an atypical configuration involving PAPP-A MoM below 0.5 combined with a normal free β-hCGMoM; and increased NT was demonstrated in most of these fetuses. In the two remaining cases, the biochemical parameter MoM values were not indicative of trisomy 21. However, their abnormal concentrations and an increased NT indicated they were high risk and led to the ultimate confirmation of Down Syndrome in the fetuses.

Additionally, we have analyzed in detail the nuchal translucency data in the selected free β-hCG and PAPP-A MoM ranges. Although the mean NT in a subgroup with known fetal trisomy 21 was 3.9 mm, which is consistent with previously reported findings [8, 9, 19], not all fetuses in this subgroup presented with an increased NT. In those latter cases, the elevated risk of trisomy 21 was primarily determined by abnormal maternal serum concentrations of free β-hCG and/or PAPP-A.

Our findings unequivocally indicate that none of the analyzed parameters on their own offers enough sensitivity to provide a conclusive finding of fetal trisomy 21. In our sample, there were cases of confirmed Down Syndrome with normal maternal serum concentrations of assessed biochemical parameters as well as those with normal NT. The analysis shows that maternal serum biochemical markers and ultrasound fetal screening are complementary and should not be considered separately in trisomy 21 diagnostics.

CONCLUSIONS

1. The analysis of maternal serum PAPP-A and free β-hCG levels along with ultrasound-based nuchal translucency measurement are independent of each other as parameters in trisomy 21 diagnostics.

2. Assessing biochemical and ultrasound parameters in combination is an indispensable condition of assessing the risk of trisomy 21 occurrence in antenatal screening during the first-trimester.

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The role of artificial nutrition in gynecological cancer therapy

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ABSTRACT

Cancer patients are at risk of developing malnutrition from underlying disease as well as from cancer treatment. Moreover, weight loss is considered as a predictive factor for disease progression and shorter survival time. As many as 10–20% of patients with cancer die from the results of malnutrition, instead of from the cancer itself. In the case of cancer-related malnutrition, it is necessary to quickly implement individualized nutritional support depending on the type and stage of the disease, metabolic changes, the patient's condition, expected survival and the function of the gastrointestinal tract. Artificial nutrition reduces the side effects of chemotherapy and improves immunity. Perioperatively it reduces the risk of infection, facilitates wound healing and shortens the length of hospitalization, thereby reducing the costs of the treatment. Initially, a malnourished patient, without gastrointestinal dysfunction, qualifies for nutritional counseling. When the energy needs cannot be met by normal feeding, nutritional supplements, taken orally, are recommended. The next step is to feed the patient by nasogastric tube or percutaneous endoscopic gastrostomy. Parenteral nutrition, which results in more side effects, is only started when enteral nutrition is insufficient to ensure adequate nutritional status or in cases of gastrointestinal tract obstruction. The benefit of parenteral nutrition is that it especially provides for those patients with gynaecological cancer who have radiation-induced intestinal damage and post-surgical complications such as short bowel syndrome. Palliative nutrition must to relieve hunger and thirst. Nutritional interventions should be individualized and focused on the changing nutrient needs of the patient and should be supported by physical activity. Regular assessment of the nutritional status of the patient should be an inherent element of the oncological treatment.

Key words: parenteral nutrition; gynecological cancers; malnutrition; enteral nutrition; nutritional treatment

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INTRODUCTION

Cancer patients are at risk of developing malnutrition from the underlying disease as well as from the cancer treatment. In addition, weight loss is considered as a predictive factor for disease progression and indicates shorter survival times. It is known that 10–20% of patients with cancer die from the results of malnutrition, instead of from the cancer itself [1]. In 2012, studies showed that doctors underestimate how malnutrition influences patients' quality of life and the cancer treatment itself [1]. The data shows that 20–70% of oncological patients are malnourished and this applies more often to older patients; but only 30–60% of patients with a high risk of developing malnutrition are treated [2]. This is caused by a lack of knowledge of the guidelines for nutritional treatment in cancer which are an important part of oncological treatment. In Poland, female patients suffering from gynecological cancers comprise 11% of all patients treated in the Nutritional Centers of Poznan alone. These are mainly patients in the terminal stage of the disease, following several methods of treatment, and when the disease is advanced and life expectancy is not long. Only one fourth of them is treated, especially with parenteral nutrition, for longer than four months. It is necessary to make screening tests among all patients with reproductive organ cancer, in order to estimate the risk of them developing malnutrition. This should be done every time

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a patient is qualified for treatment, and tests should include BMI, estimated weight loss, and muscle mass. Blood tests should be also considered. The European Society for Clinical Nutrition and Metabolism (ESPEN) analysed all the causes and effects of malnutrition in cancer patients and have provided specific guidelines for such cases [3]. Nutritional interventions should be individualized and focused on the changing nutrient needs of the patient and on the reduction of inflammation marker levels and should be supported by physical activity [4].

CURRENT STATE OF KNOWLEDGE

Mechanism of malnutrition

Among cancer patients the most frequent causes of malnutrition are: loss of appetite, food intolerance, nausea, vomiting, symptoms associated with local tumour growth, hypoalbuminemia, anaemia, as well as side effects of the oncological treatment [5]. Chemotherapy may cause gastrointestinal mucositis, mouth ulcerations, secondary haemorrhage, diarrhoea, dysgeusia (taste disturbance), and nausea. All the above lead to a reduction of food intake and increased risk of malnutrition [6]. Similarly, the adverse effects of radiotherapy mainly affect surrounding tissues, and in patients receiving treatment for cervical cancer or endometrial cancer these adverse effects are enteritis and malabsorption disorder [3, 5]. The tumour itself, causes an increased inflammatory response, mediated by IL-6, which plays an important role in the development of malnutrition, with catabolic effects [7]. Pro-inflammatory cytokines cause malabsorption of nutrients and interfere with the metabolism of carbohydrates, fats and proteins, and they affect the central appetite control system leading to anorexia. Cytokines also affect hepatic overproduction of pro-inflammatory acute phase proteins, which leads to the worsening metabolism of anticancer drugs and increases their toxicity. Activation of inflammatory factors causes the breakdown of tissues and, as a result, weight loss and the reduction of muscle mass [7]. Loss of muscle mass is associated with worsened prognosis and also occurs in obese people. Among those patients, despite having a high BMI, muscle mass loss also occurs, along with all the malnutrition consequences [5, 8]. BMI is a less valuable indicator, because obesity is becoming a more serious problem. Doctors need to pay more attention to recent weight loss or weight loss within a short period, and to the patient's reduced food intake.

Diagnosis of malnutrition

Weight loss is an important sign of malnutrition [8]. Special scales are used to assess the patient's nutritional status. In hospitals, the most common ways to assess nutritional status are the nutritional risk score (NRS) (Tab. 1) and the subjective global assessment (SGA) of nutritional status [9]. Further advanced assessments of nutritional status are performed by body composition tests using bioelectrical impedance analysis, computer tomography, magnetic resonance imaging, biochemical tests and anthropometrical indices, such as measuring the thickness of the skin fold over the triceps muscle or the circumference of arm muscles [9]. According to ESPEN, malnutrition is diagnosed when the patient's BMI is < 18.5 kg/m^2 or when the patient reports

Table 1. Screening of risk assessment related to malnutrition - NRS 2002 adults (above 18 years of age)

Impaired nutritional status		**Severity of the disease (increase in requirements)**	
Score = 0	normal nutritional status	Score = 0	normal nutritional requirement
Mild Score = 1	weight loss > 5% in 3 months or food intake below 50–75% of normal requirement in preceding week	Mild Score = 1	e.g. hip fracture, chronic diseases, especially in patients with acute complications (eg cirrhosis of the liver, COPD), radiotherapy
Moderate Score = 2	weight loss > 5% in 2 months or BMI 18.5–20.5 + impaired general condition or food intake 25–50% of normal requirement in preceding week	Moderate Score = 2	major abdominal surgery, stroke, elderly patients - long-term treatment, postoperative renal failure, chemotherapy
Severe Score = 3	weight loss > 5% in 1 month or BMI < 18.5 + impaired general condition or food intake = 0–25% of normal requirement in preceding week.	Severe Score = 3	head injury, bone marrow transplantation, intensive care patients
if > 70 years: add 1 to total score above			
Score:		Score:	Total points:

Instructions:
1. select one appropriate degree of disturbance of the state of nutrition and the severity of the disease
2. sum points
Score:
≥ 3 — indicated nutritional treatment
< 3 — consider a conservative procedure, repeat the test in a week

unintentional weight loss (> 10% over an unknown period or > 5% over 3 months), and in connection with the patient's BMI (< 20 in patients under 70 years and < 22 in patients over 70 years), or with a low fat-free mass index (FFMI) of < 15 kg/m^2 for women and < 17kg/m^2 for men. (Fig. 1). We also assess CRP and albumin levels using the Glasgow Prognostic Score. We identify the nutrition as inadequate when the patient has not eaten for a week or when the food intake covers less than 60% of the energy demands over 1–2 weeks. A change in appetite is the first symptom of being at risk of malnutrition, and normal nutrition does not meet the body's needs in cancer. Nutrition support must be introduced gradually to avoid refeeding syndrome, and especially for patients with large deficits, because it can lead to electrolyte, hormonal and metabolic changes and consequently can cause neurological disorders and cardiological complications [10] (Fig. 1).

Consequences of malnutrition

The consequences of malnutrition in oncological patients are weight loss and muscle mass loss, weakening of the immune system, increased frequency of infections, more complications and less tolerance to chemotherapy. Malnutrition is associated with a greater number of complications of chemotherapy and radiotherapy, which may even lead to the necessity to stop treatment and reducing its effectiveness. It has been clearly shown that malnutrition influences the faster progression of the disease, higher mortality rates and poorer quality of life. The consequences of malnutrition are also pain, weakness and depression. Patients with stable body weight have a longer survival time [11]. Nutritional status is an important predictor of the treatment's tolerance and of increased mortality. Therefore, it is important not only to recognize malnutrition, but also to identify and monitor patients at risk of its occurrence, in order to start early nutritional treatment [12–14].

Artificial nutrition

The goal of nutritional treatment in cancer patients is to prevent any further deterioration of their nutritional status, as well as to support the oncological treatment [15]. It is a supportive treatment that improves the patient's functional ability and overall fitness state, increases the body's immune system, improves tolerance to chemotherapy and reduces its side effects. However, in order to achieve the desired goals, it must be introduced early enough, and if this is achieved, it reduces the risk of infections, enables wound healing, shortens hospitalization and reduces the costs of treatment. Physical activity is also important and prevents loss of muscle mass. Artificial nutrition includes nutrient supplements introduced via the gastrointestinal tract (oral or enteral) or by intravenous line. (Fig. 1). If an oncological patient with an expected survival time longer than several months who does not have gastrointestinal dysfunctions, is unable to cover their energy demands with a normal diet, nutritional treatment is induced. This treatment is based on the diagnosis of the type and stage of the disease, its severity, the type of treatment planned, as well as taking into consideration the individual preferences and general condition of the patient. The first step is dietary counselling. If this is insufficient, the next step is the introduction of oral nutrition supplements followed by feeding the patient by nasogastric tube or percutaneous endoscopic gastrostomy [16]. Parenteral nutrition, which has more side effects than the abovementioned treatments, is only started when enteral nutrition is insufficient to ensure the patient's adequate nutritional status and when malnutrition will shorten the survival time compared with the prognosis of death due to cancer disease itself. (Fig. 1).

Parenteral nutrition in gynecologic oncology

Around 50% of patients referred from gynaecological oncology units for parenteral nutrition treatment are patients suffering from cervical or endometrial cancer with radiation-induced enteritis and secondary malabsorption syndrome. Acute radiation-induced enteropathy occurs within a few days after the therapy and affects only the mucous membrane. The subacute condition occurs during the first year after radiotherapy and the mucous and submucous membrane are affected. However, the chronic condition occurs several years after radiotherapy and affects all layers of the intestine wall. The risk of enteropathy increases with age, co-morbidities, and after previous surgical procedures. About 80% of patients treated with radiotherapy focused on their pelvic area experience side effects associated with their digestive system and suffer weight loss. About 20% of them will develop chronic intestinal inflammation after radiotherapy. Intestinal failure develops in about 5% and this is a group that should be treated with parenteral nutrition as they will benefit the most from this type of nutrition. Nutritional support, preferably enteral nutrition, during the entire treatment of patients with cervical cancer and endometrial cancer, will either avoid or reduce side effects and the interruptions of treatment that are caused by the side effects of radiotherapy [17].

The conditions for patients with advanced cancer qualifying for parenteral nutrition are: expected overall survival time > 3 months, > 50 points in the Karnofsky score and no irreversible damage of the liver, kidneys and lung functions. The main indications for parenteral nutrition in gynecologic oncology include:

— obstruction of the gastrointestinal tract in advanced, metastatic ovarian cancer (secondary dysphagia, when enteral nutrition is impossible);

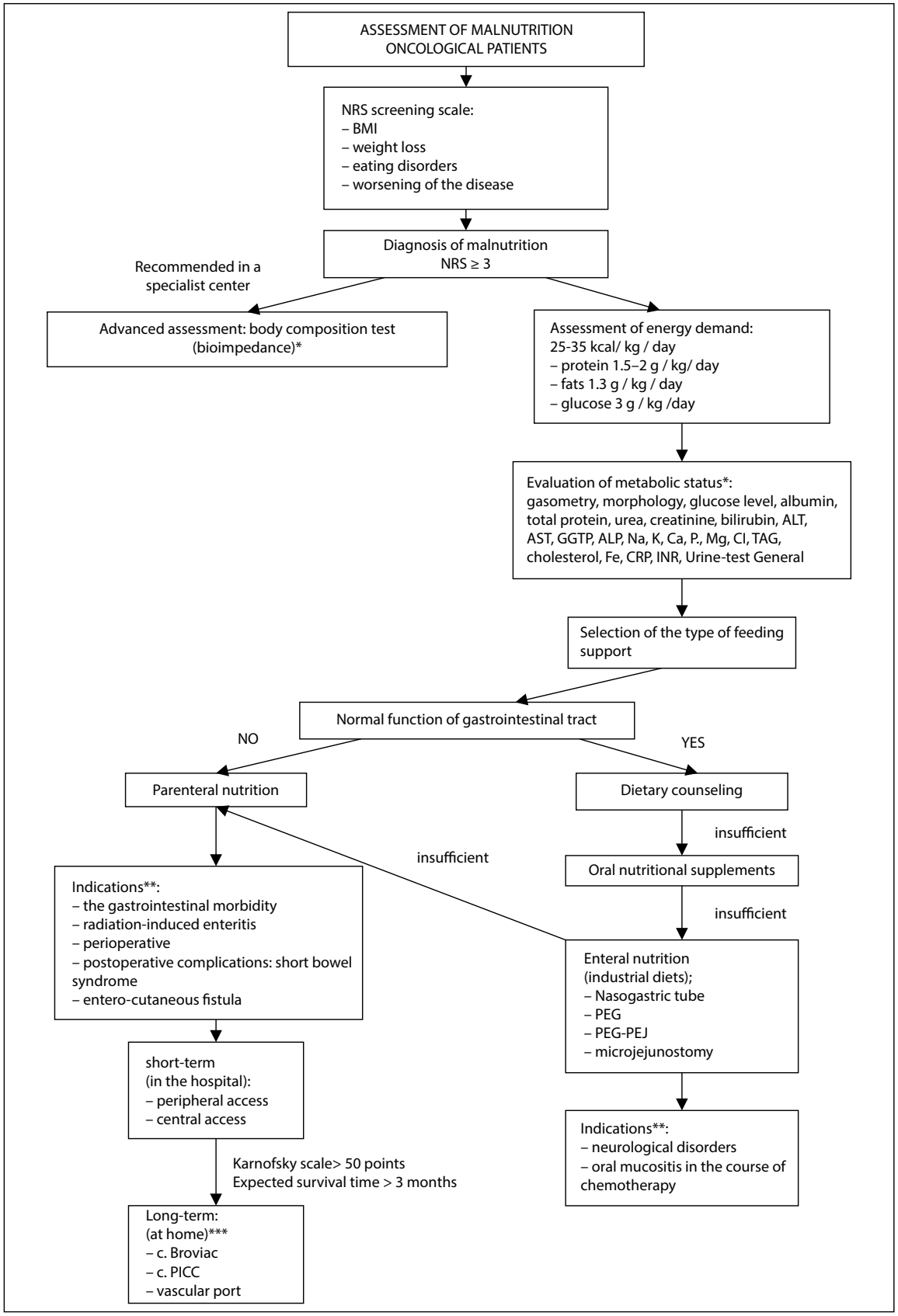

Figure 1. A brief description of the procedure in the event of suspected malnutrition. PEG-PEJ — percutaneous endoscopic gastrostomy-percutaneous endoscopic jejunostomy; PEG — percutaneous endoscopic gastrostomy. *Marking 1–2 a week or more often depending on the needs and type of disorder. **The most common selected indications in oncological gynecology. ***Referral to a Nutritional Treatment Center

— malabsorption syndrome among patients with enteritis after radiotherapy (cervical and endometrial cancer);
— post-surgical complications (short-bowel syndrome, entero-cutaneous fistulas);
— perioperative nutrition support to reduce the number of complications.

Parenteral nutrition can be divided into 2 parts: short-term, used in the perioperative period in malnourished patients, which reduces perioperative risk and strengthens the immunological response; and long-term, used in the home environment with patients with chronic gastrointestinal insufficiency. Different types of central venous lines are used: Broviac catheter-central venous catheter with subcutaneous tunnelling, inserted through the jugular vein, the subclavian vein or the femoral vein; PICC catheter-peripherally inserted central catheter, inserted through the cephalic vein or through the basilic vein; and ports. However, in the case of a port, there is a higher risk of infections compared with the former two methods. All three methods mentioned above can also be used for administering chemotherapy while maintaining the principles of high sterility.

Artificial nutrition in palliative care

Often patients are referred for nutritional treatment too late, when they are disqualified from other forms of treatment and cachexia is irreversible. Cachexia is considered to be a condition that is resistant to treatment in the last stages of life. In palliative care, non-invasive feeding support, adequate for the patient's needs, is administered, with the goal of improving the patient's comfort and quality of life [18]. Palliative nutrition must relieve hunger and thirst. Parenteral nutrition has no proven efficacy in this group of patients. Only patients in an otherwise good general condition who have a gastrointestinal obstruction will gain some benefits from this method of nutrition. The psychological aspect is also very important. Patients with advanced gynaecological cancer complicated by intestinal obstruction live for 40–93 days [19]. These patients are often referred for parenteral nutrition, but this treatment usually only lasts from a few days to several weeks [19]. It should also be remembered that, according to ESPEN, parenteral nutrition is associated with a greater risk of side effects, which occur in 4–54% of patients, including: infections associated with the feeding port, deep vein thrombosis, deterioration of liver functions, worsening organ failure, and reduced quality and comfort of life through increasing amounts of effusion fluids in patients with ascites or pleural effusion.

SUMMARY

Cancer patients are at risk of developing malnutrition from the underlying disease as well as from their cancer treatment. Malnutrition increases the number of side effects of chemotherapy and shortens patient survival time. The main goals of artificial nutrition, whether oral, enteral or parenteral, are to prevent further weight loss, improve muscle strength, restore lost tissues and subsequently cause weight gain. The benefit of parenteral nutrition is that it especially provides for patients who have radiation-induced intestinal damage and post-surgical short bowel syndrome. Palliative nutrition must relieve hunger and thirst. Regular assessment of the nutritional status of the patient should be an inherent element of the oncological treatment.

Conflicts of Interest

The authors declare that there are no conflicts of interest.

Contributions of Authors

We confirm that all the co-authors have been included, have contributed to the final manuscript and have approved it. MS and EG designed the study, analyzed the data, wrote the manuscript and prepared figures for this manuscript. ENM and KM critically reviewed the manuscript.

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The role of disordered angiogenesis tissue markers (sFlt-1, PlGF) in present day diagnosis of preeclampsia

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ABSTRACT

Preeclampsia and conditions associated with impaired placental perfusion develop in almost 10% of all pregnancies. Pathologic angiogenesis is one of the processes observed in preeclampsia. sFlt-1, PlGF and the sFlt-1/PlGF ratio are new and promising angiogenesis-related biomarkers. Our paper describes the present status of, and clinical practice opportunities for, these factors.

According to present data, sFlt-1, PlGF and the sFlt-1/PlGF ratio are very useful tools in assessing placental angiogenesis abnormalities associated with preeclampsia and can be use in clinical practice.

Key words: sFlt-1; PlGF; preeclampsia

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INTRODUCTION

Preeclampsia and conditions associated with impaired placental perfusion develop in almost 10% of all pregnancies [1]. The last two decades have seen a 25% rise in the prevalence of these pathologies in the United States [2]. According to the statistical data, clinical syndromes developing secondarily to placental ischemia account for almost 50% of iatrogenic premature births, 50% of hospitalizations in pathological pregnancy departments and 25% of intensive care stays among pregnant patients [3]. Every year, preeclampsia causes nearly 60 thousand deaths among pregnant women [4]. Presently, we are unable to successfully treat these conditions, and the only effective therapy available is termination of the pregnancy. However, recent years have witnessed the emergence of diagnostic methods that have considerably improved our ability to predict pathological symptoms and thus the quality of our monitoring of women and fetuses.

Currently, literary sources concerned with this topic distinguish between early- and late-onset forms of preeclampsia [5]. The early-onset form develops prior to 32–34 weeks of gestation and is definitively connected with impaired trophoblast invasion. The insufficient transformation of the spiral arteries leads to ischemia, uteroplacental compartment hypoxia, and subsequently, to pathological processes such as elevated oxidative stress, inflammation or angiogenesis disorders arising. As a consequence of this, generalized endothelial damage occurs and various clinical symptoms develop, such as arterial hypertension, proteinuria, increased liver damage marker levels, eclampsia and intrauterine growth restriction [6]. The late-onset form of preeclampsia, which has a similar clinical presentation, develops after 34 weeks' of gestation and, according to the current data, there is only a slightly inadequate transformation of the spiral arteries, and the main role is played by maternal factors, e.g. metabolic syndrome [7]. It is also possible that a contributing factor for the development of late-onset preeclampsia syndromes is patient-specific programmed placental senescence.

CURRENT STATUS

Formerly, preeclampsia diagnosis was mainly based on recognizing clinical symptoms and studying the analytical parameters of laboratory tests that revealed the degree of organ damage. However, these analytical criteria were frequently so ambiguous that making the right diagnosis was difficult and required a process of elimination, which took a substantial amount of time. A consequence of the approach was a marked delay in diagnosis and, frequently,

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very serious consequences for the mother and her child. Presently, we are aiming to work out a more precise diagnostic process which is capable of exploring the earlier stages of the condition's development. Determining the presence of angiogenesis disorder-related markers in the uteroplacental compartment is one method to achieve that objective. Already, fms-like tyrosine kinase (sFlt-1 — soluble tyrosine kinase receptor) and placental growth factor (PlGF) laboratory kits have been marketed. sFlt-1 is produced by the syncytiotrophoblast, and its concentrations are only a few times the concentrations of PlGF in physiological pregnancies [8]. In hypoxia, or impaired perfusion of the placenta, the trophoblast produces massive amounts of sFlt-1, and the concentrations recorded in maternal circulation are at least several dozen times the levels of PlGF [9]. Such elevated levels of sFlt-1 have a dysfunctional effect that are responsible for most of the clinical and laboratory symptoms observed in preeclampsia [10].

PlGF has a stabilizing impact on endothelial function. It exerts a positive effect on, for example, placental function, but as sFlt-1 damage to the trophoblastic structures increases, its concentration is gradually reduced. Moreover, sFlt-1 is responsible for neutralizing PlGF and restricting its availability [11]. The situation observed under homeostatic conditions in normal pregnancies on the one hand, and in angiogenesis disorders accompanying preeclampsia on the other, is best represented by the diagram below (Fig. 1).

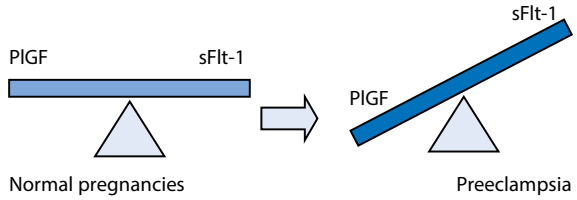

Figure 1. Diagram of the balance of angiogenesis markers in normal pregnancies and their imbalance in preeclampsia [12]

Changes in the sFlt-1 and PlGF concentrations precede the appearance of clinical symptoms and the biochemical parameters of preeclamptic organ damage by approximately 5 to 6 weeks [13].

In diagnosing preeclampsia, PlGF can be used as early as the first trimester. Combining biophysical examinations with biochemical marker assessments has enabled the discovery of an optimal model for detecting those patients with a higher risk of developing early-onset preeclampsia. This risk assessment algorithm uses the pregnant patient's medical history data, mean arterial pressure (measured twice on both the arms — MAP), uterine arterial pulsatility index, and PAPP-A and PlGF concentrations [14]. The model was modified in 2016 by proposing that a two-stage prediction process should be performed between 11 and 14 weeks, and between 19 and 24 gestational age, using MAP, UtA-PI and PlGF. Thanks to this modification, detection rates (DR) of 75% and 85% were achieved for the first and second trimesters, respectively; each with a false positive rate (FPR) of 10% [15]. For the purposes of comparison, the model currently proposed by ACOG results in a DR of 90% with an FPR of 67% [16].

Later in the pregnancy, the highest predictive and diagnostic value starting from 20 weeks gestational age is achieved by measuring sFlt-1 and PlGF levels simultaneously. The sFlt-1/PlGF ratio derived from this data is considered predictive at a cut-off point of 85 [17].

At the earliest, trophoblast invasion disorders lead to the development of clinical symptoms after 20 weeks gestational age. Research reported in the literature has shown that among patients with existing predictive factors for preeclampsia such as chronic hypertension, chronic renal conditions, diabetes mellitus andantiphospholipid syndrome, or with a history of preeclampsia, the sFlt-1/PlGF ratio test allows us to single out that group of patients who are at risk of developing a severe obstetric pathology at a given time. The test is similarly beneficial if conducted in pregnant patients who demonstrate any of the clinical or laboratory symptoms of preeclampsia [18]. Positive sFlt-1/PlGF ratio values, from tests repeated over a period at precise time intervals, allow us to dispel any diagnostic doubts that might persist in such situations.

2015 saw the presentation of the PROGNOSIS test that was carried out in 30 centers around the globe and that included 1.050 pregnant patients with suspected preeclampsia who were between 24- and 37-weeks gestational age. The study was designed to assess the usefulness of sFlt-1/PlGF ratio values for a short-term prognosis, of between 1 week and 4 weeks following the emergence of preeclampsia. Based on the study outcomes it was found that ratio values of less than 38 ruled out the emergence of preeclampsia within the following 7 days (an NPV of 99.3%). The study showed that in patients below 34 weeks gestational age, with ratio values greater than 85, and in those over 34 weeks gestational age, with ratio values greater than 110, there was a very high likelihood of them developing preeclampsia or another condition caused by an ischemic placenta.

In the high-risk cases mentioned above, the ratio values should be monitored and assessed for any indication of progression in the changes. In severe cases of early-onset preeclampsia with a ratio of > 655, and in late-onset preeclampsia with a ratio of > 201, there are strong implications for pregnancy termination within 48 hours of the test results. sFlt-1/PlGF ratio values between 38 and 85 (110) indicate that

there may be abnormal placental perfusion, therefore the authors suggest that in patients with these results prior to 34 weeks gestational age the ratio should be monitored, and in patients after 34 weeks gestational age the ratio should be monitored, and early labor induction considered [19].

Based on present studies, in 2016 the National Institute for Health and Care Excellence (NICE) of the United Kingdom found the sFlt-1/PlGF test to be a promising tool for ruling out preeclampsia in pregnant patients between 20- and 35-weeks gestational age. The Institute ruled, however, that there was a need for further study and that the current state of knowledge was insufficient for recommending the sFlt-1/PlGF test as a routine tool in NHS practice [20].

In 2016 and 2017 more reports on the usefulness of the sFlt-1/PlGF ratio test for ruling out preeclampsia were published. Zeisler et al. presented their results of a multi-center study, where they proved that an sFlt/PlGF ratio cut-off level of 38 had a negative predictive value of 99.3% [21]. In another study of over 4.000 pregnant women with a low risk of developing preeclampsia, Sovio et al. [22] found that the sFlt-1/PlGF ratio was very useful for detecting preeclampsia after 36 weeks gestational age. In addition, the same study found that positive ratio values in women after 28 weeks gestational age correlated with a direct risk of the need to terminate the pregnancy due to evidence of clinical preeclamptic features. Dragan et al. presented the results of their research on the sFlt-1/PlGF ratio in more than 12,000 pregnant patients. The researchers showed that an sFlt-1/PlGF ratio of 38 or less provided a certainty of 99.97% that the patient would not deliver her child within a week of the test, due to preeclampsia. Moreover, the negative predictive value for a ratio of > 38 was very high, at 99.91% [23].

As mentioned above, high sFlt-1/PlGF ratio values correlate positively with the manifestation of serious clinical symptoms necessitating pregnancy termination [18]. It has also been shown that higher sFlt-1 and lower PlGF concentrations are associated with the emergence of more severe clinical syndromes. In early-onset preeclampsia the ratio values are decidedly higher than in the late-onset form of this condition [24]. sFlt-1 concentrations are directly proportional to the severity of proteinuria and inversely proportional to the platelet count [25].

As the research carried out so far indicates, assessing angiogenesis disorder-related markers may prove to be a valuable support for and addition to the diagnosis of preeclampsia, and to the monitoring methods currently in use. The studies mentioned in our paper indicate clearly that the sFlt-1/PlGF ratio value also correlates with the severity of the clinical symptoms. Very high ratio values directly precede the emergence of symptoms necessitating pregnancy termination. Despite these facts, further studies are required before the sFlt-1/PlGF ratio can be introduced as an independent tool. This year has seen the publication of several reports that have included the sFlt-1/PlGF ratio in algorithms for predicting the development of early- and late-onset forms of preeclampsia. It has been proven possible to classify patients depending on their risk of preeclampsia already at 19–24 weeks gestational age [26], and then to compare the results at 30–34 [27] and at 35–37 [28] weeks gestational age. Historically, the highest sensitivity and specificity have been achieved by combining physical (MAP) and imaging (UtA-PI) examinations with biochemical (sFlt-1/PlGF) tests. The possible clinical applications of sFlt-1, PlGF and sFlt-1/PlGF ratio test results are shown in Figure 2.

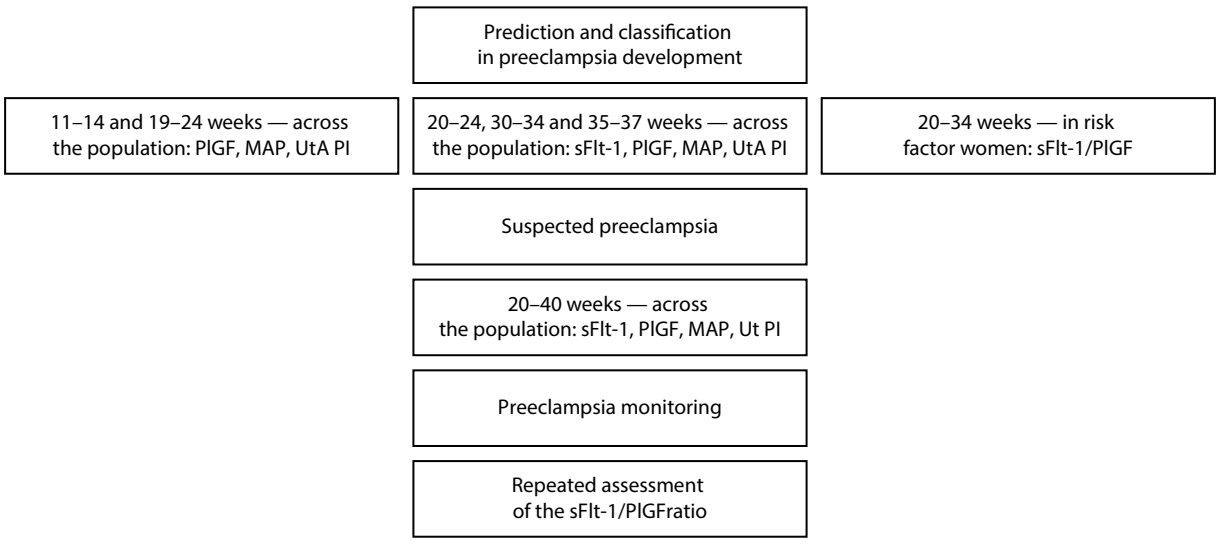

Figure 2. Possible applications of sFlt-1, PlGF and the sFlt-1/PlGF ratio in prediction, diagnosis and monitoring of preeclampsia

Our paper focuses on preeclampsia because most reports on the usefulness of the sFlt-1/PlGF ratio as a diagnostic tool have concentrated on this clinical syndrome. It must be emphasized, however, that the sFlt-1 and PlGF angiogenesis -related disease markers also demonstrate irregularities in other conditions related to placental hypoperfusion and ischemia. The markers show similar variation profiles in intrauterine growth restriction syndromes (IUGR) [29], and in some cases of placental abruption [30].

SUMMARY

Preeclampsia develops as a result of placental insufficiency. New angiogenesis markers sFlt-1 and PlGF provide an opportunity to predict, diagnose and monitor the status of placental angiogenesis abnormalities, including preeclampsia. According to present data, sFlt-1, PlGF and the sFlt-1/PlGF ratio permit the creation of a new model for preeclampsia management. The sFlt-1/PlGF ratio seems to be an especially valuable tool for use in clinical practice.

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Perinatal care in a patient with diagnosed Westphal's disease

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Hypokalemic periodic paralysis (HOKPP) belongs to the group of genetically conditioned myopathies, inherited in an autosomal dominant manner. Pathology is associated with a fall in blood potassium levels (hypokalemia). The disorder is linked to the region of chromosome 1q 31–32 in the gene encoding the dihydropyridine (DHP) receptor and the unit of the alpha-1 calcium channel. Impaired function of ion channels and sodium-potassium pump lead to secondary depolarization of cell membranes and further lack of muscle reaction to nervous stimulation. The Westphal*'s disease* is characterized by the occurrence of quadriplegic paralysis associated with hypokalemia. In the severe form of the disease, a generalized paralysis may occur with involvement of respiratory muscles and arrhythmias. The factors causing the seizure include: sudden temperature changes, cold, long-term immobility, vigorous physical exercise, stress, viral infections. Prevention consists of avoiding risk factors and treatment based on the supply of potassium preparations and the use of mechanical lung ventilation.

CASE REPORT

A 27-year-old female patient came to the hospital, at 41st week pregnant with the first child to induce labor. The course of pregnancy was uncomplicated. The patient did not report any symptoms at the time. Patient's medical history included Westphal's disease, diagnosed in her childhood. She inherited a pregnant illness from her father who has been ill since he was 12 years old. Since the first episode in the third year of life, the patient was under constant care of the Neurological Clinic, hospitalized several times and treated conservatively with potassium preparations. The patient admitted to being supplied with potassium at time of hospital admission.

Due to the 41st week of pregnancy, the decision was made to insert Foley catheter to pre-induce, then to provide oxytocin for labor induction. Before pre-induction, the potassium level blood test was carried, measuring 4.00 mmol/L. During the procedure, the patient reported numbness in the limbs, which according to previous experience of the patient could suggest a decrease in potassium concentration. An ECG was performed in which no disturbances were found. Blood tests showed hypokalaemia at 3.2 mmol/L. 20 mEq KCl was given intravenously as a result of which the symptoms disappeared. After a few hours of induction, amniotomy and administration of diastolic drugs (buskolysin) decelerations occurred in the CTG record. Due to the risk of fetus life, the pregnancy was terminated by caesarean section. A son with a mass of 3400 g Ap 10 was born. In the puerperium period, potassium was supplemented by monitoring its concentration. During the hospitalization period, the patient did not report any recurrence of neurological symptoms. On the fifth day after delivery, she was discharged home with recommendations for neurological control in an outpatient procedure and urgent report to the hospital in case of alarming symptoms.

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